Impulse pattern, innervation density and two point discrimination of skin and mucosal afferents in humans. Considerations for a sensory reinnervation of urinary bladder and anal canal in spinal cord lesions. IV (IV)

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Abstract

1. *Single fiber action potentials (Ap's) were recorded with 2 pairs of wire electrodes from a coccygeal nerve root. Simultaneous impulse patterns of 3T0+6T1+3T2+11T3+5T4 and 4P single skin afferent units were separated by their different Ap wave forms and conduction velocities. For a rapid touch or pin-prick the afferent units fired on average with 2 Ap's.*
2. *The touch units had most likely the following receptor properties. T1: rapidly adapting, medium high threshold, sensitive to skin traction over a distance of more than 10 cm. T2: rapidly adapting, high threshold. T3: slowly adapting, lowest threshold among T afferents for a light touch with no movement along the skin. T4: slowly adapting, lowest threshold among T afferents for a light touch with a movement component parallel to the skin surface. The T1 to T4 afferent receptors are the PC, RA, SAI and SAII receptors respectively. The correspondence is not safe.*
3. *With nerve fibre diameter distribution histograms (morph), myelinated fibre numbers, conduction velocity distribution histograms (electro) and Ap occurrence patterns, innervations were determined. With estimated dermatome areas, innervation densities i of skin dermatomes were calculated for nerve fibre diameters larger than 5 μm:*

   $i(\text{electro, morph; Co}) = (0.6T0+1.2T1+2.8T2+2.4T3+1.2T4+1.6P)/cm^2$,

   $i(\text{morph; S4}) = (0.4T0+1T1+0.8T2+1.1T3+0.5T4)/cm^2$,

   $i(\text{electro; S4}) = 0.4T0+2.3T1+2.1T2+2T3+1.5T4)cm^2$,

   $i(\text{morph; T9) (lateral)}) = (0.8\ (T0 \text{ or hair follicle})+1.7T1+0.9T2+0.7T3+0.4T4)/cm^2$.
4. *Innervation densities of mucosal afferent units M of urethra, trigonum vesicae and anal canal through S3 and S4 roots had the following lower limits:*

   $i(\text{electro; urethra+trigonum}) = 2\ M/cm^2$,

   $i(\text{electro; anal canal}) = 3\ M/cm^2$.

   The innervation density of skin like receptors of the anal canal through an S4 ventral root was with

   $i(\text{electro; anal canal}) = (0.5T0+2.4T1+1.6T2+1.2T3+0.8T4)/cm^2$

   at least as high as the innervation density of the S4 dermatome. The urethra posesses no skin like receptors in the mucosa. Mechanoreceptor afferents of the mucosa (M) of urethra and anal canal had thresholds similar to those of T3 and T4 afferents.
5. *The two point discrimination of a volunteer was for a light touch 30 mm in the S3 and S4 dermatomes and reduced to 25 mm with faster and stronger touch. In the direction of the anus and the os coccygeum the two point discrimination reduced to 25 mm. In the axillary line of the T9 dermatome the two point discriminations were 35 mm (transverse axis) and 45 mm (longitudinal axis).*

6. *By comparing the innervation densities with the two point discriminations it was found that in the rather untrained situation the discrimination sensitivity increased with the innervation density. Summing up the touch unit innervations from T0 to T4 one obtains the following correlation between the two point discrimination and touch innervation density: coccygeal skin (25 mm 2 point discrimination/7.2 innervations/cm^2), S4 dermatome (30 mm/6 innervations), T9 dermatome (40/4.5 innervations). It is calculated that there are 7 to 8 touch unit innervations between the two points of the two point discrimination.*
7. *It is shown that the Ap amplitude decreases, if the single nerve fibre is further away from the recording electrodes in the root cross-section.*
8. *In the Clinical implications it is discussed that the T1 afferents can serve as an information transport across the level of lesion if motor functions are restored in spinal cord injury patients.*
9. *20% of the afferent fibres may only be needed for a reinnervation of bladder, anal canal and sacral dermatomes. Because of similar properties of the receptors of T4 afferents and flow receptors the sense of bladder fullness may also be reconstructed.*
10. *It is discussed that a tract reconstruction should be tried in the PNS and that for a CNS regeneration improvement, the pyrogen Piromen should be reconsidered. Quantitative and realistic evaluations are necessary to find practical treatment between the "no hope" and the "false hope" standpoints in spinal cord lesions.*

Key-words: Skin afferents — Impulse pattern — Innervation density — Two point discrimination — Spinal cord lesion.

1. Introduction

For a sensory reinnervation in spinal cord lesions, receptor properties of skin, urinary bladder and anal canal afferents have to be further clarified and innervation densities calculated for quantitative comparisons of available donor nerve fibre numbers and necessary innervation densities of the to be reinnervated targets.

Even though there is the general belief that everything is known about skin afferents in humans (31, 32, 33, 40, 41, 66, 81), the knowledge about group conduction velocities and group nerve fibre diameters is poor. Very little is known about innervation densities (31). Receptor thresholds of different skin afferents (31, 33) were not measured simultaneously. Receptor properties of skin afferents have not been compared with those of bladder afferents.

Skin, anal canal and bladder afferents were characterized by their group conduction velocity and their group nerve fibre diameter (66): Skin afferents: T0 (49 msec^{-1}/-13.0 µm), T1 (44/11.2), T2 (39/10.1), T3 (31/9.1), T4 (20/8.3), P (13/?); mucosal afferents: M (12.5/?); flow receptor afferents: S2 (12.5/?). The simultaneous registration of impulse patterns from 32 single skin afferents in this paper will give a good understanding of the population response (32) and will be used for further analysations of innervation densities and two point discriminations.

Even though many calculated values of innervation densities are rather approximate, quantitative considerations are necessary if one wants to reinnervate urinary bladder, anal canal and skin in spinal cord lesions on rational grounds.

In the Clinical implications some first treatments and further research directions are suggested.

2. Method

The impulse pattern measurements are from the brain dead human cadaver HT6. For the

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calculations of innervation densities, measurements from different cadavers are used. For ethics and details of the method see references 64-68. The arrangement for recording single fibre action potentials is shown in figure 9.

3. Results

3.1. *Nerve fibre diameter distributions of the skin like nerve root dCo*

Figure 1 shows the cross-section of a dorsal coccygeal root, which will be analysed electrophysiologically in detail in the following sections. The cross-section of figure 1A shows mainly thick, thickly myelinated fibres and thin, thinly myelinated fibres. The corresponding nerve fibre diameter distribution histograms (Fig. 1B) support this overall view. A large number of fibres is contained in the myelin sheath thickness range d between 1.8 and 2.3 µm. Only few fibres have myelin sheath thicknesses between 0.8 and 1.8 µm. The large populations of thin ($\varnothing \sim 3$ µm) thinly myelinated ($d < 0.8$ µm) nerve fibres are not measured here, because of their smallness their action potentials (Ap's) are to small to be recorded and the fibre diameters can therefore not be compared with the corresponding conduction velocities.

By comparing the nerve fibre diameter distributions of figure 1 with the ones of figure 7 of the first paper (70) it is concluded that this coccygeal root has similarity with a skin nerve. Thick proprioceptive afferents are mainly missing. Electrophysiologically no dorsal root efferents could be found, probably because this dorsal coccygeal root was caudal to the motor outflow of the conus medullaris. Therefore also motoneurons with diameters larger than 5 µm could not have contributed to the spectra of figure 1B. With the help of the known group nerve fibre diameters (66) some peaks of skin afferents were identified and designated in figure 1B.

3.2. *Conduction velocities of thick skin afferents in the dCo root*

Conduction velocity distributions of the coccygeal root following touch and pin-prick are shown in figures 2A and 2B. Because of the unknown low temperature the peaks of the different skin afferents fused and the typical

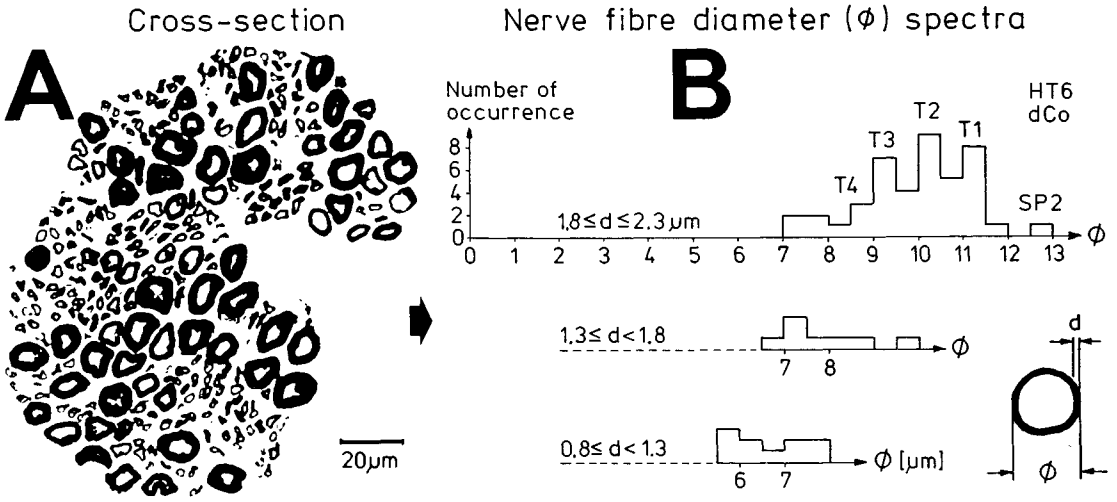

Fig. 1. — A. Cross-section of a dorsal coccygeal nerve root (dCo), HT6. vCo did not exist. B. Corresponding nerve fibre diameter frequency distribution histogram, classified by the myelin sheath thickness range "d". Fibre diameter class borders ≤ and <. The very thin fibres $d < 0.8$ µm are not measured.

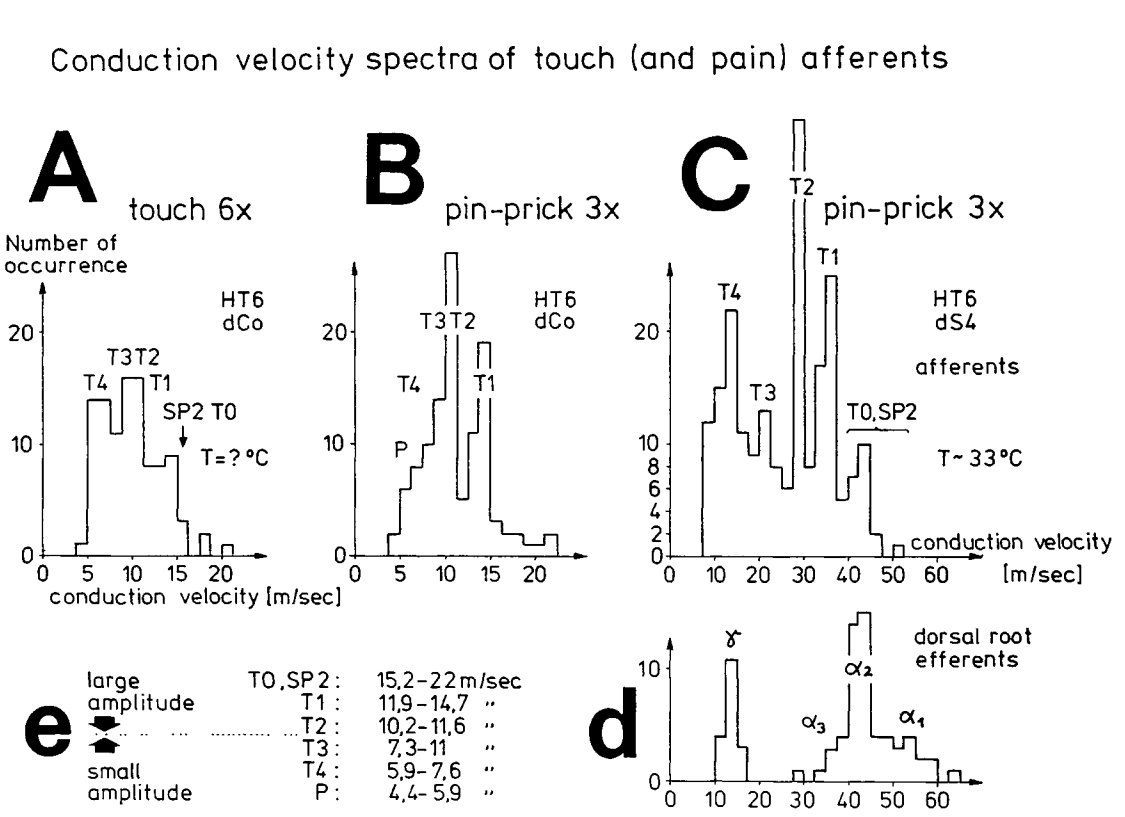

Fig. 2. — A, B. Conduction velocity frequency distribution histograms of the dCo root of figure 1 following touch (A) and pin-prick (B). The one active secondary spindle afferent fibre is marked in "A" with SP2. Notice, the touch with a ball (∅ = 5 mm) activated a different selection of touch afferents (different population response) than the pin-prick. Touch afferent peaks are designated, HT6. C, d. Conduction velocity distribution histograms of afferent (C) and efferent nerve fibres (d) of the same HT as in "A" and "B", but from a different root (dS4). e. Conduction velocity ranges of touch afferent groups, indicated in "A" and "B", of the coccygeal root used in the following figures.

peak distribution did not occur. To obtain the velocity ranges of the different skin afferents, the velocity ranges of a S4 dorsal root of the same HT (Fig. 2C), calibrated by the simultaneously recorded motoneurons (Fig. 2d), were used for comparison. Further, the conduction velocity of a continuously firing secondary spindle afferent fibre (SP2) and the different Ap amplitudes of the skin afferents were used to establish the velocity ranges of figure 2e. A few uncertain cases remained and are marked in the following impulse patterns.

