Oscillatory firing of single human sphincteric α_2 and α_3-motoneurons reflexly activated for the continence of urinary bladder and rectum. Restoration of bladder function in paraplegia

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Abstract

1. By recording with 2 pairs of wire electrodes from human sacral nerve roots (S3-S5) rhythmic as well as occasional firing was observed in α_2 and α_3-motoneurons in response to physiologic stimulation of the urinary bladder and the anal canal. The rhythmic firing consisted of periodically occurring impulse trains, most likely produced by true spinal oscillators which drove the motoneurons.

2. α_2-motoneurons, innervating fast fatigue-resistant muscle fibres, were observed to fire with impulse trains of about 2 to 4 action potentials (Ap's). These impulse trains occurred every 110 to 170 msec (5-9 Hz). α_3-motoneurons, innervating slow fatigue-resistant muscle fibres, fired about every 1400 msec ($\sim$0,7 Hz) with impulse trains of about 11 to 60 Ap's. α_1-motoneurons, innervating fast fatigue muscle fibres, and γ-motoneurons were not observed in the continuous oscillatory firing mode.

3. Sphincteric motoneurons were observed most likely in the oscillatory firing mode in response to the sustained stretch (reflex) of the external anal sphincter or to retrograde filling of the bladder (urethro-sphincteric guarding reflex), in order to preserve continence. A urethral sphincteric α_2-motoneuron increased its mean activity from 0.5 to 18 Ap's/sec during retrograde filling by changing its firing pattern from the occasional spike mode via the transient oscillatory firing mode to the continuous oscillatory mode. Up to a filling of the bladder of 500 ml the mean activity of the stretch receptors, measuring probably mural tension, increased roughly proportionally and the sphincteric motoneuron increased its activity to about 1 Ap/sec in the occasional spike mode. Up to 600 ml, the motoneuron responded in the transient oscillatory mode with mean activities of up to 5 Ap's/sec. With higher bladder fillings, the flow receptors afferents fired additionally, probably according to pressure symptoms, and the motoneuron switched into the continuous oscillatory firing mode and increased its activity up to 18 Ap's/sec at 700 ml. When the bladder was about 800 ml full, the stretch afferent activity decreased, the flow receptor activity increased strongly and the α_2-motoneuron activity decreased; the overflow incontinence had probably started. Micturition was not observed, probably because of brain death.

4. It is suggested that one adequate stimulus for an α_2-motoneuron of the external anal sphincter to jump into the oscillatory firing mode, was the activity from secondary spindle afferent (SP2) fibres from external anal sphincter muscle spindles. The interspike intervals (II's) of the SP2-fibres were often similar to the length of the oscillation period or to the half of it. 2 adequate stimuli of an α_2-motoneuron of the external urethral sphincter for switching into the high activity mode of oscillatory firing, was the increased activity from stretch and flow receptors. Similarities in the II's of the afferents and the oscillation period of the motoneuron were not found till now. A clear adequate stimulus of a sphincteric α_3-motoneuron to switch into the oscillatory firing mode was not found.

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5. The neuronal networks which drive sacral motoneurons in the oscillatory firing mode lie in the spinal cord. These spinal oscillators oscillated independently of each other. Out of 4 oscillatory firing modes of 4 α_2 and α_3-motoneurons analysed in detail, 3 showed quite a large dynamic range in response to different afferent inputs, with changes in the oscillation frequency and the number of Ap's per impulse train in order to decrease or increase the mean activity. The oscillatory firing mode of one α_2-motoneuron was very stable with respect to oscillation frequency, Ap's per impulse train and length of the II's in the impulse train.

6. In the impulse trains the II's increased in the range from 3.5 msec up to about 15 msec for α_2 and α_3-motoneurons; 3.5 msec is the known shortest soma-dendritic II in rats and cats. Longer impulse trains had shorter first II's and longer last II's. Typical II's of impulse trains of 3 Ap's of α_2-motoneurons were 4.5 and 7.4 msec long. In comparison with animal data, it was found that the length of the impulse train mainly depended on the amplitude of the depolarization produced by long current pulses and not on the length of the depolarization. The strength of the depolarization is already manifested in the length of the first II. With increasing depolarization the length of the impulse train increases and the length of the first II decreases. From further comparison with animal data, it is suggested that the oscillation cycle of a motoneuron, consisting of the impulse train part and followed by an inactive part, is produced by a drive potential, consisting of a short depolarizing part from excitatory post-synaptic potentials, and followed by a longer hyperpolarizing part from inhibitory post-synaptic potentials.

7. It is proposed that the drive potential in a motoneuron is produced by exciting and inhibiting impulse trains from different oscillatory interneurons of a true spinal oscillator. Further properties of spinal oscillators are summarized in the discussion section.

8. The external urinary bladder and anal sphincters are mainly innervated by α_2-motoneurons and probably by a few α_3-motoneurons. Electrophysiological evidence for a muscle spindle could be found in the external anal sphincter.

9. The possibility of reconstructing the urinary bladder function in paraplegia by a nerve anastomosis from the lower intercostal nerves to the cauda equina on the basis of anatomy, nerve fibre counts, mismatch, functional aspects and neuronal plasticity is discussed.

Key-words: Human — Spinal oscillators — Continence — Sphincteric motoneurons — Adequate afferents — Activity level — Urinary bladder — Paraplegia.

1. Introduction

The new observation in this second paper is that α_2 (FR-type) and α_3 (S-type)-motoneurons (75) in humans start periodically to fire with impulse trains when under physiological conditiones, a high activity level is needed. The analysis of this oscillatory firing mode will give more understanding about the range of activity of motoneurons and will give the mebrane property of firing repetitively (3, 47) in human a physiological meaning.

Hodgkin (47) classified the motoneurons in liligo into 3 groups with respect to the repetitive activity of membranes following intracellular applied current pulses. In the first group, the motoneurons showed strong repetitive activity. With long near threshold rectangular current pulses, the motoneurons responded with long impulse trains, whose interspike intervals and impulse train lengths, depending on the depolarization strength, are strikingly similar to the properties of impulse trains obtained from α_3-motoneurons when the anal canal and the urethra are constantly stretched. The α_3-motoneurons innervate muscle fibres which are responsible for posture, weight carrying of the lower abdomen and perhaps the continuous

low level activity of the external anal sphincter. Hodgkins second group contained motoneurons whose membranes showed reduced repetitive activity. These motoneurons probably correspond to the α_2-motoneurons, who fire with short impulse trains of about 3 action potentials (Ap's). As will be seen in the third paper (78), these α_2-motoneurons respond more specifically than the α_3-motoneurons, and guard in external (striated) sphincters the continence of rectum and bladder. Hodgkins third group contained motoneurons, which showed no or only little repetitive activity, which probably correspond to the α_1-motoneurons (FF-type) from which no repetitive activity has been recorded so far. But there were only a few α_1-motoneurons in the lower sacral nerve roots. It may be that α_1-motoneurons also show some reptitive activity, especially the thinner, more slowly conducting ones, belonging to the F (int) subgroup (55), called α_{11} in the first paper (77). But thicker, faster conducting α_1-motoneurons may not fire repetitively (65).

The correlation between the strength of the repetitive activity, the oscillation frequency of the driving oscillators and the mean activity for the different α-motoneurons found in this paper, indicates that α_1, α_2 and α_3-motoneurons do not only drive their own muscle fibres (FF, FR, S-type) but that they are also rostrally driven by their own central neuronal network to obtain their own activity pattern and level (see also discussion of the third paper (78)).

In Restorative Neurosurgery it may be crucial to reconstruct sphincter function with respect to activity levels in order to safeguard continence. After an introduction to possible biological treatments in spinal cord lesions in the part concerning clinical implications, the results of all 3 papers will be discussed with respect to the restoration of bladder function by nerve anastomoses in paraplegia.

2. **Method**

The clinical material is similar as in the first paper. The measuring of single action potentials (Ap's) (afferent Ap's = upwards; efferent Ap's = downwards) and the calculation of single fibre conduction velocities is also the same. The calculation of activity levels (Ap's/1.2 sec) from a certain group of afferents is done by counting the number of occurring conduction velocities under a certain distribution peak (curve all conduction velocities are taken) from a conduction velocity distribution histogram (Fig. 9C). Some inaccuracy enters this calculation since distribution peaks of afferent groups overlap. Some new problems arose form the poor digitalisation of the storage oscilloscope, since long time periods had to be considered in order to analyse the oscillatory firing mode of motoneurons (for definition see section 3.2).

On a fast time base the digitalisation is good (at least 4 digitalisation points per Ap), but the overall view is bad; on a slow time base the digitalisation is poor (sometimes no digitalisation point per Ap = Ap lost), but the overall view is good. Sometimes a piece of recording was taken several times from the video tape to obtain the optimum of reasonable digitalisation and an overall view with expansion and compression of the time base.

The given sacral segments in this and the other 2 papers are from human. Cats have a different segmentation and, to avoid confusion, they are never stated explicitly. For an explanation of the histogram when all conduction velocities are used (open plus hatched histogram parts) and the histogram when each conduction velocity value is taken only once (hatched part of the histogram) see Ref. 75, page 36.

3. **Results**

3.1. *Rhythmic activity*

By recording from an S5 dorsal root (HT4) with about 20-30% myelinated afferents it was observed that, a few seconds after bladder and anal catheter stimulation there was a rhythm in the efferent activity like the one in figure 1. The time interval between peaks of increased activity was in the range of 180 msec. Such rhythmic activity changed with time, but the time inter-

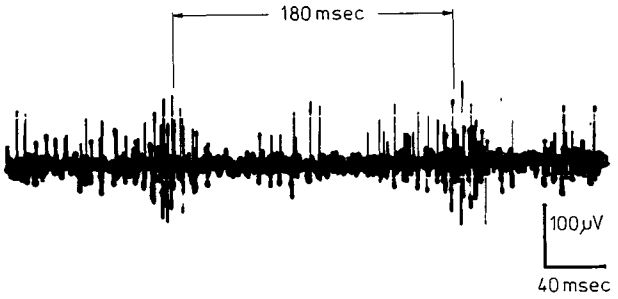

Fig. 1. — Efferent activity (mainly) recorded from an S5 dorsal root 20 sec after pulling the bladder and anal catheters. Rhythmic activity interval is marked by a 180 msec distance. HT4.

vals were rather similar. Myographic recordings from the pelvic floor and the sphincter externus of the urinary bladder show similar rhythmic activity (Fig. 1 of Ref. 51). Such rhythmic activity will be analysed in the following. It will turn out that α_2 (innervating fast fatigue resistant muscle fibres) and α_3-motoneurons (innervating slow fatigue resistant muscle fibres) can switch from the occasional spike mode of low mean activity into the oscillatory firing mode (for definition see below) of high mean activity. The activity of the recording in figure 1 was analysed. At least 2 motoneurons were in the oscillatory firing mode, but not in phase with respect to each other. About 50% of the occasionally active α and γ-motoneurons fired at about the same time as the motoneurons in the oscillatory firing mode as if they were coactivated. The rest of the motoneurons seemed to be active irregularly.

Since merged Ap's often have large amplitudes and will be very prominent in a recording like the one in figure 1, summed inpulse activity shows only partly the real activity patterns of single fibres. Poor digitalisation also changed the activity pattern like the one in figure 1 a little (see method).

3.2. *Oscillatory firing mode of α_2 and α_3-motoneurons*

The oscillatory firing mode of a motoneuron is a periodically occurring repetitive firing (Table 1). The repetitive firing has the pattern of a impulse train with regular increasing interspike intervals (see below). Each impulse train is followed by a time interval where the motoneuron is inactive. The time period from the beginning of one impulse train to the next is called the oscillation period, since it is reasoned later on that the oscillatory firing mode is produced by oscillating oscillators (Fig. 10). In the transient oscillatory firing mode a motoneuron is occasionally active (occasional spike mode) and fires in addition transiently in the oscillatory firing mode (Table 2).

In 4 HT's (HT4 to HT7) and in 1 patient repetitive efferent activity has been observed (Table 1). In the patient, the repetitive activity was recognized by a wave form analysis. But, since only a few impulse trains were documented (early measurements), the identification is only partly certain. In the ventral root recording from the HT7, motoneurons in the oscillatory firing mode were observed, but the overall activity was too high to be quantified until now. In the dorsal root recording of the HT4 an oscillatory firing mode could be quantified for 2 motoneurons, but could not be followed up over a long time to get a correlation with the afferent activity changes. There were still to many efferents in that S5 dorsal root ($\sim$20-30%). But 4 α-motoneurons of the HT5 and HT6, called here O_1, O_2, O_3 and O_4, could be identified definitely over long periods of time ($\sim$1 hour) in reaction to afferent input due to physiological stimulation and will be analysed in detail in this and the following paper.

