Action potential patterns of intrafusal γ and parasympathetic motoneurons, secondary muscle spindle afferents and an oscillatory firing α_2-motoneuron, and the phase relations among them in humans

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Abstract

1. *Single-fibre action potentials (APs) were recorded from a S4 root of a brain-dead human and a patient with a spinal cord lesion, with 2 pairs of wire electrodes, and distribution histograms of conduction velocity frequencies were constructed. By plotting the intrafusal velocity main γ peak on a logarithmic scale, the peak splitted into one dynamic ad two static γ-peaks and an additional peak of parasympathetic fibres.*
2. *Apart from the doublet firing, a single γ_1 (dynamic) and a single γ_{21}-motoneuron (static) fired with shortest interspike intervals of 80 msec, similarly as a simultaneously firing secondary spindle afferent fibre; with 13 msec the doublet interspike interval of the γ_1-motoneuron was very similar to that of the spindle afferent fibre. The intrafusal motoneurons fired with patterns very similar to those of secondary spindle afferents, and they did not fire in the oscillatory mode for high activations as α_2 and α_3-motoneurons do.*
3. *The stability of the oscillatory firing of a sphincteric α_2-motoneuron increased with the increasing phases of approx. 50 msec between the APs of the γ-motoneurons and the impulse train of the motoneuron following bladder catheter pulling. Moreover, in a certain phase range the number of phases between the APs of a γ_1-motoneuron and a secondary spindle afferent fibre increased upon stimulation and, as shown earlier, also the number of phase correlations between the APs of some secondary spindle afferents and the impulse train of the oscillatory firing α_2-motoneuron increased. Phase relations between the APs of two spindle afferents also increased upon the bladder catheter pulling. During the oscillatory firing of the α_2-motoneuron a phase loop seemed to exist from the APs of the α_2-motoneuron to the APs of certain γ-motoneurons, to the APs of certain secondary spindle afferent fibres and back to the APs of the α_2-motoneuron, in similarity to the phase recoupling of electronic oscillators.*
4. *Single γ-motoneurons changed their activity levels rhythmically, similarly as the secondary spindle afferents, often with a frequency of 0.3 Hz. Parasympathetic intrafusal motoneurons fired at a constant activity level for about 10 sec, and activated up to 6 single encoding sites of a parent secondary spindle afferent fibre. Shortly after the recruitment of a new encoding site, the interspike intervals of the parent fibre were similar again. The parent spindle afferent fibre raised its activity in response to the parasympathetic activation with a time constant of 3 sec (e-fit) and decreased it with a time constat of 40 sec.*
5. *The clinical implication of the methods include nerve anastomoses and regeneration aimed at the restoration of the urinary bladder functions in patients with spinal cord lesions. A rat model is introduced with a structure-function coupling for measuring regeneration stages.*

Key-words: Human — Impulse patterns — Motoneurons — Intrafusal — Extrafusal — Parasympathetic — Spinde afferents — Phase relation — Spinal oscillator — Stretch reflex.

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Introduction

The general scope of the author's research project has been to develop biological treatment to partly cure spinal cord lesions. It is the merit of Guttmann (26) from Breslau who developed, after the World War II in Stoke Mandeville, a treatment procedure to save the life of patients with spinal cord lesions. However, a further step has been missing, i.e. improvement of the quality of life of the patients. In the first 20 to 30 years following the war basic research and surgical techniques were not advanced enough to provide for essential progress. In spite of recent advances in research and microsurgical techniques, there is little interest to organize the necessary clinical research; prejudices and pseudo-ethics are being put forward instead of specific knowledge (see Acknowledgements). The American neurosurgeon Freeman stated already in the 1960's: "It is difficult to find persons who want to do research in paraplegia and it is difficult to get money for the research — probably World War II is already too far away".

Following spinal cord lesion the control over the urinary bladder, rectum and sexual functions is lost, and walking is not possible any more. The loss of the bladder function is most critical, since patients may die of ascending infections of the bladder. Kidney transplantation is useless because of the infections. With a badly functioning bladder paraplegics have difficulties in taking part in the social life. The possible method of reconstruction of the urinary bladder functions by a nerve anastomosis is summarized in the Clinical implication section (57, 58, 59, 60). Improvements of regeneration measurements are also outlined there. However, functions of the human nervous system can only be repaired on the long term, based on a thorough knowledge of these functions, of neural networks exerting these functions, as well as on the possibility of establishing the diagnosis during the surgery (which nerves or nerve roots functions take). The continence of the rectum, as the main focus here, is closely connected to that of the bladder, is easier to measure and is a first step towards the understanding of the urinary bladder continence and storage functions. Bladder functions and their relationship to anorectal continence properties were partly analysed elsewere (65).

Continence functions are slow and may have to last up to hours in some similarity and relationship (pelvic floor) to postural control, where muscles have to work constantly against gravity. Highly specialized muscle spindle receptors could be activated in the constant stretch reflex (81) of the anal sphincter as in some neck muscles (43). Some medium fast components are also needed as, for example, to secure continence of the bladder with coughing and to secure continence of the rectum with the differentiation between gas, fluid and solid substances. In this paper the constant stretch reflex is under consideration. The term constant stretch reflex is not accurate, since this tonic reflex activated by rectal distension will probably decrease within minutes to hours (39).

In a previous paper (63) it was shown that the constant stretch reflex of the external anal sphincter is driven by constantly firing oscillators (52), which consist of the motoneuron itself and many interneurons (63). Probably, only a part of the sphincteric motoneurons will fire in the oscillatory firing mode. Others will still fire in the occasional firing mode (61, 62).

Previously it was shown that a spinal oscillator is excited by afferent action potentials (APs) of secondary muscle spindle afferents, which have a certain phase to the APs of the oscillatory firing α_2-motoneuron (64, 65). Constant stretch reflex was induced by rectal distension with an anal catheter. With additional stimulations (bladder and anal catheter pullings), the phase relations between the secondary spindle and oscillatory firing motoneuron APs changed transiently, and the spinal oscillator stopped firing transiently (65). A transient break of oscillation occurred probably due to reduced occurrence of phases in a certain range between the secondary spindle afferent APs and the motoneuron APs. The reduced number of occurring phase relations was in turn probably due to a hysteresis effect of the secondary spindle afferents (64, 65) caused by creep and other after effects of the intrafusal muscle

fibres (20). The 3 secondary muscle spindle afferents SP2(1), SP2(2) and SP2(3), contributing to the drive of the oscillator in brain-dead human HT6, showed pronounced sensitivity to anal catheter pulling, bladder catheter pulling and painful pin-prick respectively (64, 65). Since the muscle spindles are not innervated by skin, mucosal, flow and pain receptor afferents, the input to these receptors has to run via the intrafusal motoneuron systems. The identification of natural impulse patterns of single intrafusal motoneurons is therefore of high importance for the understanding of the drive of the oscillatory firing α_2-motoneuron by the intrafusal motoneurons via the secondary muscle spindle afferents (final common path). With the identification of the impulse pattern of two single intrafusal motoneurons in the present paper, it will be shown that the intrafusal motoneurons respond differently to changing afferent input from skin and mucosal receptors and drive differently the secondary spindle afferents. It will be further shown that there are certain phase relations between the APs of the γ and the oscillatory α_2-motoneurons, the γ-motoneurons and the secondary spindle afferents and, as shown earlier (64, 65), between the spindle afferents and the α_2-motoneuron. A phase loop seems to exist for excitation of the spinal oscillator in phase.

Even though exact measurements of human spinal oscillators with their mainly secondary spindle afferent drive and the phase loop is a complete new development for the understanding of the constant stretch reflex (81), these findings are partly in accordance with the current opinions concerning the function of muscle spindles. It is the Matthews' standpoint that secondary muscle spindle sensory endings induce a powerful excitation in human stretch reflexes (36), which in the case here is the oscillatory firing α_2-motoneuron in the constant stretch reflex.

Since secondary spindle afferents predominantly innervate nuclear chain muscle fibres (5), and chain fibres can contract locally (12) and can oscillate up to 60 Hz (7, 8), the chain fibre activity provides a mechanism for maintaining a high level input to α-motoneurons that is independent of changes in muscle length (11). Hulliger and Prochazka proposed a concept of fusimotor set (80), claiming that fusimotor firing levels, and the balance between γ_1 (dynamic) and γ_2-motoneurons (static), is set in a way characteristic of, and specific to, a particular movement. Though the α-motoneuron output must also have a characteristic pattern in any movement, the α and γ-motoneuron patterns are usually independent unless the movement is powerful (24).

With the identification of impulse patterns of intrafusal γ-motoneurons it will be shown that somatic γ-motoneuron activities alone cannot explain a strong long lasting activity increase of secondary spindle afferent fibre SP2(2), caused by strong bladder pulling. A parasympathetic muscle spindle activation was therefore introduced and has to be included into the concept of fusimotor set. This autonomic spindle innervation was in accordance with certain activity changes of fibres whose conduction velocities laid in the expected parasympathetic peak in the conduction velocity distribution. Both histological (1, 2, 70) and functional (38) indication for autonomic muscle spindle innervation have been found in animals.

Materials and methods

Measurements were performed on a brain-dead human cadaver (HT6) and a paraplegic patient. For details of the method see previous papers (61, 62).

Results

Identification of peaks of γ-motoneurons and parasympathetic fibres in conduction velocity distributions on log scale

One of the drawbacks in this research project so far has been that it was impossible to clearly identify the different intrafusal motoneuron peaks in distribution histograms of con-

duction velocity frequencies and to identify impulse patterns of single γ-motoneurons. These problems will be approached now. On a linear scale velocity peaks fused and could be separated by their different functions (54, 55) only partly. By constructing first histogram classes for conduction times however, and plotting them on a log scale from the column values, the velocity peaks separated. Figure 1A, B shows that the fused γ-peaks of the linear plots (61, 62) (Aa, Ba) split up into different peaks on the log scale. Since first histogram classes of conduction times were constructed using a linear scale, it was possible to study the dynamics of peaks or peak values also upon stimulation.

Figures 1Ab and Bb show several distribution peaks in which the γ_1 and γ_{21}-peaks could by identified from earlier functional considerations (54, 55, 56). By comparing now (Fig. 1B) the velocity distributions obtained upon stimulation with those without stimulation, and assuming reasonably that the dynamic intrafusal motoneuron peaks are higher upon stimulation (Fig. 1Bd) and the static ones are higher with no stimulation (Fig. 1Bc), a second static

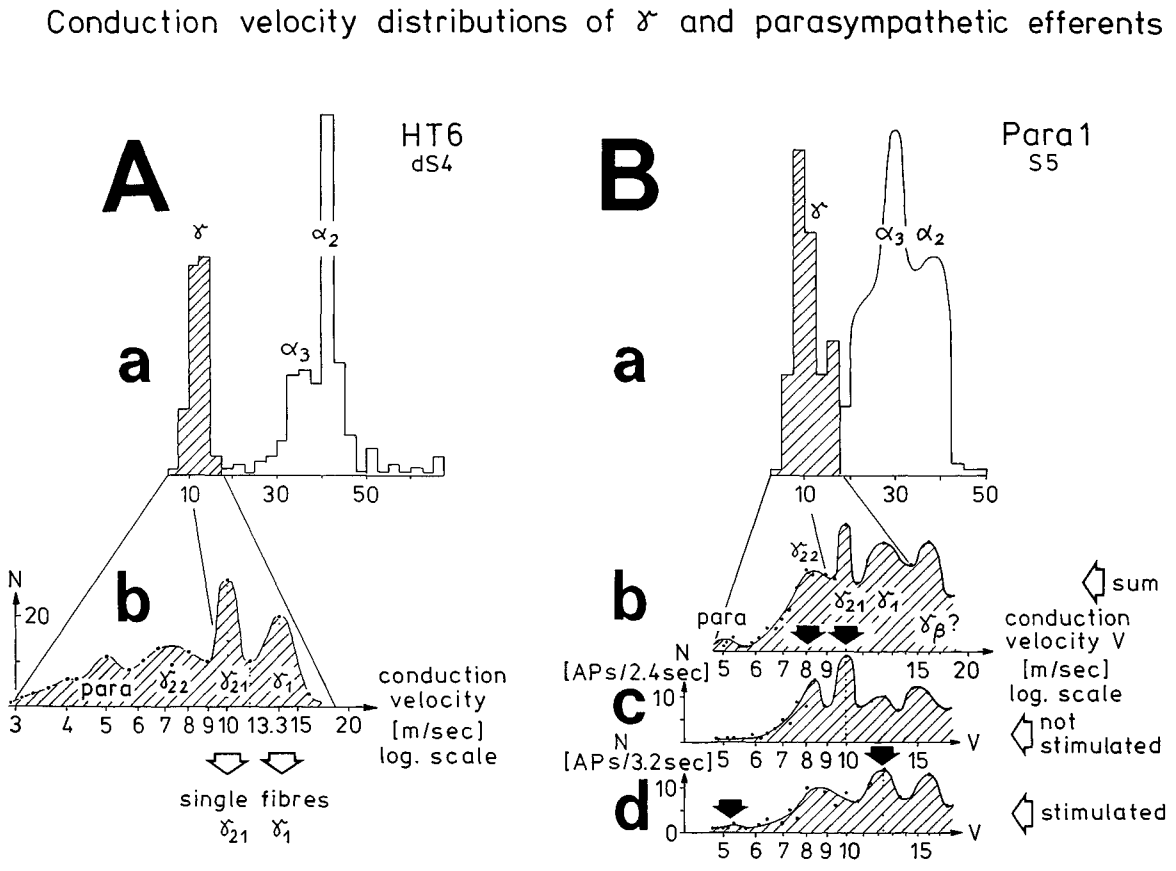

Fig. 1. — Conduction velocity frequency distributions of motoneurons in the brain-dead human HT6 (A) and in the paraplegic 1 (B). To make intrafusal motoneuron and parasympathetic peaks visible, the main γ-peak of Aa and Ba was replotted on a log scale in Ab and Bb. The distribution peaks are labelled with the groups, they most likely represent. In B, the distribution Bb is split into the distribution upon no additional stimulation (Bc) and upon additional stimulation (Bd). Note that with the nonstimulated distribution (Bc) the static γ-motoneuron peaks (γ_{22}, γ_{21}) are highest, whereas under stimulation (Bd) the parasympathetic (para) and the dynamic γ-motoneuron peaks (γ_1) are highest. The activities of the single fibres γ_{21} and γ_1 are not contained in distribution Ab. When plotting the velocities in Ab and Bb logarithmically, the conduction times were first grouped by a conduction time histogram and the column values were then used (conduction distance = 8 mm) to construct conduction velocity distribution curves.

