THE EXCITATION OF MUSCLE STRETCH RECEPTORS

BY SUXAMETHONIUM

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by

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SUMMARY

1. Changes in the response of cat soleus muscle spindle primary, secondary and "intermediate" sensory endings to ramp stretching during intravenous and intra-arterial infusions of suxamethonium (SCh) in the intact anaesthetised animal have been studied. The effects of SCh on the spindle sensory endings have been related to the known action of SCh and ACh on the two nuclear bag intrafusal muscle fibres of isolated cat muscle spindles in vitro (Gladden 1976).

2. The application of repetitive short-duration ramp-and-hold test stretches to the soleus muscle during continuous slow infusion of SCh enabled the gradual activation of the spindle sensory endings to be studied in detail. Typical muscle spindle primary sensory endings were activated in three consecutive stages during infusion of SCh, which will be termed Phases I, II and III of excitation. In Phase I of excitation, a gradual facilitatory effect of SCh on the discharge of the Ia sensory endings accompanied by a progressive reduction in the sensitivity of the endings to muscle shortening was observed. This occurred without a potentiation of, and usually a decrease in, the dynamic and position sensitivities of the Ia endings to muscle stretch. The Phase I facilitatory effects of SCh on Ia endings appear not to be caused by the contraction of intrafusal muscle fibres, and are probably the result of a direct or indirect depolarising action of SCh on the sensory nerve terminals of the Ia afferent axon. In Phase II of excitation, the sensitivity of the Ia endings to the dynamic phase of the ramp stretch increased dramatically, and the response of the endings to stretch was very similar to that of Ia endings during strong dynamic fusimotor activation. This increase in the dynamic sensitivity is very

likely the result of the recruitment of the dynamic nuclear bag (DNB) fibre, which has the lower threshold of SCh of the two nuclear bag fibres (Gladden 1976), and which is made to contract by dynamic fusimotor axons (Boyd, Gladden, McWilliam & Ward 1977). In Phase III of excitation, a marked increase in the position sensitivity of the Ia endings was superimposed on the already enhanced dynamic sensitivity, and the response of the Ia endings to stretch became very similar to that during combined stimulation of powerful dynamic and static fusimotor axons. The increase in the position sensitivity of the Ia endings in Phase III of activation no doubt reflects the contraction of the static nuclear bag (SNB) fibre, which has the higher threshold to SCh of the two nuclear bag fibres (Gladden 1976). The characteristic response to stretch of Ia endings in Phase III of excitation is thus the result of the combined activation of the dynamic and static nuclear bag fibres by SCh.

3. Unlike soleus muscle spindle primary sensory endings, secondary endings showed only a gradual facilitation of their discharge during infusion of SCh, and behaved in a similar way to Ia endings in Phase I of excitation. While Ia endings subsequently experienced large increases in their dynamic and position sensitivities following the recruitment of the two nuclear bag fibres, secondary sensory endings did not show similar effects. The activation of typical secondary sensory endings by SCh therefore appears to be entirely the result of a direct or indirect depolarising action of SCh on the afferent nerve terminals, without any apparent contribution from the contraction of the two nuclear bag fibres.

4. The majority of muscle spindle sensory endings with afferent axon conduction velocities between 60 and 80 m/sec ("intermediate"

conduction velocity afferents) behaved either like primary endings or like secondary endings when activated by SCh (cf. Rack & Westbury 1966). However, a significant minority of "intermediate" sensory endings were found in these experiments to behave neither like primary nor like secondary sensory endings in the presence of SCh, and thus appeared to be a "truly intermediate" form of spindle sensory ending. These "truly intermediate" sensory endings initially showed a gradual facilitation of their discharge in a very similar way to typical secondary endings during SCh infusion, but then experienced a significant increase in either their dynamic sensitivity or their position sensitivity to stretch. This behaviour indicates that the "truly intermediate" sensory endings lie mainly on the nuclear chain fibres of the muscle spindle like secondary sensory endings, but also receive a collateral input from one but not both of the nuclear bag fibres. Of five "truly intermediate" sensory endings encountered in these experiments, four appeared to receive an input from the SNB fibre, and one from the DNB fibre.

5. Infusion of SCh was also found to produce a gradual facilitation of the discharge of Golgi tendon organs in the soleus muscle (cf. Granit et al 1953), similar in form to the Phase I effects of SCh on the Ia endings and the effects of SCh on secondary endings. The extent of the facilitation of the discharge of tendon organs by SCh was however much smaller than the effects of SCh on the muscle spindle sensory endings, and appeared to depend on the thresholds of the tendon organs to passive muscle stretch (Stuart et al 1970), so that tendon organs with lower thresholds to passive stretch were most affected by SCh and those with higher thresholds less so, some apparently not being affected

at all. Nevertheless, the finding that the discharge of tendon organs may be facilitated by SCh adds weight to the proposal that SCh, directly or indirectly, can have a depolarising action on the sensory nerve terminals of mammalian afferent axons.

6. The contraction first of the DNB fibre and then of the SNB fibre in soleus muscle spindles during SCh infusion, provides an important new experimental means of investigating the role of the individual sensory terminals of the Ia afferent axon on the two bag fibres in the generation of the Ia afferent discharge. The changes in the response to stretch of Ia endings when the SNB fibre is made to contract by SCh in the presence of DNB contraction, indicate that the Ia sensory spirals on the two nuclear bag fibres interact competitively with one another to determine the discharge of the Ia afferent axon, so that the sensory terminal with the greater output at a given time dominates the Ia afferent discharge ("pacemaker switching", Matthews 1972 Ch. 6).

ADDITIONAL PAPERS

Dutia, M.B. (1977a). The response of cat muscle spindle primary sensory endings to stretch during infusion of suxamethonium. J. Physiol. 268, 24-25P.

Dutia, M.B. (1977b). Activation of cat spindle secondary sensory endings by intravenous infusion of suxamethonium. J. Physiol. 273, 89-90P.

INTRODUCTION

The intensive investigation of the structure and function of mammalian muscle spindles in recent years has emphasised their complexity as sense organs. Muscle spindles, known to histologists and physiologists for over 100 years, are muscle stretch receptors which are intimately involved in the maintenance of normal muscle tone. An important aspect of their function is that their sensitivity to muscle stretching is variable, under the control of the central nervous system.

The internal working of the cat muscle spindle, and the pattern of innervation of its intrafusal muscle fibres by gamma motor axons from the spinal cord, have been the subject of much research in the last 15 years. The great majority of these experiments have involved the stimulation of gamma fusimotor axons, to produce contraction of the intrafusal muscle fibres on which the spindle sensory endings lie. Recently, however, Gladden (1976) showed that the two nuclear bag intrafusal fibres of a typical spindle are made to contract in the presence of acetylcholine, while the remaining nuclear chain intrafusal fibres appeared to be paralysed by acetylcholine and did not contract. Suxamethonium, like acetylcholine, also has a similar action on the intrafusal muscle fibres. This finding presents a potential alternative "chemical" means of activating the nuclear bag fibres of the spindle, independently of the nuclear chain fibres, in a selective manner that the conventional experimental approach does not provide.

The initial aim of the present work was to reach a suitable set of circumstances in the intact animal in which the nuclear bag fibres of soleus muscle spindles could be regularly recruited by continuous slow infusion of suxamethonium. Once this was achieved, using infusions of suxamethonium into the aortic bifurcation, it was possible to examine in detail the contribution of the activated nuclear bag fibres to the afferent discharge of the spindle primary and secondary sensory endings. This

revealed a significant amount of new information about the internal working of the mammalian spindle, which could not be readily obtained using the conventional experimental approach (see Discussion).