In figure 2, the repetitive activity of the α_2-motoneuron O_1 is shown. The impulse train consisted of 2 Ap's, 5.9 msec apart. The duration of the oscillation period $T(O_1)$ is given in the insertion of figure 2A with 110 msec. This α-motoneuron was of α_2 type, since its conduction velocity was $v = s/t = 8$ mm/0.22 msec = 36 m/sec (see Fig. 4C of the following paper (78)). It had a recurrent collateral as shown in figure 2A with a conduction velocity of $v = 8$ mm/0.38 msec = 21 m/sec, which branched off from the axon trunk about 11 mm distal to the measuring place ($s = vt = t\,1/2(v_1 + v_2)$ = 0.38 msec 28.5 mm/msec =

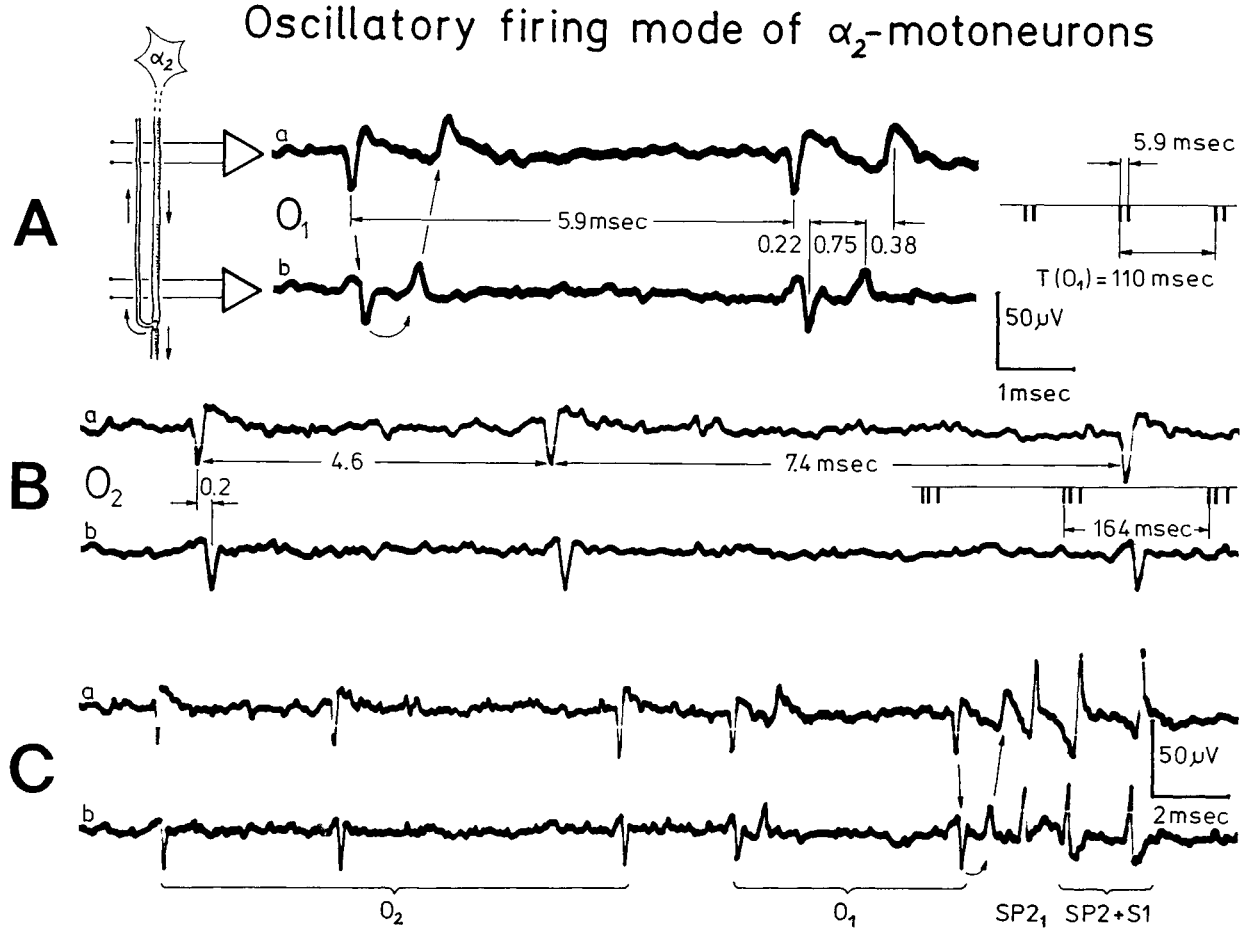

Fig. 2. – Recordings from the α_2-motoneurons O_1 and O_2, firing in the oscillatory mode with impulse trains of 2 (A) and 3 (B) action potentials (Ap's). The durations of the oscillation periods are 110 (A) and 164 msec (B). The interspike intervals of the impulse trains are 5.9 msec (A) and 4.6 and 7.4 msec (B). The motoneuron O_1 (A) conducted with 36 m/sec. Its recurrent fibre conducted with 21 m/sec. The measuring arrangement is schematically shown in A (see also Ref. 75). The schematic insertions in A and B show the oscillatory firing modes; they are not drawn to scale. The impulse trains of the α_2-motoneurons O_1 and O_2 are shown in C together with the Ap's of the identified secondary muscle afferent fibre $SP2_1$ and 2 other spindle or bladder stretch receptor (S1) afferents. S4 dorsal root. HT6. For temperature see Table 1.

11 mm). This recurrent fibre is of general interest for the recording method because it shows that if there are recurrent fibres, then their activity is time locked to the one of the mother fibre. The recurrent fibre is of importance here, since it marked uniquely the spikes of the α_2-motoneuron O_1 and made it possible to identify each single Ap in various situations.

Another α_2-motoneuron (O_2) (v = 8 mm/0.2 msec = 40 m/sec) of the same HT (HT6) is shown in figure 2B. Its oscillation period had a duration of 164 msec (see insertion of Fig. 2B) and the impulse train consisted mostly of 3 Ap's, 4.5 and 7.4 msec apart. As can be seen from the wave forms, the Ap's of the motoneurons O_1 and O_2 are similar on the traces "a" and "b" but not same, since noise and artefacts, poor digitalisation and real Ap differences made them a bit different. In figure 2C the impulse trains of the α_2-motoneurons O_1 and O_2 are shown together in connection with Ap's from secondary spindle afferents ($SP2_1$, SP2) and stretch afferents (S1) of the urinary bladder. For the identification of the afferents see figure 9C, and figure 13 of the first paper (77).

Figure 3 shows the repetitive activity of the oscillatory firing α_3-motoneuron O_3. As can be

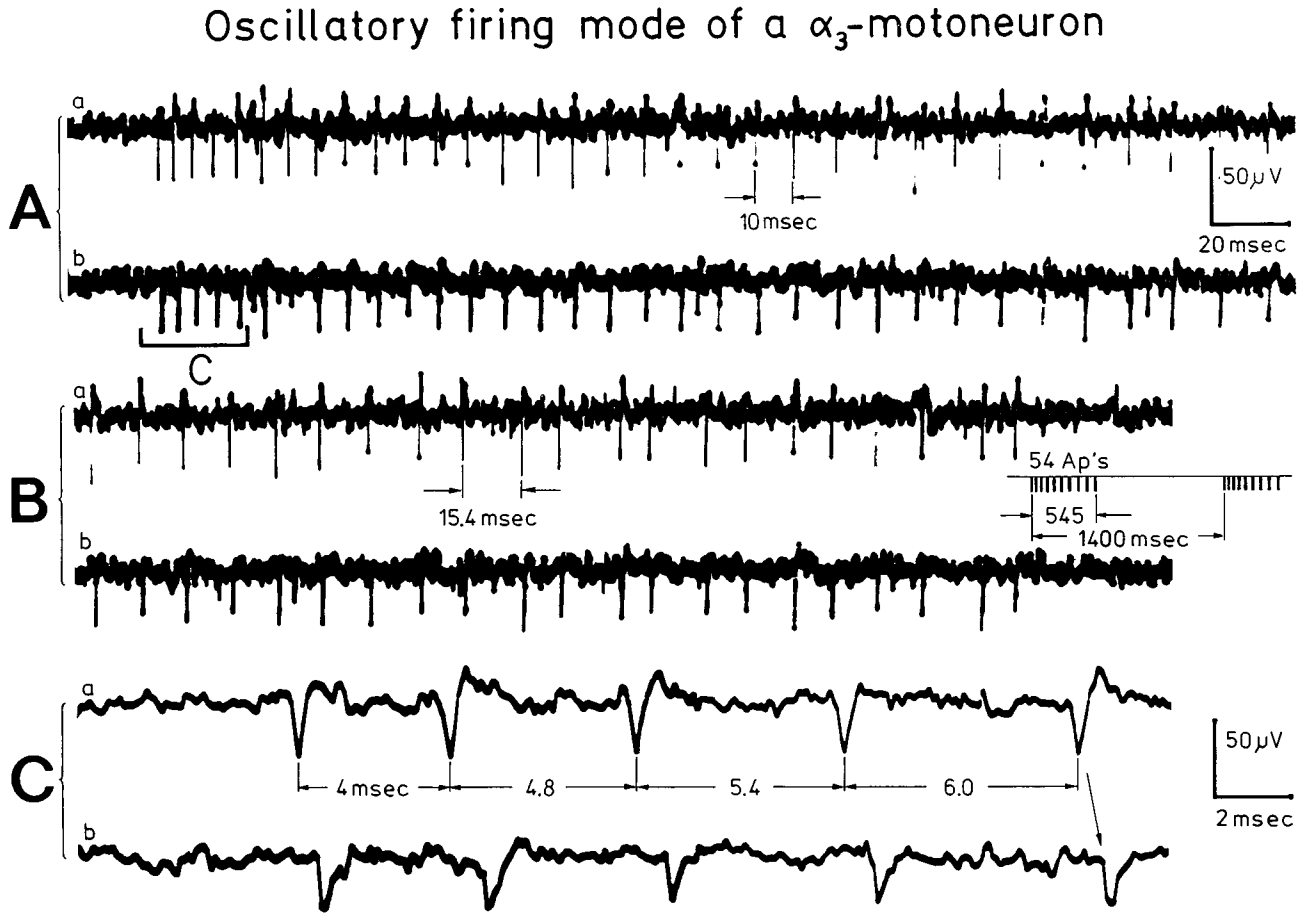

Fig. 3. — Impulse train (54 Ap's) of the oscillatory firing α_3-motoneurons O_3 . "B" is the continuation of "A". The duration of the oscillation period was about 1400 msec (insertion "B"). The start of the impulse train is shown time-expanded in C.

seen from the schematic insertion in figure 3B, the oscillation period was about 1400 msec here and this impulse train needed 545 msec for the 54 Ap's. The different Ap amplitudes of the impulse train in figures 3A and B are mainly due to poor digitalisation. The interspike intervals increased from 4 to over 10 msec (Figs. 3A, B, C). From about of the middle of the impulse train onwards, irregularities in the interspike interval occurred.

The α_2 and α_3-motoneurons identified earlier by their conduction velocity and nerve fibre diameter (75, 77) have a different oscillatory firing mode. All measured motoneurons in the oscillatory firing mode are summarized in Table 1.

3.3. *γ-motoneurons*

Figure 4 shows γ-motoneuron activity. The amplitudes and durations of Ap's of γ_1, γ_2 and α_2-motoneurons can be compared with one another in the time and amplitude-expanded figures 4B and C. The amplitude and conduction velocity increased from the γ_2-motoneuron to the γ_1 and γ_β (not shown) to the α_2-motoneuron, whereas the duration decreased. As has been reported, there are exceptions to that rule (75). In the HT5 measurement, the α_3-motoneuron (Fig. 3) had a slower conduction velocity but an amplitude twice as high as that of the α_2-motoneuron.

γ-motoneurons were not observed in the

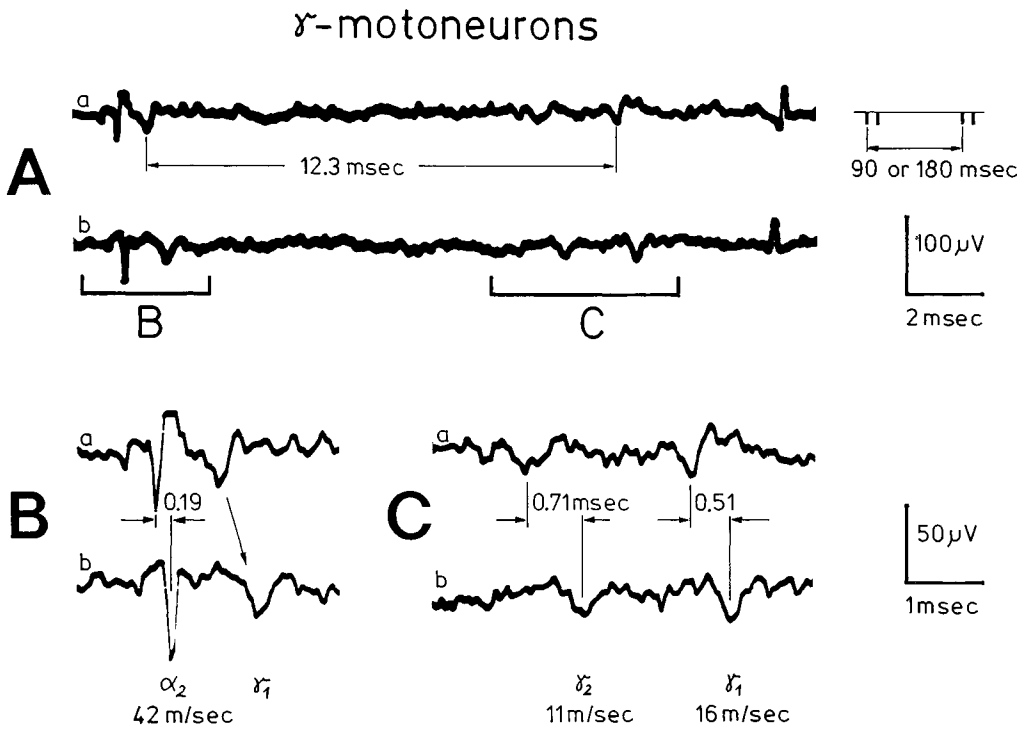

Fig. 4. — Activity from 2 γ-motoneurons and an α_2-motoneuron. The γ_1-motoneuron may fired in the oscillatory mode for a few cycles with a period duration of 90 msec or 180 msec.

A Interspike intervals of the possible impulse train, consisting of 2 Ap's, is indicated with 12.3 msec. The schematic insertion shows the possible oscillation cycle period.

B, C Time and amplitude expansions of A. Conduction velocities are indicated. Note, that with increasing conduction velocity, the Ap amplitude increases and the duration decreases.

constant oscillatory firing mode. It seemed that 2 to 3 oscillations could be recognized for the γ_1-motoneurons. But there is still a good statistical chance that the activity was accidently regular. But if this regular activity was a transient oscillatory firing, then the time relations were the ones given in figure 4 and table 1. Also, the Ap wave form identification was not certain, as can be seen from the wave forms of the γ_1-motoneuron in figures 4B and C.

γ_2-motoneurons probably do not oscillate because of their cumulative effect on muscle spindles (39, 78).

3.4. *Some properties of the oscillatory firing mode*

Table 1 summarizes the measured oscillatory firing modes.

It can be seen that the α_2 and α_3-motoneurons show a different activity pattern. The α_2-motoneurons oscillated with a cycle period of between 110 and 170 msec and an impulse train of about 2 to 4 Ap's, whereas α_3-motoneurons oscillated with a cycle period of about 1400 msec and an impulse train length of 11 to 60 Ap's. The duration of the oscillation period and the number of Ap's per impuls train of α_2 and α_3-motoneurons differed by a factor of about 10. The motoneuron 2 of the HT4 measurement of table 1 was probably an intermediate case.