γ-peak (γ_{22}) can be identified and at least one further rather dynamic motoneuron peak (para) can be seen. This peak distribution observed in the paraplegic patient could also be found in the measurements in HT6 (Fig. 1Ab). That the "para" peak contains activity from parasympathetic fibres will be shown later.

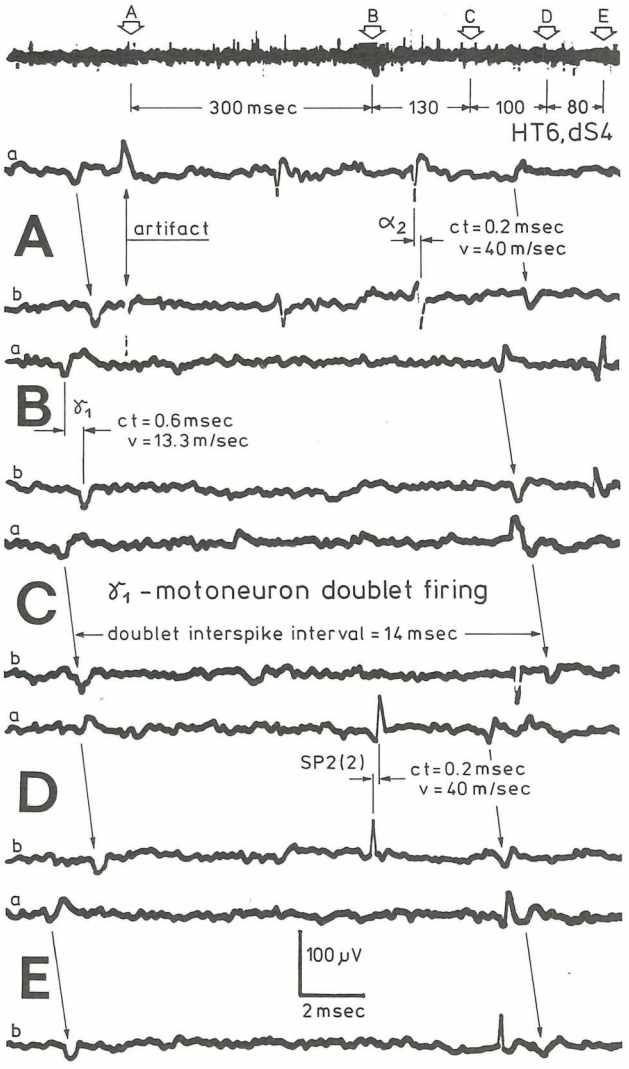

Fig. 2. — Doublet firing from a single γ_1-motoneuron (intrafusal, dynamic). From the sweep on the top of the figure, successive AP doublets are shown on an expanded time scale in A to E. Conduction times (ct), conduction velocities (v), a doublet interspike interval and interspike intervals from doublet to doublet are indicated. An artifact (A) can clearly be distinguished from real action potentials by the mirror picture potentials and the missing of the conduction time. HT6, dS4.

Impulse patterns of intrafusal motoneurons

By looking repeatedly through the HT recordings at high γ-motoneuron activation, it was possible to identify the impulse patterns of a single dynamic γ-motoneuron by the action potential (AP) wave form, duration, conduction time and doublet firing. Because of the importance of the finding, five successive doublet interspike intervals (IIs) are shown in figure 2. The approx. IIs from doublet to doublet are

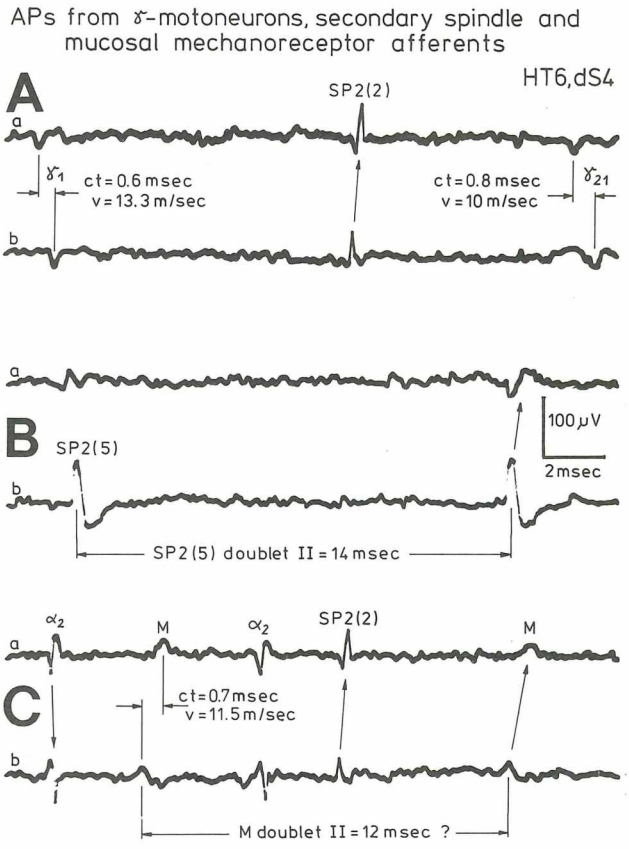

Fig. 3.

A. Recording of a single γ_{21}-motoneuron action potential (AP) (intrafusal, static) in comparison to a single identified γ_1-motoneuron AP.

B. AP doublet of the secondary muscle spindle afferent fibre SP2(5), recorded at the same time period as the APs of the single γ_1 and γ_{21}-motoneurons. Note, that the SP2(5) doublet has the same duration as the γ_1 doublet in figure 2 (14 sec).

C. APs recorded from a mucosal afferent fibre (M). Conduction time (ct) and conduction velocity (v) are indicated. APs from other fibres are intermingled.

shown in the upper part of figure 2 (see also (Fig. 6A). The γ-motoneuron doublet II had very similar durations of about 13 to 14 msec.

Before plotting the doublet IIs and the IIs from doublet to doublet, let us throw a look on original registrations of other nerve fibres (Fig. 3). It was further possible to identify the impulse pattern of a single γ_{21}-motoneuron. An AP of it is shown in figure 3A together with an AP of the γ_1-motoneuron. Figure 3B shows a doublet II of a simultaneously firing secondary muscle spindle afferent fibre SP2(5). Only the second AP of the doublet is partly conducted to the proximal electrode pair (trace a).

So far only muscle spindle afferent fibres were analysed as candidates for the afferent excitation of the oscillatory firing of motoneurons activated for the constant stretch reflex of the external anal sphincter. However, mucosal afferent APs could also contribute to the oscillatory firing of the motoneuron. Figure 3C shows two mucosal APs with an II duration in the range of those of SP2 doublets. Probably, this M-doublet occurred only accidentally. It has not been possible so far to pick up the impulse patterns of single mucosal receptor afferents.

Figure 4 shows the impulse patterns of a γ_1 and a γ_{21}-motoneuron in the form of IIs between doublets (Fig. 4A, B) and of IIs of the doublets (Fig. 4C, D). The dynamic (γ_1) and the static (γ_{21}) intrafusal motoneurons fired with a

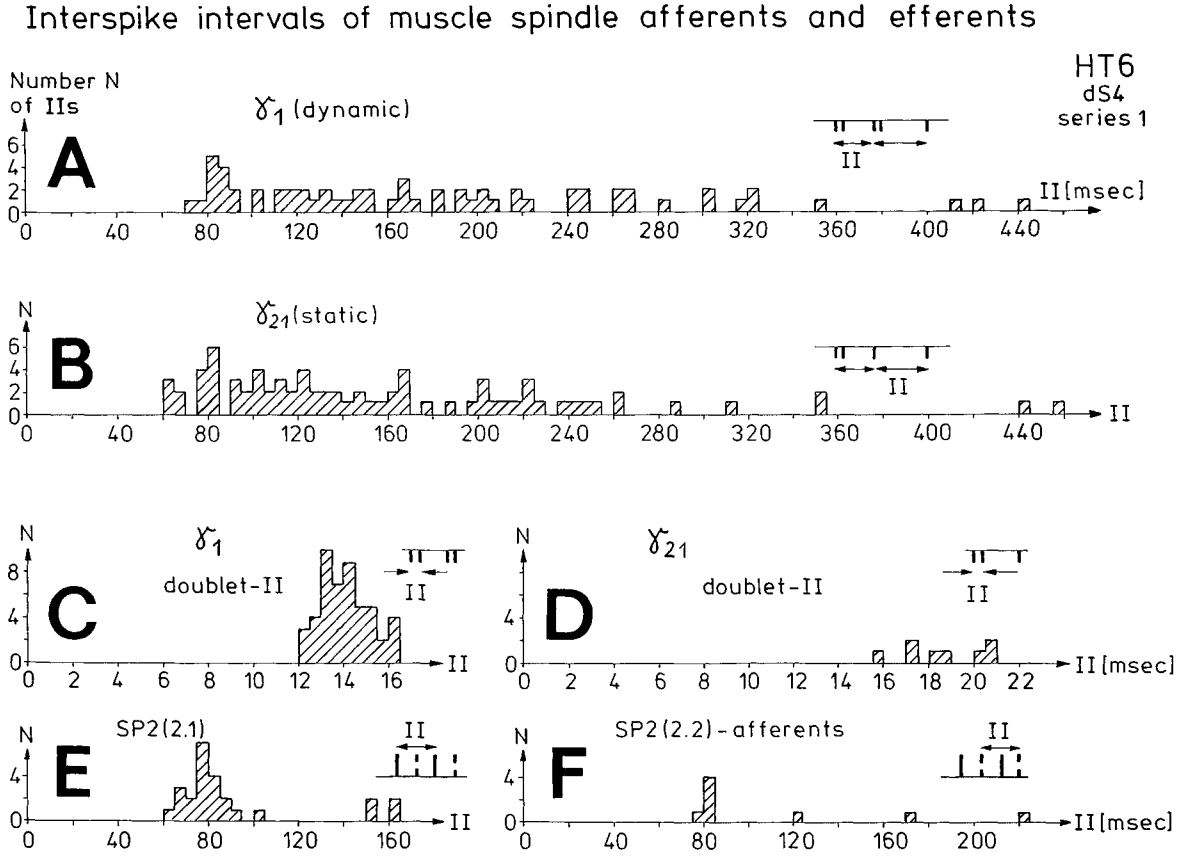

Fig. 4.

A, B. Interspike interval frequency distribution histogram of a single γ_1(A) and a single γ_{21}-motoneuron (B). The way how the intervals were measured is shown.

C, D. Doublet interspike interval distribution histograms of a single γ_1(C) and a single γ_{21}-motoneuron (D).

E, F. Interspike interval distribution histograms of the two single endings SP2(2.1) (E) and SP2(2.2) (F) of the single parent secondary muscle spindle afferent fibre SP2(2) measured at the same time interval as the γ interspike intervals in A to D.

shortest II of about 80 msec. Also, the single encoding sites of APs of secondary muscle spindle afferents fired with a shortest II of about 80 msec (64, 72). The doublet II distribution for the γ_1-motoneuron showed a peak between 13 and 13.5 msec (Fig. 4C). The γ_{21}-motoneuron fired only sometimes with doublets of durations of about 18 msec (Fig. 4D). Maybe, the γ_{21}-motoneuron neural network was not as much excited as that of the γ_1-motoneuron.