Towards the end of this study, a short series of experiments were done in collaboration with Dr. W.R. Ferrell, in which the effects of intra-arterial infusion of suxamethonium on the discharge of Golgi tendon organs in the soleus muscle were also examined. With this exception, the work described in this thesis was carried out by myself, under the supervision of Professor I.A. Boyd in the Institute of Physiology, University of Glasgow. Preliminary results of the muscle spindle work were presented to the Physiological Society in February, 1977 (Dutia 1977a) and in September, 1977 (Dutia 1977b).

LITERATURE REVIEW: PART 1

The Structure and Function of Muscle Spindles.

Matthews (1964, 1972) has referred to the "classical picture" of muscle spindle structure, as opposed to the still-evolving "present picture". The "classical picture" became established following the morphological and histological studies of Sherrington (1894) and Ruffini (1898), and remained prevalent until the late 1950's. The historical derivation of the "classical picture" of the structure of muscle spindles from the time of their discovery by Kolliker in 1862 has been reviewed in detail by Matthews (1972, Ch.1) and will not be dwelt on here.

Ruffini (1898) studied the microscopial structure of the nerve endings in cat muscle spindles stained with gold chloride. He was able to distinguish three types of nerve endings lying on the intrafusal muscle fibres, and named them the primary (annulospiral) ending, the secondary (flower-spray) ending, and the plate ending. The primary ending lay in the centre of the spindle, supplied by a large diameter nerve fibre which branched several times to form spirals or rings around each of the intrafusal muscle fibres. The secondary ending was supplied by a smaller diameter axon, which formed filaments which ran irregularily along the intrafusal fibres. The secondary ending always lay to one side of the centre of the spindle. The plate endings were usually found on the outer regions of the intrafusal muscle fibres, supplied by nerves of even smaller diameter.

On morphological grounds, Ruffini proposed that each of the three types of nerve ending in the muscle spindle was sensory in nature. Earlier, Sherrington (1894) had proved that the muscle spindle was indeed a sense organ, by showing that after the severing of the spinal nerve roots from the cord proximal to the sensory ganglion, the larger of the afferent nerve axons which remain in the muscle nerve do in fact innervate muscle spindles. The central primary ending which was supplied by a large diameter axon as described by Ruffini was therefore probably an afferent nerve ending. Onanoff

in 1890 had done a similar experiment in the dog; he had shown not only that destruction of the dorsal root ganglion causes the greater part of the nerves in the muscle spindles to degenerate, but also that cutting the ventral spinal roots alone causes some of the nerve fibres in the spindle to atrophy. Clearly, the muscle spindle was a sense organ, and the observations of Onanoff suggested that it was also supplied by motor nerves from the spinal cord.

Sherrington (1894) though at the time unaware of the work of Onanoff (1890), stained muscle spindles of the cat and monkey with gold salts and looked for motor nerve endings on the intrafusal muscle fibres. Though he did not find any, he went further and carried out a degeneration experiment, in which the sciatic nerve of a cat was sectioned and the skeletal muscle of the hindlimb were allowed to degenerate for 150 days. The intrafusal muscle fibres of the spindles in these muscles however did not degenerate, indicating an absence of a motor nerve supply. However, Sherrington remained cautious and did not conclude one way or the other on the question of a motor nerve supply to the muscle spindle.

Evidence for a motor innervation of the intrafusal muscle fibres was provided by Cippolone (1898), who followed the course of motor nerves in muscles of the lizard and showed that some of the motor axons had motor end-plates on both extrafusal and intrafusal muscle fibres. Cippolone also showed that transient compression of the aorta in the rabbit caused the smaller nerves in the muscle spindles to atrophy while the large afferent endings remained intact, and on this basis suggested that the small nerves were motor.

It was in 1927 that Boeke showed that the plate endings on the intrafusal muscle fibres degenerated after the spinal nerve roots had been cut proximally to the dorsal root ganglion. Hinsey also in 1927, and Hines &

Tower in 1928 proved that the plate endings were definitely motor: they persisted after removal of the sympathetic ganglia, and the removal of the dorsal root ganglia which caused the central sensory endings to atrophy; the plate endings only degenerated when the ventral spinal roots were cut. These experiments and the subsequent confirmatory work of Cuajunco (1932) clearly established the motor nature of the plate endings at the poles of the intrafusal muscle fibres, and the sensory nature of the primary ending at the centre. The secondary ending was also very probably sensory, as Hinsey (1927) stated that it persisted after ventral root section and atrophied after dorsal root section.

In 1948, Barker published a detailed account of the structure of the muscle spindles of the rabbit, which added a new feature to the "classical picture" of spindle structure. He found that the central region of the rabbit intrafusal muscle fibres always contained a large number of nuclei, and a correspondingly small amount of contractile material. The concentration of nuclei was greatest in the equatorial region, and diminished towards the poles. Barker named the central region the "nuclear bag" region of the intrafusal fibre, and the adjoining regions the "myotube" regions.

B.H.C. Matthews in 1933 modified and extended the original technique of Adrian & Zotterman (1926) for recording the electrical activity of nerves, and was able to record the afferent discharge of single stretch receptors in various muscles of the cat. Earlier, Fulton & Pi-Suner (1928) had deduced that muscle spindles, which lie in parallel with the extrafusal muscle fibres would be silenced by the contraction of the muscle, and that tendon organs, which lie in series with the extrafusal fibres would be excited during muscle contraction. The differences in the behaviour of the A and B type endings of Matthews (1933) gave experimental support to this view.

Matthews was also first to demonstrate experimentally the excitation of muscle spindles by the activation of motor nerve fibres. He found that the afferent discharge of some of his A type endings was elevated when a repetitive stimulus was applied to the muscle nerve at a slightly higher strength than that required to produce a maximal contraction of the muscle. Matthews suggested that this excitation of the A type endings was caused by the recruitment of the small higher-threshold motor nerve fibres to the intrafusal muscles, which Ruffini had first described and which subsequently had been proved to be motor nerves (Hinsey 1927; Hines & Tower 1928).

In 1945, Leksell located a small wave in the compound action potential of the L7 ventral root evoked by the stimulation of the gastrocnemius muscle nerve. He proved that this wave was caused by a group of motor nerves which had a higher electrical threshold than the main group of motor fibres, and which conducted at a slower rate than the main motor nerves. Earlier, Langley (1922) and Eccles & Sherrington (1930) had demonstrated a bimodal distribution of the diameters of the myelinated motor axons in the ventral roots, and Langley (1922) had proposed that the smaller motor nerves supplied the muscle spindle intrafusal muscle fibres. Leksell (1945) was able to block selectively the conduction of action potentials in the large motor nerves by applying pressure to the sciatic nerve, and showed that the activation of the remaining small motor axons did excite muscle spindle sensory endings. Erlanger & Gasser (1937) had termed the large motor axons in the ventral roots the "alpha" motor nerves, and Leksell named the smaller motor nerves the "gamma" motor axons.

Leksell (1945) was however unable to determine conclusively whether the gamma motor axons also innervated the extrafusal muscle fibres.

In 1951, Kuffler, Hunt & Quilliam introduced the now common technique for the preparation of "single-unit" filaments of the dorsal and ventral spinal nerve roots, and showed that simultaneous stimulation of six gamma motor fibres produced no detectable increase in the isometric tension of the whole muscle, proving that the gamma fibres did not innervate the extrafusal muscle fibres. They also confirmed and extended the findings of Leksell (1945) and showed that stimulation of single gamma axons in the ventral roots increased the rate of discharge of single muscle spindle afferent axons in the dorsal roots. Later, Hunt & Kuffler (1951a; Kuffler & Hunt 1952) demonstrated that all muscle spindle afferents could be excited by at least one gamma motor axon, some by as many as five, and that conversely a single gamma motor fibre might excite several muscle spindle afferent axons. Clearly, the muscle spindle had been shown to be a sense organ under efferent control from the spinal cord.