The oscillation frequency and the time course in the impulse train were very stable in the α_2-motoneuron O_2 in comparison to the ones of the α_2-motoneuron O_4 (Table 1). For the α_2-motoneuron O_2, the standard deviation of the oscillation period of 164 msec was ± 4 msec, whereas for the motoneuron O_4

Table 1. — *Oscillatory firing modes of α_2, α_3 and γ-motoneurons measured from 3 HT's and 1 patient (Pat). m = male, f = female, age in years, temp = central temperature, d = dorsal, v = ventral, S = sacral, f_{osc} = oscillation frequency, $\overline{II}$ = mean interspike interval, activ. = activity (Ap's/sec), s = sec, ms = msec. Downward deflections in the schematically drawn activity modes indicate the Ap's of the repetitive activity. Time from impulse train to impulse train indicates the duration of the cycle period in msec. II = interspike interval in msec, ± = absolute error (standard deviation, number of measurements between 50 and 100). O_1, O_2, O_3, O_4 = designation of motoneurons, which will be referred to in all figures. non- = occasional spike mode, transiently oscill. = transient oscillatory firing mode, constantly oscill. = constant oscillatory firing mode*

Case root sex age temp.	γ_1-motoneurons	α_3-motoneurons firing mode	$f_{osc.}$ [1/s]	$\overline{II}$ [ms]	activ. [1/s]	α_2-motoneurons firing mode	$f_{osc.}$ [1/s]	$\overline{II}$ [ms]	activ. [1/s]
HT4 dS5 f 56 32°C		1. constantly oscill. 11 Ap's — 1400 ms — II = 2,4 ··· 8,6	0,7		8	transiently oscill. 3 Ap's — 170 ms — II = 4,7/6,4 ms	6		17
		2. constantly oscill. 4 Ap's — 410 — II = 5/5,6/6,3	2,4		10				
HT5 dS3 f 58 38°C	γ's present	O_3 constantly oscill. 45 Ap's — 1400 ± 110 — 430	0,6–0,83	9,6	24–50	O_4 constantly oscill. a) 2 Ap's — II = 5,4	4,8–7,1	6,15	9,6–28,6
						b) 3 Ap's — 170 ± 13 — II = 4,6/7,7 ± 2			
						c) 4 Ap's — II = 4,2/6,3/8			
HT6 dS4 f 37 35,5°C	transiently oscill. ? 1. 2 Ap's II = 12,4 — 90 or 180 — 2. 3 Ap's II = 4/8 — 370					O_1 non-; transiently and constantly 1-2 Ap's oscill. — 110 — II = 6,0	7,6–9,0	6,0	12–18
						O_2 constantly and transiently oscill. 3 Ap's — 164 ± 4 — II = 4,5/7,45 ± 0,35	6,1	6,0	18,3
Pat 24 vS3 m 10 37°C	γ's present					transiently oscill. 3 Ap's — 144 — II = 3,5/5,4	6,9		21

(case b) the standard deviation was ± 13 msec. The interspike intervals (II's) of the 3 Ap's showed similar different variations. The α_2-motoneuron O_2 had a standard deviation of ± 0.35 msec for the second II whereas the α_2-motoneuron O_4 had one of ± 2 msec. The different stability in the oscillating firing mode als turned out in the number of Ap's per impulse train. The α_2-motoneuron O_2 nearly always fired with 3 Ap's per oscillation cycle, whereas the α_2-motoneuron O_4 fired more often with 2 or 4 Ap's per oscillation cycle. Therefore, the α_2-motoneuron O_2 was stable in the oscillation cycle period, the number of Ap's per impulse train and the length of the II's of the impulse trains. The α_2-motoneurons O_1 and O_4 and the α_3-motoneuron O_3 were not so stable in these parameters.

The II's of the impulse trains of the α_2 and α_3-motoneurons showed a certain rule, which can be seen from the impulse patterns of the α_2-motoneuron O_4 of table 1. If the impulse train consisted of 2 Ap's (case a), then the II was 5.4 msec long. If the impulse train consisted of 3 Ap's (case b), then the first II became shorter (4.6 msec) and the second lon-

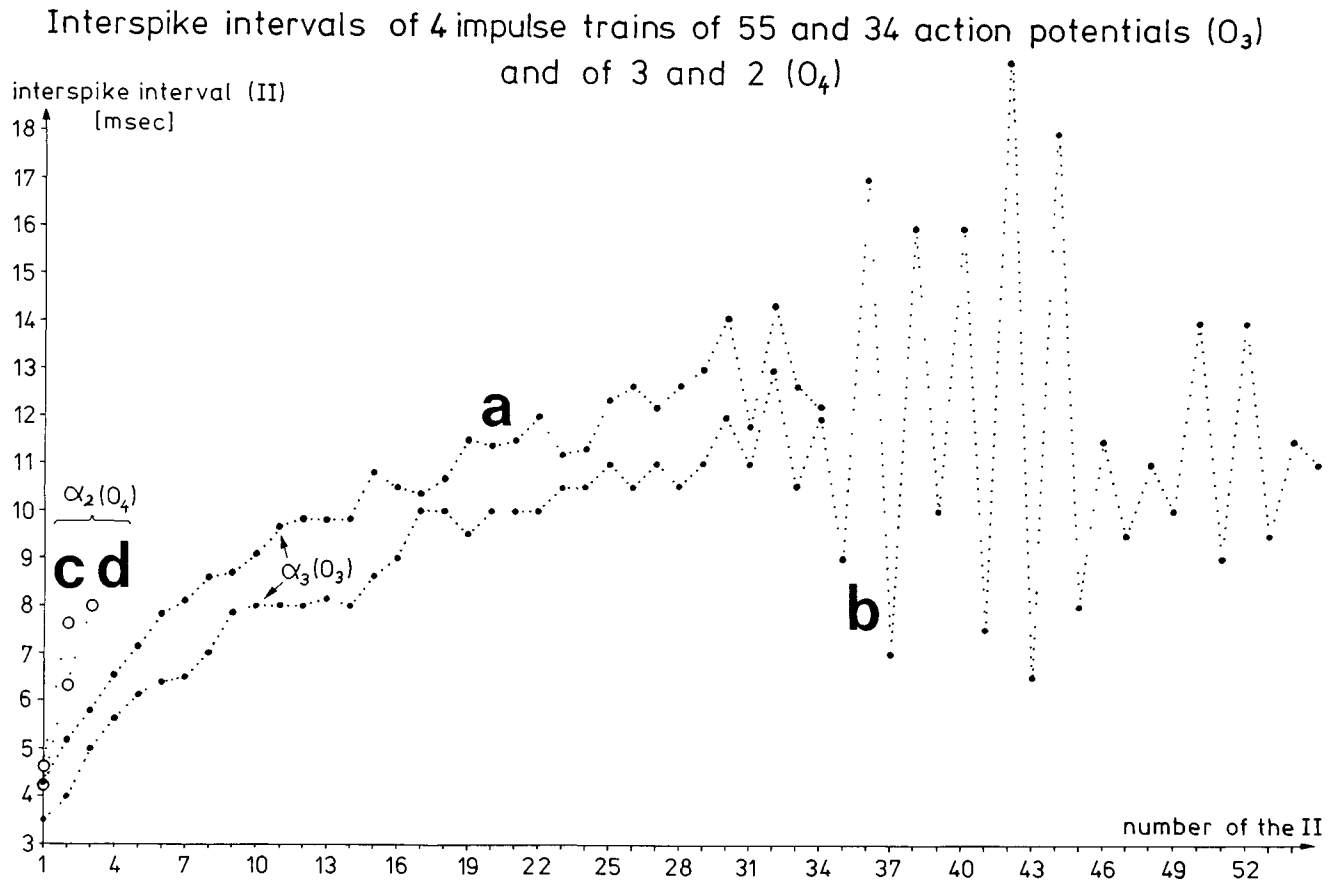

Fig. 5. — Interspike intervals (II's) of successive Ap's of a short (a) and a long impulse train (b) of the α_3-motoneuron O_3 and II's of the α_2-motoneuron O_4 of impulse trains consisting of 3 Ap's (c) and 4 Ap's (d). The large dots give the values of the II's and the dotted lines connect successive II's for the α_3-motoneuron O_3. The circles give the values of the II's and the dotted lines connect the II's for the α_2-motoneuron O_4. Note that the II's from the impulse train "b" are very unequal from the 34th II on. Notice also, that the shortest II's converge towards values of between 3.5 and 4 msec. HT5. S3 dorsal root.

ger (7.7 msec). If the impulse train was 4 Ap's long, the first II became even shorter (4.2 msec) and the last one even longer (8.0 msec) (Figs. 5c, d, Table 1). This same rule also held true for the α_3-motoneuron O_3. With longer impulse trains, the first II became shorter and the last one longer. Strong irregularities occurred for long impulse trains from about the 30th Ap on, similar to Hodgkins measurements (47). Figures 5a, b show 2 sets of II's from the α_3-motoneuron O_3. It can be seen that the II's increased from the beginning to the end and a longer impulse train started with a shorter II (Fig. 5a). That means that for the impulse trains of α_2 and α_3-motoneurons, with the first, or first few II's, the length of the impulse train is given. As will be analysed in the discussion section, the Ap train length and the duration of the first II are correlated to the strength (amplitude) of the depolarization. This means, that in the first II the information is contained as to how much the motoneuron cell soma was depolarized if the repetitive activity was produced by a depolarization (see discussion).

The number of Ap's per impulse train of the α_3-motoneuron O_3 is shown in figure 6. 42 Ap's per impulse train occurred most frequently. In the lower part of figure 6 mean II's of impulse trains are given. It can be seen, that the longer impulse trains had slightly longer mean II's, even though the mean II converged against a value of about between 9.8 and 10 msec. Since

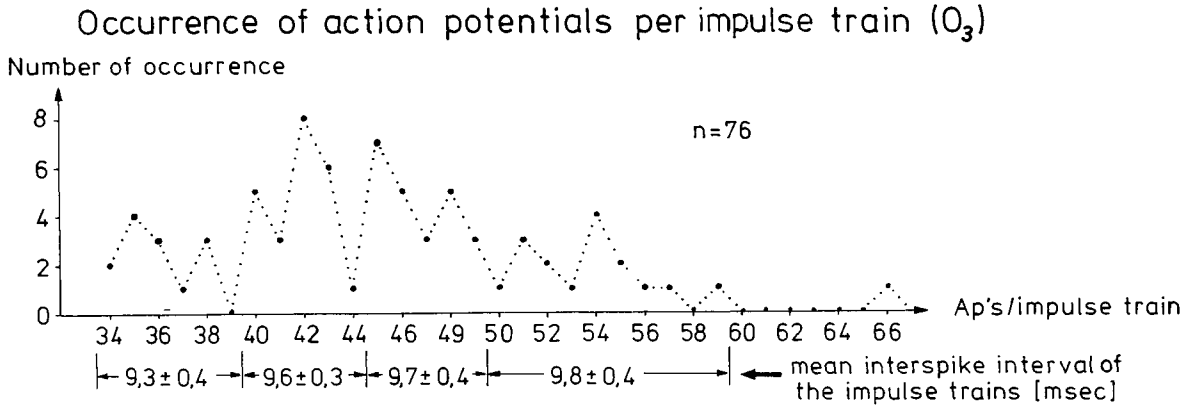

Fig. 6. — Occurrence of Ap's per impulse train. The large dots give the numbers of how often an impulse train of a certain number of Ap's occurred; the dotted lines connect the values. Notice that the occurrence of numbers of Ap's per impulse train does not build a gaussian distribution. The lower part of figure 6 gives mean interspike intervals for ranges of impulse train lengths.

it seemed that the impulse trains were normally uninterrupted, it may be that the mean II is also slightly correlated to the length of the impulse train.

From figures 5c, d, it can be seen that the α_2-motoneuron increased its II's faster than the α_3-motoneuron (Figs. 5a, b). This maybe means that in α_2-motoneurons, the repetitive activity inactivates faster than in α_3-motoneurons. The membrane properties of α_2 and α_3-motoneurons are probably different, therefore, in accordance with the results of the first paper (77), where different membrane properties of α_2 and α_3-motoneurons were concluded from a different temperature dependence of their conduction velocities (for another explanation for increasing II's see the discussion section).

As table 1 summarizes, the oscillatory firing mode is different for the α_2 and α_3-motoneurons. The oscillation frequency is lower for the α_3-motoneurons with 0.7 impulse trains per second than for the α_2-motoneurons with about 7 impulse trains per second. The mean II was nearly 10 msec for the α_3-motoneurons and about 6 msec for the α_2-motoneurons. The mean number of Ap's (mean activity) varied between 24 and 50 Ap's/sec for the α_3-motoneuron O_3 and between 10 and 29 Ap's/sec for the α_2-motoneurons. These ranges of mean activity seem to be the approximate dynamic ranges in which the motoneurons can respond to changes of afferent input in the continuous oscillatory mode and it will turn out in the following paper that the motoneurons in the not-so-stable oscillatory firing modes can respond more smoothly to changes in the afferent input.

The 2 γ-motoneurons, most likely of γ_1-type, which may have been transiently in the oscillatory mode (Table 1), bear more similarity to the activation mode of the α_2-motoneurons than to the α_3-motoneurons. This to some extent supports the consistency argument of the previous paper, that the γ_β-motoneurons correspond to the α_1, the γ_1 to the α_2 and the γ_2 to the α_3-motoneurons.

No α_1-motoneurons were observed in the oscillatory firing mode. But in these measurements from lower sacral roots, only a few Ap's from α_1-motoneurons (and γ_β-motoneurons) were observed. No conclusion can be drawn for the α_1-motoneurons. As was said in the introduction, the α_1-motoneurons probably show no or only a little repetitive activity. But if a subgroup of the α_1-motoneurons would fire oscillatory, then one could expect an oscillation period of 10 to 20 msec and an impulse train of 1 to 2 Ap's.

3.5. *Change of the firing mode*

On the one hand, one has the known occasional spike mode of motoneurons and on the other, the oscillatory firing mode reported in

this paper. The question is now, how do the motoneurons change from the occasional spike mode to the oscillatory firing mode. From the mean activities of the motoneurons of table 1, it can be seen that motoneurons in the oscillatory firing mode are in a highly activated stage. One would have to give a motoneuron a slowly increasing adequate stimulus to see how the activity pattern changes. Filling the urinary bladder and recording how the sphincteric motoneurons are responding seems to be such a situation, since with the filling of the bladder the afferent activity from stretch and flow receptors (S1, S2, ST) increased and the activity of the external sphincter motoneurons also increased to preserve bladder continence (guarding reflex).