By firing with shortest IIs of 80 msec and doublets of 12 to 21 msec, single γ_1 and γ_{21}-motoneurons fired with the pattern of the secondary spindle afferents rather than with that of α_2-motoneurons in the high activity mode of oscillatory firing. An α_2-motoneuron, firing with an impulse train of 2 APs, about 6 msec apart (52), would fire with an oscillation period of 130 msec (63). The two γ-motoneurons showed, at the moment of firing with doublets and a shortest II of 80 msec between the doublets, a higher activity than did the α-motoneuron, firing in oscillatory mode with impulse trains consisting of 2 APs.

The two γ-motoneurons fired in the way the secondary spindle afferents did. The II distributions of 2 encoding sites of the simultaneous firing SP2(2) fibre are shown in figure 4E, F. It will be discussed in the discussion section whether the intrafusal motoneurons drove the secondary spindle afferents via the intrafusal fibres, or whether the secondary spindle afferents drove the γ-motoneurons. The single encoding site SP2(2.1) of the secondary spindle afferent fibre SP2(2) showed more IIs of 80 msec duration (Fig. 4E) than did single intrafusal motoneurons γ_1 and γ_{21} (Fig. 4A, B); its degree of regularity was therefore higher at the time of these measurements.

Successive interspike intervals (IIs) of the dynamic (γ_1) and the static (γ_{21}) intrafusal motoneurons are shown in figure 5. The changes of the γ_{21}-motoneuron were slowlier and longer lasting than that of the γ_1-motoneuron, supporting the identification of static and dynamic patterns by the velocity distributions (Fig. 1). The successive IIs of these 2 γ-motoneurons (Fig. 5) were similar to those of

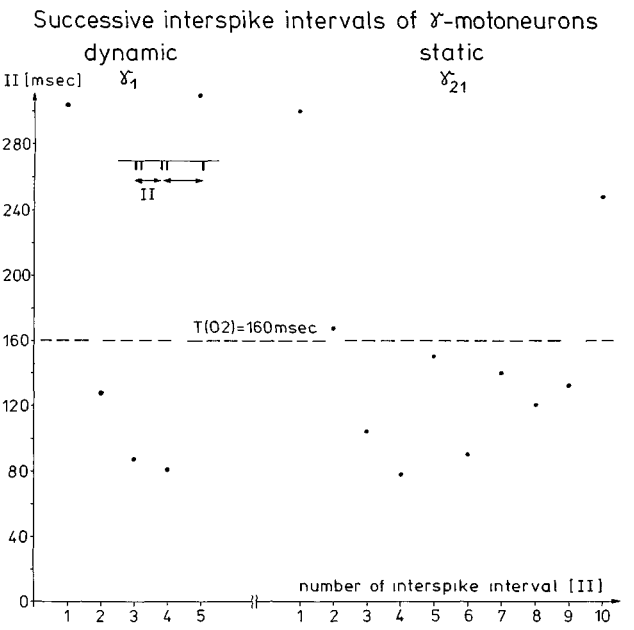

Fig. 5. — Successive interspike intervals (IIs) of single γ_1 and γ_{21}-motoneurons. The way how IIs were measured is indicated. The oscillation period of the oscillatory firing α_2-motoneuron O2 is indicated.

certain secondary spindle afferents (Fig. 4 of Ref. 64).

Figure 6 shows the impulse patterns of single γ_1 (dynamic) and γ_{21}-motoneurons (static) simultaneously with the impulse patterns of the secondary muscle spindle afferent fibres SP2(2) and SP2(5) (and SP2(4)) and the continuously oscillatory firing α_2-motoneuron O2 in HT6. It can be seen from these direct patterns that the γ-motoneurons did not show oscillatory firing as did α_2-motoneuron O2 (no coactivation). On recordings shown in figure 6A the γ_1-motoneuron is mainly firing with doublets following bladder catheter pulling. The marked part of it is shown in figure 2. Before the bladder catheter pulling (Fig. 6B) the γ_1-motoneuron was only sometimes firing with doublets. Thus, repeated bladder catheter pulling may have activated the doublet firing. The increase in activity following bladder catheter pulling (Fig. 6A, 25 APs) as compared to that following pin-prick (Fig. 6B, 20 APs) is only slight. Since this repeated bladder catheter pulling activated the parasympathetic spindle innervation (see below), the increase in the

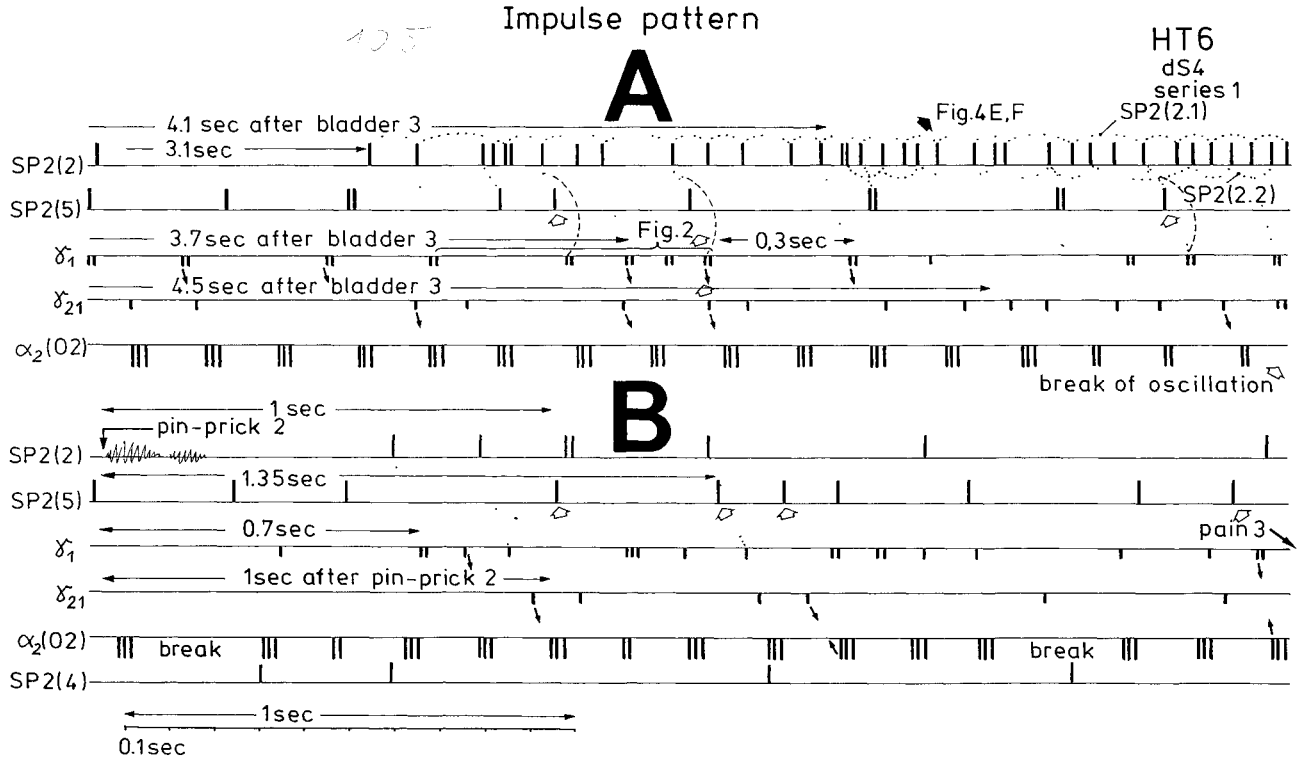

Fig. 6. — Impulse patterns of simultaneously recorded γ-motoneurons (γ_1 and γ_{21}), secondary spindle afferent fibres (SP2(2), SP2(4), SP2(5)) and the oscillatory firing α_2-motoneuron O2 following bladder catheter pulling (bladder 3) (A) and pin-prick 2 (B). B was recorded before A. In A the impulse patterns of the 2 encoding sites SP2(2.1) and SP2(2.2) (not necessarily identical to the endings of Fig. 4E, F) of the single parent afferent fibre SP2(2) are indicated by the dotted curves. Times to the activity increases of γ-motoneurons and secondary spindle afferents following stimulation are indicated. Similar time intervals between the occurrence of γ-motoneuron APs and the SP2(5) fibre APs (phase relation) are indicated by the open arrows, and similar time intervals between γ-motoneuron APs and α-motoneuron APs are indicated by small arrows. Similar time intervals between the APs of fibres SP2(2) and SP2(5) are indicated by the double dotted lines, between γ_1-APs and the SP2(2) fibre APs by a dotted line and between the γ_1-APs and the SP2(2)-SP2(5) correlations by a curved dashed line.

doublet firing maybe due to an increase of the low level parasympathetic activity. Also, the spindle afferent fibre SP2(5) raised its doublet firing from no doublets (Fig. 6B) to occasional doublets (Fig. 6A). Upon strong activation of the parasympathetic nervous system (Figs. 7, 8) this SP2(5) fibre showed about 10 min later low activity, consisting of only doublets. Also, fibre SP2(2) fired after about 10 min following this parasympathetic activation with doublets (Fig. 8 of Ref. 64).

The γ_{21}-motoneuron fired with doublets but occasionally. As can be seen from figure 6, the dynamic γ_1-motoneuron raised its activity more rapidly following pin-prick (0.7 sec) and bladder catheter pulling (3.7 sec) than did the static γ_{21}-motoneuron (1 sec and 4.5 sec respectively). The spindle afferents SP2(2) and SP2(5) raised their activity following pin-prick later than did γ_1 and γ_{21}-motoneurons (Fig. 6B, 1 sec and 1.35 sec). However, the spindles were most likely innervated by more intrafusal motoneurons (β-motoneurons were nearly not activated (Fig. 1)). Some of them may have raised their activity earlier than γ_1 and γ_{21}-motoneurons, so that the time correlation of the two single γ-motoneurons with the spindle afferents is conclusive but partly. As can be seen from figure 7B, the remaining γ-motoneurons (γ-rest) raised their activity slightly earlier than did γ_1

and γ_{21}-motoneurons, indicating that there may have been a γ-motoneuron (or parasympathetic fibre), which had raised its activity slightly earlier than did γ_1 and γ_{21}-fibres.

The strong activity increase of fibre SP2(2) (Fig. 6A) was not induced by γ_1 and γ_{21}-motoneuron activity or by that of the remaining γ-motoneurons (Fig. 7B). It was due to the parasympathetic spindle innervation, as will be analysed below. The dotted lines link the impulses of single encoding sites of parent fibre SP2(2).

Phase relations between extra- and intrafusal motoneurons and secondary spindle afferents

Following bladder catheter pulling the oscillatory firing α_2-motoneuron O2 was more stable (Fig. 6A) than before pulling (Fig. 6B) following pin-prick. Two breaks and 2 impulse trains of 2 APs each occur in figure 6B, and there is no break in figure 6A. The activity of γ_1 and γ_{21}-motoneurons is slightly higher following bladder catheter pulling. Figures 2, 3 of Ref. 65 show that there were less breaks in oscillation with higher spindle afferent activity. With a phase of 50 ± 10 ($n = 5$) (mean $\pm$ st.d.) for γ_1 and 42 ± 15 msec for γ_{21}-motoneuron between γ-motoneuron and α_2-motoneuron O2, 9 phase-correlated APs occurred in figure 6A and 4 (phase = 44 ± 20 msec) are seen in figure 6B. The number of phase correlations between γ-motoneurons and α_2-motoneuron O2 increased more rapidly than did γ APs occurrence. The strength of the drive of oscillation therefore can be better measured by the number of phases occurring in a certain range between γ and the α-motoneurons than by the number of γ or SP2 fibre APs. In previous work (Fig. 7 of Ref. 55) it seemed that corecruitment of γ_1 and α_2-motoneurons in the occasional firing mode also increased with the strength of stimulation.