The "present picture" of muscle spindle structure began to emerge in the late 1950's and early 1960's, when detailed histological examination of human muscle spindles by Cooper & Daniel and of cat muscle spindles by Boyd, led to the realisation that the intrafusal muscle fibres were probably of two types, which differed on several counts (Cooper & Daniel 1963; Boyd 1958a, 1960, 1962). Boyd named the smaller and shorter type of intrafusal muscle fibre the "nuclear chain" fibre, which differed from the larger "nuclear bag" fibre (Barker 1948) in that the nuclei in the equatorial region were fewer and arranged in a single file. Boyd also described further differences between the microscopical structure of the nuclear bag and the nuclear chain fibres of the cat spindle, which included differences in their diameter and innervation (Boyd 1962). The central primary sensory ending had its afferent nerve terminals on all of the intrafusal muscle fibres, while the secondary sensory ending lay mainly on the nuclear chain fibres with

occasional collateral terminals on the nuclear bag fibres. Boyd (1958a, 1960, 1962) also observed that while the motor innervation of the nuclear bag fibres consisted of plate endings like the ones originally described by Ruffini (1898), the motor endings on the nuclear chain fibres appeared to consist of a diffuse "network" of nerve terminals. These diffuse endings were definitely motor, since they persisted after removal of the dorsal root ganglia. Boyd (1962) proposed that the two different forms of motor nerve ending were supplied by different populations of gamma motor fibres, one (γ_1) supplying the plate endings on the nuclear bag fibres and another (γ_2) supplying the diffuse motor endings on the nuclear chain fibres. Boyd also noticed that the γ_1 motor axons had a larger diameter than the γ_2 axons close to the spindle, and suggested that the two kinds of gamma axons were derived from two types of stem fibres in the muscle nerve.

In 1962, Boyd & Davey presented evidence at the Hong Kong Symposium on muscle receptors which showed that in some de-afferentated muscle nerves, the small gamma motor axons could be divided into two groups on the basis of their myelin thickness. They proposed tentatively that the thickly and thinly myelinated gamma axons in the muscle nerve were the stem fibres of the γ_1 and γ_2 axons, which innervated the nuclear bag and the nuclear chain fibres respectively. However, Boyd's view of the independent motor innervation of the nuclear bag and nuclear chain fibres was strongly disputed by Barker (1962), who felt that the nuclear chain fibres could also be innervated by γ_1 axons and the nuclear bag fibres by γ_2 axons. The ensuing debate between Barker and Boyd at the Hong Kong Symposium was the start of a controversy that has yet to be completely resolved.

Adal & Barker (1965) undermined the relationship suggested to exist by Boyd & Davey (1962) between the thickly and thinly myelinated small axons in the muscle nerve and the γ_1 and γ_2 motor axons, when they followed

the small diameter axons for long distances in teased muscle preparations and found no consistent correlation between the diameter of an axon in the muscle nerve and its diameter close to a muscle spindle. However, this did nothing to refute Boyd's picture of the mutually independent motor innervation of the nuclear bag and nuclear chain fibres, which was again the subject of debate at the Stockholm Symposium in 1965. Barker & Ip (1965) did not find a true "network" of motor nerve terminals on the nuclear chain fibres as described by Boyd (1962), and at the Stockholm Symposium it was decided to modify the terminology from "γ_1 and γ_2 motor ending" (Boyd 1962) to "γ-plate" and "γ-trail" endings, thus referring more to the form of the motor endings on the intrafusal muscle fibres.

Jansen & Matthews (1961, 1962) meanwhile had recorded the response to stretch of single muscle spindle afferent endings in the decerebrate cat with the ventral roots intact, and for comparison the response of the endings to stretch after the ventral roots were cut. They found that with the ventral roots intact, the response of some primary endings to the dynamic phase of a ramp stretch was much enhanced compared to the response after de-efferentation, while other primary endings appeared to be much less dynamically sensitive than when subsequently de-efferentated. The normally small dynamic responses of secondary endings were even less with the ventral roots intact than after de-efferentation. Jansen & Matthews suggested that the nuclear bag fibres were responsible for the greater dynamic responsiveness of the primary ending, while the nuclear chain fibres upon which the secondary ending predominantly lies (Boyd 1962) increased the static sensitivity of the primary ending. Matthews (1962) went on to study the effects of functionally single efferent fusimotor axons on single primary and secondary sensory endings, and found that the gamma fusimotor axons could be divided into two functional classes on the basis of their action on the primary

endings. Stimulation of some fusimotor axons increased the dynamic responsiveness of the primary endings, while other fusimotor axons decreased the dynamic sensitivity and increased the static sensitivity. Matthews named these two groups the "dynamic" and "static" gamma axons, according to which component of the response to stretch of the primary ending was enhanced the most.

Crowe & Matthews (1964a, b) further studied the "dynamic" and "static" classification of gamma fusimotor axons in the soleus muscle. They introduced the term "dynamic index", to quantify the measurement of the dynamic responsiveness of the primary ending, and defined it as the decrease in the discharge rate of the ending which occurs over 0.5 sec immediately after the end of the dynamic phase of stretch, while the muscle is held extended. Fusimotor axons which when activated increased the dynamic index were classified as "dynamic", while others which decreased the dynamic index were classified as "static". Significantly, the action of a given fusimotor axon was found to be either static or dynamic on each of the primary endings that it influenced, indicating that this was indeed the property of the motor axon rather than due to differences between individual spindle sensory endings (Crowe & Matthews 1964b).

Brown, Crowe & Matthews (1965) extended the functional classification of gamma fibres to muscle spindles in the tibialis posterior muscle, and restated Matthews (1962) suggestion that the dynamic and static gamma axons corresponded to the γ_1 and γ_2 axons of Boyd (1962), innervating the nuclear bag and nuclear chain fibres respectively. They also established that the conduction velocities of the dynamic and static fusimotor axons overlapped considerably, though the slower gamma axons with conduction velocities below 25 m/sec tended to be static in their action. The "static" and "dynamic" functional subdivision thus appeared not to correspond to the

subdivision of gamma axons on the basis of their diameters and degree of myelination (Boyd & Davey 1962) and on the basis of their conduction velocities (Boyd & Eccles 1963).

Appelberg, Bessou & Laporte (1966) studied the simultaneous action of single dynamic and static fusimotor axons on primary and secondary sensory endings which were sensitive to small surface deformations of the same area of the tenuissimus muscle, and which were therefore probably located in the same muscle spindle. They found that dynamic axons did not excite the secondary sensory endings, while static axons regularly excited both primary and secondary sensory endings. These findings fortified the suggestion of Matthews (1962) and Brown, Crowe & Matthews (1965) that the dynamic fusimotor axons innervate the nuclear bag fibres and the static axons the nuclear chain fibres, and fitted in well with Boyd's (1962) picture of the selective independent innervation of the nuclear bag and nuclear chain fibres.

Direct observation of the isolated cat and rat muscle spindle (Boyd 1958a, 1966; Smith 1966) showed that the nuclear bag fibres contracted more slowly than the nuclear chain fibres, as had been suggested on indirect evidence by Crowe & Matthews (1964b). Bessou, Laporte & Pages (1968a) developed a method of averaging the response of a sensory ending to fusimotor stimulation, which consisted of superimposing many successive sweeps of a display of the instantaneous frequency of discharge of the ending on a storage oscilloscope, while keeping the stimulus synchronised with the sweep. They named the composite picture which resulted from upto 30 superimpositions the "frequencygram". Modulations in the frequencygrams of primary endings during static fusimotor stimulation suggested that the static gamma axons produced fast twitch contractions of the intrafusal muscle fibres, while dynamic gamma axons appeared to produce slower contractions which "fused" at low frequencies of stimulation. However,

because of the variability in the frequencygrams elicited by static gamma stimulation (Bessou et al 1968b), the authors preferred not to propose that the fast nuclear chain fibres were responsible for the static fusimotor action and the slower nuclear bag fibres for the dynamic fusimotor action.