Table 2 shows the activity increase of the sphincteric α_2-motoneuron O_1, identified by its guarding function, in response to the retrograde filling of the bladder through a bladder catheter (see also Fig. 9). Up to a filling of 550 ml, the α_2-motoneuron O_1 occasionally fired and the mean activity increased slowly up to 2.5 Ap's/sec. With further filling, followed by an increase of the stretch receptor activity (Fig. 9), the motoneuron O_1 jumped into the oscillatory firing mode transiently. Such transient oscillatory firing was also observed with anal canal stimulation. When the bladder was 620 ml full, the sphincteric α_2-motoneuron O_1 started to fire in the continuous oscillatory mode with an impulse train of 1 Ap or 2 Ap's alternately. The oscillation cycle period following the impulse train consisting of 2 Ap's was longer (143 msec) than the one following an impulse train consisting of 1 Ap (114 msec). With a 700 ml filling the impulse train consisted more often of 2 Ap's and with a filling of 750 ml the impulse train always consisted of 2 Ap's, but the oscillating mechanism still seemed to have the information about when the impulse train consisted of 1 Ap before, since that oscillation period was still shorter, namely 109 against 112 msec. This means the mechanism responsible for the oscillation, did not directly have the information about the number of Ap's per impulse train, which had been carried out. The mean activity increased from 12 Ap's/sec to 18,1 because of an increase of the oscillation frequency and an increase of the number of Ap's per impulse train. With further filling, the activity pattern went backwards again and also the mean activity was reduced to

Table 2. — *The occasional spike mode, the transient and the constant oscillatory firing mode of the α_2-motoneuron O_1 of the external urethral sphincter in response to filling of the bladder. In the "activity pattern" column changing durations of oscillation periods are given. The oscillation frequencies in brackets give the frequencies at the moment of oscillation for the transient oscillatory mode. Downward deflections are schematised Ap's. Interspike intervals of close Ap's ≈ 6.0 msec. HT6*

fluid in bladder [ml]	activity pattern [msec]	oscillat. frequency [impulse trains/sec]	mean activity [Ap's/sec]	firing mode
200			0,5	occasional spike mode
500			1,0	
550			2,5	
anal-stimulat.	144	(6,9)		transient oscillatory mode
580	112 long short	(8,9)	5,0	
620	143 114	7,8	12,0	continuous oscillatory mode
700	134 116	8,0	14,0	
750	112 109	9,0	18,1	
800	127 111	8,4	16,8	
830	134 124 104	7,8	13,8	

13.8 Ap's/sec. More details about that bladder filling will be given later on in connection with figure 9.

Only in the α_2-motoneuron O_1 all 3 firing modes were observed (occasional spike mode, transient oscillatory firing mode and continuous oscillatory mode). The α_2-motoneuron O_2 was observed in the constant and in the transient oscillatory firing mode. It does seem, therefore, that with the increasing afferent input at certain levels, the motoneurons change from the occasional spike mode via the transient oscillatory firing mode to the constant oscillatory firing mode. This is a property of an oscillator when it gets an increasing stimulus of adequate strength and phase.

3.6. *Damping of α_3-motoneurons*

Figure 7 shows the mean activity and the oscillation frequency, as time goes on, of the α_3-motoneuron O_3. There was no stimulation before this recording, apart from the constant stimulus from the bladder and the anal canal and a possible mechanical stimulus caused by lifting the root onto the electrodes. The shape of the increase and decrease of the mean activity over a period of time looks very similar to the shape of damped oscillations, which are schematically shown in the insertion in figure 7. The strength of damping to avoid the swinging of the mean activity (produced by oscillation) is not quite as strong as the aperiodic damping. The damping in the spinal cord circuitry projecting onto the α_3-motoneurons, seems to be the same as has been used in ideally damped, that means strongly damped, galvanometers, but not so strong that the end value changes, or, in the language of galvanometers, the pointer has to perform about 1 swing before stopping. In the following 3rd paper (78) other recordings can be seen, where it seemed that ideal damping occurred. Such damping seems to be necessary since it can be seen in the following paper (78) that the activities of α_3-motoneurons in the occasional spike mode and in the oscillatory firing mode have the tendency to go up and down, that means to swing.

Recurrent inhibition may stabilize the slow swinging of stretch-sensitive tonic α-motoneurons in the cat (40, page 323). The lack of recurrent inhibition in the cat has only been reported for sphinteric α_2-motoneurons (60).

3.7. *Origin of the oscillatory firing mode*

The system generating the oscillatory mode cannot lie supraspinal as for respiratory motoneurons of intercostal muscles (82), since the oscillation was observed in HT's. The oscilla-

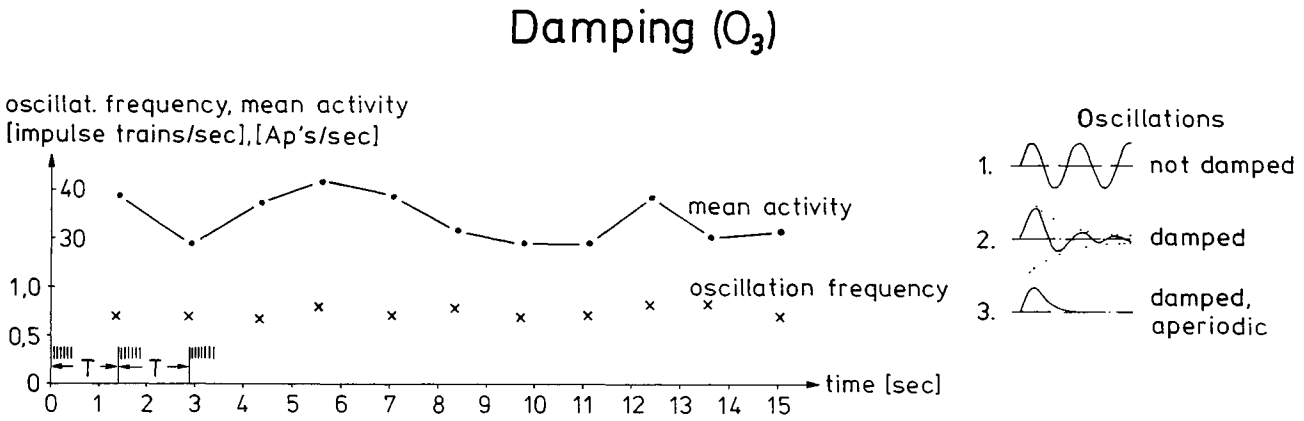

Fig. 7. — Oscillation frequency (~0.7 impulse trains/sec; crosses) and mean activity (~35 Ap's/sec; dots) with ongoing time. Insertion on the right shows schematically wave forms of non-and damped oscillations. Notice, the shape of the mean activity with time is similar to that of damped oscillations of between case 2 and 3 in the insertion. The left lower part of figure 7 shows schematically the impulse train and the oscillation cycle period T.

tors, giving rise to the oscillation patterns of table 1, cannot lie in the periphery either, since no afferent activity with exactly the same firing pattern as the one of motoneurons in the oscillatory mode was observed from afferents thicker than 5.5 µm (limit of the measuring method). The questions remain, whether afferent activity of statistical or rhythmic distribution stimulates the spinal oscillators to oscillate and whether there are specific kinds of afferents, which stimulate certain oscillators.

3.8. *Adequate afferent stimuli of spinal oscillators*

The α_2-motoneuron O_2 fired in the ocillatory mode very precisely with an oscillation cycle period of 164 msec and an impulse train of 3 Ap's. Its activity pattern were therefore suitable for a comparison with the afferent activity pattern, especially since some interspike intervals (II's) of the existing secondary muscle spindle activity seemed to have a length of about 160 msec. The α_2-motoneuron O_2 was identified as innervating the external anal sphincter by the recto-sphincteric-reflex (79, 80), which is activated when rectal contents push against the distal rectum. The internal sphincter (smooth muscle (80)) is relaxed to let the contents into the anal canal for identification (see first paper (77)) and the external sphincter contracts to secure continence. In figure 5B of the third paper (78) it is shown that the α_2-motoneuron O_2 was most sensitive to the pulling of the anal catheter with its ballon in the rectum. The secondary muscle spindle activity was identified as being mainly or at least partly from muscles spindles of the external anal sphincter, since it reduced transiently following anal catheter stimulation with the contraction of the external anal sphincter motoneurons in the occasional spike mode (Figs. 5A and 7B of the third paper (78)). In the measuring situation the external anal sphincter was statically stretched with a catheter of 10.5 mm in diameter and the external bladder sphincter was probably stretched a bit by the bladder catheter; the bladder was empty. Out of the secondary afferent spindle activity the activity from one fibre ($SP2_1$) was picked up by a wave form analysis (Figs. 8B, C). The $SP2_1$-fibre activity, contributing more than half of the secondary spindle afferent activity, was assumed to be the activity from the external anal sphincter spindle, which was stimulated by the sustained (tonic), stretch. The external bladder sphincter may not have spindles (98), and if it has, then the afferent fibres would only have low activity, because the external bladder sphincter was not or was only stretched a little by the bladder catheter. The oscillatory activity of the external anal sphincter α_2-motoneuron O_2 was therefore assumed to be stimulated by the sustained anal stretch reflex to secure continence ("guarding reflex") (80), which means by the activity of secondary spindle afferents, mainly from the $SP2_1$-fibre in this recording situation. By comparing the activity of the α_2-motoneuron O_2 with those of the $SP2_1$-fibre, the oscillatory reflex activity of an external anal sphincter α_2-motoneuron, during the sustained stretch reflex, is compared with its (or an) adequate stimulus from an external anal sphincter muscle spindle afferent fibre (Fig. 8).

The $SP2_1$-fibre activity increased and decreased, while the sphincteric motoneuron O_2 fired constantly in the oscillatory mode. The occurrence pattern of the Ap's from the $SP2_1$-fibre was, therefore, not directly correlated to the one of the α_2-motoneuron O_2. The Ap's of the $SP2_1$-fibre sometimes appeared with the impulse train of the α_2-motoneuron O_2 (Figs. 8B, C) and sometimes they did not. A direct phase correlation (time locking) was not observed. To analyse how similar their frequencies were, an interspike interval (II) frequency distribution histogram was constructed from a few sweep pieces of the $SP2_1$-fibre activity. It can be seen from figure 8D that most of the $SP2_1$-II's had a length similar to the oscillation period $T(O_2)$ (14 times), to half of it (43) or longer (9). From the frequency aspect ($f = 1/T(O_2)$), the $SP2_1$-fibre activity may be able to stimulate the oscillator driving the α_2-motoneuron O_2. But such an oscillating system would also need to be able to oscillate for a few cycles without that afferent drive, since longer

II's were also observed (Fig. 8D). From mechanics and electronics it is known, that critical oscillators only sometimes need rhythmic energy in phase and that they can select their "in phase energy" out of the mixed energy offered.

A further secondary spindle afferent fibre seemed to have an impulse pattern with similar II's than the $SP2_1$-fibre, but its activity could not safely be extracted from the activity of the roughly 2 remaining spindle afferents, probably from pelvic floor muscle spindles, since their wave forms were very similar.

The regularity of the discharge from the secondary spindle afferent $SP2_1$-fibre is not unexpected. It has been reported that secondary spindle afferents maintain a highly regular discharge, especially at higher discharge frequen-

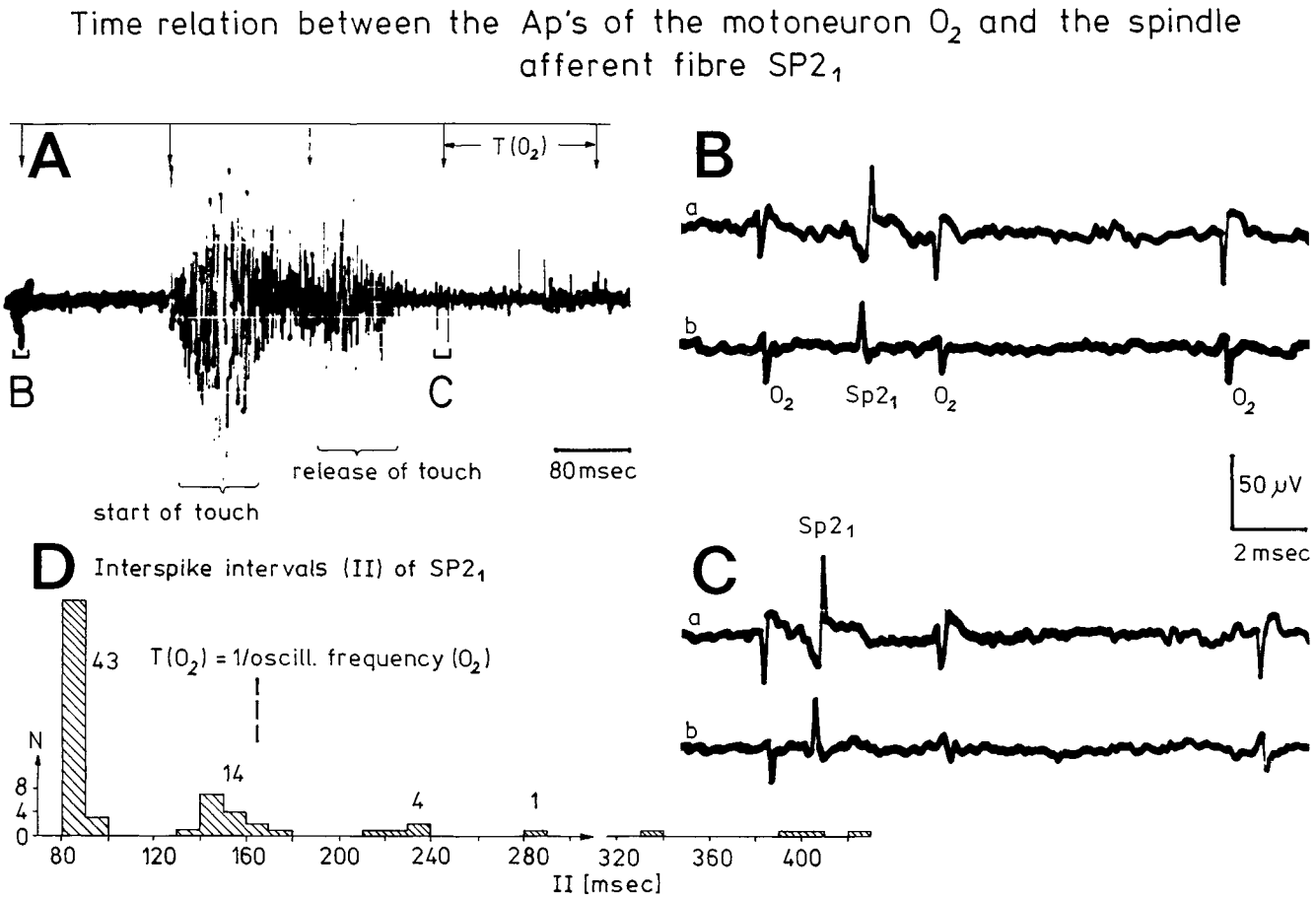

Fig. 8. — Time relation between the occurrence of the action potentials (AP's) of the α_2-motoneuron O_2 in the oscillatory mode and the secondary spindle afferent fibre $SP2_1$. HT6. S4 dorsal root recording.

A Overall view of the used sweep piece; only trace "a" shown. 4 oscillation cycle periods of the motoneuron O_2 are indicated ($T(O_2)$). The Ap's of the impulse train can only partly be recognized, because of slow time base and bad digitalisation. One impulse train (dashed arrow) is lost in the touch stimulated activity, which consists of the touch (large overall amplitude) and the release part (lower overall amplitude).

B, C Sweep piece from A, time stretched. In B, motoneuron impulse train Ap's marked with O_2, spindle afferent Ap's are marked with $SP2_1$. Notice that the Ap's of the spindle fibre are not time-locked to the Ap's of the motoneuron. Digitalisation 4 times better than in A, but still rather poor, as can be seen from the low amplitudes of the motoneuron Ap's on trace "b" in C.

D Occurrence of interspike intervals of the secondary spindle afferent fibre $SP2_1$. The oscillation period of the motoneuron O_2 is indicated by a short dashed line. The numbers give the amount of II's in each distribution peak.

cies (10, cat). The II length were in the range of between 50 and 100 msec (10) and had approximately normal distributions with a mild positive skew towards longer II's. The difference of the $SP2_2$-fibre discharge pattern to those of Burke et al. (10) is, that the in this measurement observed II's preferred several specific values, whereas the ones measured by Burke et al. preferred only one specific value.