In figure 6B, there were 3 phase correlations between γ_1 and γ_{21}-motoneurons and the 10 SP2(5) fibre APs. In the higher excited stage of figure 6A 4 phase correlations occurred between the APs of the two γ-motoneurons and the 12 SP2(5) fibre APs. The fibre SP2(5) thus received only little drive from encoder sites by single γ_1 and γ_{21}-motoneurons. Nevertheless, the activity of fibre SP2(2) was strongly correlated to that of the single γ_1-motoneuron. Already 3 phase correlations occurred for 7 afferent APs (67 ± 11 msec) following pin-prick 2 (Fig. 6B). The second γ APs of the doublets contributed further phase correlations. There is indication for the single γ_1-motoneuron driving the single encoding site of fibre SP2(2), active at the time shown in figure 6B. About 6 phase correlations occurred (Fig. 6A) between the APs of γ_1-motoneuron and fibre SP2(2) (phase = 52 ± 13 msec). However, additionally there were at least parasympathetic intrafusal motoneurons (see below), which additionally drove encoding sites of the SP2(2) parent fibre (right side of Fig. 6). With stronger oscillation of α_2-motoneuron O2 (Fig. 6A) there were more phase correlations occurring between γ_1-motoneuron and fibre SP2(2) and between γ_1-motoneuron and oscillatory firing α_2-motoneuron O2. With stronger afferent input, the number of phase correlations between APs of γ_1-motoneuron and α_2-motoneuron O2, increased as did those between γ_1-motoneuron and the secondary afferent fibre SP2(2) (Fig. 6); as shown previously (65), there were also more correlations between fibre SP2(2) and α_2-motoneuron O2. As the afferent inputs from the bladder, anal canal and skin were not constant (51), and in response to it γ-motoneurons changed their activity levels (Figs. 6, 7B), synchronisation with the activity of the extrafusal motoneurons was often transiently lost. This loss of synchronisation will probably also depend on the kind of intrafusal muscle fibre (bag or chain fibre) and on whether there is increasing or decreasing activation (hysteresis effect (64, 65)). Even with many APs from muscle spindle afferents, the oscillation can transiently break (Fig. 4 of Ref. 65). Apart from these dynamic changes, with the increasing drive from the bladder, anal canal and skin afferents, the APs of γ-motoneurons and the oscillatory firing α_2-motoneuron O2 were closer phase-correlated, and thus the single encoding sites of the secondary spindle afferent fibre

SP2(2) and the α_2-motoneuron O2 were also correlated, as was shown for fibre SP2(2) (Figs. 7, 8 of Ref. 64).

In figure 6A there were many SP2(5) APs phase correlated to SP2(2) APs (indicated by the double dotted lines; phase = 35 ± 9 msec, $n = 6$). Most phase relations occurred between SP2(5) APs and the encoding site SP2(2.1). Since phase correlations also occurred to other SP2(2) fibre APs, it is likely that the splitting of the SP2(2) fibre activity into APs of single encoding sites was only approximately correct. A correction is possible (Fig. 6A), but was not performed. The increase of phase correlations between APs of fibre SP2(2) and those of SP2(5) indicates that partly the fibres were activated by the same intrafusal motoneurons. Since 3 phase relations occurred between the γ_1-doublets and the SP2(2)-SP2(5) phase relations (indicated by the bended dashed line in Fig. 6A), it is likely that the γ_1-activity contributed essentially to the SP2(2.1) encoding site and slightly to the SP2(5) afferent fibre, so that SP2(2)-SP2(5) phase relations occurred. Thus, the γ_1-motoneuron probably innervated intrafusal muscle fibres of the muscle spindles, afferently innervated by SP2(2) and SP2(5) afferents. Since fibre SP2(2) responded mainly to bladder stimulation, and fibre SP2(5) responded nonspecifically (65), it is unlikely that afferents SP2(2) and SP2(5) innervated the same muscle spindle.

Parasympathetic muscle spindle innervation

In previous work it was argued that the strongly increased spindle afferent fibre activity (lasting for more than 10 min), following strong bladder catheter pulling was due to the cumulative response of static γ-motoneuron activity (53, 56). With the identification of impulse patterns of the single dynamic and static γ-motoneurons, it will turn out that this long lasting increased summed SP2 fibre activity was due to the activity increase of fibre SP2(2) alone, secondary to parasympathetic activation of the secondary spindle afferent fibre.

Figure 7A shows that fibre SP2(5) changed only very little its activity level, whereas the activity of fibre SP2(2) strongly increased following strong bladder catheter pulling. About 10 min later, the activity still did not fully return to prestimulation level. This long lasting activity increase cannot be due to the activity increase of the single dynamic γ_1-motoneuron, since there was a similar increase in γ_1-motoneuron activity following pin-pricking (left part of Fig. 7B) with no increase in that of fibre SP2(2). Either the single static γ_{21}-motoneuron cannot be responsible for this long lasting activity increase of fibre SP2(2), since after bladder catheter pullings the γ_{21}-activity was nearly as high as with anal catheter pulling, but fibre SP2(2) activity decreased slowly instead of strongly increasing. It is also very unlikely that another γ-motoneuron is responsible for this strong activity increase of fibre SP2(2), since activation of the remaining fibres of the same root with low and very low conduction velocities (γ-rest) was nearly identical upon both anal catheter pulling (Fig. 7B, right) and bladder catheter pulling (Fig. 7B, middle), but the SP2(2) fibre activity dit not increase. Still another possibility is that there were slowly conducting fibres which contributed to the activity of "γ-rest" fibres, which had a different effect on the intrafusal muscle fibres innervated by the myelinated afferent endings of SP2(2). In figure 1A, B there is a conduction velocity peak at about 5 m/sec which probably contained activity of parasympathetic fibres. Since this very slowly conducting fibres responsed more dynamically (Fig. 1Bd) and it can be expected that the parasympathetic fibres (1st motoneuron) being contained in a S4 root (49) conduct only slightly slowlier than the static γ-motoneurons (the fibre diameter of the static γ-motoneurons is about 5 to 6 µm and that of the parasympathetic fibres is about 3 to 5 µm (49, 51, 54)), it is likely that fibre SP2(2) was also activated by parasympathetic motoneurons. Nevertheless, this possibility needs to be proven. It can be seen from figure 7B (middle part) that the single γ_1 and γ_{21}-motoneurons increased and decreased their activity following stimulation with a rhythm of about 3 sec. It could well be that parasympathetic fibres, belonging to another division of the

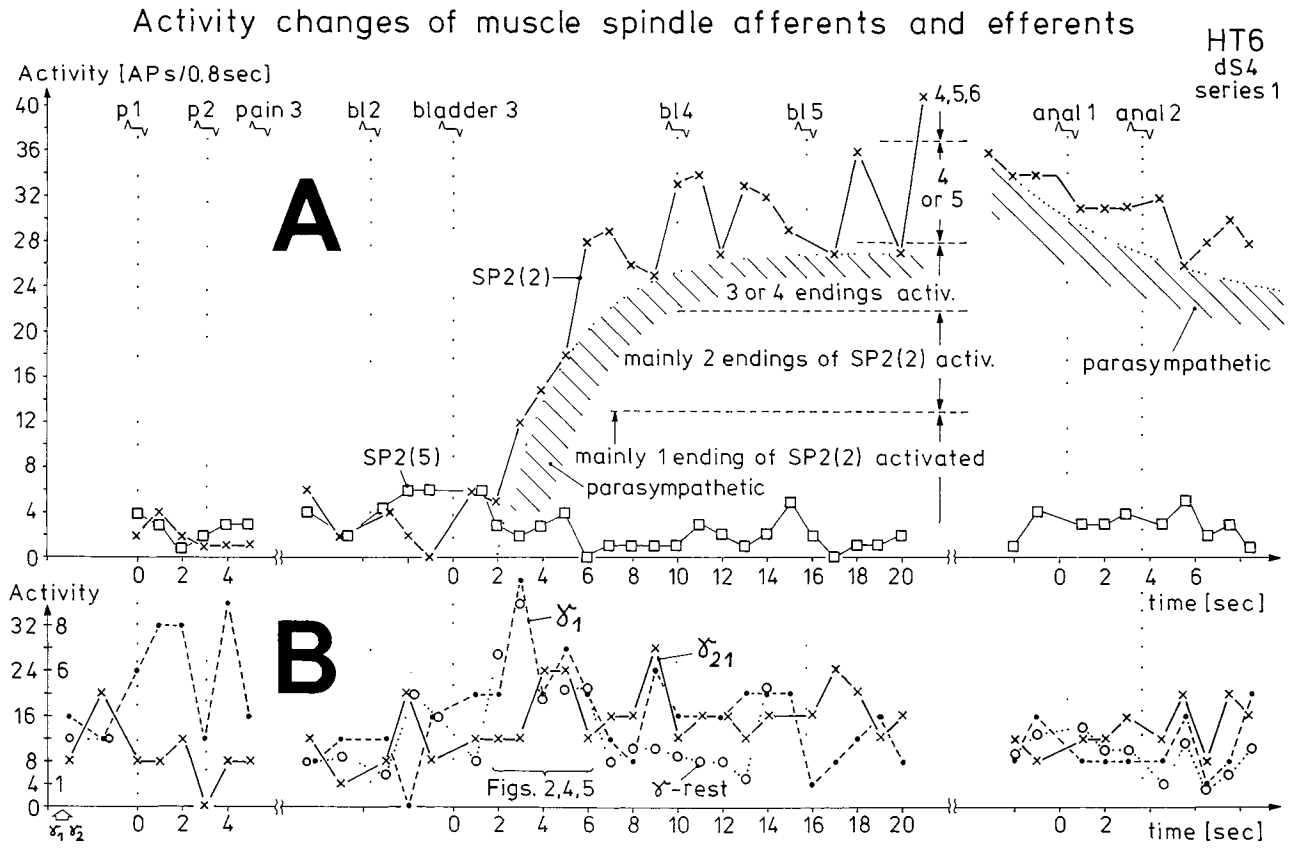

Fig. 7. — Activity changes of the secondary muscle spindle afferent fibre SP2(2) (and SP2(5)) (A) in relation to the simultaneously measured activity changes of the single intrafusal motoneurons γ_1 and γ_{21} and the remaining intrafusal motoneurons γ-rest (including parasympathetic efferents) (B). The very strong long lasting base line activity increase of fibre SP2(2) following very strong bladder catheter pulling (bladder 3) is indicated by the dotted and the cross-hatched lines and represents, most likely the activity increase due to parasympathetic muscle spindle activation. It is indicated in A, how many single endings of fibre SP(2) were activated. p1, p2, pain 3 = pin-pricks; bl 2, bladder 3, bl 4, bl 5 = bladder catheter pullings; anal 1, anal 2 = anal catheter pullings. In B the activity 0 to 8 holds for the γ_1 and γ_{21}-motoneuron and the scale 0 to 32 for the rest of efferent fibres (γ-rest).

nervous system, are activated with different impulse patterns. This possibility was tested by plotting the activity changes of motoneurons conducting with different velocities (low ranges) in relation to the activity increase of fibre SP2(2) suspectedly caused by parasympathetic fibres (Fig. 8). To obtain the proportion of the activity increase of fibre SP2(2) mainly due to parasympathetic fibre activity (Fig. 7A), fibre SP2(2) activity following bladder and anal catheter pulling was compared with the activity level and its changes before the catheter pullings. The strong baseline activity increase, most likely due to parasympathetic activity, is indicated in figure 7A by the dotted line and the partly cross-hatched area. Based on shortest interspike intervals of 80 msec of single encoding sites of human secondary spindle afferents (Fig. 4E, F; Fig. 5 of Ref. 64), the parasympathetic fibres could be assumed to activate up to 6 single encoding sites (Fig. 7A).

Figure 8 shows the activity increase of fibre SP2(2) due to parasympathetic activation, replotted from figure 7A into a different scale. Figure 8L shows the velocity distribution of γ-motoneurons and probably parasympathetic fibres from figure 1Ab. Figure 8M shows the conduction velocity distribution histogram at the beginning (or increasing) of parasympathetic activation measured by the afferent response (Fig. 8A). Figures 8B to K show the activity changes of fibres with conduction ve-

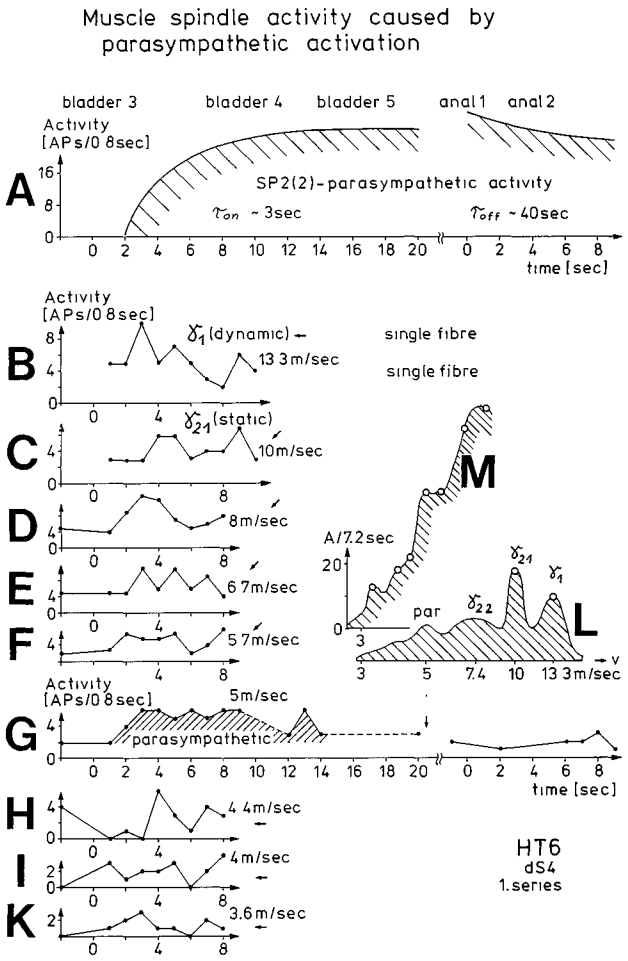

Fig. 8. — Long-lasting activity changes of the single secondary muscle spindle afferent fibre SP2(2) in relation to the activity changes of the efferents, most likely including the efferent innervation of the spindle which is innervated by SP2(2) fibre. A. Changes of the baseline activity, taken from figure 7A (different scale). B. to K. Activity changes of the efferents in the dorsal S4 root of HT6, conducting at different group peak conduction velocities (or certain intermediate values) indicated by circles on the conduction velocity frequency distribution curves M and L. L. Velocity curves of figure 1A, taken from measurements at different times. M. Velocity curve from the measurements used for the construction of figures B to K. B and C are single-fibre activity changes, taken from figure 7B. D to K. Activity changes from probably several fibres. Note that the activity changes in G are long lasting, the other ones in B to K are not; only the activity in F is similar, with probably the activities of 1 or 2 parasympathetic fibres intermingled. Note further that at the time of anal-catheter pulling, where fibre SP2(2) shows still parasympathetic induced activation, there is no or no increased parasympathetic efferent activity. v = conduction velocity.