With the 3 criteria "Ap wave form on trace 'a'", "Ap wave form on trace 'b'" and the "conduction velocity of a single Ap", the simultaneously occurring impulse patterns of about 32 active skin afferent units will be extracted from the population response. The patterns will be given in the following figures.

3.3. *Comparison between fibre numbers obtained from diameter distributions and Ap occurrence patterns*

Thirty two patterns of single fibres were extracted from the following population responses (Fig. 4). In the diameter distribution for myelin sheath thicknesses $1.8 \leq d < 2.3$ µm (Fig. 1B) 37 touch and pain fibres are contained. The number of fibres measured morphometrically and identified electrophysiologically are in good agreement. Probably not all afferents from the dCo dermatome leading through the dCo root were stimulated.

The correlation between nerve fibre numbers obtained from impulse patterns and nerve fibre diameter distributions also hold within the skin afferent groups. It can be seen from figures 4a and b that with strong pin-pricks 4 fast

conducting pain fibres and 5T4 afferents were activated. In the fibre diameter spectrum of figure 1B for $1.8 \leq d < 2.3$ µm and $7 \leq \varnothing < 9$ µm 4 pain fibres and 4T4 afferents are contained. The T3 impulse patterns of figure 4A contains 11 fibres; in the fibre diameter peak of figure 1B also 11 fibres are contained. In the T2 group (Fig. 4a) 3 fibres were stimulated; the morphometry group of figure 1B contains about 14 fibres. In the T1 and T0 group 9 fibres were stimulated (Fig. 4a); the corresponding group of figure 1B contains 9 fibres. Apart from the T2 group, fibre numbers from the diameter spectrum $1.8 \leq d < 2.3$ µm and the occurrence patterns are in good agreement. Taking the few fibres of the diameter spectrum $1.3 \leq d < 1.8$ µm into account, does not change the good agreement very much. The discrepancy in the T2 group is a bit unexpected, since one would expect uncertainties more for the thin, slower conducting fibres. That the T2 fibres accidently innervated another, not stimulated skin area is possible, but such situation would probably not account for the whole discrepancy. Further analysation will show, that the T3 and T4 skin afferents are very sensitive to light skin touch. They were therefore easily stimulated and all recruited. The T1 afferents with much higher thresholds were also sensitive to skin traction. They were therefore easily accessible to stimulation. One is left with the likely explanation, that many T2 afferents were not stimulated because of their high thresholds and their short range of receptive fields.

For the comparison with the diameter spectra the occurrence patterns of figure 4 were used and not the conduction velocity distributions. The reason is, that the velocity histograms of figures 2A and 2B contain the velocities of all occurring Ap's, and not the velocity values of single fibres only. Velocity histograms of single fibres can be constructed (see hatched histogram parts "each conduction velocity value only taken once" in Ref. 65), but the fibre numbers obtained in such a way are not as accurate as the ones from impulse occurrence patterns.

3.4. *Adaptation and thresholds of skin afferents*

Figure 3A shows the population Ap occurrence pattern during and following pin-prick 3. For the identification of certain single Ap's and their reoccurrence the recording was analysed on an expanded time scale as in figures 3B, C. The obtained impulse patterns of single skin afferent units from the population response following that pin-prick are shown in figure 4a. Many skin afferents were active. The different afferents in each group with their impulse patterns were put in order mainly according to the delay of the first Ap following pin-prick. Only receptors of afferents firing with a short delay in each skin afferent group were most likely rather focally stimulated and will show characteristic properties. In the following the adaptation and the thresholds will be compared between the different skin afferent groups. The adaptation will be judged by comparing the number of Ap's per impulse train at the beginning and the end of the pin-prick or touch and by the overall activity. Schematically, the stimulations were of trapezoidal form.

Figure 4a shows that the receptors of the $T1_1$ and $T1_2$ afferents adapted fast following the rather long lasting pin-prick 3, since the release activity part consisted of fewer Ap's. Following short strong pin-prick (Fig. 4b) the $T1_1$ receptor showed no adaptation since pin-prick and pin-prick release impulse trains consisted both of 3 Ap's. In figure 4a it seems as if the T2 afferent receptors also adapted fast. From the long lasting pin-prick of figure 4a it can be seen that the receptors of the T3 afferents did not adapt fast. That the T3 receptors adapted much more slowly than the T1 receptors can also be seen by comparing the overall activity for long (Fig. 4a) and short (Fig. 4b) pin-prick. The T1 afferents fired with 16 Ap's for the long and with 15 Ap's for the short pin-prick. The T3 afferents fired 21 Ap's for the long and with 8 AP's for the short pin-prick. This shows that the activity of the T1 afferents did not depend on the duration of the stimulation, whereas the activity of the T3 afferents did very much. Since the T3 receptors have a lower

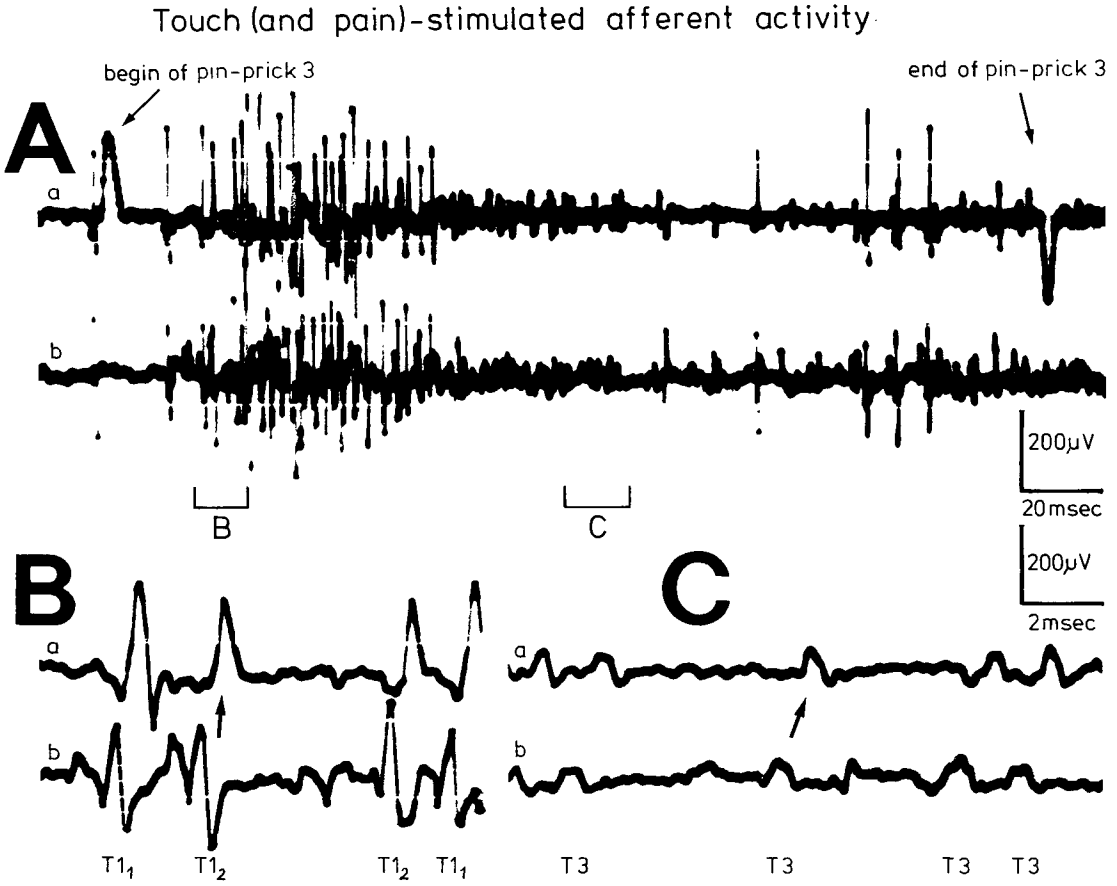

Fig. 3. — Touch activity stimulated by pricking S5 or Co dermatomes with a pin and recording extracellularly from a dorsal coccygeal root (HT6). T1 and T3 mark action potentials (Ap's) from touch afferents. Subscripts 1 and 2 mark single identified fibres. A. Whole sweep shown at a slow time base. Large upward artifact on trace "a" marks electronically the beginning of the pin-prick. Large downward artifact on trace "a" marks the end of the pin-prick. Note that 2 intervals of high activity of large Ap's occur, one after the beginning of the pin-prick with 1 Ap in front, and a second before the end of pin-prick; potentials with small amplitude follow the potentials of large amplitude. The touch afferent Ap before the beginning of the pin-prick could be a spontaneous Ap or was stimulated accidently by other means. Time intervals B and C are shown in a time-expanded form in figures B and C. B, C. Time expanded sweep pieces of A. Ap's from identified touch afferents are indicated. Different T1 afferents are marked by subscripts. Note in B, that the single fibre identification of the T1 afferents in safe. The identification of all single touch units of figure 1A on a similar scale as in B and C will be given in figure 4a.

threshold than the T1 receptors, as will be shown below, the stimulation threshold will not disturb the adaptation difference between T1 and T3 receptors. For the T4 receptors the situation is more complicated. It seems as if they are slowly adapting (see below), but for the short pin-prick the activity consisted of 6 Ap's and for the long pin-prick of 5 Ap's. This would point towards a fast adaptation. An explanation could be, that the T4 receptors are adapting slowly, but their threshold could be velocity dependent (see below). The impulse patterns of the pain afferents (P) in figure 4b give no clear answer about their adaptation speed.