Meanwhile, Barker and his colleagues continued to challenge the prevailing "simple" picture of the independent motor innervation of the nuclear bag and the nuclear chain fibres (Boyd 1962). Barker & Ip (1965) and Barker, Stacey & Adal (1970) found histologically that individual gamma axons often innervated both nuclear bag and nuclear chain fibres. Barker et al (1970) described in detail the form of the plate and trail endings of the fusimotor axons as revealed by light and electron microscopy, and subdivided the plate endings into p_1 and p_2 types on the basis of differences in their microscopical structure. The p_2 and trail endings on the intrafusal muscle fibres are thought to be derived from gamma motor fibres, but the p_1 endings probably are terminations of beta motor axons, which innervate extrafusal and intrafusal muscle fibres (Adal & Barker 1965; Bessou, Emonet-Denand & Laporte 1965).

An elegant series of experiments performed by Barker, Emonet-Denand, Laporte, Proske & Stacey (1971, 1973) left no doubt that non-selective innervation of the nuclear bag and nuclear chain fibres by individual gamma axons can occur. In these experiments, a single gamma axon to the tenuissimus muscle of the cat was located in an intact ventral root filament, and the remaining filaments of the ventral roots were cut. Then, after 7-12 days to allow for the degeneration of the cut motor axons, the remaining gamma axon was classified as static or dynamic in its action by observing its effect on the integrated electroneurogram of the tenuissimus muscle during simusoidal stretching. The muscle was then histologically prepared

to allow the remaining single gamma axon to be traced, and the nature of its terminations as well as the intrafusal muscle fibres it innervated were established. Only static gamma axons were encountered in this series of experiments, and they were all found to terminate in trail endings. However, poles of the muscle spindles in which the nuclear chain fibres or the nuclear bag fibres were selectively innervated by the static gamma axons were only half as common as those where the innervation was shared non-selectively.

These experiments disagreed to a large extent with the observations of Boyd (1971) and Boyd & Ward (1975) on isolated muscle spindles, where the large majority of fusimotor axons recruited in the muscle nerve by increasing stimulus stength were found to be selective in their intrafusal distribution, and produced contractions either in the nuclear bag or the nuclear chain fibres only. 86% of the fusimotor axons were selective in their action, while only 11% produced contraction of both the nuclear bag and the nuclear chain fibres.

Brown & Butler (1973, 1975) determined the nature of the intrafusal muscle fibres in tenuissimus muscle spindles whose glycogen content appeared to be diminished or eliminated by repetitive stimulation of single static or dynamic fusimotor axons over a period of 3 hours, with the blood supply to the muscle occluded for some of this time. Their results (1973) showed that stimulation of dynamic fusimotor axons always depleted the glycogen levels of the nuclear bag fibres and that static gamma stimulation always depleted the glycogen levels of the nuclear chain fibres, but also that the static gamma axons frequently produced glycogen depletion in the nuclear bag fibres. Later, Brown & Butler (1975) in a series of experiments on the peroneus longus muscle confirmed that static gamma axons always depleted the glycogen levels of the nuclear chain fibres but that 50-75% of

the time, one of the two nuclear bag fibres of the spindle was also affected. This bag fibre was found to be always the larger of the two bag fibres in the spindle.

In 1975, Bessou & Pages published a detailed account of the nature of the intrafusal muscle fibre contractions produced in tenuissimus spindles by stimulation of dynamic and static fusimotor axons. The spindles were isolated from the muscle for observation, but their afferent and efferent connections remained intact, and their blood supply was maintained adequately. They found that of the eleven dynamic fusimotor axons studied in their experiments, all produced a localised contraction in the nuclear bag fibres, and in this they agreed with a preliminary report by Boyd, Gladden, McWilliam & Ward (1973). The nuclear bag fibres activated by dynamic fusimotor axons never received any static gamma innervation. Of a total of 38 static fusimotor axons, however, one-third produced contraction of the nuclear chain fibres only, and three static axons selectively produced contractions of the bag fibres. Twelve further static axons also produced contractions of the nuclear bag fibres, but a possible collateral innervation of the nuclear chain fibres in these cases was not investigated. The remaining eleven static axons innervated both the nuclear bag and the nuclear chain fibres. The contraction of the nuclear bag fibres which were activated by dynamic fusimotor axons were slower and smaller than in those nuclear bag fibres which contracted during static fusimotor stimulation. The nuclear chain fibres contracted and relaxed more rapidly than the nuclear bag fibres (see also Boyd et al 1973).

Meanwhile, histological and ultrastructural evidence was emerging that supported the existence of two kinds of nuclear bag fibre in mammalian muscle spindles. Ovalle & Smith (1972) named the nuclear bag fibre which contained acid-stable, alkaline-labile myosin ATPase the "bag_1" fibre, and the other

nuclear bag fibre which contained acid-stable, alkaline-stable myosin ATPase the "bag_2" fibre. Banks, Barker, Harker & Stacey (1973) and Barker & James (1974) described differences in the equatorial diameter, histochemistry and ultrastructure of the cat and rabbit intrafusal muscle fibres. They named the longer and thicker of the two nuclear bag fibres of the cat spindle the "typical" bag fibre, which also had medium to high levels of glycogen, succinic dehydrogenase (SDH) activity and actomyosin ATPase activity. The other nuclear bag fibre was named the "intermediate" bag fibre, and was shorter, thinner and had low levels of glycogen and actomyosin ATPase activity with medium SDH activity. Gladden (1974) showed that the numbers and relative thicknesses of the elastic fibres associated with each of the two nuclear bag fibres in the cat spindle was significantly different, indicating that the two bag fibres may behave differently during and after stretching of the spindle. Gladden (1976) has also shown that one of the two bag fibres of isolated cat muscle spindles is more sensitive to topically applied acetylcholine than the other (see page 29).

The observations of Brown & Butler (1975) and Bessou & Pages (1975) had suggested that though static and dynamic fusimotor axons could both produce contractions in the nuclear bag fibres, the nature of the bag fibres made to contract by static axons was different from those bag fibres made to contract by dynamic fusimotor axons. Boyd, Gladden, McWilliam & Ward (1975b, 1977) and Boyd (1976a, b, c) studied the contractions produced in the intrafusal muscle fibres of isolated tenuissimus muscle spindles by stimulation of dynamic and static fusimotor axons, and from a large number of observations concluded that all muscle spindles contain two distinct types of nuclear bag fibre, which differ in their contractile characteristics and their innervation. Dynamic gamma axons, and beta axons, produced focal contractions in only one of the two nuclear bag fibres of the muscle spindle,

and this nuclear bag fibre was never activated by static fusimotor axons. Boyd et al named this bag fibre the "dynamic nuclear bag" fibre, or DNB for short. Static gamma axons were found to be less specific in their intrafusal distribution, and produced contractions either in the nuclear chain fibres alone, or in the second of the two nuclear bag fibres alone, or in this bag fibre and the nuclear chain fibres. The nuclear bag fibre innervated by static gamma axons, which usually was the larger and stronger of the two in the spindle, was named the "static nuclear bag" fibre, or SNB for short. Boyd et al (1977) correlated their observations with histochemical data, and showed that the DNB and the SNB correspond to the bag_1 and bag_2 fibres respectively (Ovalle & Smith 1972). Further, Boyd (1976c) and Boyd, Gladden & Ward (1977) showed that the mechanical behaviour of the two bag fibres differed significantly immediately following an extension applied to the muscle spindle. The DNB fibre exhibited a slow "creep" towards the equator of the spindle after the completion of stretching, so that the extension of the primary afferent axon sensory spirals on the DNB decreased by about 20% over 0.5 to 1 sec after the end of stretching. This "creeping" of the DNB was accentuated by dynamic fusimotor stimulation, or the application of succinylcholine (Boyd et al 1977). The SNB and the nuclear chain fibres did not show a similar "creeping" action. Boyd et al (1977) suggested that this mechanical "creeping" of the DNB contributes to the adaptation of the Ia afferent discharge after the end of stretching.