locities indicated in figure 8M. The activity changes of the single γ-motoneurons of figures 8B and C are partly those seen in figure 7B. Time-related changes of fibre groups with selected conduction velocities are shown in figure 8D to K. It can be seen from figures 8B to K that following bladder catheter pulling the activities of all fibre groups increased and decreased similarly as that of single γ-motoneurons (Fig. 8B, C) with the exception of the (assumedly) parasympathetic fibre group shown in figure 8G. The parasympathetic fibre activity remained a certain level up to 9 sec following bladder catheter pulling. Irregularities occurred because of further bladder catheter pullings. The only other fibre group which showed an increased activity were fibres represented in figure 8F. However, the fibres giving rise to this increased activity (Fig. 8F) are a mixture of parasympathetic fibres and γ_{22}-motoneurons. This measurement allowed to identify, by the long lasting activity increase, the parasympathetic motoneurons generating the strong long lasting activity increase of muscle spindle afferent fibre SP2(2). The γ-motoneurons showed no constant activity increase; they increased and decresed their activity with a rhythm of 0.3 Hz. The actual activity patterns of single parasympathetic fibres could not be identified so far. As figures 8M and L further show, there seem to be further groups, conducting at velocities between 3 and 5 m/sec at 33.5 °C. Nothing can be said so far about whether parasympathetic motoneurons split or not into extrafusal and intrafusal fibres.

By comparing figure 8A with figure 8G it can be seen that the parasympathetic fibres were only active at the time of the activity increase of afferent fibre SP2(2) and not during the slowly decrease of fibre SP2(2). The parasympathetic fibres seem to induce a very strong cumulative response on fibre SP2(2). Using the well known fits of the natural exponential function ($Ao(1-e^{-t/\tau_{on}})$ and $Aoe^{-t/\tau_{off}}$) the time constant τ for the activity increase and decrease of fibre SP2(2) can be calculated:

τ_{on}: if $t=\tau_{on}$, then $Ao(1-1/e) = Ao(1-0.37)$ = 27 APs/0.8 sec × 0.63 = 17 APs/0.8 sec.

The value of A = 17 APs/0.8 sec was reached after 3 sec (Figs. 7A, 8A), τ_{on} = 3 sec

τ_{off}: if $t = \tau_{off}$, then $A_o e^{-1}$ = 34 APs/0.8 sec × 0.37 = 12 APs/0.8 sec. The reduction from A = 34 APs/0.8 sec to A = 12 APs/0.8 sec was reached 40 sec later (Figs. 7A, 8A), τ_{off} = 40 sec.

The time constant for the reduction of fibre SP2(2) activity was with τ_{off} = 40 msec more than 10 times longer than the corresponding time constant for the activity increase (τ_{on} = 3 sec). Since fibre SP2(2) decreased and increased its activity quickly in parallel with the activity changes of γ-motoneurons (Fig. 7A), the extremely slow reduction of the fibre SP2(2) activity following parasympathetic activation is most likely due to the very slow relaxation of the intrafusal muscle fibre area innervated by parasympathetic motoneurons (see discussion).

Relation between conduction velocity, action potential amplitude and action potential duration

Even though it has been denied, the conduction velocity of a myelinated fibre is related to action potential (AP) amplitude and AP duration. With increasing conduction velocity (and the increasing diameter) AP amplitude increases and AP duration decreases (47, 48, 49, 51, 60). The scatter in these relations is large because different fibres in a root are at different distances from the recording electrodes. Also, nerve fibres change their diameter slightly from internode to internode (49). And, as a matter of fact, damaged nerve fibres have strongly reduced conduction velocity and increased AP duration. Poor digitalisation and too strong filtering will reduce large AP amplitudes. Nevertheless, good recordings clearly demonstrate that average AP amplitude decreases and AP duration increases with the reduction of conduction velocity when changing from one nerve fibre group to another. These relations are of interest here, since with known expected conduction times, AP amplitudes and AP durations, it is much easier to identify or to pick up certain APs on traces *a* and *b*, in particular in the presence of small amplitudes and high levels of noise and artefacts.

From figures 9A and 2 it can be calculated that the AP duration increased from α_2 through γ_1 to parasympathetic motoneurons (1:3:6), and that the AP amplitude decreased in the same sequence (1:1/3:1/8) (Fig. 9B).

Discussion

Natural stimulation of the stretch reflex

The constant stretch reflex of the anal sphincter is considered. Upon constant stretch of the anal sphincter by an anal catheter of 12 mm in diameter, sphincteric α_2-motoneurons

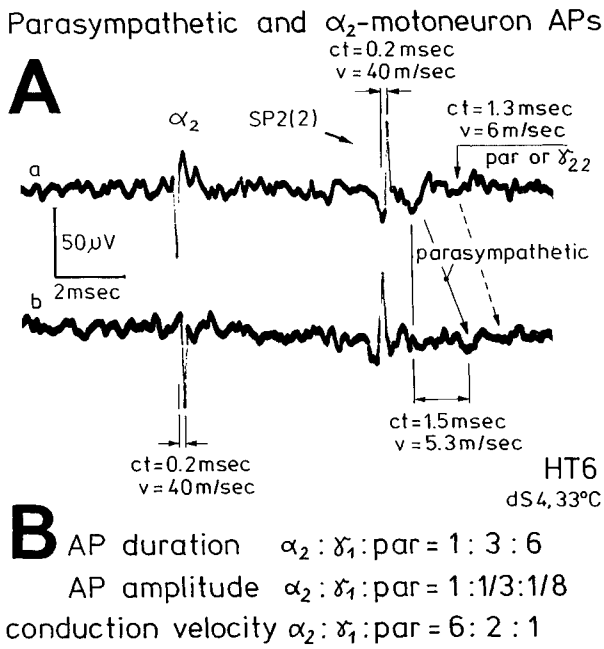

Fig. 9.

A. Wave form and conduction time (ct) of a parasympathetic action potential (AP) in comparison to the wave forms and conduction times of the AP of an α_2-motoneuron and the secondary muscle spindle afferent fibre SP2(2). v = conduction velocity, par = parasympathetic, γ_{22} = static intrafusal motoneuron.

B. Approximate relations of AP duration, AP amplitude and conduction velocity between α_2-motoneurons (extrafusal), γ_1-motoneurons (intrafusal, dynamic) and parasympathetic (par) efferents.

(FR) and α_3-motoneurons (S) responded partly by firing continuously in the oscillatory firing mode. This oscillatory firing (63) was stimulated, when the catheter was not pulled, mainly by the activity of secondary muscle spindle afferents, activated by the sphincter distension. Apart from mucosal afferents, other afferents in the same dorsal S4 root with diameters larger than 5 μm did not fire (limit of recording method). This finding is in accordance with the Matthews' opinion that secondary spindle afferents cause a powerful autogenic excitation in human stretch reflexes (36). In a first approximation, the anal sphincter contracted isometrically, since the catheter determined approximately constant length.

To explore this rather constantly acting recto-sphincteric-reflex (81), stimulations such as pin-prick, anal and bladder catheter pullings, were used to increase or decrease the reflex to study the reflex function. Of interest were particularly breaks in continuous oscillation, i.e. transient breaks of constant stretch reflex, since the oscillator, of which the sphincteric motoneuron is a part, must have transiently lost adequate afferent input from the secondary spindle afferents. Previously (64, 65) it was shown that 5 single secondary spindle afferents could be identified, 3 of them responding preferentially to certain natural combinations of afferent input, namely painful pin-prick, anal and bladder catheter pullings. In previous publications (51, 60) painful pin-prick was shown to stimulate, within the limits of the recording method T1 (v = 44 msec^{-1}/$\varnothing$ = 11.2 μm), T2(39/10.1), T3(31/9.1) and T4(20/8.3) skin afferents (maybe PC, RA, SAI, SAII) and fastest pain afferents P(13 msec^{-1}/$\varnothing$ = ?). Anal catheter pulling stimulated skin afferents T1 through T4 of the anal canal and mucosal afferents M(17.5 msec^{-1}/$\varnothing$ = ?). Bladder catheter pulling stimulated mucosal afferents innervating the trigonum vesicae and the urethra (and maybe flow receptors S2(17.5 msec/$\varnothing$ = ?)), and strong pulling additionally stimulated pain afferents, the fastest component of which could be measured (P) (51). The T4 afferent receptors seem to be especially sensitive to touch movement along the skin (Streichel-receptors (60)). As shown in figure 6 and figures 7, 8 of Ref. 64, the strength of stimulation changed the firing patterns of the secondary spindle afferents. But also the stimulated areas will change the response of the secondary spindle afferents (60). Spindle afferent fibre SP2(2) was strongly activated by pulling of the bladder catheter, i.e. mainly by the activity of the mucosal and pain afferents innervating the urethra and the trigonum vesicae. Fibre SP2(1) was strongly activated by the anal catheter pulling (Fig. 2 of Ref. 65), i.e. by the activity of the mucosal and pain afferents of the anal canal and the rectal ampulla, and the skin afferents of the anal canal. It is obvious that bladder catheter pulling, by which the mucosal and pain afferents are stimulated, and a simultaneous touch of the S3 and S4 dermatoms by which the skin afferents are stimulated, will not activate strongly fibre SP2(1), which was strongly activated by the afferent input from skin, mucosal and pain receptors following anal catheter pulling. Electrical stimulation of groups of afferents is therefore far from reality to mimic natural spindle activation. Already Sherrington advocated the need for a well balanced peripheral input (67).

Impulse patterns of intrafusal axons and secondary spindle afferents

Since the skin, mucosal and pain afferents are not innervating the muscle spindles themselves, the different drives of the secondary muscle spindle afferents are channeled through the efferent muscle spindle innervation, consisting of the somatic dynamic and static γ-motoneurons and, as measured in the present work, of parasympathetic motoneurons. According to the different afferent inputs from mechanoreceptors of the skin, the urethra, the trigonum and the anal canal (51, 60) the γ and parasympathetic motoneurons changed their activities, with secondary spindle afferents showing action potential (AP) patterns as shown in figure 6 and figures 7, 8 of Ref. 64.

In addition to activities of afferent fibres SP2(2) and SP2(5), figure 6 shows the natural

impulse patterns of a single dynamic (γ_1) and a single static γ-motoneuron (γ_{21}). In the second series of measurements, where all 5 secondary afferents were strongly activated, it was difficult to identify the γ-motoneurons, probably because of an insufficient blood supply, following recording for more than 20 min from the root. As figure 4 shows, the interspike intervals of the γ-motoneurons and the secondary muscle spindle afferents are similar (see also Fig. 2 of Ref. 64). It is therefore not clear, whether the γ-motoneurons drove single encoding sites of the secondary spindle afferents or whether the parent secondary spindle afferent fibres drove partly neural networks, which produced the impulse patterns of the dynamic and the two static γ-motoneuron groups. A second static γ-motoneuron group was proposed by Boyd (9). Since secondary spindle afferents predominantly innervate nuclear chain fibres in cats (5), and contractions of chain fibres can follow frequencies up to 60 Hz (7, 8), it may well be that the muscle spindle capsule is rather constant, whereas the chain fibres show local movements according to the activity patterns of the γ-motoneurons (12). These local contractions will increase or decrease the stretch of the equatorial region, innervated by the secondary spindle afferents. Single encoding sites will send impulse patterns in competition with, or in addition to, other encoding sites via the parent afferents, to γ-neural networks to form a loop (Fig. 10) and to the spinal oscillators, consisting of α_2 and α_3-motoneurons and many interneurons (63). Owing to the time needed, the existance of a loop from the γ-neural networks to the spindles and backwards is possible, since the activation of micturition and defecation is in the time range of seconds to minutes. The proposed loop is too complex to follow up the AP patterns. Many fusimotor axons will activate nuclear chain and nuclear bag fibres, and different encoding sites of chain and bag fibres will compete with one another. As figure 7B shows, the overall activity patterns of the single γ_1, single γ_{21} and γ-rest-motoneurons are similar, but the actual AP patterns of the γ_1 and γ_{21}-motoneurons were different (Fig. 6).