Figure 5 shows the impulse patterns with light and rather long lasting pin-prick. Mainly only T3 afferents were stimulated. This indicates that the T3 afferents have the lowest threshold among skin afferent receptors measured in this experiment. No pain afferents were stimulated. The pain activity property found in figure 4a and figure 5 are in accordance with normal feeling. With light pin-prick

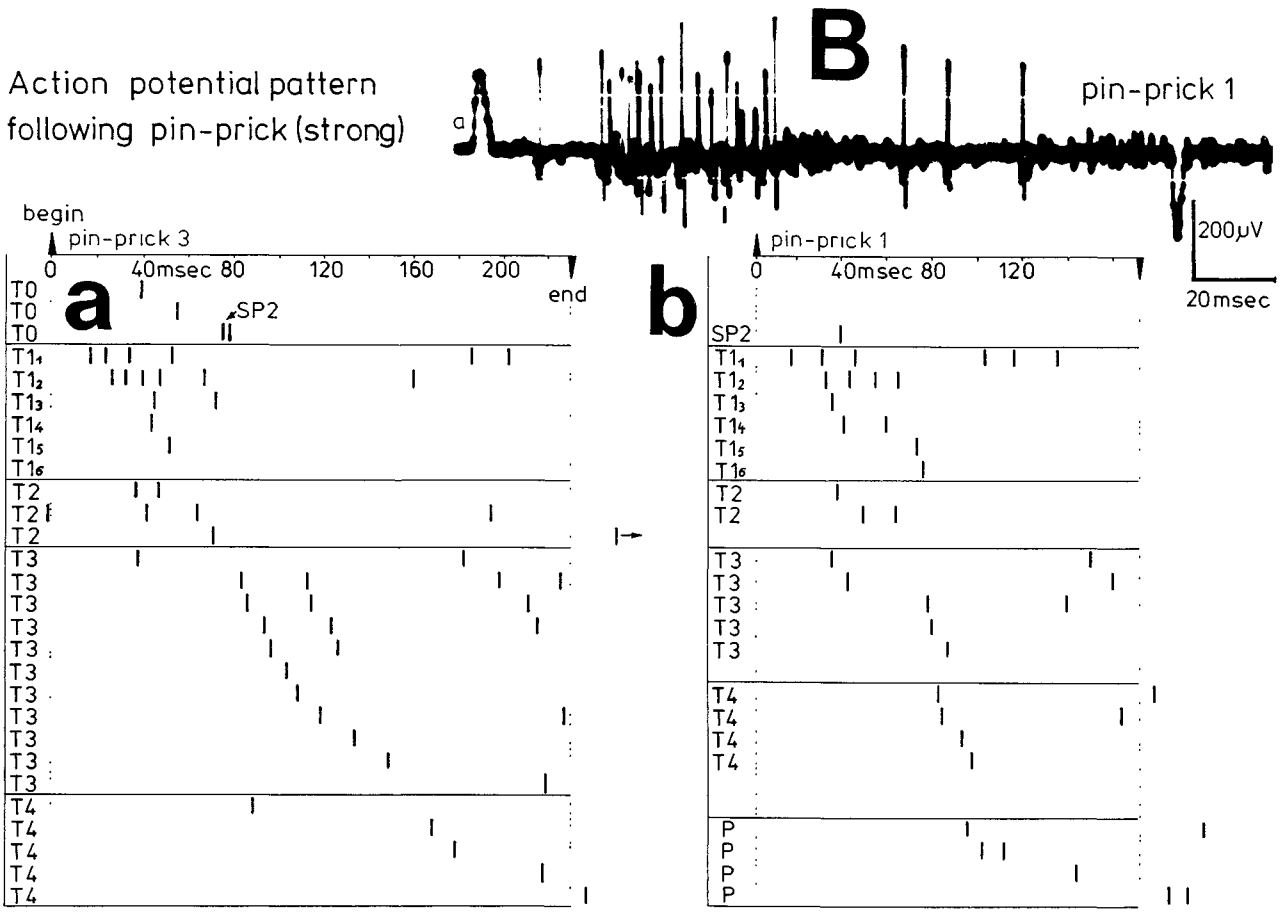

Fig. 4. — Action potential (Ap) occurrence patterns of single touch fibres following strong long pin-prick 3, analysed from the pin-prick sweep of figure 3A. The single fibre Ap activity of the different touch groups are identified by the Ap forms on the traces "a" and "b" and the conduction velocities. The single touch afferents of the T1 group are marked with subscripts and can be followed up in all the stimulations of the following figures. The one active secondary spindle afferent fibre (SP2) could always safely be identified and is marked in this and the following figures. B. Original recording of pin-prick 1 (only trace "a" shown) with single fibre analysation in "b". b. Single fibre Ap occurrence patterns of the strong short pin-prick 1 shown in B. Notice, the $T1_1$-unit adapts in "a" following the strong and slow pin-prick (release activity is reduced), but not in "b" following the strong and short pin-prick (release activity is not reduced).

no pain is felt, probably no receptors are activated (high threshold). With rather strong pin-prick it is sometimes possible to miss pain receptors sensing fast pain (Fig. 4a).

Touching the skin at the former place of the pin-prick (Fig. 6) with a ball gives similar skin afferent impulse patterns as by pin-pricking (Fig. 4), apart from the pain afferent activity and the overall population responses (compare Fig. 2A with Fig. 2B). For rather long touch $T1_1$ and $T1_2$ receptors adapted (Fig. 6a) (release impulse part is much shorter than the touch part) but for the short touch they did not (Fig. 6b). The $T3_1$ receptor showed less adaptation with the longer touch (Fig. 6a) than the $T1_1$ and $T1_2$ units. With the shorter touch the T3 afferents fired mainly only with threshold Ap's . It seems that the slowly adapting T3 receptors needed also more time to build up an impulse train than the T1 receptors. The slower adapting receptors are also slower in responding. The overall touch stimulated activity of the T1 receptors was 9 for the long and 9 for the short touch. The T1 afferent response activity was therefore as for the pin-prick independent of the length of the touch. The T3 afferents fired with a slightly higher activity for the longer lasting touch (11 against 9). With the

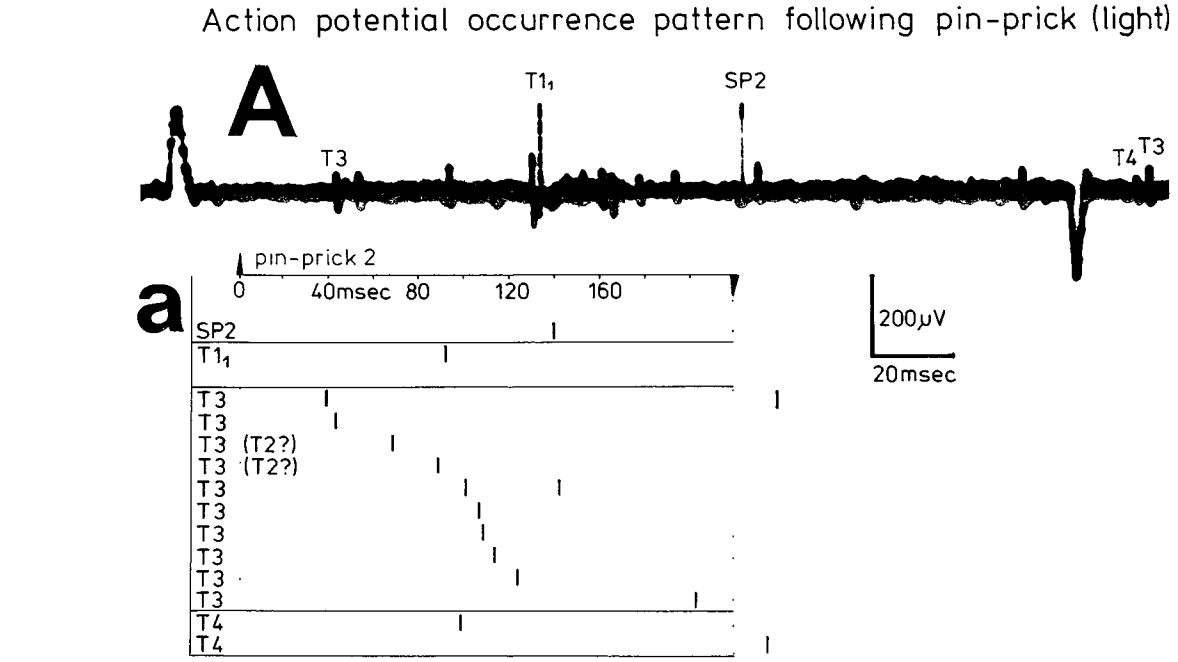

Fig. 5. — Ap occurrence patterns following light and long pin-prick 2. Original recording in A; single fibre analysis in "a". Notice, mainly only T3 touch afferents were stimulated.

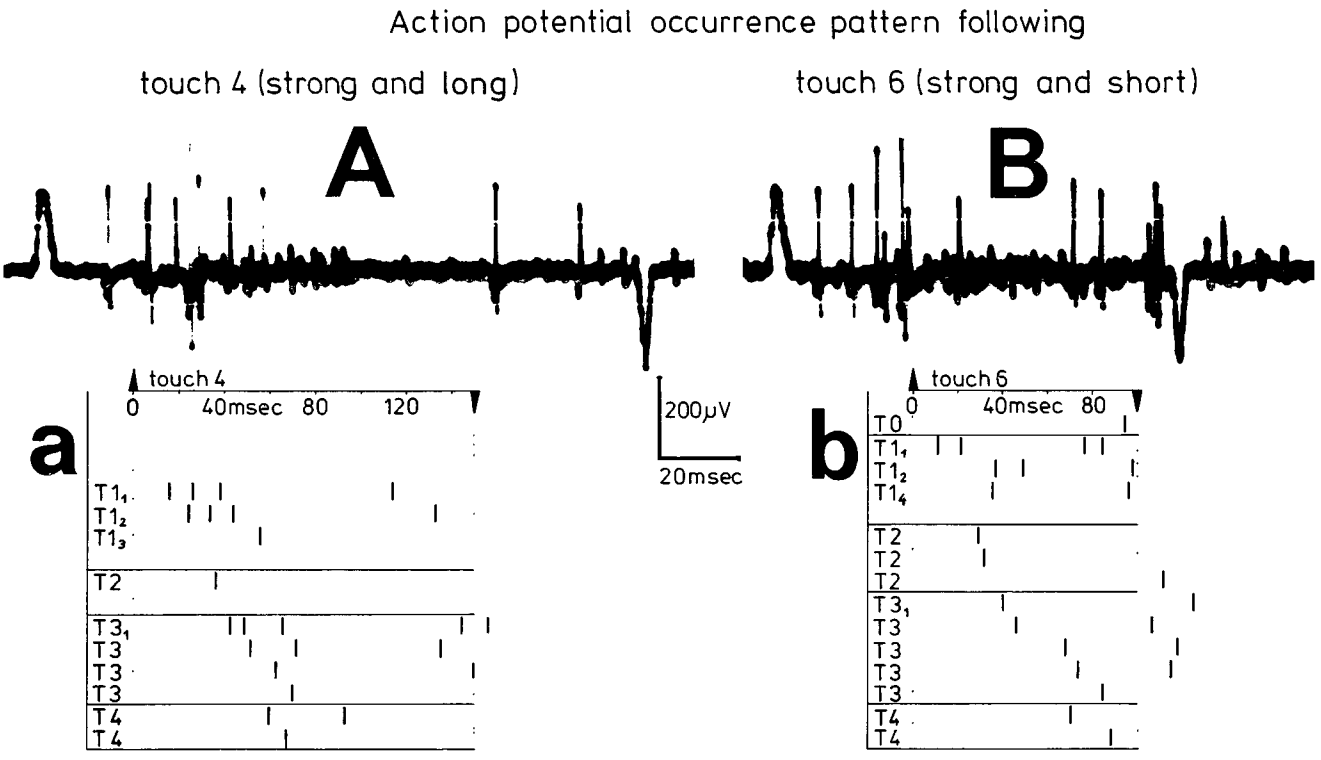

Fig. 6. — Ap occurrence patterns following strong and long touch 4 with a ball of 5 mm in diameter and a strong and short touch 6 (B, "b"). Notice, the stimulated $T1_1$-unit adapted in the case of the strong and long touch (A, "a") (release activity strongly reduced) and not for the strong and short touch (B, "b"), notice further, the $T3_1$-unit adapted more slowly than the $T1_1$-unit ("a").

skin touch not as many afferents were stimulated as with the pin-prick. A likely explanation is, that the pin-prick was normally stronger than the touch and the stimulated skin area increased with a stronger touch or pin-prick, since a larger area will be indented with a stronger touch or pin-prick (see below). This interpretation is supported by the choice of T1 receptors stimulated. With touch (Fig. 6) only those 4 T1 receptors were stimulated, which showed the shortest delay with pin-prick (Fig. 4), which had therefore on average the lowest threshold with respect to the point of stimulation and which were therefore on average nearest to the point of stimulation (see also Fig. 9b). Figure 7 shows for touch as figure 5 showed for pin-prick, that with light and long touch mainly only T3 receptors were stimulated, which means that the T3 receptors have the lowest threshold for slowly applied rather long lasting touch.