A similarity between the II's of the stretch (S1, ST) receptor and the flow (S2) receptor afferent activities, and the duration of the oscillation cycle period of the oscillatory firing sphincteric α_2-motoneuron O_1 (T = 110 msec) of the urinary bladder has not yet been found. In the next section it will be shown, that the stretch and flow receptor activities are most likely adequate stimuli for the α_2-motoneuron O_1.

3.9. *Activity increase of the α_2-motoneuron O_1 of the sphincter externus of the bladder in response to the activity increase of stretch (S1, ST) and flow receptor (S2) afferents due to the filling of the bladder — Urethro-sphincteric guarding reflex*

With the identification of afferents and efferents in the first paper and the activation pattern of motoneurons in this paper, functional correlations between the activities of afferents and efferents due to physiological stimulation are directly possible. They will be shown in this and the following paper.

The activity increase of the α_2-motoneuron O_1 of the external urethral sphincter in response to the afferent input from stretch and flow receptors will now be analysed in detail. The nerve fibre connection are schematically shown in figure 9D. The axon of the sphincteric motoneuron leads from the dorsal S4 root to the external sphincter of the urinary bladder. The flow receptor afferents (S2), coming from different mucosa parts of bladder and urethra, are pictured as one afferent fibre from a receptor of the trigonum vesicae, since the density is believed to be highest there (7). The 2 kinds of stretch receptor afferents S1 and ST, probably measuring tension, are schematically drawn into the detrusor. The oscillation frequency and the mean activity of the sphincteric α_2-motoneuron O_1 is shown in figure 9B. With the conduction velocities of the stretch (S1, ST) and flow receptor afferents (S2), collected during a time interval of 1.2 sec at a 750 ml filling of the bladder, a conduction velocity frequency distribution histogram is constructred in figure 9C as in the first paper (77). With the velocity limits of the afferents, given in figure 9C, the number of occuring conduction velocities of S2 afferents (27 Ap's), ST afferents (33 Ap's) and S1 afferents (59 Ap's/1.2 sec) are counted from the hatched plus open part of the histogram of figure 9C and plotted as activity values of S1, ST and S2 afferents at 750 ml into figure 9A. Activity values during other fillings of the bladder are obtained from similar velocity histograms.

The activities, recorded from the 3 kinds of afferent units, did not continuously increase, but increased intermittently and decreased during the time interval of 1.2 sec. The number of active afferent units will probably also have changed a bit with the filling of the bladder. Very approximate numbers of the afferent units, activated at 750 ml, can be obtained from the hatched part of the histogram in figure 9C. Since 3 histograms of 400 msec had been added, one has to divide the number of conduction velocities in the hatched parts of the histograms by 3. The number of the S1 units is 4, of the ST units 4 and of the S2 units 6. These units lead from the bladder through the S4 dorsal root on one side.

The dependence of the activity of the S1, ST and S2 afferent units on the filling of the bladder is shown in figure 9A. In a first approximation, the activities of the stretch afferent units S1 and ST increased proportionally with the filling of the bladder up to 750 ml and then reduced. The slight bending of the S1 activity dependence probably comes from a few intermingled secondary spindle afferent Ap's. It was not attempted to seperate them out. The 2 deflections from the rougly straight line at about 400 ml and 620 ml in the S1 dependence may not be artifacts. The second activity reduc-

tion between 600 and 650 ml fillings of the bladder can be explained by the reduction of vesical pressure due to the stopping of the filling of the bladder. It is known that the vesical pressure rises gradually when the bladder is filled continuously from a reservoir and that the pressure subsides, or "adapts" when the volume is maintained constant (22). With further filling, the S1 activity turned back to the dependence line as if there had been no stop to the filling. For the fluctuation at 400 ml there is no meaningful explanation for the time being. Maybe the filling speed was changed transiently by manipulating with the catheter bag. The ST activity dependence shows less reaction to the stopping of the filling of the bladder between 600 and 650 ml and no response at 400 ml. The receptor properties of the S1 afferents cannot

Sphincter motoneuron activity depending on bladder afferent input

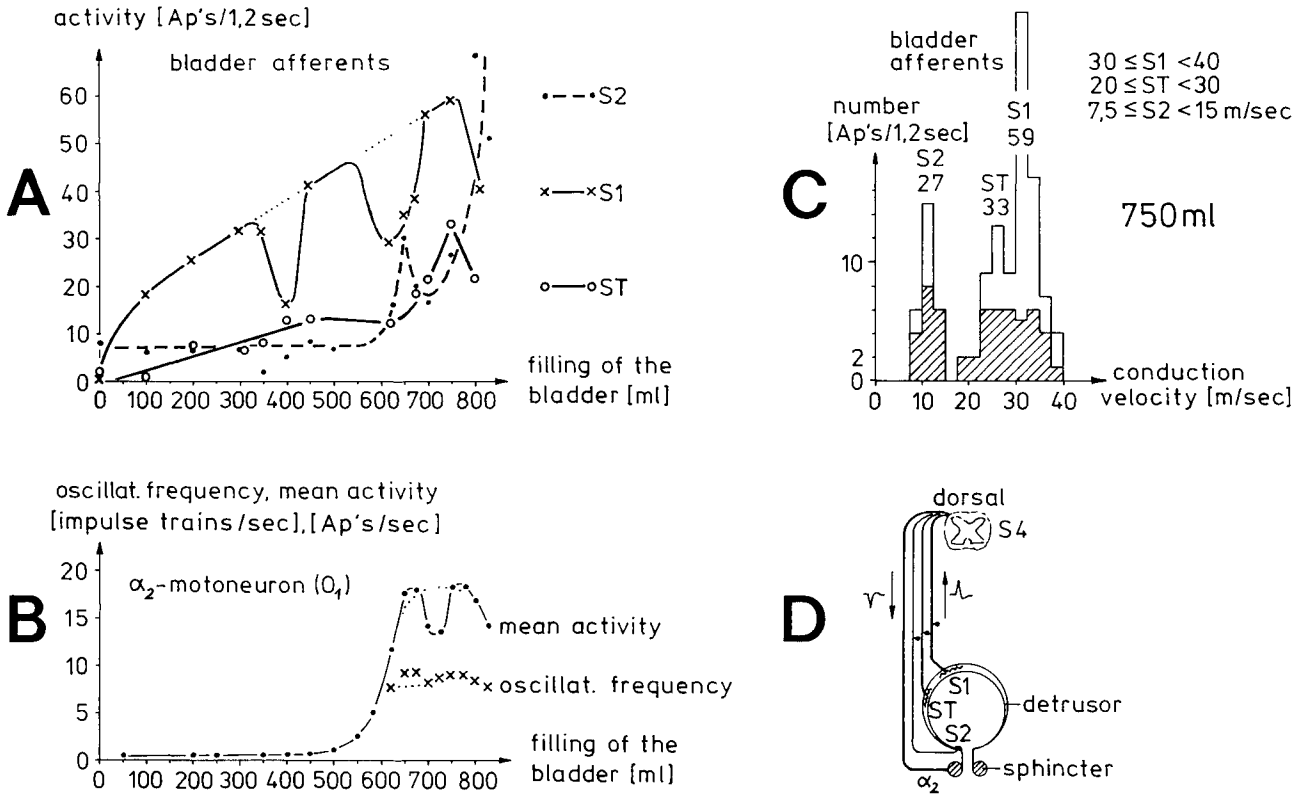

Fig. 9. — Activity levels of stretch (S1, ST) and flow receptor (S2) afferents (A) and the sphincteric α_2-motoneuron O_1 (B) in response to the retrograde filling of the bladder. HT6. S4 dorsal root recording.

A The activity values of the S1, ST and S2 afferents are taken from histograms like the one in C. Filling of the bladder was stopped once between 600 and 650 ml.

B Small dotted lines suggest mean activity (Ap's/sec) and oscillation frequency (impulse trains/sec) of the α_2-motoneuron O_1 if bladder filling were not stopped in between. Notice that the mean activity increases continuously with the filling of the bladder from 550 to 650 ml, even though the motoneurons started to fire in the oscillatory mode from 620 ml on (Table 2).

C Conduction velocity frequency distribution histogram of stretch and flow-receptor activity at 750 ml. The receptor activities of the S1, ST and S2 afferents are quantified by counting the occurring conduction velocities under the peaks (open plus hatched part), with the conduction velocity limits given in the insertion. The counted numbers (27, 33, 59) are given below the peak designations S1, ST, S2 and plotted into A for the afferent activity at 750 ml.

D Schematic drawing of the anatomical arrangement of the afferents and the α_2-motoneuron O_1.

be derived from this one measurement. The reduction of the activity at the stop in the filling of the bladder between 600 and 650 ml points towards tension dependence. The existence of the ST stretch receptors is unsafe. It could be that the ST units are a subgroup of the S1 units. The later start to the increase and the similar behaviour following the filling of the bladder suggests that these ST units also monitor mural tension and are maybe responsible for avoiding overfilling of the bladder, just as the Golgi tendon organs respond to tension to avoid overstretch.

The S2 mechanoreceptors of the bladder, responding to pressure in the bladder for fillings of the bladder larger than 600 ml and fluid movements via disturbances at the bladder wall, showed a transient activity increase between 620 and 650 ml filling of the bladder, because of a stoppage of further filling in that range. The baseline activity of the S2 receptor afferents for bladder fillings lower than 600 ml was probably due to the stimulation of S2 receptors by the catheters lying in the urethra and anal canal. Whether the mucosal mechanoreceptors M are identical to the S2 receptors is not clear (see first paper (77)). If the interpretation of the urinary bladder afferents is right, then the S1, ST and S2 receptors supply an elaborate control system for urin storage and micturition, by monitoring tension (stretch), pressure and fluid movement.

The simultaneously measured activity of the α_2-motoneuron O_1 is shown in figure 9B. Up to a filling of the bladder of 500 ml the occasional activity of the α_2-motoneuron O_1 was very low and increased slowly (Fig. 9B). With further filling the occasional activity increased strongly and the motoneuron started to respond transiently in the oscillatory firing mode to increase the activity and then changed into the constant oscillatory firing mode for an even greater increase in activity (Table 2). In the constant oscillatory firing mode, the sphincteric motoneuron increased its activity with further filling of the bladder by increasing the frequency and by increasing the number of Ap's per impuls train. Since the motoneuron in the oscillatory mode seemed to have only the possibility of responding with 1 or 2 Ap's per impulse train, alternation and other mixtures of 1 or 2 Ap's per impulse train were used to produce the needed activity level (Table 2). The pointed lines in figure 9B give the suggested mean activity and oscillation frequency in dependence on the filling of the bladder without filling stoppage.

The start of further filling between 620 and 650 ml after a stop in filling gave a strong activity increase in the flow receptor (S2) afferents (Fig. 9A, Fig. 9 of the first paper (77)). The sphincter motoneuron also seemed to further increase the activity to secure continence, probably because the increased S2 activity "told" the spinal cord that urine was entering the proximal urethra. After the reduction of the S2 activity (after 650 ml, Fig. 9A) the mean sphincter activity reduced transiently at about 700 ml, because the S2 receptors were not "signalling" any more fluid is entering the proximal urethra and the additional contraction to preserve continence was reduced.

At an 800 ml filling of the bladder the reduction of the activity of the S1 and ST afferents and of the sphincteric α_2-motoneuron O_1 and the strong increase in the activity of the S2 flow receptor afferents is probably due to the start of the overflow incontinence. The micturition reflex did not seem to start at a certain stage in the filling of the bladder probably because the brain stem micturition centre was damaged (HT measurement) and the sacral micturition centre had not been built in (21) during the short time of brain death, as is similar to about the first 2 weeks following a spinal cord lesion when complete retention of urine exists. But the urethrosphincteric guarding reflex (61) seemed to work in this HT. Effects from a partial spinal shock cannot be excluded.

The activity of the α_2-motoneuron O_1 perhaps showed how the whole external urethral sphincter roughly responded to the filling of the bladder if it consisted only af fast fatigue-resistant muscle fibres (FR-type) when the urethrosphincteric guarding reflex was acting (61) and the micturition reflexes were not. Comparing the activity curve of the α_2-motoneuron O_1

in figure 9B with the cystometrically measured pressure curve of figure 1B of reference 105, then it seems that in the accomodative phase (storage phase), where the pressure in the bladder increases only little (till about 450 ml filling), the sphincteric α_2-motoneuron O_1 showed only little activity. In the non-accomodative phase (105), where the pressure in the bladder increases more steeply (till about 550 ml), the mean activity of the sphincteric α_2-motoneuron O_1 increased more strongly and the motoneuron started to respond transiently with oscillatory firing (Table 2). According to this comparison the motoneuron increased strongly its mean activity by changing into the constant oscillatory firing mode for fillings from uncomfortable full to the overflow incontinence (filling range from about 600 ml to 850 ml). By comparing now figure 9B with figure 9A it seems that at about 600 ml filling the sphincteric α_2-motoneuron O_1 changed into the high activity mode of oscillatory firing, when the flow receptor afferents (S2) increased their activity most likely in response to the pressure in the urinary bladder and not or not so much in response to mural tension, monitored by the stretch receptor afferents (S1, ST). In further research it has to be compared at high fillings of the bladder the activity patterns of the flow receptors afferents (S2) and α_2-motoneurons of the external bladder sphincter to see whether there are frequency similarities as has been found between the activity patterns of the secondary spindle afferent fibre $SP2_1$ and the α_2-motoneuron O_2 of the external anal sphincter.

The γ-motoneuron activity reduced along with the filling of the bladder as in the cat (28), probably due to a relaxation of the perineal and pelvic floor muscles to reduce additional pressure on the bladder. The activity changes are not shown, since the γ-activity had decreased in general, probably because of poor blood supply to the root after a long measuring time ($\sim$1 hour). The γ-motoneurons seemed to be more sensitive to a reduction or arrest of blood supply than the α-motoneurons. The SP2 afferent activity also reduced with the filling of the bladder.

4. **Discussion**

4.1. *Repetitive activity — Action potential impulse trains*

The analysis of the oscillatory firing mode will be started by considering the repetitive activity (impulse train part of the oscillatory mode) and afterwards it will be discussed, what circuitry could be resposible for the oscillatory mode.