The single γ_1-motoneuron seems to innervate a single encoding site of the secondary spindle afferent fibre SP2(2) since i) the γ_1-motoneuron had a doublet interspike interval distribution peak at 13 msec (Fig. 4C) similar to one subpeak of fibre SP2(2) (Fig. 6 of Ref. 64, labeled γ_1), and ii) many phase relations occurred between γ_1 APs and SP2(2) APs (Fig. 6). However, the impulse patterns of γ_1-motoneurons and fibre SP2(2) were not identical and time-locked either. Since identical peaks of doublet interspike interval distributions existed at 13 msec, the doublet firing may have been generated in SP2(2) fibre endings by the pacemaker switching of the two encoding sites, and that this doublet firing pattern projected into the γ-neural networks. The shortest interspike interval of about 80 msec, with the exception of the doublet IIs, may be generated in the neural network generating γ-motoneuron activity. Also, the doublet and the 80 msec IIs may be generated in γ-neural networks as a preform of self organisation in similarity to the self organisation of α_2 and α_3-oscillators. The activity level of a γ-motoneuron firing with a doublet every 80 msec is higher (25 APs/sec) than that of an oscillatory firing α_2-motoneuron, which fires with 2 APs every 130 msec (15.4 APs/sec). If α_2-motoneuron fires in the oscillatory mode with 3 APs every 160 msec, which often occurs (52, 63), the activity level is still lower with 19 APs/sec.

Oscillatory firing and β-motoneurons

The principal observation has been that γ_1 and γ_{21}-motoneurons did not fire in oscillatory mode for high activation as α_2 and α_3-motoneurons can do. The α-neural networks in the spinal cord are thus different from those of γ-neurons. The α_2 and α_3-motoneurons can organize spinal oscillators, the γ_1 and γ_{21}-motoneurons cannot. Unclear is whether α_1-motoneurons can form spinal oscillators and how the impulse patterns of β intrafusal motoneurons are. Both motoneuron types contributed no or only very little activity to the micturition

and defecation function, so that nothing can be said about them based on these measurements. If α_1-motoneurons are also able to fire in the oscillatory mode, the interesting question occurs concerning the kind of the β-motoneurons. Being of the intrafusal type, they are not expected to be able to fire in the oscillatory mode, but being of the extrafusal type, they are expected to do so (β-motoneurons are supposed to innervate simultaneously extra- and intrafusal muscle fibres). The rather stereotyped oscillatory firing would probably not be very suitable for intrafusal motoneurons to subserve sensory input from the skin, the urinary bladder and the anal canal to the muscle spindle. The important question remains, whether β and α_1-motoneurons are able or not to fire in the oscillatory firing mode.

Population of intrafusal motoneurons

The question was rised by Boyd whether there exist two types of static γ-axons (9). Previous work of the author seemed to suggest more than one group of static γ-motoneurons. The distributions of conduction velocity frequencies obtained for HT6 and paraplegic 1 (Fig. 1) show 3 γ-peaks two of which seem static. Towards lower conduction velocities a peak of parasympathetic fibres appeared at about 5 m/sec (T = 33.5 °C). However, as figures 1B and 8M indicate, there was one or two other conduction velocity peaks, suggesting further types of motoneurons. In compound action potentials of peripheral nerves, with the dorsal roots previously cut (6), several very slowly conducted peaks occurred. It has to clarified further, whether the peaks at conduction velocities of about 3.2 and 4 m/sec represent additional motoneuron types. In particular it needs to be known, whether there is but a single type of parasympathetic motoneurons or several ones, and whether there are different parasympathetic motoneurons for extrafusal and intrafusal innervation. In the present work, the identification of the parasympathetic fibres was mainly based on the identification of AP patterns of a single γ_1 and a single γ_{21}-motoneuron. The impulse patterns of single γ_{22} and parasympathetic motoneurons need now to be separated from the summed impulse traffic of dorsal or ventral sacral roots. This seems to be possible if these fibre types can be strongly activated. Neurogenic bladder dysfunction (discoordinated action of the detrusor and the sphincter system; called also dyssynergia of the bladder, spastic bladder, cord bladder or autonomic bladder (71)) has to be analysed in a paraplegic during surgery, using retrograde filling of the bladder. It should also be possible to clearly record APs from the somatic and parasympathetic division, because anaesthesia needs only to be light. Mostly no pain is felt below the level of lesion. Also an improvement of the method of recording of single fibre APs from unaltered nerve roots seems possible.

Phase relations and spinal oscillators

As a comparison between figures 6B and 6A indicate, the number of phase relations (phases in a certain range) between single-fibre APs of γ-motoneurons and certain secondary spindle afferents increased with bladder catheter pulling. Also the number of phase related γ and oscillatory firing α_2-motoneuron O2 APs increased, which suggest a certain kind of α-γ coactivity. In a previous paper (64) it was shown that the number of phase related APs between secondary spindle afferents and oscillatory firing motoneuron O2 increased. A phase loop seemed to exist from the oscillatory firing α_2-motoneuron O2 through γ-motoneurons to the secondary spindle afferents and back to the oscillatory firing motoneuron (see Fig. 10). This phase loop is similar to recoupling in phase from output back to input as used in electronic oscillators. The analogy is only partly correct, since γ-motoneuron systems probably do not get the phase from the α-systems. Probably, the phase relation occurs because of α-γ coactivity (or more exactly, α_2-γ_1 coactivity) for high activations. The absolute phases may not be so important for the drive of the spinal oscillator, since interneurons could serve as delay components to adapt to the right phase. These rather

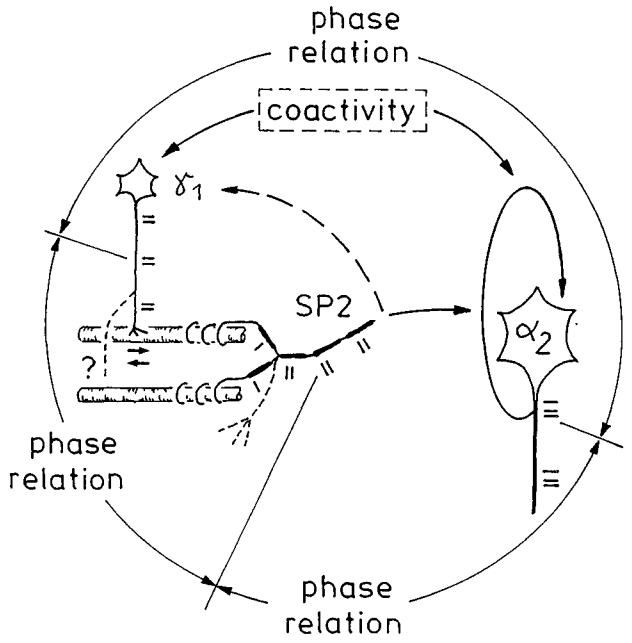

Fig. 10. — Schematised existing phase relation between α_2 and γ_1-motoneurons and a secondary muscle spindle afferent fibre (SP2). Parallel existing phase relations between other parent afferents and the α_2-motoneuron and between parent secondary spindle afferents are not shown. Phase relation means, the increased occurrence of phases in msec in a certain phase range between the action potentials (APs) of the two compared nerve fibres. The complex afferent and efferent muscle spindle innervation was not tried to show. Small arrows at intrafusal muscle fibre indicate local contraction, which is in nuclear chain fibres readily transmitted to the place of afferent innervation. A possible reason of the doublet firing of the SP2 fibre is pictured to occure from single APs (schematised by bars) of 2 myelinated endings, not necessarily from pacemaker switching. More endings of the parent SP2 fibre and γ_1-motoneuron are indicated by dashed line branches. "Coactivity" indicates a correlation between γ and α-motoneuron spinal cord circuitries for higher activations.

qualitative considerations concerning phase relation have to be quantified in future. Phase correlation distributions have to be constructed by plotting APs of α and γ-motoneurons vs those of secondary spindle afferents; moreover, it would be essential to know the in-phase ranges which drive the spinal oscillators, and to hopefully get more information about the neural networks of the human spinal cord, which makes such activities possible. Since also the number of phase correlated APs between fibres SP2(2) and SP2(5) increased with the bladder catheter pulling (Fig. 6A), certain systems seem to become more synchronized or regularized with the increasing activation (of the constant stretch reflex) of the particular part of the nervous system.

Fusimotor and skeletmotor activity

During voluntary movements in man, Hagbarth and Vallbo measured the impulse rate in spindle afferents to run reasonably in parallel with the skeletomotor activity as estimated from EMG activity (27, 73). During the constant stretch reflex of the external anal sphincter some α_2 and α_3-motoneurons fired in the high activity oscillatory firing mode (52, 63). Transiently, the identified impulse patterns of single γ_1 and γ_{21}-motoneurons showed here higher activity levels, when firing with doublets every 80 msec, than the oscillatory firing α_2-motoneuron O2 (HT6) firing with impulse trains of 3 APs every 160 msec. On a reasonable assumption that the highly activated intrafusal motoneurons were functionally connected to the oscillatory firing α_2-motoneuron, as supported by an increase of phase relations between their APs with the increasing activation, the activity level changes of these extra- and intrafusal motoneurons run in parallel only sometimes. In the occasional firing mode following stimulation, α_2 and γ_1-motoneurons were activated in parallel also only sometimes (53). α_3-motoneurons changed their activity level differently from those of α_2-motoneurons (53, 55).

As the actual impulse patterns show (Fig. 6), there was no or no strongly linked α-γ coactivation. α_2-motoneuron O2 fired in the oscillatory firing mode and γ-motoneurons did not. The fusimotors had impulse patterns very similar to the secondary spindle afferents. Since APs of the highly activated fusimotors are more easier to pick up from the summed impulse traffic than APs of only little activated neurons, highly activated fusimotors of the dS4 root therefore most likely did not escape detection.

From the plasticity of the central nervous system of animals and humans one would expect more variability in the dissociation of

functions (23) in the human central nervous system (CNS). Sperry transposed the nerve supplies of flexor and extensor muscles in a rat (68) and a monkey (69): the monkey relearned the task after some time, the rat did not. Surprisingly few trials were required for poliomyelitis patients to use transposed tendons successfully (75).

The voluntary movement probably activates the human CNS differently than the constant stretch reflex.

Time course of activation of a secondary spindle afferent fibre activated by parasympathetic fibres

From conduction velocity frequency distributions (Fig. 1) and the time course of activation of fibre SP2(2) following strong bladder catheter pulling 3 (Fig. 7, 8) intrafusal parasympathetic action could be identified. This autonomic muscle spindle activation is of parasympathetic type: parasympathetic fibres emerge from the spinal cord via the lower sacral roots (where measurements were performed), to partly form the pelvic nerves (58), whereas sympathetic fibres leave the spinal cord through levels between TH12 and L2 and innervate the urinary bladder via the hypogastric plexus (58). About the autonomic innervation of animal muscle spindles has been reported elsewhere (1, 2, 38, 70). A time constant τ of 3 sec has been calculated here for the activity increase of fibre SP2(2). The plateau of activation was reached within 10 to 15 sec (Fig. 7). This value is in accordance with animal measurements, where sympathetic stimulation increased muscle spindle afferent activity to a plateau value within 10 to 15 sec (38) as well. Following parasympathetic activation (Fig. 8G) fibre SP2(2) decreased its activity very slowly with a time constant of 40 sec. The time constants for the increase and decrease of the SP2(2) fibre activity differed by more than a factor of 10, which indicates that the parts of the intrafusal muscle fibre which contracts with the parasympathetic activity, relaxes very slowly. Frog skeletal slow muscle fibres, used as a reference for contraction and relaxation speeds of intrafusal muscle fibres, do not relax following nerve stimulation as slowly (not a K^+-contracture!). The time constant for the increase of the isometric tension in the frog rectus abdominis following selective small axon stimulation of motor branches of spinal nerves, which innervate extrafusal slow muscle fibres, was about 1.3 sec. A plateau was reached 10 to 15 sec following stimulation (21). Upon switching off the 60 Hz tetanus the isometric tension decreased with a time constant of approx. 3.5 sec. In kittens (16) the slow muscle extensor digitorum longus (ELD) reduced its isometric tension following tetanic stimulation with a time constant much shorter than 1 sec. The area of the human intrafusal muscle fibre activated by parasympathetic fibres has very slow properties. Creep and other after effects (10, 20) cannot account for such low time course. It could be that parts of the intrafusal muscle fibres have properties similar to those of smooth muscle. Human muscle spindles of the external anal sphincter and the musculus pubococcygeus (Fig. 7 of Ref. 65) need to be examined histologically and histochemically. Still, intrafusal muscle fibres may have normal morphology and contract slowlier because of the parasympathetic fibres exerting a trophic action and changing the excitation contraction coupling. For frog slow muscle fibres it has been shown that the action potential mechanism of the membrane, and the contraction and relaxation speeds are under neural control (37). The excitability of the membrane is under neural control even in parts of the slow muscle fibre, probably via a "trophic" effect (44).