So far no properties could be obtained of the T4 afferents. With the stimulations shown in figure 8 the T4 afferents were more activated than the T3 afferents. Since 4 T1 receptors were also stimulated, the strength of touch was medium and the T3 afferents should also have been activated strongly. But they were not. The impulse patterns of the T4 afferents in figure 8a show a more slowly adapting nature, whereas the slowly adapting T3 afferents in figures 8a, b show only threshold activation. The slowly adapting nature of the T4 afferents can also be seen, if one compares their overall activity of the rather long touch 2 with the shorter touch 3. For the longer touch the T4 afferents fired with 11 Ap's and for the shorter touch with 8 Ap's. The fast adapting T1 afferents fired with 6 and 5 Ap's roughly with the same activity. The velocity of touch is probably also not the reason for the activation of the T4 afferents, since the activity with shorter and probably higher speed of touch was shorter. It is concluded, that the T3 and T4 receptors are both slowly adapting, both have a low threshold, but sometimes the T3 receptors are more activated and sometimes the T4 receptors are more activated. Therefore there must be a difference in the adequate stimulus of the T3 and T4 receptors. Looking once again over all stimulations it can be seen from figures 4 to 8 that with sticking with a needle the T3 afferents were always activated the most and with the touch of the skin with a ball sometimes the T3 and sometimes the T4 afferents were activated more. Since touching with a ball also a movement component parallel to the skin is possible and for the pin-prick not (only skin traction) it is concluded that the T4 receptors are very sensitive to touch movements along the skin,

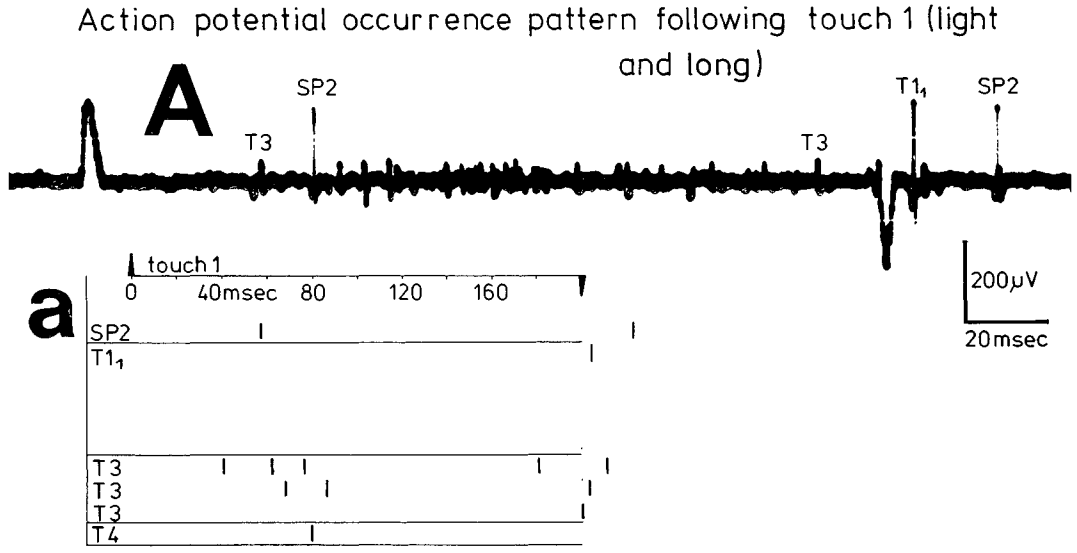

Fig. 7. — Ap occurrence patterns following light and long touch 1. Notice, mainly only T3 units were activated.

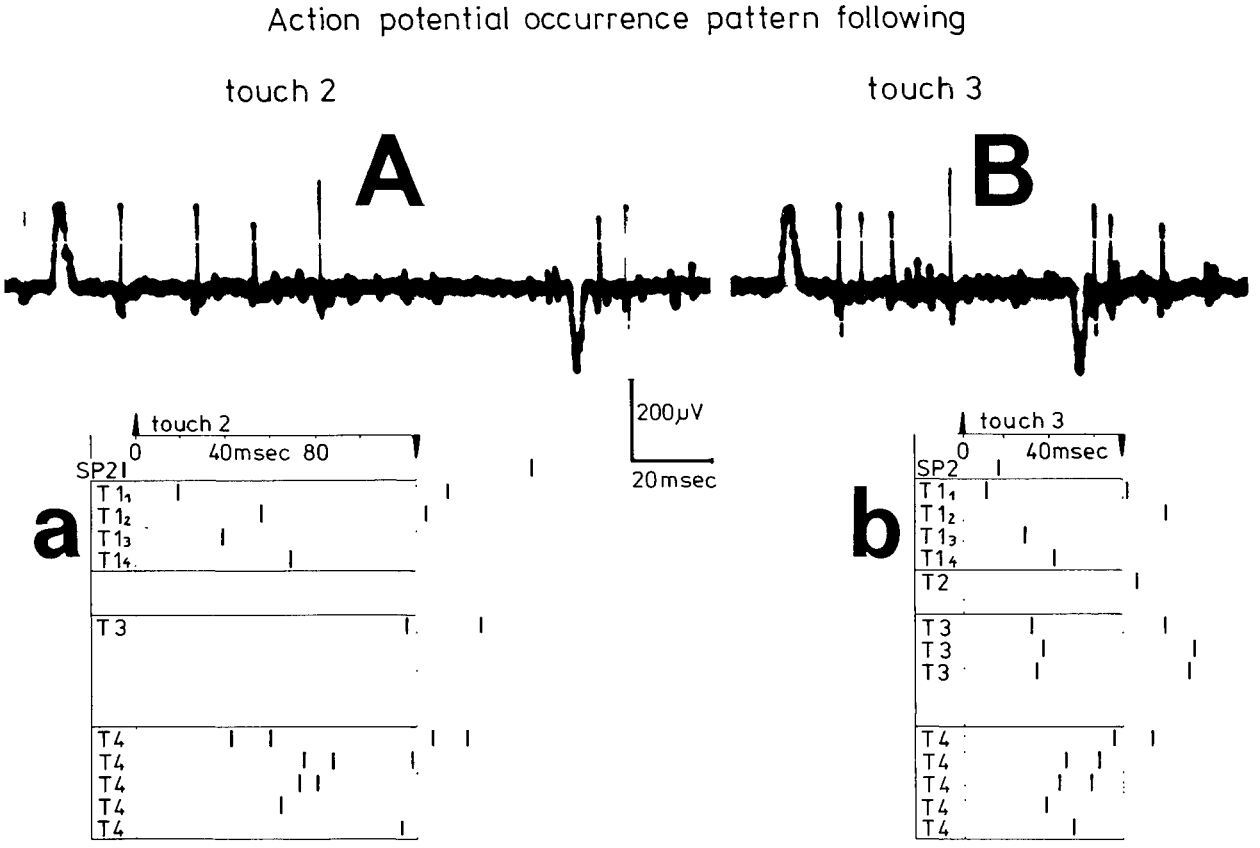

Fig. 8. — Ap occurrence patterns following different touch stimulations. Notice, the T4-units are more activated than the T3-units, especially in "a", in difference to the stimulations of the figures 3 to 7.

whereas the T3 receptors are more sensitive to a touch without a movement along the skin. The T4 receptors are therefore the "Streichel receptors" (caress receptors).

The analysis of the adaptation of touch receptors by comparing the "on" impulse train with the "off" part is questionable. Normally adaptation is judged by applying long lasting skin indentation and measuring whether a receptor stops firing rapidly or slowly.

No special properties could be found for the T0 afferents. Even though they have the highest group conduction velocity (66), they never fired first. Probably they were not adequately stimulated. The T0 afferents could innervate hair receptors, because of their high conduction velocity, or they could be developmental rudiments. That the T0 afferents innervate pressure receptors is unlikely since none of them fired strongly with pin-prick.

Since the T2 receptors were activated most with strong pin-prick, they will have a higher threshold than the T1 receptors and probably do not respond so much to skin traction as the T1 receptors do, as will be analysed below. Since further only 3 T2 afferents were activated (Fig. 4) of the about 14 present (Fig. 1B), whereas nearly all of the T1, T3 and T4 afferents were activated, it is likely that the T2 receptors obtained only little adequate stimulus, namely pressure. It will be difficult to apply pressure to a small defined skin area on top of the gluteus maximus.

3.5. *Receptors of T1 afferents are sensitive to skin traction*

Following bladder and anal catheter pulling no clear activity could be found of mucosal

afferents. The coccygeal root seems to be more like a skin nerve and originates more caudally than the nervous outflow to the bladder and the anal canal. With anal-catheter pulling several kinds of the above skin afferents including T1 units fired. Because it is not clear from the anatomy (Fig. 9a) which activity was due to skin traction and which to skin touch from right and left body parts, the bladder-catheter pulling will give more clear answers than anal-catheter pulling about skin traction. Figure 10A shows on a fast time scale the end of a sweep piece of a bladder-catheter pulling. By comparing the wave form of the Ap of figure 10A with those of the skin stimulation of figure 3B it can be seen, that the Ap of figure 10A was conducted by the $T1_2$ afferent fibre. With this bladder-catheter pulling no low threshold T3 afferents were activated. A stronger touch of the skin by the touching of adjacent skin parts is therefore unlikely. The $T1_2$ receptor was therefore stimulated from far away (at least 10 cm, see Fig. 9a) by skin traction, which was caused by the pulling of the bladder-catheter.

Since further the $T1_6$ receptor was not stimulated, which seemed to be most far away from the place of pin-prick and nearest to the meatus of the urethra (activated by anal-catheter pulling) (Fig. 9b), it seems that not all T1 receptors had the same sensitivity to skin traction. The sensitivity to skin traction probably also depends on the receptor arrangement itself and on the direction of skin traction and how the skin is folded or bended.

3.6. *Summarized receptor properties of the T1, T2, T3 and T4 skin afferents*

The T1 and T2 skin afferent units were rapidly adapting and the T3 and T4 afferents were slowly adapting according to the measure for adaptation used. With skin touch and no movement component along the skin the T3 receptors had the lowest threshold among the 4 receptor kinds. For a touch with a movement component parallel to the skin the T4 afferent receptors had the lowest threshold. T1 and T2 receptors had higher thresholds. The T2 receptors probably had the highest threshold. T1 receptors could be stimulated by skin traction from more than 10 cm away. Since the Ap's from one T1 receptor were often clearly leading (Fig. 3B) the T1 units seem to have a very sensitive single focus and receptive fields which are not sharply deliniated. T2 afferent receptors probably have small receptive fields. High thresholds and small receptive fields could explain that only few T2 afferents were activated with pin-prick and touch with a ball of 5 mm in diameter. The T3 receptors had very low thresholds to skin indentation, did not respond very much to skin traction or touch movement along the skin, but many of them were activated simultaneously with a single

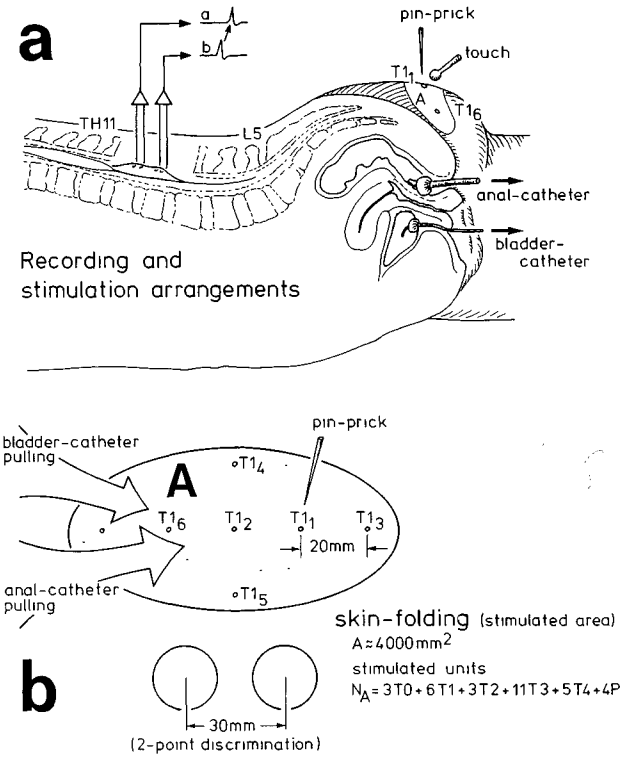

Fig. 9. — Recording and stimulation arrangement for measuring simultaneously many single touch and pain units. A = by skin folding stimulated area, which is drawn more in detail in "b". $T1_1$, $T1_6$ = suggested touch points of the $T1_1$ and $T1_6$-units. b. Drawing of the very approximate by skin folding stimulated skin area. $T1_{1\text{-}6}$ = suggested focal T1 touch points. Two point discrimination indicated for comparison. N_A = number of stimulated units in the dorsal coccygeal root of figure 1. Skin tractions, evoked by anal and bladder-catheter pulling, are indicated by large open arrows.