The recent recognition of the fact that the mammalian muscle spindle contains two different nuclear bag fibres, however, has not lessened the debate over the intrafusal distribution of the motor terminals of the static gamma axons. Boyd, Gladden, McWilliam & Ward (1977) stressed their finding that the DNB and the SNB were independently controlled by dynamic and static fusimotor axons respectively, and proposed that two independent systems of

efferent control of the spindle existed, the "dynamic" system and the "static" system. Glycogen depletion studies (Barker et al 1975b, 1976) and direct observations (Bessou & Pages 1975) agree with the findings of Boyd et al as regards the motor nerve terminals of the dynamic fusimotor axons, which lie on the "dynamic" or bag_1 fibre. However, the glycogen depletion studies provide evidence which conflicts with the direct observations of Boyd et al as regards the innervation of the intrafusal fibres by static gamma axons. Brown & Butler (1975) found that the glycogen content of only one of the nuclear bag fibres was depleted during static gamma axon stimulation, and that this nuclear bag fibre was always the larger of the two, suggesting that it was the "static" bag_2 fibre. This agrees with the findings of Boyd et al (1977). However, Brown & Butler (1973) had earlier found that static gamma axons frequently depleted the glycogen levels of both nuclear bag fibres, and Barker et al (1975b, 1976) found that bag_1 (dynamic) fibres as well as bag_2 (static) fibres were depleted of glycogen during static gamma stimulation. The depletion of bag_2 (static) nuclear bag fibres by static fusimotor axons agrees with the findings of Boy et al, but not the depletion of bag_1 (dynamic) nuclear bag fibres. Boyd et al (1977) have suggested that the depletion of the bag_1 fibres during static gamma stimulation may be indirectly caused by the pattern of intermittent activation and ischaemia used in the experiments of Barker et al, and not by the presence of static gamma axon motor terminals on the bag_1 fibre. On the other hand, Barker et al have stressed the possibility that some weak contractions of the intrafusal muscle fibres may have been masked by stronger simultaneous contractions of other intrafusal fibres in the experiments of Boyd et al.

A recent report by Barker, Bessou, Jankowska, Pages & Stacey (1978) presented results from 37 experiments where visual observations of the

intrafusal contractions produced by dynamic and static gamma stimulation and the recording of intrafusal membrane potential changes were followed up by histological determination of the fibre type innervated by each fusimotor axon. These results showed that thirteen intrafusal fibres innervated by static axons were either bag_2 or chain fibres, and that seven of nine fibres innervated by dynamic axons were bag_1 fibres, in good agreement with the findings of Boyd et al (1977). However, Barker et al (1978) found that two of nine intrafusal fibres innervated by dynamic axons appeared histologically to be a bag_2 and a long chain fibre respectively. For the moment at least, the directness of the observations of Boyd et al compared with the indirectness inherent in the histochemical methods employed by Barker et al, favours the picture of the independent motor innervation of the "static" and "dynamic" systems of the cat spindle envisaged by Boyd et al (1977).

Recently, however, the broadly accepted functional subdivision of the gamma efferent axons into "static" and "dynamic" types according to their effects on the response of primary sensory endings to stretch (Matthews 1962, 1972) has been critically re-examined by Emonet-Denand, Laporte, Matthews & Petit (1977). Using large triangular and ramp stretches, Emonet-Denand et al applied a series of criteria only one of which was the change in the dynamic index (their pages 844-846) to the action of fusimotor axons on the discharge of muscle spindle Ia sensory endings in the peroneus brevis muscle of the cat, and searched for fusimotor effects that could be recognized to fall between the well known static and dynamic types. When individual fusimotor axons were studied and their actions on several of the spindles they innervate were taken into account, their functional division into "static" and "dynamic" types was found to be "virtually complete". Thus, every fusimotor axon was consistent in being predominantly static or dynamic

in its action, though its action on an individual primary ending may or may not be absolutely clear. When the actual effects of fusimotor axons on individual primary endings were considered, then only about two-thirds of the fusimotor actions were found to be purely "static" or "dynamic". Emonet-Denand et al subdivided the actual effects of fusimotor axons into six categories, where the two extreme categories I and VI were "pure dynamic" and "pure static" respectively. Category III contained fusimotor effects which were apparently "unclassifiable" as either "static" or "dynamic", while the remaining categories included various admixtures of apparent static and dynamic actions. Such "mixed" actions could be simulated by the concomitant stimulation of "pure dynamic" and "pure static" fusimotor axons. These findings led Emonet-Denand et al to propose that "the distribution of the motor innervation to the different intrafusal muscle fibres shows a degree of overlap, rather than a complete dichotomy", and consequently that their observations "serve to soften any conceptual difficulty experienced on finding that a given fusimotor fibre includes the unexpected kind of intrafusal fibre in the distribution of innervation, provided that it primarily supplies the expected kind of intrafusal fibre". However, the observed "mixed" actions of some fusimotor axons were perhaps too readily attributed to a "mixed" innervation of several intrafusal fibres by those axons, and the possibility exists that some of the apparently "mixed" effects may result from differences in the strength and location of the intrafusal contractions produced in different spindles by individual gamma axons. This possibility is discussed in the light of the results of the present study, on page 101.

A line of investigation parallel to but separate from the question of the motor innervation of the intrafusal muscle fibres has been centred around the obvious complexity of the muscle spindle as a sense organ, and the

mechanical and electrical factors which might interact in the generation of the afferent discharge of the compound primary sensory ending (see Matthews 1972, Ch. 6). The concept that the separate spiral sensory endings of the Ia axon on different intrafusal muscle fibres may signal different aspects of the mechanical forces acting on the spindle, has been generally accepted for some time. How two or more such signals may be mixed for transmission via the single Ia afferent axon, however, has not yet been extensively explored experimentally. The precise pattern of branching of the Ia axon close to the primary ending, and the degree of myelination of each branch, appears from a preliminary study made by Banks et al (1977) not to be stereotyped and predictable, unlike the frog "single-type" muscle spindle afferent axon (see Ito et al 1974). Two possible alternative means of mixing the electrical signals originating in the individual spirals of the Ia axon exist, and have been discussed in detail by Matthews (1972). One possibility is that the receptor potentials generated at each of the Ia sensory terminals add together at a unique pacemaker site where the Ia afferent impulses are initiated. The Ia afferent discharge would in this case reflect the instantaneous sum of all the receptor potentials acting on the one pacemaker site. Alternatively, it is possible that each, or some, of the Ia sensory terminals has its own pacemaker which initiates action potentials in the branch of the Ia afferent axon that supplies it, and the Ia afferent discharge is then determined by the interaction of several trains of action potentials at branch-points of the Ia axon. In this case, the Ia afferent discharge would be the same as that of the pacemaker with the highest instantaneous frequency of discharge (Matthews 1972; Eagles & Purple 1974).