Repetitive activity produced by sudden application of constant current pulses into nerve cells is a well known phenomenon (3, 42, 43, 44, 47, 54, 65). This response is not explained by the permeability equations in the form developed for the squid axon (48). A clear physiological explanation has not yet been given for humans. By comparing the impulse trains of the α_3-motoneuron O_3 of figures 3 and 5 with the repetitive activity produced by depolarizing current pulses of a crustacean nerve of plate I of reference 47, one is struck by the similarity. It is concluded, that the impulse trains of the α_3-motoneuron O_3 are mainly produced by a long depolarization, which can be produced by rectangular current pulses slightly higher than the rheobase current (threshold current). It is further concluded, that if the depolarizations are only slightly stronger than the rheobase, then the impluse trains are rather short and the interspike intervals (II's) increase quite regularly as in figure 5a. With increasing depolarization, the impulse trains become longer and the II's become irregular after about the middle of the impulse trains as in figures 3 and 5b (3, 47). Further in accordance with the crustacean nerve (47), the first II's become shorter and the last ones longer with stronger depolarization. Since the patterns of the increasing interspike intervals (II's) of the crustacean nerve of plate I of reference 47 following very long current pulses and the human α_3-motoneuron O_3 of figures 3 and 5a are so similar, it is further concluded that the length of the impulse train is mainly given by the strength of the depolarizing pulse and the increasing inactiviation of the repetitive activity (see later), and not by the length of the depo-

larizing pulse. The repetitive firing of rat and cat motoneurons (42, 43, 44), caused by injected currents, are similar to the measurements of Hodgkin (47). Compare for example the upper 2 traces of figure 4 of reference 43 with the ones of plate I of reference 47 and figures 3 and 5a and b. Only Granit et al. (42, 43, 44) were more concerned with stronger depolarizations. These human measurements show that the physiological range of repetitive activity is rather close to threshold depolarizations, namely in the primary range of motoneuron firing caused by injected currents (44, cat). This is also the motoneuron firing range where post-synaptic activation is summed up algebraically (44). In the primary range of repetitive firing, the impulse rate (Ap's/sec) is roughly proportional to the depolarizing current strength (44) in the rat and the cat. In human the physiologically driven α_3-motoneurons had no constant impulse rate during repetitive firing. The impulse rate decreases with increasing II in the impulse train. The corresponding parameters are the length of the first II and the length of the impulse train. It is likely that also in human in the primary range the depolarizing current pulse amplitude is roughly proportional to the impulse rate of α_3-motoneurons, if it is calculated from the first II (impulse rate = 1/first II).

Till now the repetitive activity of motoneurons from artificial stimulation has been compared with the repetitive activity of natural synaptic drive in this paper, assuming that depolarizations from current pulses can imitate synaptic potential changes. It has been shown that depolarizations from current pulses can imitate drive potentials from spatially and temporally summed exitatory post-synaptic potentials (13, 44).

As figures 2 and 3 show, and table 1 summarizes, α_2 and α_3-motoneurons show different repetitive activity. The impulse trains of α_3-motoneurons consist of about 11 to 60 Ap's, and the ones of α-motoneurons of about 2 to 4 Ap's. According to the comparison with Hodgkins measurements (47) it is very likely that the short impulse trains of the α_2-motoneurons are driven by similar current pulses. That means, also for α_2-motoneurons hold, that the drive potential, produced by the current pulse or synaptic potentials, is probably longer than the impulse train and the length of the impulse train and the length of the first II are mainly given by the amplitude of the drive potential in relation to the membrane potential (85). Furthermore, the length of the first II is correlated to the length of the impulse train (Fig. 5) and inverse proportional to the strength of the depolarization. Vice versa, it may also hold, that the depolarization of the nerve cell soma is correlated to the first II and the impulse train length, if an impulse train depolarizes a neuron via exciting post-synaptic potentials and temporal summation (13) (see traces "b" and "c" of Fig. 10).

Hodgkin (47) sometimes observed an irregularity at the beginning of the impulse train. Granit et al. (43) never saw any "warming up" or frequency increase during stimulation. Such irregularities have sometimes been observed in α_2 and α_3-motoneurons.

Calvin (12, 13, 14) classified repetitive firing mechanisms into an occasional spike mode, a rhythmic firing mode and an extra spike mode. In the occasional spike mode occasional waves of depolarization cross the accomodating threshold to elicit occasional output spikes. In the rhythmic firing mode sustained depolarizing currents hold the membrane potential above threshold, resulting in a sustained rhythmic discharge at a rate proportional to the current level. In the extra spike mode the depolarizing afterpotentials immediately following a spike may rise through the falling threshold to elicit an extra spike within about 1 to 2 msec (11, 14) of the original spike. In this paper the measured activity modes are the occassional spike mode, the transient oscillatory firing mode (plus the occasional spike mode) and the continuous oscillatory firing mode. The extra spike mode produced by the short afterdepolarization has not been looked for in these measurements, but has not been observed during the repetitive firing part of the oscillation cycle of motoneurons in the oscillatory mode. The rhythmic firing mode corresponds to the impulse train part of the oscillatory firing mode and is pro-

duced according to Calvin (11, 81) by the hyperpolarizing Ap afterpotential lasting 50 to 100 msec, which is in concurrence to the sustained depolarization produced by synaptic or artificially applied current. Following the first crossing of the threshold, the intracellular afterhyperpolarization will interact with this sustained depolarization. As the hyperpolarizing afterpotential wears off, the membrane potential will intersect the threshold again. The larger the synaptic or current depolarization, the sooner one might expect this intersection to occur.

With the explanation for the generation of impulse trains with constant interspike intervals (II's) given by Calvin, it will now be attempted to understand the increasing of the II's which could originate from enhancing afterhyperpolarizations and/or inactivation. If the afterhyperpolarization is generated by the somatic and proximal dendritic membrane, then perhaps the extent of antidromic invasion of the proximal dendrites determines the amount of hyperpolarization (11, 81). After a given current pulse, antidromic invasion of the dendrites (29) might increase with each successive spike, thus deepening the afterhyperpolarization, until the maximum possible invasion for that depolarizing pulse level is obtained and a steady state is reached. This would be an explanation for the increase of the II's in the impulse train (Fig. 5).

The shortest interspike interval (II) of the impulse train of the α_3-motoneuron O_3 was about 3.5 msec (Fig. 5b). The shortest II's of repetitive activity of α_2-motoneurons was also 3.5 msec (Table 1, Pat 24). The shortest soma-dendritic II elicited by antidromic paired shocks was reported to be 3.4 msec in intercostal motoneurons of the cat (82) and about 3.5 msec in rat motoneurons (42). If the shortest II of soma-dendritic spikes of human α_2 and α_3-motoneurons were also about 3.5 msec and this is what is assumed here, then they are roughly equal to the shortest II's of repetitive activity produced by sustained depolarization. This equality would suggest that the repetitive activity is produced in the motoneuron soma, the dendrites and the axon hillock including the first stretch of the non-myelinated axon. The similarity of the first II's of the α_2 and α_3-motoneurons due to strong depolarization indicates that the generating mechanism for repetitive activity is first concentrated in the soma with little spread into the dendrites and proximal axon and that the soma properties of the α_2 and α_3-motoneurons are similar. With increasing afterhyperpolarization (and increasing II's), the antidromic invasion of the dendrites and the orthodromic invasion of the first axon stretch increases. The dendrite trees and membrane properties of the first axon stretch are probably different in α_2 and α_3-motoneurons and will result in different increases of II's in α_2 and α_3-motoneurons.

In the introduction and the first part of the discussion, a close correlation between the repetitive activity properties of the crustacean (invertebrates) axon membrane and the human repetitive centre (soma, dendrites, first stretch of axon) has been found. Hodgkin and Cajal (47) pointed out, that the similarity of the phylogenetic far away crustacea lies in the fact that the thinly myelinated axons of crustacea may behave in a manner like the first short stretch of non-medullated axon in mammals, including man. The similarity of the human repetitive activity with those of crustacean axons indicates that the first short stretch of the proximal axon contributes essentially to the summing-up point at the axon hillock, where the Ap's are probably also generated in the repetitive activity mode. The increasing inactivation of the excitability of the first proximal axon stretch may be more important for the increase of the II's than the increasing antidromic invasion of the dendrites and can also explain the end of the impulse train. But the unregularity in the II's of long impulse trains of the α_3-motoneuron O_3 (Fig. 5b) may indicate that 2 mechanisms or systems are responsible for the generation of the II.

4.2. *Possible spinal oscillators*

The impulse trains generated by the motoneurons in the oscillatory firing mode are

repeated again and again after certain time intervals, that means a system in the spinal cord is oscillating.

Artificial trigger points can be excluded as the origin of the oscillation, since they produce mostly mirror picture potentials on the traces "a" and "b", which show no specific features, whereas the oscillating systems responded specifically to spindle, stretch receptor, flow receptor and other afferent activities.

The α_2-motoneurons fired in the oscillatory mode with shorter action potential (Ap) trains ($\sim$3 Ap's/train) at higher frequencies ($\sim$7 Hz) than the α_3-motoneurons (11-60 Ap's/train; 0.7 Hz). This correlation between oscillation frequency or period and impulse train length of α_2 and α_3-motoneurons suggests, that the motoneurons may oscillate in themselves. There is an indication that depolarization is shifted from the axon hillock into the dentrites (11, 29, 42) (see discussion of repetitive activity). The afterspike hyperpolarization in sphincteric motoneurons of the cat are in the range of 40 to 110 msec (56, 60) and are even longer for tonic fibres (23). But the afterhyperpolarization of intracellularly recorded Ap's was used before for a possible explanation of the repetitive activity and an oscillation period of 1400 msec for α_3-motoneurons seems to be too long for such movements.

It is more likely that the motoneurons oscillate with a few interneurons among themselves in a pool of α_2 or α_3-motoneurons with specific functions via recurrent fascilitation and inhibition (24, 46, 70, 95), as has been observed in gastric and pyloric functions of the lobster (86). Recurrent collaterals are likely to be of greater importance for the tonic than for the phasic activity (39, 40). The frequency range of the operation of recurrent inhibition (5 to 40 shocks/sec (41), cats) is similar to the mean activity range of α_2 and α_3-motoneurons (5 to 40 Ap's/sec, Table 1). For the α_2-motoneuron O_1, a recurrent collateral could even be found in the ventral root (Fig. 2A). But, it has been reported that cat sphincteric motoneurons lack Renshaw inhibition (60) and crossed disynaptic inhibition (49). Therefore, it is most likely that mainly spinal interneurons oscillate among themselves and drive with their oscillation in the high activity mode (Table 1, Fig. 9) α_2 and α_3-motoneurons, innervating striated sphincters and functionally associated perineal and pelvic floor muscles.

4.3. *Oscillatory drive potential*

The oscillation in these measurements has always been observed in connection with the repetitive activity. Oscillation with repetitive activity has been recorded extracellularly from inspiratory and expiratory intercostal motoneurons (18, 84, cat). Intracellular "central respiratory drive potentials" could be recorded, which gave rise to the repetitively occurring impulse trains (83, 85). The drive potentials had a depolarizing and a hyperpolarizing part, of which the depolarization stimulated the repetitive discharges.

As analysed earlier, the impulse trains are produced by depolarizing drive potentials, which have similarity to the ones produced by rectangular current pulses. This depolarizing potential will most likely be followed by a hyperpolarizing potential to fully activate the membrane again after the long depolarization. By recording from the pudendal motor nerves of cats, when the afferent fibres of the pelvic or contralateral pudendal nerves were stimulated, it was found that the initial excitatory phase of pudendal nerve activity was followed by a second inhibitory phase of between 150 and 2500 msec duration (63). Intracellular drive potentials could be recorded from pudendal α_2-motoneurons (8), which consisted of a short depolarization part from excitatory post-synaptic potentials followed by a hyperpolarizing part from inhibitory post-synaptic potentials. The time course of this drive potential is similar to the time course of the oscillation cycle period, consisting of the repetitive activity part and the silent part of α_2-motoneurons (Table 1). It is concluded that the oscillatory drive potential of one cycle giving rise to the impulse train followed by an inactive part consists of a depolarizing part from excitatory, post-synaptic potentials and hyperpolarizing

part from inhibitory post-synaptic potentials (Fig. 10, trace "b").

4.4. *Oscillatory spinal interneurons*

McMahon and Morrison (62) recorded with tungsten electrodes from sacral spinal interneurons of cats which responded to pelvic and pudendal nerve stimulation. The interneurons had receptive fields in bladder, colon, perineum and adjacent structures and often showed a duration of the inhibitory response of about 500 msec. These interneurons showed various patterns of responses following nerve stimulation, namely excitation only, excitation followed by inhibition, excitation followed by inhibition followed by excitation and excitation followed by secondary excitation after a time interval. The time courses and the properties of these interneurons are compatible with oscillations. If, for example, the group of interneurons, responding to a stimulus with excitation, inhibition and excitation, were to get a new stimulus at an appropriate time, the alternation of excitation and inhibition would continue.

But these interneurons must not be the principal components of the spinal oscillators. Functionally nearby interneurons may resemble the oscillator cells in some properties. In the medicinal leech it was found that the basic swimming rhythm was generated mainly by rings of a few small oscillatory interneurons (32), which oscillated with impulse trains. The fundamental principle to which the network owed its oscillatory character was the recurrent cyclic inhibition of the neuronal loop (93). The cycle period of the basic rhythm had durations in the range of 400 to 2000 msec and the time required for each interneuron to recover from inhibition was between about 30 and 150 msec (32).

Even though rhythms can be generated by several kinds of mechanisms (86), it is assumed as a working hypothesis that the true spinal oscillators consist of an ensemble of spinal interneurons which are activated or inhibited by peripheral and/or central input. In the HT measurements, the afferent input stimulated the oscillators; the central inhibition was maybe reduced. A network of synaptic connections link the sets of oscillatory interneurons to the motoneurons commanding the sphincters and functionally associated muscle groups (Figs. 10).

4.5. *Properties of the oscillators with their afferent input and motoneuron drive*

Figure 10 shows a drawing of how a sacral spinal oscillator could in principle drive the motoneurons. The afferent inputs from urinary bladder, anal canal, skin (mainly from peri-anal and perineal regions) and other sources are probably split by connectivity and activity pattern into adequate and unspecific stimuli, and drive the motoneurons mainly mono- and disynaptically, via more complex pathways, through the oscillators and, via yet more complex pathways, through integrative spinal activity pattern generators. Afferent pathways through higher or supraspinal levels are not drawn. It will be shown in the third paper (78) that these different afferent pathways which are suggested seem to have measurable consequences in long response latencies, especially since the monosynaptic pathway to the external anal and bladder sphincters is not very pronounced in the cat (56, 60) and the human (78). Not much is known about the spinal oscillators and their connections. But probably they consist of an ensemble of interneurons, of which each interneuron has its own phase in the oscillation cycle. The different phases in the cycle allow the oscillatory interneurons to excite and inhibit the motoneurons at different phases as shown schematically by the single traces "c" and "d" in figure 10. Suggested properties of the oscillators are summarized in the following.

1. Sacral spinal oscillators can probably be occasionally active (see also under point 10). They can oscillate transiently and continuously. The mean activity in the driven motoneurons increases from the occasional spike mode via the transient

oscillatory firing mode to the continuous oscillatory firing mode.