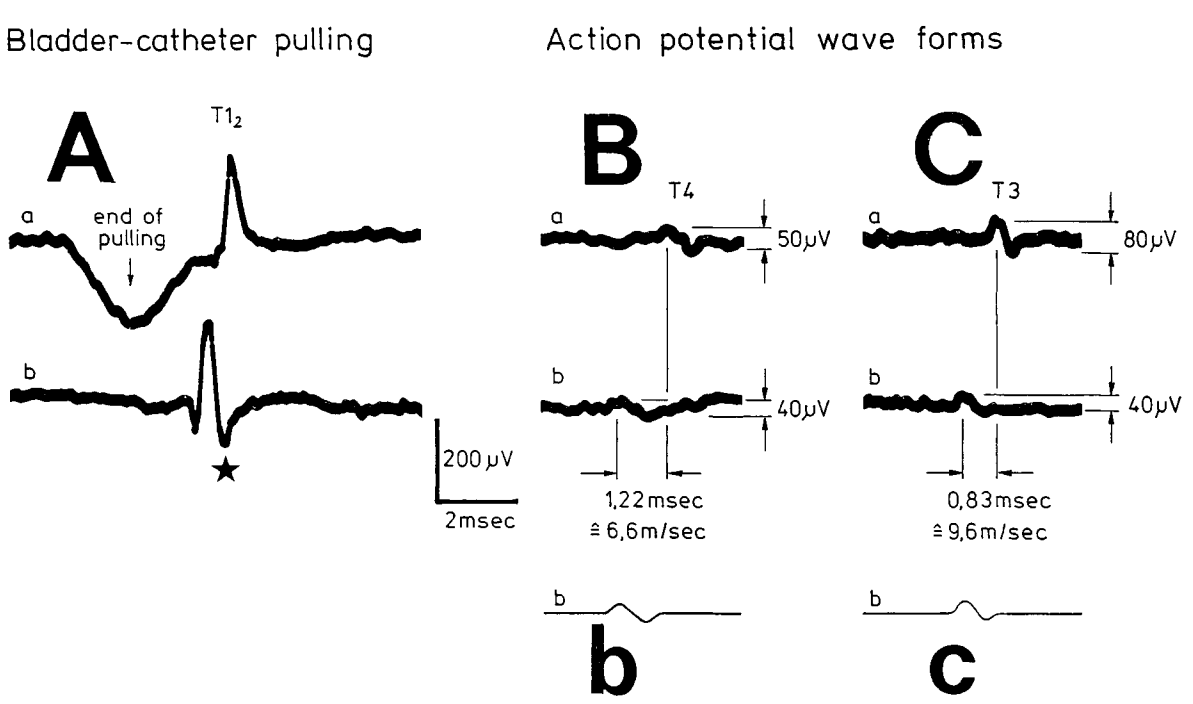

Fig. 10. — A.Ap occurrence pattern following bladder-catheter pulling 1. Two potentials of T4 or M-type occurred (not shown) and this $T1_2$ touch afferent fibre Ap at the end of the pulling, which was also mostly stimulated following pin-prick and touch. For the wave form identification of the $T1_2$-Ap compare with figure 3B. B, C. Action potential wave form analysis and comparison of T3 and T4 touch afferents. Rather focal recorded T4-Ap's are shown in B and idealised in "b". The T4 identification is done by the conduction velocity (see Fig. 2e). The T3-Ap (compare with the velocity ranges of Fig. 2e) is rather focally recorded with the proximal electrode pair (trace "a", amplitude = 80 µV) and non focally recorded with the distal electrode pair (trace "b", amplitude = 40 µV). The non focal registration is schematically redrawn in C. Notice, a focal to a non focal registration reduces the amplitude from 80 µV to 40 µV. Root diameter 0.13 mm; electrode pair distance = 8 mm.

touch or pin-prick. May be their receptive fields are large and there is a large overlap of the receptive fields or T3 receptors are very sensitive to skin folding or bending.

3.7. *Innervation and innervation densities of skin afferents for Co, S4 and T9 dermatomes*

To calculate different innervation densities of sacral and thoracal skin segments, first the innervations "I" were determined from nerve fibre diameter distribution histograms, myelinated fibre numbers, conduction velocity distribution histograms and action potential (Ap) occurrence patterns. From the diameter spectra of figure 1B for myelin sheath thicknesses $1.3\ \mu m \leq d$ the innervation of the coccygeal dermatome on one side was about I (morph; Co) = 9(T0+T1)+14T2+12T3+6T4+8P. From the Ap occurrence patterns of figure 4 an innervation I (electro; Co) = 3T0+6T1+3T2+11T3+4T4+4P could be obtained. As analysed before, the agreement is good between the values obtained from the morphometry and the electrophysiology. Only the values of the T2 afferents show a big discrepancy, which was explained by the high threshold of the receptors and their small receptive fields.

To calculate innervation densities "i" dermatome areas and stimulated skin areas have to be known. Lower sacral dermatomes were measured by Bohm (4) by cutting dorsal roots. In certain areas the sensibility was reduced and in small areas absent. The remained reduced sensibility can be explained by the existance of ventral root afferents (64, 65, 66). Likely is, that the ventral root afferents contributed to the

remained sensibility for example of the S4 dermatome following the cutting of the dorsal S4 root. But probably there is also a large overlap and variation in the lower sacral and coccygeal dermatomes. Therefore only very rough estimations can be obtained for sacral dermatomes and stimulated skin areas. The coccygeal dermatome area is assumed to be 5 cm^2 large on one side. The stimulated skin area was with 40 cm^2 (Fig. 9) much larger than the coccygeal dermatome and it seems as if nearly the whole coccygeal dermatome on one side was stimulated. The calculated innervation density from the electrophysiological and morphometric measurements for the coccygeal dermatome is about i(electro, morph; Co) = (0.6T0 + 1.2T1 + 2.8T2 + 2.4T3 + 1.2T4 + 1.6P)/cm^2.

From the nerve fibre diameter distribution histogram of a S4 dorsal root of figure 11 of reference 66 (same HT) with identified skin afferent peaks the following innervation on one side was obtained for myelin sheath thicknesses 1.3 μm ≤ d I (morph; S4) = 8T0 + 20T1 + 22T2($-6\alpha_2$) + 22T3 + 14T4($-3\alpha_3$).

"$-6\alpha_2$" and "$-3\alpha_3$" indicate that some α_2 and α_3-motoneurons of that dorsal root were subtracted. A few misjudged other afferent fibres were probably also intermingled. If one assumes a S4 dermatome area of 20 cm^2 on one side then one obtains an innervation density of i (morph; S4) = (0.4T0 + 1T1 + 0.8T2 + 1.1T3 + 0.5T4)/cm^2 (ventral root afferents are not taken into account). In these calculations the main uncertainty comes from the assumed dermatome area.

More difficult is to calculate the innervation density from conduction velocity frequency distribution histograms. Since the activity of skin afferents following skin touch was very large in dorsal roots, many single fibre Ap's merged and the obtained velocity histograms (Fig. 2B of Ref. 66) gave no representative selections and can therefore not be used for calculations of innervations. The innervation density will therefore be calculated from the skin afferents of a ventral S4 root (Fig. 2A of Ref. 66). Taking 5 touch stimulations and 20% ventral root afferents into account, one obtains the following number of nerve fibres I (electro; S4) = 8T0 + 46T1 + 42T2 + 40T3 + 30T4. With the assumed dermatome area on one side of 20 cm^2 one obtains the innervation density i(electro; S4) = (0.4T0 + 2.3T1 + 2.1T2 + 2T3 + 1.5T4)/cm^2. Because ventral roots are thinner than dorsal roots (63) and dorsal and ventral root afferents have to be taken into consideration, i(electro; S4) is probably underestimated.

From the myelinated nerve fibre number of the skin branches of the intercostal nerve (3000) to the lateral skin (Fig. 4b of the first paper (70)) and the corresponding nerve fibre diameter distribution histograms (Fig. 7 of the first paper (70)) for 1.3 μm ≤ d and 8 μm ≤ ∅ (36% of 3000) the following innervation is obtained I (morph; T9) = (19(T0 + hair follicle) + 40T1 + 21T2 + 17T3 + 10T4) (3000 × 0.36)/310 × 80). With an assumed lateral T9 dermatome area of 80 cm^2 (20 cm × 4 cm (assumed dermatome broadness)) the innervation density results to i (morph; T9 (lateral)) = (0.8(T0 + hair follicle) + 1.7T1 + 0.9T2 + 0.7T3 + 0.4T4)/cm^2.

3.8 *Mean innervation density of urethra and trigonum vesicae and anal canal*

From the figures 4, 6 and 8 it can be calculated that T1, T2, T3, T4 and P afferent units fired on average 2 times following rather short touch or pin-prick. From figure 6C of reference 66 (same HT) it can be calculated that 20 Ap's from mechanoreceptors of the mucosa (M) were recorded from a S4 dorsal root following bladder-catheter pulling. A similar number of Ap's was recorded from a S3 dorsal root. A lower limit for the innervation of the mechanoreceptors of the mucosa of urethra and trigonum vesicae through S3 and S4 dorsal nerve roots on one side, assuming an activation number of 2 Ap's as above to hold also for the mucosa, is about I(electro; S3 + S4) = 20 M((20 + 20)/2). These values are compatible with the nerve fibre diameter distribution histograms of figures 11 and 12 of reference 66, even though the peak group nerve fibre diameter of mucosal afferents is still unknown. The stimulated area of urethra and trigonum vesicae is in

the range of 10 cm^2 on one side (urethra: $\varnothing$ = 0.4 cm, L = 4 cm; trigonum side length = 3 cm). The lower limit for the mean innervation density would then be i(electro; urethra + trigonum) = 2 M/cm^2.

The estimated innervation densities of the T4 afferents varied between 0.4 and 1.5 per ^{2}. The lower limit of the innervation density of the mucosal afferents of urethra and trigonum vesicae is therefore higher than the one of the T4 afferents of the skin.

From figure 7 of reference 66 it can be further estimated in the same way that the innervation of M units of the anal canal is about I(electro; anal canal) = 25 M. Since the mucosal receptors are distributed only till to the linea arcuata, the area will be smaller. The lower limit of the innervation density of the anal canal (diameter = 1.2 cm, L = 4 cm, A = 15/2cm ^{2}) is with i(electro; anal canal) = 3 M/cm^2 in the same range than the one of urethra and trigonum.

From figure 7 of reference 66 it can be further estimated that the innervation of skin receptors of the anal canal through an S4 ventral root (Ap occurrences of figure 7B of reference 66 devided by 4(4 stimulations)) is about I(electro; anal canal) = 4T0 + 18T1 + 12T2 + 9T3 + 6T4. With a stimulated mucosal area of 15/2cm^2 on one side an innervation density of about i(electro; anal canal) = (0.5T0 + 2.4T1 + 1.6T2 + 1.2T3 + 0.8T4)/cm^2 is obtained. The skin mechanoreceptor innervation density of the mucosa of the anal canal is at least as large as the innervation density of the S4 dermatome, since afferents from the anal mucosa could also lead through S3 and S5 roots.

3.9. *Two point discrimination*

A 25-year-old female volunteer was analysed for the shape of skin indentation and two point discrimination. Two, not too sharp pencils were used for the touching. It was tried to stimulate in the same way and at similar places as was done during the HT measurements. The skin touch with one pencil resulted more laterally in a round shaped skin indentation and more medially in an elliptic shaped indentation with the long axis in direction of the anus, as is shown rather schematically in figure 9. The area of skin indentation (indentation amplitude 20 to 40 mm) due to a rather strong touch was measured and resulted to about 40 cm^2, as indicated in figure 9b.

Then the two point discrimination was measured, which was for a slow rather light touch 30 mm in the S3 and S4 dermatomes. Figure 9b shows the two point discrimination with the 2 circles of skin indentation according to scale. With faster or stronger touching the two point discrimination reduced to about 25 mm. The two point discrimination reduced when the skin was stimulated more close to the anus and was 25 mm on top of the os coccygeum. The two point discriminations in the axillary line of the T9 dermatome were about 35 mm (tranverse axis) and 45 mm (longitudinal axis). The measured values are in accordance with the literature (72). A further detailed analysis in the direction of the anus was not possible since firstly it was difficult to measure at the anal region without touching other skin parts and secondly the volunteer refused cooperation after some time. A measurement of the two point discrimination in the anal canal and bladder was not possible with such simple means.

3.10. *Comparison between innervation density and two point discrimination*

The two point discrimination increased from the lateral T9 dermatome (40 mm) to the S4 dermatome (30 mm) and the coccygeal dermatome (25 mm). With the used innervation density:

$$i = 1/cm^2 \sum_{v=0}^{v=4} n_v Tn$$

$$= 1/cm^2(n_0T0 + n_1T1 + n_2T2 + n_3T3 + n_4T4)$$

Tv = kind of afferent fibre, n_v = number of innervations of a certain kind, the summed up innervation density N equals then to:

$$N = 1/cm^2 \sum_{v=0}^{v=4} n_v$$
$$= (n_0 + n_1 + n_2 + n_3 + n_4)/cm^2$$

N increases from the T9 dermatome (N = 4.5 touch points/cm^2) to the sacral (8.3, 3.8; mean = 6) and coccygeal dermatome (7.2). The increase of the two point discrimination (shorter distance) with a stronger or shorter touch is in accordance with the number of recruited afferents in figures 4 to 8, since with slow and light touches mainly only the receptors of the T3 (may be T4) afferents were activated, whereas with stronger and faster touch also the receptors of the T1 and T2 afferents were activated.