Experimental investigations carried out to date have sought to characterise the effects on the Ia discharge of the combined simultaneous

stimulation of static and dynamic fusimotor axons, and from the changes observed to deduce the nature of the interaction between the intrafusal fibres activated by the fusimotor axons (Crowe & Matthews 1964b; Lennerstrand 1968; Schafer 1974; Hulliger, Matthews & Noth 1977a, b, c). Hulliger et al have shown that the effects of static and dynamic fusimotor activation summed to some extent during dynamic extension of the spindle, but that the static activation appeared to occlude the dynamic activation during shortening. These findings complemented and extended the earlier results of Lennerstrand (1968). Hulliger et al felt that the summation observed during extension of the spindle was probably caused by electronic spread of generator potentials to a common pacemaker site, but the occluding effects seen during shortening could either be caused by the interaction of mechanical forces between individual intrafusal muscle fibres which might cause one of them to be unloaded, or by the "switching" of the site of the pacemaker for the Ia afferent axon (Crowe & Matthews 1964b).

These recent experiments have supported the view that several different pacemakers probably exist in the cat muscle spindle (see for example Hulliger et al 1977c), as there appear to be in the frog spindle (Broshenka & Westbury 1973, 1974a, b, 1976b; Ito et al 1974). However, a limitation is placed on the interpretation of the effects of concomitant dynamic and static fusimotor activation in these experiments by the fact that it is not known which of the intrafusal muscle fibres of the spindle are activated, and how strongly, by each of the fusimotor axons employed (see Boyd et al 1977; Barker 1976). This point is taken further in the light of the results of the present study, on page 104.

LITERATURE REVIEW: PART 2

The excitation of muscle stretch receptors by Suxamethonium.

Granit, Skoglund & Thesleff (1953) were the first to report that SCh excited muscle spindle sensory endings in the cat. Earlier, Hunt (1952) had reported that acetylcholine increased the rate of discharge of muscle spindle sensory endings in the soleus muscle of the cat, and suggested that the contraction of the intrafusal muscle fibres was the most likely reason. Granit et al studied the effects of bolus injections of SCh into either the ipsilateral deep femoral artery or via the contralateral femoral artery into the aortic bifurcation, on the discharge of muscle spindles in the gastrocnemius, soleus and tibialis anterior muscles of the cat, at different static muscle lengths.

The concentration of SCh required to excite muscle spindles was found to vary from animal to animal, ranging from 10 µg to 100 µg SCh injected into the aortic bifurcation. Nevertheless, high-frequency discharges could always be elicited from spindles in a completely slack muscle, providing a large enough dose of SCh was given. This finding, and also the fact that sufficiently high concentrations of SCh could still excite muscle spindles in the presence of d-tubocurarine, led Granit et al to conclude that their results were "very much in favour of the view that SCh, whatever effects it may have on the gamma end-plates, also stimulates the sense organs directly" (their page 148). Thus, while Hunt (1952) had suggested that ACh caused the contraction of the intrafusal muscle fibres which stretched the central sensory endings, Granit et al felt that SCh probably also had a further electrical action on muscle spindle sensory endings.

In the same experiments, Granit et al also examined the effect of intra-arterial injections of SCh on the static discharge rates of Golgi tendon organs in the soleus, tibialis anterior and gastrocnemius muscles. They were unable to detect any effects of SCh on the discharge of the tendon organs, even after large doses of SCh (up to 500 µg) were made. From this

they concluded that the electrical action that SCh appeared to have on muscle spindles, did not extend to the tendon organs.

Some years later, Brinling & Smith (1960) studied the effect of SCh on Ia afferent axons from the gastrocnemius muscle of the cat, with the intention of establishing the site of action of the drug in the muscle spindle. They tested the effects of continuous infusions as well as injections of SCh into the external jugular vein on the static discharge rates of primary sensory endings. They found no evidence for tachyphylaxis or cumulation of the effects of single injections, provided that a sufficient time was allowed to elapse between administrations of the drug. This varied from 10 to 30 minutes, depending on the dose of SCh injected. The dose-response curve of gastrocnemius muscle spindle Ia endings had a skewed sigmoid shape, leading the authors to suggest that SCh may have more than one site of action in the muscle spindle. What these possible sites of action might be, however, the authors did not elaborate.

Intravenous infusions of SCh at rates of 200 and 400 µg SCh/Kg body weight/minute raised the static discharge rates of Ia endings gradually to a sustained plateau frequency which appeared to depend on the rate of SCh infusion. Higher rates of infusion of SCh produced an initial "high-frequency response" between 80 and 90 imp/sec in the example illustrated in their paper, with a subsequent plateau at a lower frequency of discharge. Physostigmine pretreatment potentiated the effects of SCh on the Ia endings, and on this basis the authors suggested that the contraction of the intrafusal muscle fibres must play a part in the excitation of the Ia endings by SCh, whether or not a further direct action of the drug on the sensory nerve terminals also occurred.

Further experiments which attempted to distinguish between the possible direct and indirect actions of SCh on muscle spindle Ia sensory endings were

carried out by Smith & Eldred (1961), who demonstrated that in gastrocnemius muscle spindles whose intrafusal muscle fibres had been made to contract irreversibly by fusimotor stimulation in the presence of rynodine, the effects of SCh on the Ia afferent discharge were reduced. The effects were not completely abolished, presumably because only one of the fusimotor axons supplying the muscle spindle was activated during rynodine administration, which left the intrafusal muscle fibres not innervated by this fusimotor axon still in a normal state. In other experiments where all the extrafusal and the intrafusal muscle fibres of the tenuissimus muscle were made to contract irreversibly by stimulating the entire ventral roots or the muscle nerve in the presence of rynodine, the effects of SCh on the Ia endings could be made to disappear. However, the authors noted from the "tightened, blanched" appearance of the muscle after this treatment that the blood circulation in the muscle, and thus the supply of SCh to the muscle spindles, was severely impaired. These experiments showed that the effects of SCh on the Ia endings were at least in part due to the mechanical shortening of the intrafusal muscle fibres since the effects of SCh were reduced when some of the intrafusal muscle fibres were made to contract by rynodine. However, the possibility of a concomitant electrical action of SCh on the sensory nerve endings, as suggested by Granit et al, was not ruled out.

Ottoson in 1961 showed that in isolated frog muscle spindles whose intrafusal muscle fibres had been cut or crushed some distance from the equatorial sensory endings, SCh or ACh did not increase the spontaneous discharge rate of the primary sensory ending. This appears to rule out the possibility that ACh and SCh have direct electrical effects on the Ia sensory nerve terminals, at least in the frog muscle spindle, and indicates that the predominant action of the drugs in the frog spindle is via the contraction of the intrafusal muscle fibres.

However, Douglas & Gray (1953) have shown in the cat that close intra-arterial injection of ACh can elicit trains of action potentials in cutaneous mechanoreceptor afferent axons, which are probably caused by a direct depolarising action of the drug on the sensory nerve terminals. The minimum concentration of ACh required to excite the cutaneous sensory endings was found to be 10^{-5}mg/ml. Further, Douglas & Ritchie (1960) found that doses of ACh as low as 2 µg given intra-arterially can produce a similar direct excitation of the discharge of both myelinated and unmyelinated cutaneous afferent axons.

Thus, it is possible that ACh and SCh also have direct electrical effects on mammalian muscle spindle sensory endings, independently of their actions on the intrafusal muscle fibres. Ferrell (1977; PhD thesis) has shown that the tonic discharge rate of some mechanoreceptors in the cat knee joint ligaments is elevated after intravenous injections of SCh of 200-500 µg/Kg body weight. This excitation is presumably caused by an electrical action of SCh on the afferent nerve terminals, since these mechanoreceptors are not associated with musculature as are muscle spindle sensory endings. However, Kidd & Kucera (1969) have shown that in the rat, a direct electrical excitation of the Group III afferent axons from muscle only occurs following injection of doses of SCh ten times higher than those required for muscle spindle excitation.