The secondary spindle afferent fibre SP2(2) increased its activity following parasympathetic activation by recruiting new encoding sites (Figs. 6, 7A and Fig. 5C of Ref. 64). The activity of the parent fibre SP2(2) became regular again (similar interspike intervals) shortly after the recruitment of a new encoding site (Fig. 6). Such a smoothing of the interspike intervals can be explained by a common pacemaker (19) for the 6 encoding sites. More likely, potentials generated in up to 6 unmyelinated endings added up at the first heminode or

penultimate node, where the action potential was produced. A pacemaker switching of myelinated endings seems to be more unlikely to produce a coordination of up to 6 encoding sites.

Clinical implications

This research was prompted by efforts, to develop biological treatment for paraplegia. The project includes a theoretical and a practical part. The 6 papers in this volume deal with theoretical problems, trying to clarify further functions of the human spinal cord under physiologic and pathophysiologic conditions. Thorough knowledge of the spinal cord functions with its circuitries, and of their pathways is essential when reconstruction is attempted of functions following spinal cord lesions, employing the regeneration approach or, if not possible, pharmacological intervention.

Pathologic spinal cord function

In a previous paper (62) it was shown that following spinal cord lesion, in the presence of dyssynergy of the urinary bladder, α_3-motoneurons (S) changed their excitation properties being recruited too fast. This may indicate a specific loss of central inhibition. In another paper (63) an α_2-oscillator, was reported to fire physiologically at a frequency of 6.25 Hz, while firing at frequencies up to 13.5 Hz under pathologic conditions (paraplegic). Such a broadening of frequency range can have consequences. It was shown elsewhere (63, 64, 65) that oscillatory firing of an external anal sphincteric α_2-motoneuron was mainly driven by certain secondary muscle spindle afferents (SP2(1 to 3)), and oscillatory firing of an external bladder sphincteric α_2-motoneuron was mainly driven by the stretch receptors most likely located in the urinary bladder wall (51, 65). If these oscillators fire at broad ranges of frequencies according to certain probability distributions (Fig. 11 of Ref. 63) instead of firing at certain resonance frequencies, these oscillators may also be excited at different frequencies. Thus, following spinal cord lesions spinal oscillators driving the bladder and anal sphincters in the high activity mode may be excited not only by their respective afferent input, but also by impulse patterns of other receptors, which normally do little or not at all contribute to drive. In dyssynergetic bladders, with parasympathetic fibres activating the detrusor for emptying the bladder, also the external or internal sphincters are transiently activated for bladder fillings exceeding 200 ml. Parasympathetic impulse patterns may have hitted pathologic frequencies of the spinal oscillators. It was shown in this paper that parasympathetic fibres also innervate muscle spindles. With the destruction of the descending tracts following spinal cord lesion, afferents serving mainly parasympathetic activation may have sprouted to sites of degenerated tract synapses and could have enhanced parasympathetic actions. It is of importance to identify the impulse patterns of parasympathetic fibres to see whether they could activate spinal oscillators via spindle activation or directly under pathologic conditions. Many functions of the spinal cord will have changed following spinal cord lesions. Unbalanced damage is probably the worst one. Unbalanced lesions of the neural network can already be induced by transient asphyxia of the spinal cord (62). Anoxia is one of the pathologic processes occurring with spinal pressure following spinal cord lesions, when the edematized cord is trapped by the rigid pia mater. It has to be tried to reduce the overreaction of the cord during the first 6 hours following the lesion by localized cord cooling (18) or by hyperbaric oxygen (22), methylprednisolone, naloxone or dimethyl sulfoxide treatment (13). The less the spinal cord is damaged, the better it can be treated e.g. by reinnervation or by electrical functional stimulation (33) with natural human impulse patterns.

Nerve anastomoses

Spontaneous healing of human spinal cord lesions has not been observed so far. Since

nerve cells are not able to divide in the adult, the central nervous system (CNS) seems to recruit other nerve cells to take over function for the destroyed ones. The substitution of a function from other parts of the CNS is only possible if the necessary connections exist or can be built and if there is enough plasticity in the human CNS for relearning of functions. In spinal cord lesions nerve cells and tracts are destroyed. Lesions of the tracts are worse since the caudal spinal cord is disconnected from supraspinal control. Regeneration efforts of spinal cord tracts are very small. Tract cells regenerate only over small distances, are impeded by scar tissue formation and form inappropriate synapses (29, 30, 42, 77, 78, 79). The normal surgical strategy to cut unhealthy tissue away and substitute healthy nervus tissue (embryonic) is not feasible. Firstly, only few spinal cord lesions are total. Resection of the damaged spinal cord parts would destroy still existing tracts. Secondly, by cutting the damaged spinal cord, e.g. in the lumbal range the caudal spinal cord will be disconnected from the blood supply and also die, because 70% of blood is supplied via the largest feeder artery (Adamkiewicz) and is distributed via the longitudinal tracts (50, 76). Also, resected scar tissue will be partly replaced by connective tissue scar (29, 30). Replacement of damaged spinal cord tissue by embryonic nervous tissue in animals is of interest for the study of the mechanism of regeneration, but has no consequences for the reconstruction of functions in humans. Since the damaged spinal cord part cannot be removed, neurosurgeons use to bypass it by performing a nerve anastomosis from the lower intercostal nerves rostral to the level of lesion to the cauda equina nerve roots caudal to the lesion (14, 17). Regeneration occurs, but no useful functions are obtained. In the most advanced operation of Carlsson (14), the regeneration of the urinary bladder function could be obtained, but the detrusor and the sphincter contracted simultaneously. The research project of the author is aimed at improving such nerve anastomosis, so that the patients gets useful functions reconstructed (45, 46, 57, 58, 59, 60). The number of total nerve fibres, of afferents and efferents of the donor nerves have to be compared with the acceptor nerves (46, 57, 58). E.g., it is useless to try to reinnervate the lower human body on one side with one intercostal nerve, which contains 10 000 myelinated fibres, if 250 000 are needed. However, the number of myelinated fibres of one intercostal nerve is sufficient for regeneration of the urinary bladder (Fig. 11). Mismatch and functional aspects have to be taken into consideration (57, 58, 60). To make a separate function of the detrusor and the sphincter possible, the bladder has to be reinnervated by the two different motoneuron pools, present in the

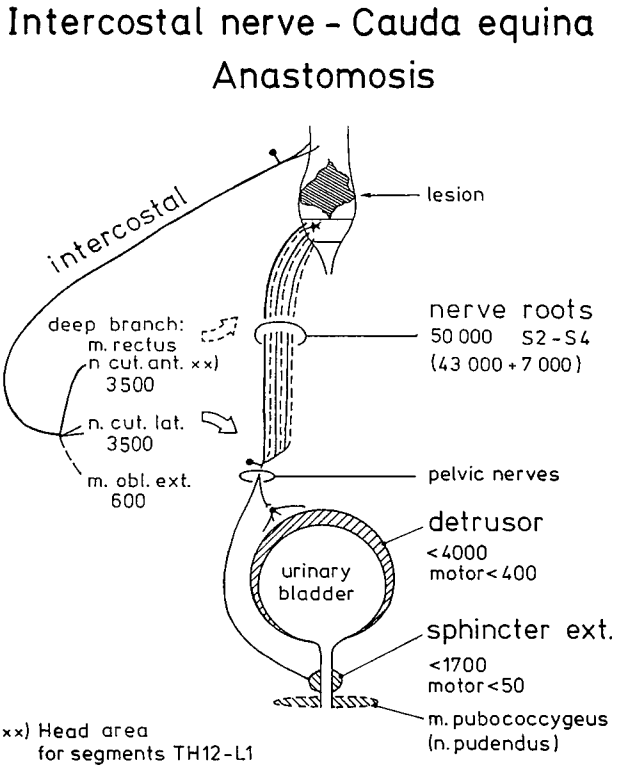

Fig. 11. — Schematic drawing of the nerve anastomosis from the intercostal nerves to the cauda equina nerve roots for a restoration of bladder function. Approximate numbers of myelinated nerve fibres from one side are indicated. The nerve root fibre number (50 000) is split up into sensory (43 000) and motor fibres (7000). For the detrusor and the sphincter externus, very approximate upper limits of motor fibres are given (motor <). Afferent pathways are not explicitly drawn. m rectus = musculus rectus abdominis, N. cut ant. = nervus cutaneus anterior, n. cut. lat. = nervus cutaneus lateralis, m. obl. exter. = musculus obliquus externus abdominis. (Only few fibres from the lower intercostal nerves innervate intercostal muscles).

intercostal nerve, by dissecting the intercostal nerve distal to its branching into two skin nerves (nervus cutaneus lateralis), a pure muscle branch supplying the musculus obliquus externus and the mixed nerve running to the musculus rectus abdominis (57). Specific bladder afferents can be reconstructed by using the skin afferents from the Head's area (ramus cutaneus anterior of the intercostals T12 to S1) (60).

A first therapy trial would be to repair the cauda equina in patients, in whom the bladder is emptied by catheterisation. Afferents may be used from T12 intercostals, since afferents do not regenerate into the spinal cord. In the higher-level conus medullaris lesions, donor nerve fibres have to be directly lead to cauda equina nerve roots, where bladder functions are represented. The most suitable roots have to be identified anatomically and electrophysiologically (45, 51). In lesions lying more rostrally it has to be clarified, whether the sacral micturition or coordination centre is functioning well. If the sacral micturition centre is functioning well, i.e. the paraplegic has a well functioning reflex bladder, reinnervation of the disconnected spinal cord through the nerve roots has additionally to be tried. This would be a tract reconstruction in the peripheral nervous system (PNS), where the nerve fibres can grow over long distances. However, only motoneurons can cross the PNS-CNS transition zone (3, 34). In animal regeneration experiments a drug has to be developed which stimulates the astrocytes to allow the sensory fibres to regenerate across the PNS-CNS transition zone (see below) (32). For spinal cord lesions at the mid-thoracic and more rostral levels, the nerve anastomosis will be less suitable, since firstly, only intercostals up to TH6 can directly reach the cauda equina, and probably the rostral intercostal nerve fibres differ more from sacral nerve root fibres and

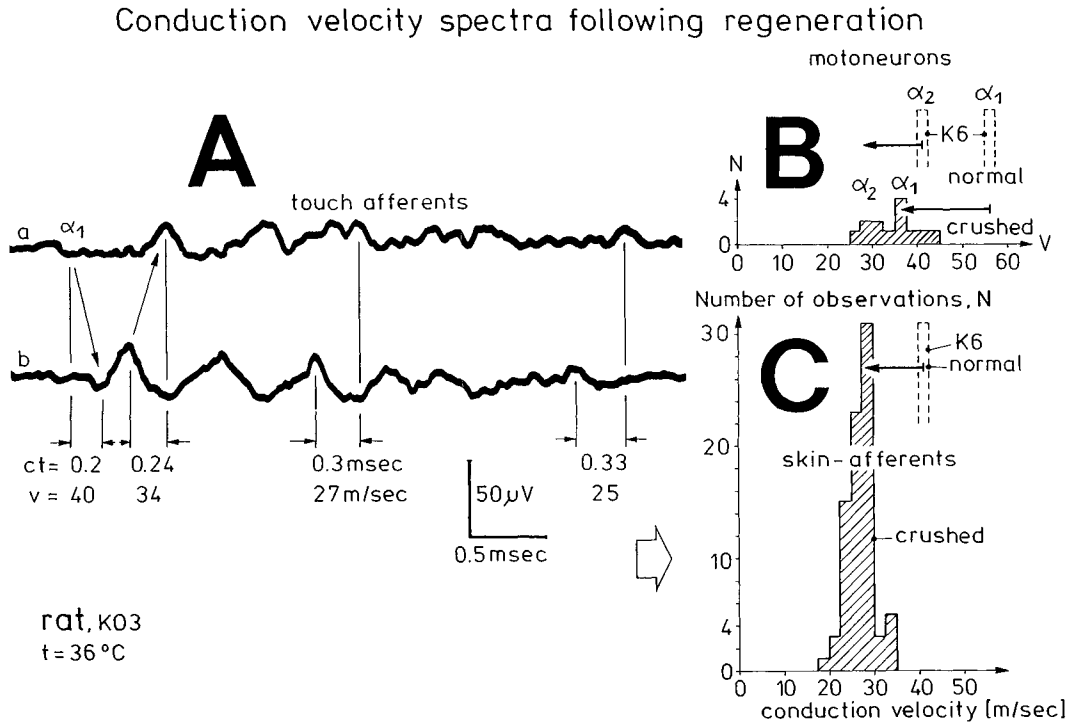

Fig. 12. — Conduction velocities of the regenerating sural nerve of a Wistar rat, 110 days old; nerve crushing 60 days previously. A. Recording of single-fibre action potentials (APs). α_1 = α_1-motoneuron AP, *ct* = conduction time, *v* = conduction velocity. B, C. Conduction velocity frequency distribution histograms of skin afferents (C) and α-motoneurons (B). Cross-hatched histograms from rat KO3 with the regenerating nerves. The dashed histograms were taken for comparison from normal rat K6 (see Ref. 61). The arrows indicate the shift of the velocity peaks due to crush and regeneration. Ether anaesthesia.