If one takes the root from the densities at the point of touch and multiplies it with the distance of the two point discrimination, then one finds that about 7 to 8 touch units are innervated between the 2 touch points (T9: $(4.5/cm^2)^{\frac{1}{2}} \times 4$ cm = 8.4). On the basis of 7 to 8 touch innervations per two point discrimination it should be possible to reduce the distance of the two point discrimination by training.

3.11. *Decrease of action potential amplitude with distance from the recording electrodes*

Figures 10B and C show the recordings of Ap's of T4 and T3 skin afferents, identified by their conduction velocity, which lie in the velocity ranges shown in figure 2e. The Ap wave forms on the traces "b" in figures 10B and C are very similar, even though their redrawn idealised wave forms in the figures 10b and c are slightly different. But on trace "a" in figure C the T3-Ap is nearly as twice as high as the T4-Ap on trace "a" in figure 10B. This clearly shows, that one trace recordings give unreliable Ap amplitudes. Furthermore this comparison shows that from a one trace recording one cannot reliably judge from the Ap amplitude to the nerve fibre diameter, even though on average the Ap amplitude increases with the fibre diameter and the conduction velocity (65, 90). The most likely explanation, that in figure 10C the T3 Ap amplitude on trace "a" is double as high as on trace "b" is, that at electrode pair "a" (Fig. 9a) the nerve fibre was very near to the electrodes in the nerve root and at the electrode pair "b" the nerve fibre was far away from the electrodes in the root. The T4-Ap amplitude in figure 10B is rather similar on the traces "a" and "b". The T4 nerve fibre had most likely about the same distance to each electrode pair in the root. This Ap amplitude explanation is supported by an Ap wave form interpretation of the figures 10b and c. The T3-Ap wave of figure 10c is more round shaped and the T4-Ap wave of figure 10b is more linear shaped. Since waves tend to reduce in amplitude, and tend to spread and get more round shaped with propagation, the more round shaped T3-Ap of figure 10c is probably generated further away from the recording electrodes in the root cross-section (Fig. 1A) than the more linear shaped T4-Ap of figure 10b. Even though a general Ap wave form analysis of both recording traces has not been undertaken until now, large Ap's as in figure 10A show artifacts on the other trace. The $T1_2$-Ap in figure 10A on trace "a" deepens the third phase of its triphasic Ap on trace "b" (indicated by a star). Also large (fast) Ap's are effected by the passing frequency range of the filter in the preamplifier (100 Hz to 10 kHz); large Ap's become roughly more round shaped after filtering. Small slow Ap's as in figures 10B and C are only slightly effected by the frequency filtering; there is also nearly no influence between the recording traces "a" and "b".

Damage and overstretch also reduce the Ap amplitude, but usually several fibres are effected and also strongly prolonged Ap's and double peaked Ap's (probably from a block of a node of Ranvier) of rather thick fibres will occur. Double peaked Ap's can be seen in figure 3B (trace "a", α_1 and α_2-motoneurons) of ref. 71.

Since the root from which was recorded here had about a diameter of 0.13 mm (Fig. 1A), it should not be concluded that

0.1 mm away from the electrodes in the root or nerve the Ap amplitude reduces to the half of its value. One factor, responsible for the reduction of the Ap amplitude is the diameter of the nerve root or nerve. The other main factor is the epi- and perineurium, soked with saline solution, which shunt the electrodes. For a recording from a nerve it is crucial for a reasonable registration to reduce the epineurium and to keep the saline solution film as thin as possible. Since the amplitude difference of the T3-Ap of figure 10C between the traces "a" and "b" was the largest one observed, it is concluded, that all Ap's from the T0 to T4 afferents were large enough, to be registered by the recording electrodes. The recording electrodes, so to say, "saw" all the fibres in the coccygeal root down to the thin T4 and P afferents. It is therefore reasonable that the agreement was rather good in section 3.7 between the innervations obtained from the electrophysiologic (I (electro); Co)) and morphometric (I (morph; Co)) measurements.

If a nerve root is lying on the recording electrodes and if the recording is going on, then there is not much danger for the root, since many kinds of damage can be seen to develop by the experienced eye.

4. **Discussion**

4.1. *Correspondence between the nomenclatures of T1, T2, T3, T4 and PC, RA, SAI, SAII afferents*

Rather safe is the conclusion that the T1, T2, T3 and T4 afferents (66) are the PC, RA, SAI and SAII afferent units (31, 32, 33, 40, 41, 81). Unclear is, which T unit corresponds to which rapidly or slowly adapting receptor type.

The T units are characterized by their peak group conduction velocity and peak group diameter, apart from an overlap of the distributions. The conduction velocity values of the PC, RA, SAI and SAII units, given by Knibestöl (40, 41), are not precise enough for a reliable correlation. For RA and PC units mean values of 55,3 and 46,9 m/sec were given (40). The velocity distributions, measured with low statistics, show for both groups peak velocities of 43 m/sec. Mean values of SAI and SAII units are given with 58,7 and 45,3 m/sec (41), but no velocity distributions were given. Unclear is, how much variation comes from the variability of the delay measurement (66) and how much from mechanical damage of the nerve fibres. The peak group conduction velocities of the T1, T2, T3 and T4 are 44, 39, 31 and 20 m/sec (66). At least the relation between the velocity values are rather reliable, since they were measured simultaneously.

The impulse patterns of the rapidly adapting PC and RA units and slowly adapting SAI and SAII units give definitive answers about the adaptation speed only for larger indentation amplitudes and longer durations. The identification of the impulse patterns of T1, T2, T3 and T4 afferents following natural stimuli of touch and pin-prick are quite safe but they give no reliable information whether they are rapidly or slowly adapting, since the indentation pressure was low and the indentation duration short. The place of measurement is given by the clinical needs. The indentation of skin, fat, and muscle at the gluteus maximus ranged up to amplitudes of about 40 mm. The applied pressure was still rather small because of the anatomical situation. The impulse patterns may be slightly different in comparison to hand measurements because of different anchoring of the receptors. More measurements with 2 electrode pairs for long indentations are needed. The problem is to have a measuring possibility.

The thresholds of the T1, T2, T3 and T4 afferents can reliably be compared, since they are measured simultaneously. But the thresholds depend on the kind of stimulus applied. The comparison between T3 and T4 thresholds showed that for a pure touch the T3 afferents had the lowest threshold. But when there was most likely additionally a small movement component along the skin, then the T4 afferents had the lowest threshold. The thresholds have to be correlated to the adequate stimulus, which is probably not just a pure indentation

for all T units. The correlation between the T-system and the PC, RA, SAI and SAII system on the basis of thresholds is also not reliably possible, especially since the thresholds of the PC (lowest) to SAII (highest) afferents (32) were not measured simultaneously.

There is a discrepance between the adaptation and the threshold correspondence of the two nomenclatures. According to the literature the rapidly adapting PC units have the lowest threshold, are sensitive to skin traction and have a single focus. The T1 units have the same properties, apart from the threshold, which is not the lowest. A simple change of the correspondence would not stop the confusion. There seem to be several uncertainties.

A correspondence on the basis of receptive fields (31, 33) is also not possible since the measurements performed here give so far only indirect knowledge about them. More simultaneous measurements of adaptation, threshold, adequate stimulus, conduction velocity and fibre diameter of skin afferents are needed. A comparison to the mechanoreceptor properties of urethra, bladder and anal canal is also needed.

4.1. *Mucosal afferents*

Todd found in cat (91) a variety of lamelled end-organs in and around the wall of the urethra. They varied from large Pacinian corpuscles, as much as 500 μm in diameter, in the peri-urethral connective tissue, down to small endings in the urethral mucosa about 30 μm in diameter. The small endings were found only in the most superficial layers of the urethral mucosa in which they lay longitudinally under the epithelium: their long axis was thus parallel to the direction of flow of the urine. They were usually situated at the summit of the longitudinal folds which develop in the urethral mucosa when the urethra is empty. They were found in groups of two to five endings (91).

For light and strong anal and bladder-catheter pulling, it was shown in figures 6 and 7 of reference 66 that for a light pulling the skin like afferent activity (at least from the T1 and T2 afferents) reduced more than the mucosal activity (The skin afferent activity occurring with bladder-catheter pulling stems from the stimulation of the skin around the ostium urethrae.). The threshold of the mucosal mechanoreceptors are therefore similar to those of the T3 and T4 afferents or lower. A closer comparison is difficult, since a strong pulling will result in movement and will stimulate more the T4 receptors, whereas a light pulling results in no or less movement along the mucosal surface and will stimulate comparibly more the T3 receptors. The mucosa of the urethra and the anal canal (apart from skin afferents) is innervated by mechanoreceptor (M), flow receptor (S2) and pain afferents (P) for nerve fibre diameters larger than about 5 μm (66). The high sensitivity of the urethra to touch and pain may also result from afferents with diameters smaller than 5μm.

It is not clear, which electrophysiologically identified afferent fibre type corresponds to what receptor structure. Since T1 and T2 afferents had higher thresholds than T3, T4 and M afferents and small afferent endings were found only in the most superficial layers of the urethral mucosa (91), it seems that the extreme sensitivity of the urethra to stimulation originates in small end-organs innervated by thin afferents. If the T1 afferents innervate Pacinian corpuscles, and this is most likely so, than the very high sensitive of the mucosa stems not from large Pacinian corpuscles. Still unclear is whether the M and S2 afferents (66) are different kinds of afferents or are only one kind of afferents which was stimulated by pulling the catheter (M) or by changing the flow of fluid during retrograde bladder filling (S2).

4.3. *Comparison of receptor properties of T4 afferents and of flow receptor afferents of urethra and trigonum vesicae*

It was shown (66) that there are flow receptors (same HT) in the urethra which responded to changes in the velocity of the flow of fluid. The interpretation for the adequate stimulus of the flow receptors was, that turbulences, occur-

ring with fluid flow changes, stimulated the receptors. These turbulences produced pressure changes and stimulated the flow receptors, which are mechanoreceptors (66, 91).

The mechanoreceptors of the T4 afferents, which are most sensitive to movement along the skin, seem to have a similar adequate stimulus than the flow receptors. This similarity may be important for a reconstruction of sensory function in the urethra, bladder and anal canal (see Clinical implications).

The movement along the skin with very light pressure ("streicheln") seems to be a certain quality of feeling. In the population response the T4 receptors probably contribute the most to that feeling. It is unlikely, that such feeling just arises from a processing in the CNS from the changing afferent input while moving a finger along the skin. A series of light touches along the skin gives rise to a different feeling, even if the touch points are set very close to mimic a "streicheln". Movement along a surface seems to be an important perception outside and inside the human body and is probably monitored at the skin, genitals, urethra and anal canal. In the walls of the intestine and the blood vessels such receptors could also be positioned.

4.4. *Innervation densities*

Johannson and Vallbo estimated innervation densities per cm^2 of 212 on the distal part of the fingers and 43 in the palm of the hand (32). Comparable innervation densities here are 4.5, 6 and 7.2 for the T9, S4 and coccygeal dermatomes respectively. These innervation densities are rather compatible if one takes the differences in the two point discrimination distances into account. It was calculated here that 7 to 8 touch point innervations were present between the two points of the two point discrimination. If on the palm of the hand the two point discrimination is 1 cm (72), then the innervation density would be $i = 7 \times 7 = 49$ touch innervation points/cm^2, which is about the value from above (43 innervations). For the distal parts of the fingers one probably has to take also training into account, which reduces the two point discrimination (72).

The high sensitivity of the mucosa of the urethra and anal canal could result from a high innervation density, rather uncovered receptors or a sensitization of the CNS. The lower limit of innervation densities of M afferents of the mucosa of the urethra and the anal canal is with 2 and 3 M/cm^2 in the range of the summed up innervation density N of the sacral and coccygeal skin (6, $7.2/cm^2$). Therefore may be the high sensitivity of the mucosa does not result from a high innervation density, but rather from less covered receptors.

Literature values of innervation densities of urethra and anal canal could not be found.