Fehr (1965) studied the effects of intravenous injections of SCh on the static discharge rates of primary and secondary sensory endings of the same muscle spindle in the tenuissimus muscle of the cat, and described several differences between them. Secondary sensory endings were excited to a much lesser degree than primary endings by the same dose of SCh, often showing only a slight increase in their discharge frequency. Further, in a given spindle, the primary sensory ending always showed a shorter lag

time to excitation following an injection of SCh, so much so that in some cases the excitation of the primary ending had reached its peak before the secondary ending of the same spindle had shown an increase in its discharge rate.

Fehr suggested that the nuclear bag as well as the nuclear chain fibres of the muscle spindles were made to contract by SCh, thus exciting both primary and secondary sensory endings by mechanical stretch. In order to explain the difference in time lag between injection and excitation of primary and secondary endings Fehr suggested that the nuclear bag fibres contract sooner and more quickly than the nuclear chain fibres following the injection of SCh. Fehr thus discounted any need for SCh to have an electrical effect on the sensory nerve terminals, though his experiments did not provide any evidence showing that electrical excitation did not occur.

All the evidence discussed so far had been obtained with muscle spindles under static conditions. Rack & Westbury (1966) took a significant step forward when they examined the effects of intravenous injections of SCh on soleus muscle spindle primary and secondary sensory endings during dynamic stretching of the muscle. Under their experimental conditions, SCh caused a large increase in the response of primary endings to the dynamic phase of a ramp-and-hold stretch, and a smaller increase in their response to the change in muscle length. This increase in the dynamic sensitivity of the Ia endings was dependent on the dose of SCh injected, but with higher doses of SCh the peak discharge frequency in response to a ramp stretch reached an upper limit, which varied from spindle to spindle. Close intra-arterial injections of SCh also increased the dynamic sensitivity of Ia endings in a similar way.

The dose of SCh required to excite primary sensory endings was found to vary not only from cat to cat as reported by earlier workers (Granit et al

1953; Brinling & Smith 1960), but also to vary from spindle to spindle in the same animal.

The effects of SCh on the discharge of secondary sensory endings were not as marked as those on primary sensory endings, as reported previously by Fehr (1965). SCh did not increase the dynamic sensitivity of secondary endings, but increased their response to both the dynamic and the extension phases of the ramp stretches by roughly equal amounts, with the result that the dynamic index did not change significantly.

The behaviour of spindle sensory endings with afferent axon conduction velocities between 60 and 80 m/sec ("intermediate conduction velocity afferents") in the presence of SCh was also studied in these experiments. Rack & Westbury found that of 16 such "intermediate" sensory endings, 11 experienced an increase in their dynamic sensitivity and thus behaved like primary sensory endings after injection of various amounts of SCh and ACh, while the remaining 6 intermediate sensory endings responded to the drugs in the same way as secondary sensory endings. They were thus able to classify all "intermediate" sensory endings as either primary-like or secondary-like, according to the effects of SCh on their dynamic sensitivity to stretching.

Rack & Westbury also examined the effects of SCh on fusimotor activity, and noted the great similarity between the effects of SCh on the Ia sensory endings and the effects of dynamic fusimotor stimulation. Dynamic fusimotor activation appeared to summate with the effects of SCh on the primary sensory endings, until the maximum discharge frequency of the sensory axon was reached. Static fusimotor stimulation in the presence of SCh however increased the primary afferent discharge at the initial and final muscle lengths of the ramp stretch, but did not affect the enhanced response of the Ia endings to the dynamic phase of stretch.

Since the effects of dynamic fusimotor stimulation were very similar to the effects of SCh on primary sensory endings, Rack & Westbury suggested that the two effects may be "mediated by the same intrafusal mechanism". Smith (1966) had earlier reported that some of the intrafusal muscle fibres of the rat spindle, like "slow" muscle fibres in amphibia and birds, went into sustained contraction in the presence of SCh. Rack & Westbury suggested that in the cat spindle the dynamic sensitivity of the primary ending may be governed by similar "slow" intrafusal muscle fibres, which when made to contract by SCh produced the typical increase in the dynamic sensitivity of Ia endings characteristic of dynamic fusimotor activation.

However, Rack & Westbury also noted in passing that the primary afferent discharge pattern often seen during the first minute following the injection of large doses of SCh was different from the typical dynamic behaviour mainly described in their paper. During the first minute after such an injection, many primary sensory endings behaved as if they were under strong simultaneous dynamic and static fusimotor stimulation. As a possible explanation, they suggested that during this period the "other intrafusal fibres which usually mediate the static fusimotor activity" (presumably they meant the nuclear chain fibres) were undergoing transient contraction, similar to the fasciculation of extrafusal muscle fibres before the onset of paralysis.

Smith (1966) visually observed the effects of SCh on the intrafusal muscle fibres of the isolated rat muscle spindle, and found that SCh produced a sustained contracture of "slow" intrafusal muscle fibres, presumably the nuclear bag fibres. "Fast" intrafusal muscle fibres, presumably the nuclear chain fibres, could be made to contract by direct electrical stimulation, but after a few minutes in the presence of SCh the response of these fibres to electrical stimulation was abolished.

Boyd (unpublished, see Gladden 1976) in his experiments on isolated

cat muscle spindles also made similar observations, though he did not see contracture of the nuclear bag fibres on every occasion. From these experiments nevertheless it began to emerge that the nuclear chain fibres were not made to contract by SCh or ACh, contrary to the suggestion made by Fehr (1965).

In 1976, Gladden while studying the differences in the characteristics of the two nuclear bag fibres of the cat muscle spindle (Boyd et al 1975), tested the effects of the direct application of ACh on the intrafusal muscle fibres of the isolated muscle spindle. Her experiments were performed with the spindles at a very short length, short enough to "kink" the nuclear chain fibres and also the nuclear bag fibres (Boyd & Ward 1975). When ACh was applied to the isolated spindle, the two nuclear bag fibres were seen to contract and straighten, whilst the nuclear chain fibres did not contract and remained "kinked". Furthermore, ACh in a concentration of 10^{-5}mg/ml caused only one of the two bag fibres to contract, showing that one of the two bag fibres was more sensitive to topically applied ACh than the other.

On the basis of indirect tests, Gladden showed that the more sensitive of the two bag fibres was the dynamic nuclear bag fibre (Boyd et al 1975). ACh in a concentration of 10^{-4}mg/ml therefore first made the more sensitive dynamic nuclear bag (DNB) fibre contract, and about 10 seconds later the other nuclear bag fibre (the static bag fibre, SNB) went into contraction.

In later experiments, Boyd & Gladden (as yet unpublished) have confirmed these findings, and also shown the DNB fibre to be more sensitive to topically applied SCh than the SNB fibre. This difference in the sensitivity of the two bag fibres to ACh and SCh has been used as a routine test in recent experiments on isolated muscle spindles where fusimotor axons were not available for stimulation (Gladden & McWilliam 1977), when the DNB fibre in the isolated muscle spindle was distinguished from the SNB fibre by its

higher sensitivity to ACh and SCh (cf. Boyd et al 1975).

From these experiments, the effects of SCh on the intrafusal muscle fibres of the cat spindle seem clear. Whether in vivo SCh also has an additional electrical action on the sensory nerve terminals themselves, however, is open to question. The excitation of secondary sensory endings by SCh (Fehr 1965; Rack & Westbury 1966), which lie mainly on the nuclear chain fibres, also remains to be explained, since the chain fibres are not made to contract by SCh. Finally, the contraction of the two nuclear bag fibres in the presence of SCh may provide a useful alternative to the stimulation of gamma fusimotor axons as a means of activating the muscle spindle sensory endings.

Referring to this kind of "chemical" activation of the muscle spindle in his closing speech at the Hong Kong Symposium on Muscle Receptors in 1962, Granit pointed out that this was "one more road of advance that hasn't been used much so far" in the study of the internal working of the muscle spindle. Since 1962, "chemical" activation has played a part in the gradual elucidation of spindle function particularly in studying the differences in the behaviour of primary and secondary sensory endings, in which context Granit had made his remark. The present work explores further this alternative "road of advance".