2. α_2 and α_3-motoneurons are driven in the oscillatory mode at different frequencies. The relative length of the impulse train is correlated to the frequency (Table 1). α_2 and α_3-motoneurons will, therefore, have their own spinal oscillators.
3. Figure 2C shows that the α_2-motoneurons O_1 and O_2 are driven with different patterns at the same time, each one stimulated with its adequate afferent stimulus. There are, therefore, several different α_2-oscillators which can oscillate at the same time according to different functions and different adequate afferent input.
4. α_2-oscillators mostly respond specifically to its adequate afferent input. The basis for excerting an adequate stimulus is probably the connectivity of the afferents and maybe the pattern of the activity. α_3-oscillators mostly respond unspecifically.

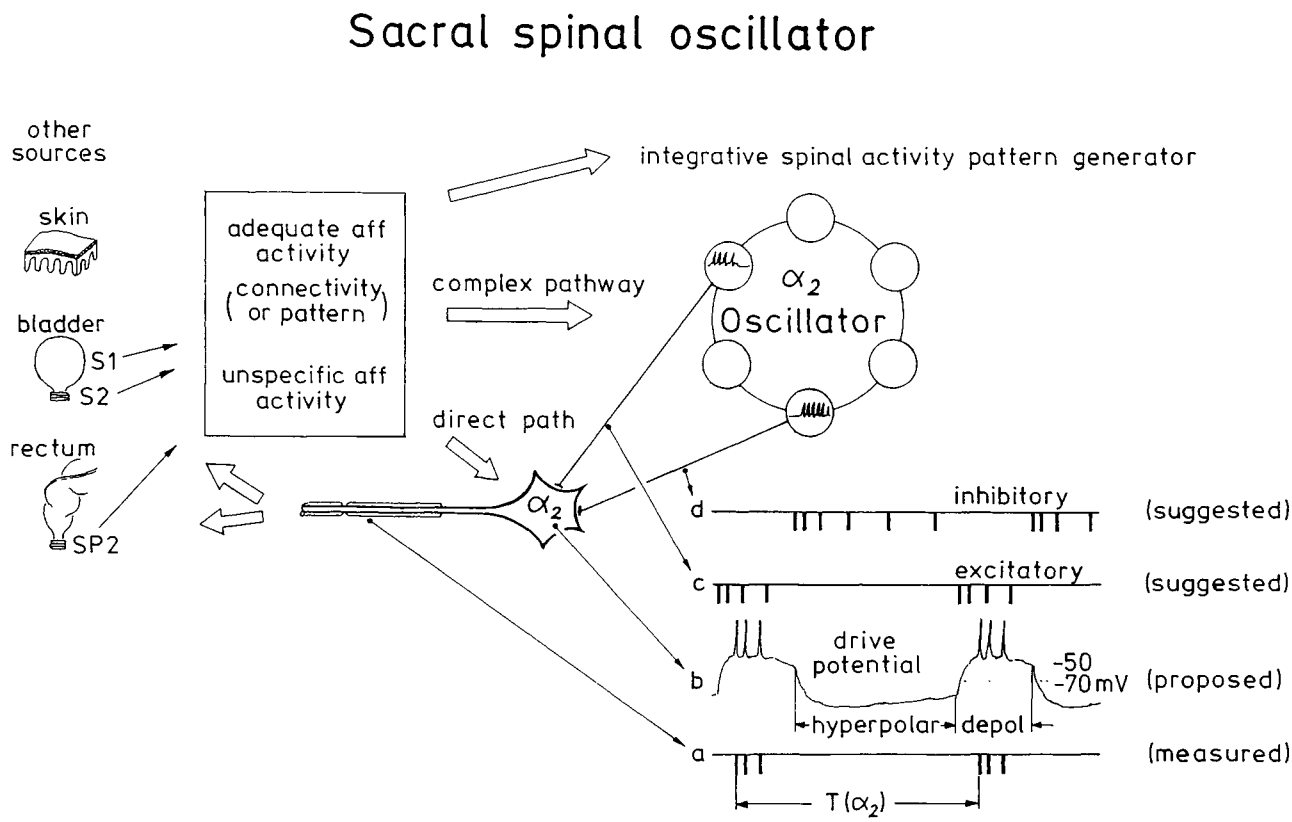

Fig. 10. — Schematic drawing of a proposed spinal α_2-oscillator with its afferent input and efferent output, not drawn to scale. On the left are the possible sources from which the S1, S2 and SP2 afferents are found as possible sources for contributing specifically to the stimulation of the oscillation. The afferent input (adequate and unspecific afferent activity) can go 3 ways to the motoneuron: direct pathway (mono- or disynaptically), complex pathway (multisynaptically) and even more complex pathways. The α_2-oscillator consists of an ensemble of interneurons, each oscillating at a different phase (indicated in 2 interneurons by different bursts), and drives the α_2-motoneuron via excitatory ("c") and inhibitory ("d") pathays of unknown number. The suggested extracellularly derived oscillatory firing patterns are shown in the traces "c" and "d". Trace "b" shows the proposed intracellularly derived oscillatory drive potential with 3 Ap's in each depolarizing part, marked with depol, and no Ap's in each hyperpolarizing part marked with hyperperpolar. Mind, the Ap amplitudes are too small by far; they should reach +30 mV! Trace "a" shows the actual extracellularly measured oscillatory firing mode at one site; $T(\alpha_2)$ = oscillation cycle period of the α_2-motoneuron. The axon of the α_2-motoneuron innervates one of the striated sphincters as indicated by the arrows.

5. One adequate stimulus of an α_2-oscillator, driving an external anal sphincter motoneuron was most likely the activity from secondary muscle spindle afferents from that sphincter. The interspike intervals were similar to the oscillation period. The adequate stimuli of an α_2-oscillator, driving external urethral sphincter motoneurons, were the activity from the stretch (S1, ST) and flow (S2) receptors. Similarities between afferent interspike intervals and cycle period were not found.
6. The oscillators probably need physiological stimulation to oscillate. Sherrington (89) advocated the need for a well balanced peripheral input.
7. The afferent input stimulates the motoneurons directly (mono- or disynaptically) and stimulates the motoneurons polysynaptically via the oscilllators, which correlate the impulse train length to the oscillation period. According to this dual pathway of afferent activity (Fig. 10), the impulse train length can probably be partly varied independently of the cycle period length according to different afferent connectivities and maybe activity pattern sensitivities of the oscillator.
8. It is proposed, that the true spinal oscillators consist of an ensemble of interneurons, which are an integrative part of the oscillator, but activated at different phases with respect to each other and different impulse train length (32).
9. The spinal oscillators drive their motoneurons most likely via exciting and inhibiting impulse trains at different phases, to produce a depolarizing and a hyperpolarizing drive potential in the motoneurons, of which the depolarizing potential part produces the impulse train in the motoneuron (Fig. 10).

   It has been concluded that the impulse train is correlated to the depolarizing drive potential and vice versa. The impulse trains of the traces "a" and "b" of figure 10 should therefore be the same as in trace "c". In figure 10 they are drawn differently because, for example, the membrane properties of the interneurons and the motoneurons could be different. In the medicinal leech (32, 68), the impulse trains of the excitatory connections from the oscillatory interneurons are different to the impulse trains of the driven motoneurons and, in the xenopus embryo, they are very similar (20). In cats, the knowledge of the central generation of locomotion (45) is not detailed enough to compare with.
10. In the inactive part of the oscillation cycle period of oscillatory firing motoneurons, where the proposed hyperpolarizing drive potential acts, no occasional activity was observed. This may mean that the occasional activity mainly uses the way through the oscillator network and, when the oscillator oscillates, the pathway is blocked in similarity to mechanical and electronic oscillators. But it could also be, that the hyperpolarizing drive potential suppresses spontaneous activity from other pathways. In the α_3-motoneuron O_3 recordings, impulse trains of 4 Ap's were observed a few times after the main impulse train. The reason for this activity could be the direct, afferent pathway to the motoneuron. The direct afferent input probably stimulated the α_3-motoneuron even in the phase part of the oscillation cycle, when the depolarizing drive potential acted, but after the impulse train. The repetitive activity was perhaps only partly inactivated, so that a superimposed excitatory post-synaptic potential gave additional Ap's.
11. It has been found that occasionally active α_3-motoneurons have a higher activity level than α_2-motoneurons (75). The data from table 1 indicate further that the α_3-motoneurons have a higher mean activity level in the oscillatory firing mode than the α_2-motoneurons. This indicates, that the different kinds of motoneurons have their own activity pathways in the central neuronal network. Low (occasional spike mode) and high (oscillatory mode) activity levels may come mainly through the same pathways (for further discussion see third paper (78)).

4.6. *Innervation of the external urethral and anal sphincters*

Motor fibres of human lower sacral nerve roots consist mainly of α_2 (FR-type) and α_3-motoneurons (S-type) (75, 77) and of intrafusal γ_1 and γ_2-motoneurons (77). Both striated sphincters are innervated mainly by α_2-motoneurons in the cat (60). But are the sphincters also innervated by α_3-motoneurons? Tonic resting myographic sphincter activity has been reported to exist in humans (16, 51, 79, 80) and cats (5, 6, 8, 35, 36). Figure 9 shows that the α_2-motoneuron O_1 of the urethral sphincter had a very low resting activity with a low filling of the bladder. The α_2-motoneuron O_2 of the external anal sphincter, identified by its function (78), was already highly activated following the constant stretch of the sphincter by the anal catheter of 10.5 mm in diameter. It is probable, that the α_2-motoneurons contribute to the resting discharge of striated bladder and anal sphincters. See also figures 3, 4, 5 of reference 78 for activity changes in the occasional spike mode. With the sustained stretch of the anal sphincter and perhaps a bit of the urethral sphincter, the α_3-motoneuron O_3 was highly activated by being in the oscillatory firing mode. Since the activity of this α_3-motoneuron O_3 was so high, it is concluded that it most likely innervated the external sphincters and not the perineal or pelvic floor muscles, and was also partly activated by the tonic stretch reflex to safeguard continence. Since defecation is different to voiding in the respect that the contents of the rectum often have to be tested to find whether they consist of flatus, liquid or feces by contracting the external anal sphincter and relaxing the internal sphincter, to let the contents into the anal canal for testing (77) where the additional skin receptors are situated, it is likely that there is more need for S-type muscle fibres in the external anal sphincter than in the external bladder sphincter where a stoppage for the discrimination of the passing contents is not necessary. Even though the α_3-motoneurons are rather unspecific in their response (78), it seems as if the oscillatory firing α_3-motoneuron O_3 increased its activity a little following the pulling of the anal catheter (and pain application) and reduced its activity a bit following the pulling of the bladder catheter (Figs. 1, 2 of Ref. 78). Since the external urethral sphincter is not, or is only slightly stretched, it is concluded, that the α_3-motoneuron O_3 innervated the external anal sphincter. Since it is known, that the α_3-motoneurons show at rest or little activation a higher mean activity than the α_2-motoneurons (75), it is further concluded that the α_3-motoneurons of the sphincters contribute more strongly to the resting discharge than the α_2-motoneurons (for further discussion see section 4.1 of Ref. 78). The external anal sphincter contains at least a few S-type muscle fibres, whereas the external urethral sphincter may not or may contain only a few. Looking at the myographic recording of figure 1 (trace 3) of reference 51 of the striated urethral sphincter, when the patient was coughing, it seems as if there were activity increases at intervals of 2000 msec. This time interval is in the range of the duration of the oscillation cycle periods of α_3-motoneurons. Clarity can be obtained, if myographic records of the external urethral sphincter, split up into single units, are obtainable.

As discussed in the first paper, the sphincters probably obtain their innervation mainly from the S4 root, some from the S5 and a bit from the S3, if no lumbalisation or sacralisation is present.

The external anal sphincter contains muscle spindles, as has been morphologically shown in the cat (17, 99) and verified electrophysiologically in this paper ($SP2_1$-fibre). The muscle spindles most likely are innervated by γ_1 and γ_2-efferents and have only secondary spindle afferents (see also Ref. 78). Whether there are muscle spindles in the external urethral sphincter is not clear. These measurements give no answer. Histologically, Todd (99) found no muscle spindles in the urethral sphincters in either sex of the cat. He observed spikes of large amplitude, meaning from rather thick and fast conducting afferents, following distension of the urethra. But these afferents could be stretch afferents (S1), which are present in the

bladder and perhaps in the urethra as well. At least discharges of rather large amplitude are no proof for the existance of muscle spindle afferents.

5. **Clinical implications**

5.1. *Restoration of bladder function in paraplegia*

5.1.1. *Biological treatment*

The human spinal cord does not regenerate after traumatic lesions because the regenerating nerve fibres in the central nervous system (CNS) cannot grow through the astrocytic scars and they only grow for short distances and form inappropriate synapses (69, 96, 97). Removing the destroyed spinal cord parts and substituting embryonic tissue will most likely not solve the problem. The growing of the CNS fibres is probably stronger and the astrocytic scar reduced, but connective tissue scar will be formed additionally in the gap (52, 53). Still, none of the 3 principal objections has been solved. Clinically there are additional problems. Firstly, where to get the human embryonic tissue from. Secondly, only a few spinal cord lesions are complete. Therefore by removing a piece of the spinal cord, remaining tracts will be destroyed. Thirdly, by removing a piece of the caudal medulla, other parts of the spinal cord will be disconnected from the main blood supply, which comes from the thickest feeder artery (Adamkiewicz) (58, 98). To restore bladder function, the strategy of the CNS can be used, namely when parts of the nervous tissue are destroyed, other parts of the CNS substitute the function. This is only possible if sufficient connections are available. In a spinal cord lesion grey and white matter are destroyed. That means the tracts (connections) are also lost. The idea of a nerve anastomosis is, to reconstruct connections, so that other parts of the CNS can substitute functions and these connections are constructed in the peripheral nervous system (PNS), where nerve fibres can regenerate over long distances as is known from nerve repair (100). Research data indicate that bladder functions can be restorated in paraplegia (15).

5.1.2. *Nerve anastomoses*

According to anatomy, nerve anastomoses in lower spinal cord lesions have been performed from the lower intercostal nerves to the cauda equina nerve roots (15, 31, 67, 101). Some success was achieved in reconstructing bladder functions (15). The task is to improve such treatment.

Intercostal nerves can reach the proximal cauda equina directly up to TH7, if they are dissected as far as the middle axillary line, where they split up into the ramus cutaneus lateralis (2 pure skin nerves), a pure muscle branch innervating the musculus obliquus externus abdomnis and the mixed ramus (deep branch) innervating the musculus rectus abdomnis and other muscles, and leading to the anterior skin (Fig. 11, 76)). The ramus cutaneus anterior of the intercostals (and spinal nerves) TH11 to S1 contains fibres to the Head's area of the urinary bladder. Cauda equina nerve roots can be partly identified anatomically in an operation (72). To connect donor (intercostal nerves) and acceptor nerves (cauda equina nerve roots) successfully, the number of myelinated nerve fibres, the number of motor fibres of the donor and acceptor nerves, the mismatching between motor and sensory fibres, and functional aspects all have to be taken into consideration.