5. **Clinical implications**

5.1. *T1 afferents and the communication across the level of spinal cord lesion*

Restoration of motor functions in patients with complete transection of the thoracic spinal cord is possible in some cases by a training to activate paralysed muscles that are innervated by the distal segment of the spinal cord (53, 54). The spinal reflexes of the isolated spinal cord are activated by muscles of the shoulder girdle, which ordinarily do not participate in lifting the leg.

One hypothesis of the mechanism for the activation of the spinal reflexes is that the skin overlying the attachment area of the lower potions of the muscles becomes displaced by contraction of the upper portions of the long muscles of the trunk. This skin displacement then acts as a stimulus for the contraction of the lower portions of the muscles. As these lower portions of the long muscles of the trunk progressively regain their ability to contract, and with the aid of supplementary exercises, EMG activity begins to appear in the gluteus medius muscle and this muscle begins to contract (54).

It has been shown in this paper (Fig. 10A) that the T1 skin afferents, innervating probably

PC receptors, can be activated by skin traction over a distance of more than 10 cm. It seems therefore that information across the level of lesion is made possible by skin displacement, since T1 afferents can be activated from far away and there is a large overlap in the innervation of adjacent dermatomes. The loss of the skin afferent input of one or two dermatomes at the level of lesion, where the spinal cord is destroyed, may not stop the communication across the lesion area. With physiotherapy, not only spinal reflexes of the isolated spinal cord are trained, and how they are activated from the supralesional levels, but also, by plasticity, the cutaneous responses may be trained to become especially sensitive to activity changes in the T1 afferents. Lesion-induced reorganization of the central nervous system (CNS) following dorsal rhizotomies has been demonstrated (14, 34, 46, 80, 85). Other kinds of afferents will also contribute, but the major candidates for the information transport across the lesion are the T1 afferents.

5.2. *Sensory reinnervation of the urinary bladder and anal canal in spinal cord lesions*

It has been shown, the number of myelinated nerve fibres and the number motor fibres of one intercostal nerve, even following mismatch, are large enough for a reinnervation of the urinary bladder by a nerve anastomosis in spinal cord lesions (63, 67, 71). Also the number of fibres of the nerve branch to the musculus obliquus externus is sufficient for a reinnervation of the external bladder sphincter (70). The number of fibres in the branch to the rectus abdominis is also large enough for a reinnervation of the detrusor (70). The skin fibres of the ramus cutaneus lateralis are sufficient for a restoration of sensory functions (67).

5.2.1. Innervation densities

That there are enough skin fibres in the ramus cutaneus lateralis for a sensory reinnervation of sacral skin (for the feeling of sitting), bladder and anal canal is supported by the results of this paper, namely that the summed touch innervation density of the T9 dermatome ($N = 4.5$ touch innervations/cm^2) is roughly the same as those of the S4 dermatome (6 touch innervations/cm^2; (mean of i(electro; S4) and i(morph; S4)) and as the skin receptor innervation density of the anal canal (6.5 touch innervations/cm^2). The lower limits of innervation densities of mucosal mechanoreceptors of the anal canal (3 M/cm^2) and urethra and trigonum vesicae (2 M/cm^2) are also in a similar range. Since it was calculated that there are in the rather untrained situation 7 to 8 receptor innervations in between the 2 points of the two point discrimination only one fifth (20%) of the innervation density probably needs to be reconstructed ($7 \times 7 = 49$; $1/5 \times 49 \sim 10$; $\sqrt{10} \sim 3$ points). For the reconstruction of efferent pathways at least 50% of the motor fibres are needed (see first paper (70)). Therefore for the reconstruction of afferent pathways the fibre number is not as crucial, as it is for the efferent ones.

5.2.2. Urinary bladder afferent pathway reconstruction

A further problem is, to reinnervate bladder, anal canal and skin with the appropriate sensory fibre types. For the reinnervation of the sacral skin or the anal canal with skin fibres of thoracal dermatomes no problem arises. But how can the CNS get information about the bladder fullness following reinnervation of the bladder with skin afferents? As analysed in the discussion section T4 afferents seem to have similar properties as the flow receptors (S2).

Flow receptors monitor changes in the flow of fluid and pressure if the bladder filling is higher than 500 to 600 ml (66). Their reinnervation with T4 afferents could make it possible to reconstruct afferent pathways which monitor urine flow and high bladder filling stages. If the used T4 afferents are from the Head's zone of the bladder (ramus cutaneus anterior of the dermatomes T11 to S1), then may be bladder

afferent pathways are reconstructed to supraspinal micturition centres (61), since skin afferents of the Head's zone and the bladder converge onto same interneurons (15, 25, 52, 76).

The outcome of such afferent pathway reconstruction is difficult to predict, because there will be mismatch between all kinds of afferents. Specific skin afferent reinnervation (84) seems not to exist in rats (26, 27, 28, 92, 93), even though it was first thought so (5). In humans, specific afferent reinnervation probably also does not exist (13, 29), but it seems that at least a sufficient afferent pathway reconstruction for a micturition is possible.

5.3. *Cauda equina lesions to be operated by a nerve anastomosis*

Patients with a few years old cauda equina lesion at about L5 are probably first cases which could be operated. Such patients empty the bladder by catheterization. They can walk a bit, but there is too little feeling in the feet. Neurosurgeons refuse to operate since a motor reconstruction will be of no help, because the denervated muscles are already atrophied and a sensory reconstruction is of no help either, because sensory fibres cannot cross the PNS-CNS transition zone (58).

A reinnervation of the urinary bladder by using the T12 intercostals (and or disconnected lower sacral roots) as donor nerves on both sides is justified because the bladder does not atrophy because of the inner plexuses. To get more sensibility into the feet to improve walking the T10 intercostals could be used on both sides.

A first therapy trial should only be started in the form of a research project, where a clinical research worker should take care of the patients in addition to the clinical routine for 2 to 3 years. Changes in the function of the urinary bladder should be followed up by urodynamics. Until the first signs of reinnervation, the intraoperative diagnosis should be analysed. With that information one could think of an additional operation, if the first operation did not result in a sufficient reinnervation. It should be quantified as well as possible the number of fibres and the groups, which were reconnected and what the obtained functions are.

Prior to the human trial it has to be found out in an animal experiment (perhaps on a dog) what the best connection is between a peripheral nerve (nerve branch of the intercostal nerve) and a thin nerve root (lower sacral nerve root), which has no epineurium and nearly no perineurium.

In cauda equina lesions (16) not older than a week, nerve roots can be identified anatomically (7, 62), by electrical stimulation (24) and from thin roots by recording single unit potentials.

5.4. *Further research*

5.4.1. Urinary bladder innervation and reinnervation

If one wants to partially reinnervate the urinary bladder then one needs to know more about the innervation of the bladder with respect to function and nerve fibre group composition of the innervating nerves (11, 12, 19, 42, 45, 49, 55, 60, 61, 87).

According to most anatomy text books the external bladder sphincter is innervated by a nerve branch from the pudendal nerve or the nervus dorsalis penis. In 5 fresh male cadavers it was tried to find this branch in a few hours dissection each. No big branches could be found leading from the nervus pudendus or the nervus dorsalis penis in direction of the prostate gland, of which the external sphincter lies distally. The branches to the external anal sphincter were easily found. Existing small branches in the direction of the bladder sphincter were removed and analysed morphometrically. The thickest nerve fibres found in the cross-sections were in the diameter range of 3 to 4 μm. Therefore no α_2 and α_3-motoneurons were contained in those nerve branches because α_3-motoneurons have a peak group diameter of 8.3 μm and α_2-motoneurons of 10.1 μm (66, 71). The nerve fibres were most likely the preganglionic motoneurons of the

sympathetic or parasympathetic division. In the continuation of the dissections, the urethra was removed from the trigonum vesicae to the external sphincter and the nerve branches leading to the sphincters analysed under the dissecting microscope. Small nerves branched and fused. An obvious innervating nerve branch could not be found. Probably the innervating nerve branch to the external sphincter runs over the prostate gland. A further detailed analysis is necessary. It seems that the external bladder sphincter is not or not always innervated through the pudendal nerve (19, 45, 55). The innervation could come through a direct branch from the S3 and S4 roots (55) or via the pelvic nerves (19).

The function of the internal sphincter needs also to be better understood. The sympathetic fibres to the internal sphincter (motor) probably prevent reflux into the bladder during ejaculation. But why does seem to increase the outflow resistance in neurogenic bladders in paraplegia with reflex micturition (86)? Bors and Comarr argued(87) that the internal sphincter is functioning in connection with the detrusor. When the detrusor contructs, the internal sphincter opens.

It has been questioned about the sense of reinnervating the detrusor, innervated by parasympathetic fibres, by somatic fibres from the intercostal nerves. Firstly, somatic fibres can reinnervate the bladder in humans (7). Secondly, the detrusor is normally mainly innervated by the three devisions of vegetative nerve fibres, the parasympathicus and the sympathicus, which probably innervate the III. vegetative division in the muscular coat. In "Morbus Hirschsprung" of the colon the III. vegetative division does not exist. Parasympathetic and sympathetic fibres do in this case directly innervate the smooth muscle fibres. The resulting function of the colon is far from normal. But this disease shows that reinnervating an end organ with another devision of fibres does not mean, that sensible function cannot be achieved. There are many publications about the reinnervation of targets with different nerves including those from different divisions (1, 43, 44, 51, 78, 79, 82, 83).

It was argued that the external sphincter and the detrusor are represented in the same roots, namely S3 and S4. A reinnervation with two motoneuron pools will therefore still result in a simultaneous contruction of the detrusor and the sphincter externus. Firstly, it seems as if the detrusor is innervated more through S3 and the sphincter externus more through S4 and S5 roots. Secondly, if one reinnervates the detrusor through the S3 root and the external sphincter through S4 and S5 roots, there is a chance that the overlap in the representations (42) is only partly. With the training of filling and emptying the bladder under visible control maybe it can be learned to enhance the separation of functions of detrusor and sphincter by plasticity, so that dyssynergia is avoided.

A nerve anastomosis directly to bladder nerves is unfavourable, because of longer distances, which make interponats necessary, and an anatomically unsuitable operational field.

In comparison with formerly performed nerve anastomoses (7, 88, 89) the new knowledge probably justifies a new human trial.

5.4.2. Function of the nervus phrenicus in cervical lesions

If the nervus phrenicus is not stimulated with the physiological impulse pattern in cervical lesions, the diaphragm may stop contracting after a few years. The nervus phrenicus has to be analysed morphometrically and electrophysiologically with respect to the nerve fibre group composition and the impulse patterns. The obtained measurements should be compared with animal data (9).

5.4.3. Tract reconstruction in the peripheral nervous system

If it should be possible to get the therapy concept of nerve anastomoses successfully working, then there are at least limitations in the method with respect to the number of nerve

fibres and the number of functions of the motoneuron pools the donor nerve can give. To restore more functions, it has to be tried in future research to reinnervate the distal disconnected spinal cord. It seems unlikely that a regeneration in the CNS can be achieved in the next 50 years because of actrocytic scar formation, missing of leading structures for regeneration like endoneurial tubes as in the peripheral nervous system (PNS) and inappropiate synapse formation (2, 20, 58, 85). A substitution of embryonic nervous tissue seems unrealistic, since it is not possible to remove spinal cord parts. Firstly, only few spinal cord lesions are complete and secondly, the arterial longitudinal system, necessary for the blood supply of the spinal cord (69, 85), would be cut. It is probably difficult to make human embryonic nervous tissue available.

A possibility to reinnervate the isolated spinal cord is, to reconstruct tracts in the PNS, since nerve fibres regenerate there over long distances and form functional synapses. Motor fibres can regenerate across the PNS-CNS transition zone, the afferent fibres cannot (58). In recent research it has been shown that probably also afferent fibres can regenerate across the PNS-CNS transition zone (3, 8, 36, 77), if embryonic astrocytes are positioned at the PNS-CNS transition zone (39). It should be attempted to reinnervate the distal spinal cord through roots (see also section 5.5) with nerve branches of intercostal nerves from rostral to the lesion.

5.4.4. Regeneration trial for C5 lesions

Even though a regeneration over long distances in the CNS can probably not be achieved in the next 50 years, it should be tried to enhance the small regenerative capacity of the human spinal cord. There is one report in the literature, where there may have been a transient regeneration in the CNS following spinal cord lesion. This regeneration took place, while there was an infection in the spinal cord with bacteria Pseudomonas. The bacterial pyrogens Piromen and Pyrogenal, derived from a Pseudomonas species, were later used in regeneration experiments for an enhancement of central regeneration may be by dissolving scar tissue. Early experiments showed an improvement in regeneration, later ones not (22, 50, 56, 57).