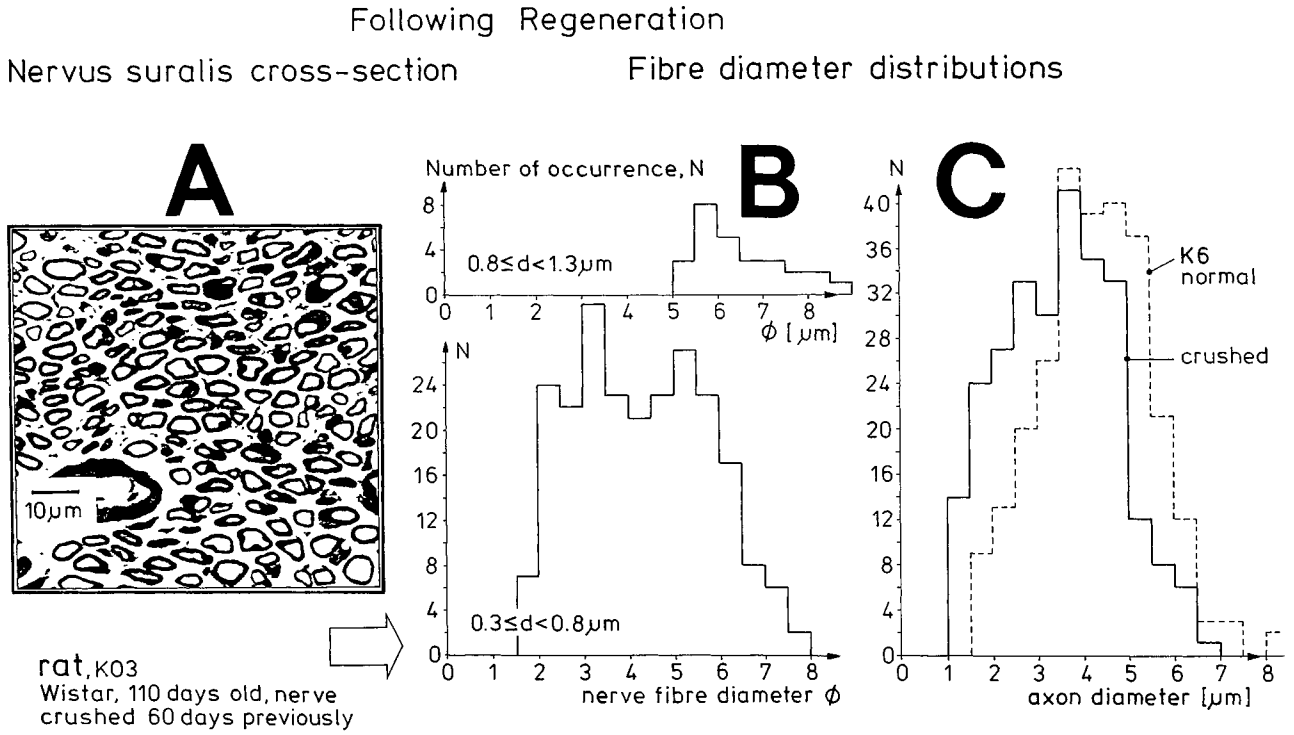

Fig. 13. — Nerve fibre diameters of regenerating fibres of the sural nerve of a rat, same as in figure 12. A. Part of the cross-section. B. Nerve fibre diameter frequency distribution histograms with the myelin sheath thickness ranges d. C. Axon diameter frequency distribution histogram; solid line = regenerated rat, dashed line = normal control rat for comparison.

higher plasticity efforts would be necessary. For lesions in the cervical range one has probably rather try regeneration in the CNS. For further details about nerve anastomosis, including references, see Refs. 57-60.

Steps in regeneration

Probably enhancement of the regenerative capacity of the nervous system has to be achieved step by step with the final goal in mind to treat the patient. Efforts to develop a drug for the regeneration of the spinal cord has been spent since World War II with no benefit for the paraplegics so far.

To enhance the regeneration capacity one first needs a powerful animal model to measure the grade of regeneration functionally and morphologically. Such a model has been developed for the peripheral nervous system and will be introduced here. Single-fibre action potentials were recorded from the sural nerve of a normal 110 days old rat, with two pairs of wire electrodes, and conduction velocity frequency distribution histograms were constructed (Fig. 3 of Ref. 61). After the recording the sural nerve was removed, fixated, embedded, stained, and morphometrically analysed, and histograms of the nerve fibre diameter distribution were constructed (Fig. 4 of Ref. 61). The same procedure was used with another rat (110 days old) with the sural nerve crushed together with the nervus ischiadicus 60 days previously. A sweep piece of the recording from the regenerated nerve is shown in figure 12A. In comparison with figure 3A (of Ref. 61) APs from the regenerated fibres (Fig. 12A) were of longer duration and were conducted slowlier. The regenerated fibres were not as matured as the normal ones. A comparison of the conduction velocity frequency distribution histograms of

motoneurons and skin-afferents of normal and regenerated fibres are shown in figure 12B, C. The regenerated fibres conducted by 13 to 19 m/sec slowlier. The morphometry of the regenerated sural nerve is shown in figure 13A, B. In comparison to figure 4 (of Ref. 61, a direct comparison is possible), it can be seen that both the myelin sheaths and the axons are thinner. A comparison of the axon diameters of the normal and the crushed fibres of the sural nerve is shown in figure 13C. The regenerated α_1-motoneurons (FF) (51) had a peak group nerve fibre diameter of 5.75 µm (Fig. 13B) and conducted with a peak group conduction velocity of 36.5 m/sec. The velocity-diameter relation of the regenerated α_1-motoneurons equals $V/\varnothing = 36.5/5.75 = 6.3$. In the normal rat the conversion factor was 6.6 at 36 °C (61). The structure-function coupling for α_1-motoneurons is roughly preserved in the rat during regeneration. If a regenerating nerve fibre is more matured, the nerve fibre diameters and the conduction velocities increase. Renegeration can therefore be measured simultaneously structurally and functionally. Administering to a third group of rats, which had their nerves crushed previously, a drug which speeds up the process of regeneration, the regenerating fibres will have larger nerve fibre diameters and show higher conduction velocities than fibres in the group receiving no drug, but still smaller diameters and lower velocities than in fibres in the normal group. It has been shown in rats that the daily administration of 3.0 mg/kg body wt uridine monophosphate and 2.5 mg/kg cytidine monophosphate (Trommsdorf, Alsdorf, Germany) enhanced regeneration by about 20 % as estimated based on nerve fibre diameters and conduction velocities (74) (clinical application and side effects were not tested).

The enhancement of the regeneration speed in the peripheral nervous system is of importance, since nerve fibres in humans regenerate at a rate of 1 to 2 mm/day (28), so that often distal muscles are already atrophied before regenerating fibres reach the muscle. Even though urinary bladder muscles do not undergo atrophy because of the inner plexus and probably reflex arcs, a speeding up of the regeneration is useful, since the patient has not to wait as long for the first signs of regeneration, which can be expected to appear in the order of a year after the surgery.

This animal model can also be used for regeneration experiments in the CNS. Measurements of conduction velocity and nerve fibre diameter can also be performed on nerve roots, if the roots are sufficiently long. Electrophysiological measurements can be performed even much better because of the missing of the epineurium and the perineurium (49), and the structure-function relationship can be better estimated, since ventral root diameter distributions with the different α and γ-peaks can be used to calibrate diameter distributions (51, 57, 58, 59). By crushing the root directly at the spinal cord one can crush the PNS-CNS transition zone, since in some animals this zone protudes into the root (4, 15, 31). Response measurements e.g. can be used to demonstrate whether afferent nerve fibres have grown into the CNS. With small parts of the spinal cord in the conus medullaris range crushed, at first steps close to the root exit, regeneration in the CNS can be measured in the roots by measuring conduction velocities, nerve fibre diameters and stimulation responses. By progressive crushing from the root towards the PNS-CNS transition zone to the spinal cord and by measuring regeneration in the root with and without the application of pharmaca (66), it may be possible to find drugs which improve regeneration at the different levels (root, transition zone, CNS). The bacterial pyrogens Piromen or Pyrogenal from a pseudomonas species (25, 35, 40, 41), which are able to dissolve scar tissue, should be reevaluated in such a regeneration model. For quick screenings of drugs the quickly performable electrophysiologic measurements can be used only. For large and expensive animals like dogs, pigs and monkeys it is possible to measure regeneration stages several times on the same animal if one restricts oneself to electrophysiologic measurements. Apart from the laminectomy, the nervous system is only little damaged with each measurement. Humans tolerate repeated laminectomies quite well.

Since there are no reports about specific regeneration in the human CNS one most likely has to take care of necessary tract fibre numbers, mismatch and functional aspects for a regeneration in the CNS, as were taken into consideration in the PNS (see above), to obtain useful functions following regeneration.

Unique anatomical situation

Progress in the treatment of spinal cord lesions seems to be possible. The new classification scheme (51, 61) in which group conduction velocities and group nerve fibre diameters (peak values) are correlated gives a more accurate basis for the exploration of the circuitries of the human nervous system and its functions. The power of this peripheral nervous system scheme rests upon the accuracy of the nerve fibre group characterization based on conduction velocities and nerve fibre diameters. So far it seems that the internal consistency of nerve fibre groups and their activities, measured in the peripheral nervous system, is still higher than the measurement accuracy. Since this classification scheme seems partly to be preserved following regeneration, a rather exact measuring of the stage of regeneration is possible, which is precondition when regeneration enhancement by pharmaca is studied.

Since further in humans there is a unique anatomical situation in the lower sacral range (firstly, bladder functions are not intermingled with tail functions in the conus medullaris and in the roots, as e.g. in the dog (54, 55, 56); secondly, lower sacral nerve roots are thin, long (45), have a good blood supply (49, 50), and afferents and efferents are partly mixed in dorsal and ventral roots (49, 51), which allows detailed measurements of nervous system functions for diagnostic and research reasons; and, thirdly, there is plenty of space for operating procedures in the lower spinal canal because of the ascensus of the human spinal cord), reconstruction of urinary bladder functions by nerve anastomosis seems possible. This is in accordance with the practical feeling of experienced neurosurgeons.

Acknowledgements

This research (45-65) has primarily been done on money saved personally, including the equipment (300 000 DM during 6 years, all the saved money), to bring this clinical research up to the level presented. In Germany, every second day a paraplegic dies because of bladder infections or by suicide. The author qualified in technical, natural and medical sciences and worked together with R. Miledi at the institute of Biophysics of Sir Bernard Katz. Instead of continuing to work on the trophic effect or on Ca channels, he changed to basic clinical research. He was advised from well known basic research workers and neurosurgeons that clinical research is worth of being done if something can be done. At the beginning reviewers argued it were not possible to record single fibre action potentials with wire electrodes in humans. Then the argument was that it should only be possible to record from thick nerve fibres, which are of no interest any more. The author had to use a computer; he has to use average values. A basic animal reviewer could not see the clinical implications and asked then for the ethics of this research, without giving reasons for his ethical considerations. Some American reviewers argued also that if it is possible to record afferents and efferents simultaneously in humans, then this will have consequences. Initially the Deutsche Forschungsgemeinschaft (DFG) supported the research, but refused to accept the application for further money because of organisational reasons. After an intervention by R. v. Weizsäcker the DFG accepted the application, but refused to allocate money because this research project has been judged unqualified and ethically unjustified; they did not want to change the decision even after more than 10 papers had appeared in different journals. Now the DFG rised the organisational argument again and argued that the author cannot apply for money for the same research project again; obviously, the DFG makes a false decision and the research worker and the patients have to suffer. The Max Planck Institution for Clinical Research was not interested in the research project, arguing that it exceeded the scope of the field covered by them. Approximately 20 other institutions refused financial or other assistance for various reasons. The "Ministerium für Forschung und Technologie, Forschung im Dienste der Gesundheit" promised financial aid for several years by establishing in the future a Neurotraumatology Research Project, but money is refused for the time being because it is needed for the reunification of West- and Middle-Germany. An institution from Switzerland and from the USA refused money basically with the argument that it is better to keep the money in the own country, even though paraplegics would use the possibility to get treatment in other countries, if available. The trial to allocate funding from private persons by an advertisement in the "Züricher Zeitung" was stopped by an ethical committee. At the rehabilitation conference IRMA VI in Madrid it was reported that in Amsterdam, it is practically impossible to get funding for research in Rehabilitation. The questions

remain, how many paraplegics have still to die until the world moral responsibility gets sensitized so that the necessary research is organized, which has to cover the range from the basic research up to the patient (question of the Spinal Cord Society, U.S.A.); and, what is the justification for killing animals in basic animal research if no clinical application is intended.

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