One lower intercostal nerve contains about 10 000 myelinated nerve fibres. The lower human body needs about 250 000 on one side, and the urinary bladder about 5000 myelinated nerve fibres on one side (73, 74, 76). On the basis of myelinated fibre numbers, it is useless to try to reinnervate the lower human body. But one intercostal has enough fibres to reinnervate the urinary bladder. From monkey denervation experiments it is known, that at least 50% of the motor fibres are needed to keep useful motor functions (26, 27). From the first paper (77) it is known, that if one touches the sacral skin with a finger, about 3 fibres of each touch group are activated in an S4 ventral root and when pricking with a pin, about 3 of

each were activated in an S4 dorsal root. One can expect that much fewer fibres are needed to reconstruct afferent functions. Maybe a third or a fifth would be sufficient. Therefore, the afferents are probably not as crucial as the efferents for reconstructing simple functions. One intercostal has about 1000 motor fibres (10%) and the bladder needs less than 500 (Fig. 11, (74)). The intercostals, therefore, also have enough motor fibres for the reinnervation of the bladder. But the mismatch has to be considered, that means how many fibres of the donor nerve grow into wrong endoneurial tubes of the acceptor nerve and are lost for function. In a very simple model, where only regenerating fibres can grow into endoneurial tubes of the acceptor nerve and not beside them, and only taking into account the mismatch between myelinated afferents and efferents, the successful number of motor fibres equals the number of motor fibres of the donor nerve times the fraction of motor endoneurial tubes of the acceptor nerve (76). In the anastomose situation of figure 11, dorsal and ventral roots should be reinnervated seperately to reduce mismatch.

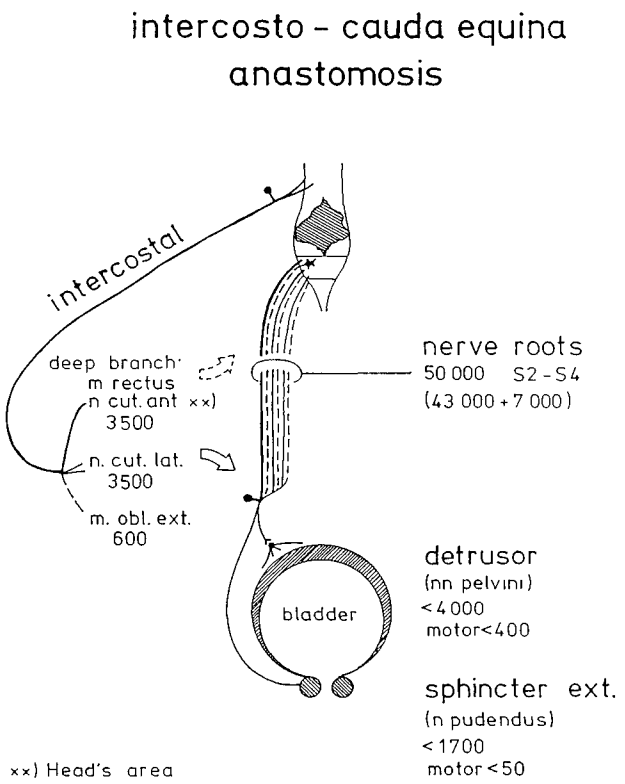

Fig. 11. — Schematic drawing of the nerve anastomose situation from the intercostal nerves to the cauda equina nerve roots for a restoration of bladder function. Approximate numbers of myelinated nerve fibres from one side are indicated. The nerve root fibre number (50 000) is split up into sensory (43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

After restoring motor functions the detrusor and the sphincter externus should not be activated simultaneously to allow urine to pass through the urethra. The detrusor and the sphincter externus have to be reinnervated by two motoneuron pools of different functions. To demonstrate the necessary reasonings it will be sought to reinnervate the detrusor by the deep branch innervating the musculus rectus abdomnis and the anerior skin and the sphincter externus by the muscle branch innervating the musculus obliquus externus abdomnis. The musculus obliquus externus can be used seperately from the musculus rectus abdomnis (33). The motoneurons innervating the obliquus externus and the rectus abdomnis belong to different motoneuron pools. Dyssynergia of the bladder should be avoided after reinnervation. The musculus obliquus externus is innervated by about 600 fibres (Fig. 11) of which 50% are motor fibres (9, 71). Assuming, for simplicity, that the external bladder sphincter is innervated through the S4 ventral root and the detrusor through the S3 ventral root (77), and if one connects now the obliquus branch with the S4 ventral root, then the 300 motor fibres (50% of 600) would be sufficient for the reinnervation of the 50 endoneurial tubes on one side leading to the sphincter externus of the bladder (74). Only a few motor fibres are lost because the muscle branch is connected with a ventral root. But the mismatch of functions has to be considered, namely that motor endoneurial tubes lead to the sphincters and which ones to other muscles, for example to the pelvic floor. Here there exists

an important difference between the human and the cat, because humans have no motoneurons leading to the tail. In the human ventral S4 and S5 roots, there will be mainly fibres to the sphincters, whereas in the cat most motor fibres in the corresponding roots will lead to the tail, so that functional mismatch in the cat should be larger. It still has to be better investigated in which root parts the sphincters are represented in humans and it should be tried to verify the representation during an operation because of variations. Also, the overlap of the representations of the external anal sphincter and bladder sphincter and the detrusor needs to be better investigated to avoid dyssynergia after reinnervation. To get the right muscle tonus into the sphincters the kind of motoneurons of the donor and the acceptor nerves also have to be compared, since nerve cells mainly keep their original functions (91). The sphincters are mainly innervated by α_2-motoneurons and a few α_3-motoneurons. α_2 and α_3-motoneurons jump into the oscillatory firing mode if high activity is needed. The musculus obliquus externus is innervated extrafusally by α_1 and α_2-motoneurons (76). The outcome if the axon of an α_1-motoneuron of the donor nerve regenerates in an α_3-motoneuron endoneurial tube is not clear. The α_1-motoneuron will probably partly change the function of the motor unit muscle fibres according to trophic influence and activity pattern. But how much functional plasticity has the spinal cord? Can also the spinal oscillators be changed? This question cannot be answered. The best thing is for a nerve anastomosis to bring motoneuron types as much as possible into accordance with one another, so as not to expect too much functional plasticity from the CNS.

Because of a lack of knowledge, the connection between the deep branch to the musculus rectus abdomnis and the S3 ventral root will not be discussed. It should only be remarked that the parasympathetic efferent fibres to the detrusor also have acetylcholin as the transmitter and that the parasympathetic system is probably not so different from the somatic division as the classification scheme would have one believe.

Concerning the reconstruction of afferent pathways, 2 lucky anatomical situations exist. The first one is that fibres of the Head's areas of the urinary bladder lead through the ramus cutaneus anterior of the intercostals Th11 to S1. Somatovisceral convergence to spinothalamic tract cells have been found in the cat (87) and the monkey (30,64). It can be assumed that somatovisceral convergence also exists in humans and this convergence is the reason for the existance of the Head's areas. By connecting skin fibres of the ramus cutaneus anterior (TH11-S1) with bladder afferents of the S3 or S4 dorsal root, the skin fibres regenerate into the bladder and because they are from the Head's areas, they converge onto true bladder afferent pathways. The anatomical problem remains of how to separate the ramus cutaneus anerior fibres from the rest of the fibres of the deep branch. The second lucky situation is, that the few ventral root afferents (75) will allow the reconstruction of a few afferent pathways of corresponding efferent ones when a muscle branch is connected with a ventral root.

With how many fibres the urinary bladder has to be reinnervated depends on the actual paraplegic case. If the conus medullaris is badly damaged and a complete malfunction is present, then the bladder has to be strongly reinnervated. If the patient has developed a reflex bladder which functions well, one has to be cautious not to destroy it. A partial anastomosis into the reflex arc is necessary. Reflex bladders are mostly overactive. By cutting an S3 or an S4 dorsal root one reduces the afferent input and hopefully enhances the reservoir function of the bladder. Reinnervating the bladder through one or two dorsal roots with skin afferents, best from the Head's areas, the patient will get some feeling in the bladder. It would be desirable to get flow receptor afferents (S2) reconstructed. There are skin mechanoreceptor afferents (T3 and T4), which are very sensitive to light touch (77) and which have similar properties to the flow receptors. Paraplegics with reflex bladders which function well would like to be operated, simply in order to have some sensitivity in the bladder, so that they could learn to recognise their partly full

bladder before the reflex bladder starts to function by itself. This would give them more possibilities to live in society.

A further step is to stop the micturition, which has been started reflexly, by reconstructing the volitional external sphincter function. Maybe a partial reinnervation of 30 to 50% of the sphincter externus motoneuron endoneurial tubes with nerve fibres from the musculus obliquus externus would be enough for voluntary control. Maybe the guarding reflex for bladder continence, probably lying in the sacral spinal cord, would then support this voluntary action. Anatomically one can reinnervate the sphincter externus partly by cutting the ventral S4 root (if the bladder sphincter were represented in S4) on one side and reinnervated it with the obliques externus branch. But the overlap of the innervation between right and left has to be known. It has been reported that there is overlap in animals (6, 88) (see also below).

A further step is to enhance the detrusor function by reinnervating it with rectus abdomnis nerve fibres in order to reduce rest urin, which is one reason for ascending bladder infections and to start micturition when desired and not to trigger the reflex bladder by tapping with fingers or other manipulations. The connection of the S3 ventral root on one side with the deep branch of the intercostal nerve give partial control over the detrusor. What is not clear, is whether it really enhances the detrusor power. More research is needed. The overlap of the innervation from right and left is more important here than for the external sphincters. It is argued, that if the detrusor is denervated on one side, and if the patient tries to micturate on volition, the urine is partly shifted to the denervated bladder part, which does not contract, instead of passing through the urethra. Even though one may also partly reinnervate the other side, the grade of overlap innervation between right and left needs to be known.

If a nerve anastomosis is performed, some cauda equina nerve roots are cut and distal parts are connected to intercostal nerve branches. But what about the proximal nerve root parts? By connecting intercostal nerve branches with the proximal stamps it can be tried to reinnervate the spinal cord distally to the lesion. It has been shown in cats that motor fibres can cross the PNS/CNS transition zone of the spinal cord (57) and functionnaly reinnervate the CNS (2). But regenerating sensory fibres cannot penetrate the CNS (57, 69). The astrocytes seem to impede the elongation of regenerating axonal sprouts. The mutual interaction between astrocytes and neurons needs to be better understood. A partial reinnervation of the lower sacral spinal cord through lower sacral roots with motoneurons needs further consideration. Such a reinnervation would be a reconstruction of tructs. 2 of the arguments from the beginning of the discussion also hold true here, namely that nerve fibres grow only for short distances and probably make no specific connections. But here there again exists a difference between cat and human. The human spinal cord in the S3 to S5 region is proportionally thinner and different to the corresponding part of the cat since the cat, in this region, has also the motoneuron pools leading to the tail. Regenerating nerve fibres in humans need only to cover a distance of about 1 mm in the CNS and the probability of reinnervating desired sphincter motoneurons and parasympathetic efferent neurons is larger than in the cat. The reinnervation of the sacral CNS with motor fibres from the spinal cord proximally to the lesion could be at least threefold, namely directly onto the motoneurons, then onto the spinal oscillators and onto more integrative structures (see Fig. 10). If one cuts dorsal root fibres, then it is known that other afferents also terminating on the motoneuron will take over the denervated synapses by sprouting (25, 66). This sprouting may result in unwanted exaggerated reflex activity (37, 59). By reinnervating these denervated synapses on the motoneuron cell bodies with supralesion efferents, one may get some desired influence on the motoneurons. If the sprouting argument also holds for the spinal oscillators, then their reinnervation would be even more crucial, since the spinal oscillators supply the sustained high activity for the sphincters. The impulse pattern of parasympathetic efferent fibres is still unknown.

5.2. *Differences between human and animal data*

For a successful performance of a nerve anastomosis to restore bladder functions, more functional, microanatomical and histological knowledge is needed. As mentioned already, the segmentation of the medulla, its structure and its roots in the lower sacral range in the human are different to those in the cat. Therefore, cat data are of no help in an operation. The power of regenerating nerve fibres in the PNS in the rat and the dog is stronger than in humans. In the rat, 50% of the fibres can cross a gap of 8 mm following sciatic nerve section (50). In the dog nerve fibres can cross a gap of 40 to 50 mm (38). For nerve repair in humans, the nerves have to be adapted. On the other hand the neuronal plasticity (19) of the human nervous system (sprouting, unmasking of neuronal pathways, synaptic changes...) is higher than that of animals. Sperry transposed the nerve supply of flexor and extensor muscles in the rat (90) and in the monkey (91): the monkey relearned the task after some time, that rat did not. In Sperry's experiment on monkeys, their learning to flex or to extend the elbow in one situation did not necessarily become generalized to other performances. This indicates that the neuronal readjustment was not localized in the spinal centres, but involved reorganisation at the supraspinal level (94). Surprisingly few trials were required for poliomyelitis patients to use transposed tendons successfully. The visualisation of the task seemed to be the prime aid for the patients (102).

Because of anatomical, regeneration power and plasticity differences it is unlikely that the anastomose situation from above can be mimiced in a rat, cat or dog model. Even a tailless monkey experiment does not allow quite certain conclusions for humans. The necessary physiotherapy, including bio-feedback following a nerve anastomosis, will probably be impossible to perform with paraplegic animals. Sperry (90, 91) already had big problems with monkeys. Dogs, for example, do not try strongly to use a non-functioning body part (limb), no, they start to eat it. With more human knowledge, one has to start to perform slight, partial anastomoses or to operate unrisky cases, where something has to be done anyway.

The powerful tool of humans to learn can only be used by them if functions are transposed. A "neurotisation" may destroy useful functions and may not reconstruct any new ones if nerve fibre numbers, mismatch and functional aspects are not taken into consideration. The spinal cords of a lizard, goldfish (4) or hibernating ground squirrel (1) regenerate spontaneously. This has never been observed in humans.

The necessity of human data has been emphasized by Desmedt (103), Kerr (104) and Sunderland (92, page 354).

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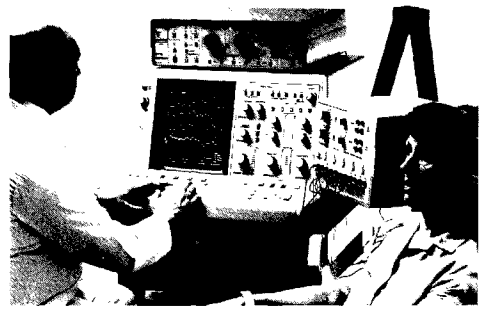

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