The effect of Piromen to enhance regeneration by dissolving scar tissue should be reevaluated in a potent regeneration model by using not so much purified batches of Pseudomonas bacteria, killed by heating, digested with trypsin and dialyzed (56). The animal regeneration experiment of the CNS probably has to be designed in a way, that one can measure the grade of regeneration in the PNS, where the quantitative research tools of morphometry and single fibre action potential recording can be used (see also paragraph 5.5).

If it can be shown, that Piromen does have an effect in enhancing regeneration in animals, then one should think of using it for C5 lesions in combination with the training of certain muscles. Especially one should concentrate on those muscles, which could start to function again if the level of lesion would be lowered by a few millimeters. To achieve the optimal muscle training of muscles with very little remained innervation, the volitional muscle activity should be picked up by electronical equipment and made visible to the patient ("bio feedback"), so that the patient can see if enhancement of regeneration is in progress. With such treatment, which relies on the plasticity of the human nervous system (10, 21, 35, 48, 94), in combination with tendon transposition by plastic surgery, may be the "grip-function" of the hand can be reconstructed.

5.5 *No hope and false hope in paraplegia*

As suggested above, it seems that progress of biological treatment in spinal cord lesions are possible if research is performed with powerful quantitative tools on the long term with the goal in mind to improve functions in the patients.

The power of regeneration is much higher in animals than in human (18 (page 242), 37, 38)

and distances are much smaller. In human the power of regeneration is very small in the CNS and in the PNS it is different in different body parts. Well known for the dentists is, that the nervus alveolaris always regenerates if the nerve is damaged with an injection needle. This author experienced himself that in the head a few touch afferents were able to cross a gap of a few millimeters. Pain afferents seem to be more powerful in regeneration than touch afferents. From nerve sutures of arm and leg it is known, that the nerves have to be adapted for regeneration. For the arm it is known that the nervus radialis, the nervus medianus and the nervus ulnaris have a different capacity for regeneration (17, 18, 30, 37, 38, 59, 74, 75). To draw conclusions from the regeneration capacity of the rat brain or tissue culture (6, 34, 73) to the human PNS or CNS is therefore only justified, if differences in the regeneration capacity are taken into consideration.

For progress in spinal cord lesions on the long term it is important to understand the mechanism of regeneration and how to enhance the regeneration, since only deep knowledge gives progress, and measurements are best performed on animals, where one has all possibilities for research. However, comparable studies are necessary to know to what extent animal data can be used in human cases. In addition, humans are highest on the phylogenetic scale, and not all human functions, for example those of the nervous system, can be mimiced by an animal model. In such cases, only human measurements can bring progress, as certainly the human anatomy and microanatomy are different than those of animals. In basic clinical research one also has to concentrate on treatments, which have a chance to succeed within the next 10 to 20 years. Even though treatments are often not very elegant and ideal, every patient has a right for hope, that means every patient has a right for qualified research if there is no treatment available.

If really a substantial regeneration of the human CNS could be achieved within the next 50 years, then the regeneration would most likely be only a partial one. Unbalanced circuitry probably would also occur. It means disregarding the complexity of the different functions in the human CNS to believe that all problems are solved if there would be regeneration. The regeneration of the spinal cord in goldfish following a lesion is only a partial one (2) and the swimming function is comparably simple in comparison with the functions of the arms, hands and legs.

It is probably better to start with small treatment steps which will need already much basic clinical research, instead of wanting all and getting nothing in the end for the patient. However, when patients with lower cervical lesions (47) don't want to get the "grip-function" of the hand reconstructed (no destructive operation with respect to CNS and PNS), which is important for eating and everyday functions, because they are waiting of basic animal research results of the regeneration of the spinal cord, then basic animal research creates "false hope in paraplegia".

An important first step in the regeneration of the CNS is probably to control the astrocytes at the CNS-PNS transition zone (3, 8, 36, 37). The spinal roots seem to be the best entrance for a regeneration of the isolated distal spinal cord, because there is no damage at the roots, therefore no scar, and regenerating fibres need not to cover long distances to reach important motoneuron pools or reflex centres in the CNS if appropiate roots are selected. Short regeneration distances are important since there are no leading structures in the CNS as in the PNS. The oligodendrocytes do not guide in the same way as Schwann cells and endoneurial tubes. For the regeneration of the spinal cord through the roots the powerful research tool of morphometry and electrophysiology exists (64, 65, 66, 67, 68). Diameter of nerve fibres, numbers of fibres, conduction velocities of afferent and efferent groups, impulse patterns of afferents and efferents, recruitment, delays and reflexes, they all can be measured. One does not need to rely on staining of nerve fibres, where one is never sure, how many of them functioned, and in what way. Compound action potentials and evoked potentials give only little information about single nerve fibres.

Following of World War II, Guttmann (23) succeeded in keeping paraplegics alive. The next step is to give them a better quality of life. The argument that nothing can be done in spinal cord lesions is an excuse to avoid responsibility to organize the necessary research (see also Acknowledgement).

Acknowledgement

This research (including Refs. 63 to 71) has been primarily done on money saved personally, including the equipment (300 000 DM during 6 years), since it was not possible, to get support.

In Germany every second day a paraplegic dies, because of bladder and kidney infections or by suicide.

Reviewers argued at the beginning: The author should use computer assistance or should average single fibre action potentials or skin afferents are of no interest any more. One reviewer did not like the measurements on humans, could not see the clinical implications, and asked whether such research is ethically justified (without giving a general definition of ethics (Kant) or giving reasons for his own ethic). Constructive criticism was the exception.

Initially the Deutsche Forschungsgemeinschaft (DFG) supported this research. Then the DFG refused to accept the application for further funding because of organisational reasons. After an intervention by R.v. Weizsäcker the DFG accepted the application but refused to allocate funds because this research had been judged as unqualified and ethically unjustified (for ethics see Ref. 66). The DFG did not want to give further reasons for its decision and did not want to change its decision even when 11 publications had been printed in different journals. It was not possible to clarify the ethics with the German Neurosurgical Society, because the institution did not respond to an inquiry. The Minister for Research and Technology refused money, because of the reunification of the FRG and the GDR, even though the author had applied for support 2 years previously. The foundation Volkswagen refused money with the argument, that the author should first organize the clinical research, then he can apply for money. Many other institutions refused money or help to develop treatment in paraplegia mainly with the organisational argument or by referring to the DFG. An institution from Switzerland and one from USA refused support with the argument, that it is better to keep the money in their own countries. At the conference IRMA Madrid '90 it was reported that rehabilitation is a part of the new University Hospital of Amsterdam, but the rehabilitation physicians cannot apply for research grants, because they don't have the funds and equipment to do the preliminary research needed for the application for money.

Even though this author did 8 years research in spinal cord lesions and presented papers at international conferences of Neurology, Neurosurgery and Rehabilitation, he was never invited by a German rehabilitation centre.

The neurosurgent L.W. Freeman (USA) stated in the 1960's after performing very many spinal cord injury experiments on dogs, "it is difficult to find persons who do research in paraplegia and to get money for such research, probably World War II is already too far away".

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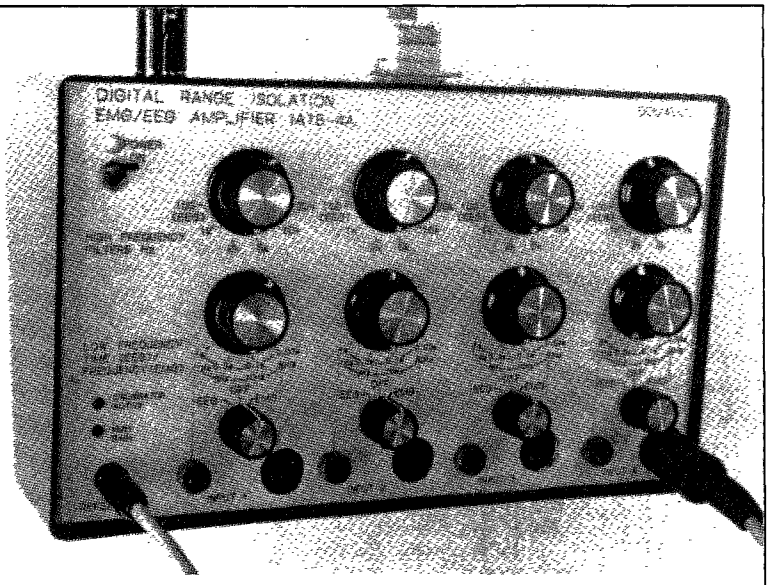

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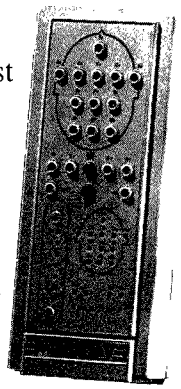

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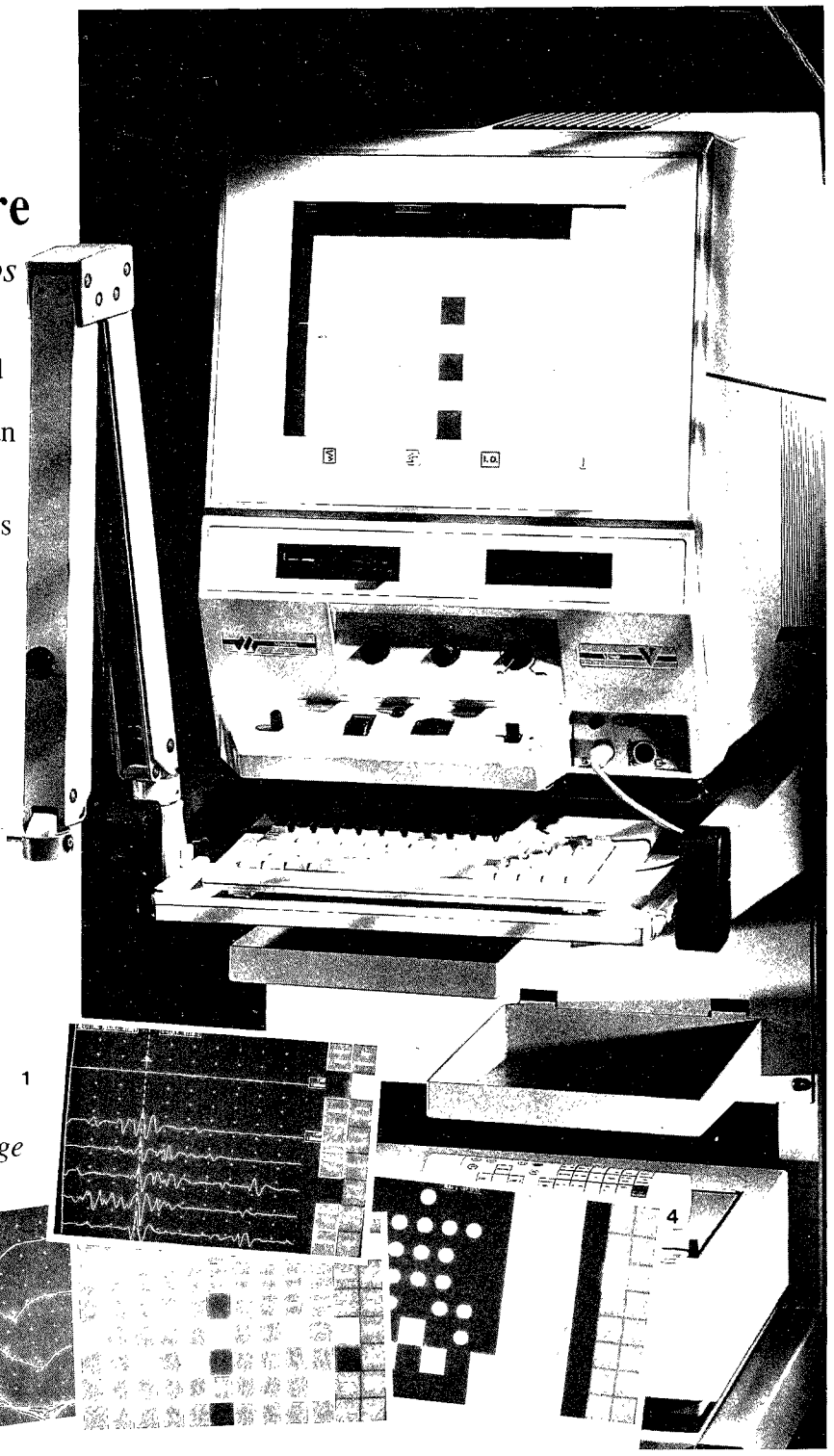

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