METHODS

A total of 68 cats over a period of three years were used in the experiments described in this Thesis. Each animal was starved for 24 hours preceding an experiment.

SURGICAL PROCEDURES

Anaesthesia

The cats were initially anaesthetised by intraperitoneal injection of sodium pentobarbitone (Sagatal or Nembutal, May & Baker, Ltd.) in a dose of 45 mg/kg body weight. During the experiments, whenever periodic checks on the depth of anaesthesia indicated the necessity, small doses of anaesthetic (6-12 mg) were given intravenously.

Tracheotomy and cannulation of the external jugular vein

The anaesthetised animal was laid supine on an operating table. The fur on the ventral surface of the neck was removed, and a midline incision 3cm long was made in the skin from the hyoid arches towards the sternum. The skin was freed from the underlying muscles by blunt dissection. The sterno-hyoid and sterno-mastoid muscles thus exposed were separated along the midline, revealing the trachea. A 15cm length of linen thread was passed under the trachea using an aneurism needle. The trachea was opened between adjacent cartilaginous rings and a glass tracheal cannula of suitable size was inserted while holding open the cut with a pair of Spencer-Wells forceps. The tracheal cannula was secured in place (Fig. 1).

The left external jugular vein was located and freed of connective tissue over about 2cm of its length. A red-luer nylon cannula (Portex Ltd.) filled with 0.9% saline was inserted into the vein. The tip was advanced about 5cm and the cannula was tied in place. The skin incision was closed with two michel suture clips.

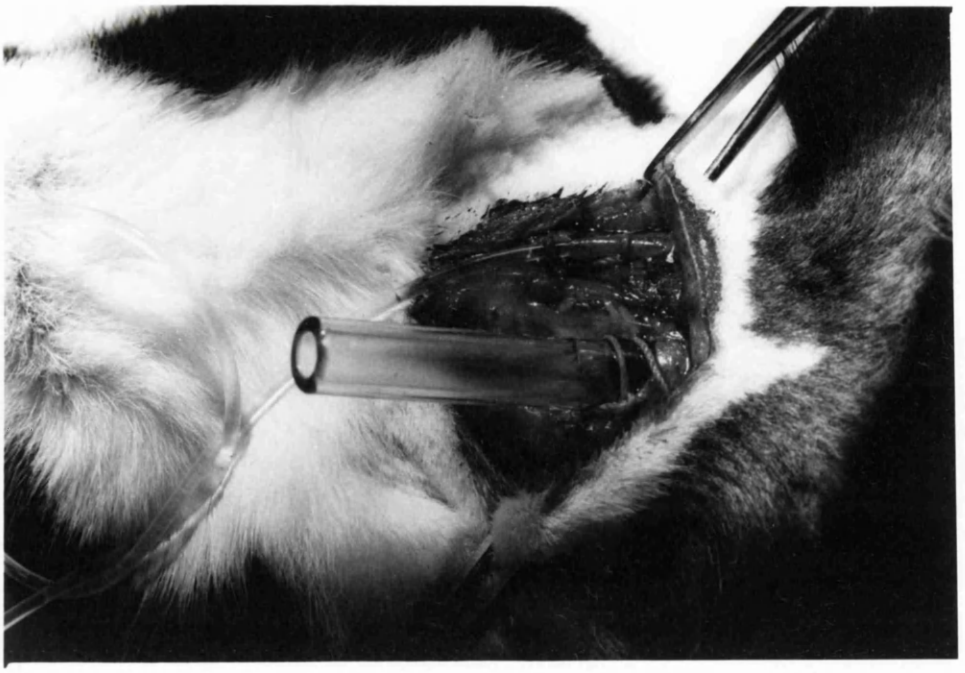

Fig. 1. Ventral aspect of the neck, showing the polythene cannula inserted into the external jugular vein and the glass cannula in the trachea.

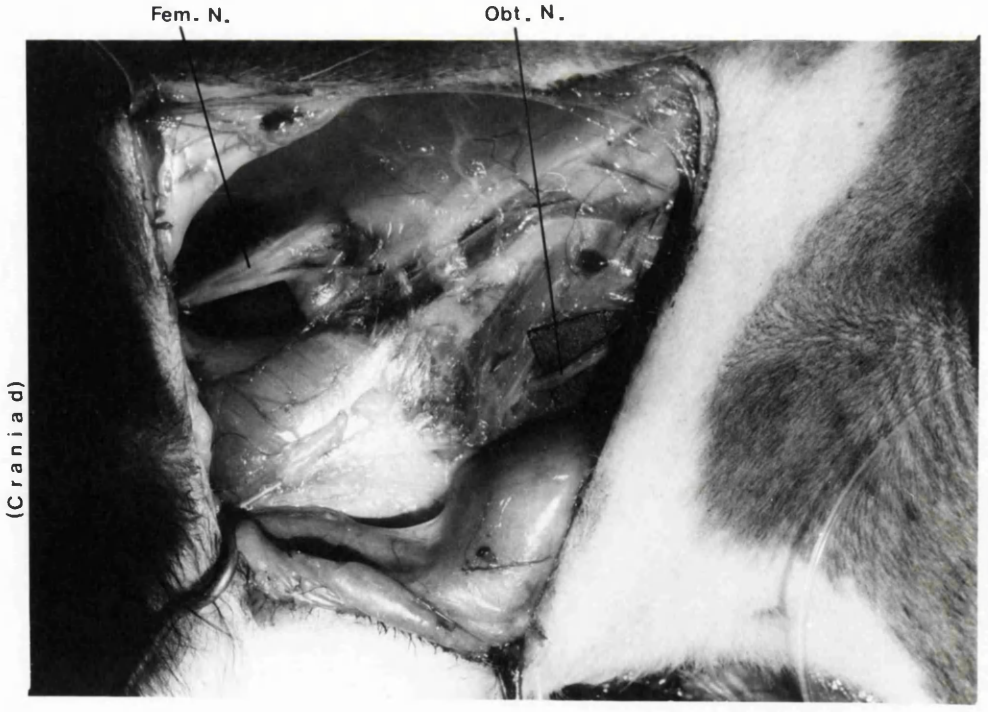

Fig. 2. Medial surface of the left leg showing the femoral and obturator nerves.

Denervation of the left hind limb: femoral and obturator nerves

The skin over the medial aspect of the left thigh was cleared of fur. A 3cm skin incision was made along the line of the femoral blood vessels, and held open by means of retracting hooks (Fig. 2). The femoral nerve was located, followed up to its point of exit from the abdominal wall at the dorsal iliopectineal arch, and there it was cut. The obturator nerve was cut as it crossed over the adductor femoris muscle (Fig. 2). The skin flaps were brought together and the incision closed with two michel suture clips.

Cannulation of the right femoral artery

The femoral blood vessels were exposed in the right thigh by making a similar incision as above (Fig. 3). The femoral artery was separated from the femoral nerve and vein over the upper half of the thigh. Two lengths of linen thread were passed under it, and the lower end of the freed artery was ligated. A pair of Spencer-Wells forceps were clamped on the artery a little above the upper ligature. The artery was opened between the ligatures and a pink-luer nylon cannula (Portex Ltd.) was inserted. The upper ligature was made firm but not tight around the cannula, and the Spencer-Wells forceps removed. The cannula was passed up the artery until the tip was estimated to be at or near the bifurcation of the aorta. The upper ligature was then made secure. A third ligature was then secured around the femoral artery as high up in the thigh as possible (Fig. 3). This ligature served to restrict the back-flow of suxamethonium when infused through the cannula. The skin incision was closed with michel suture clips, and the animal was turned over to lie prone on the operating table.

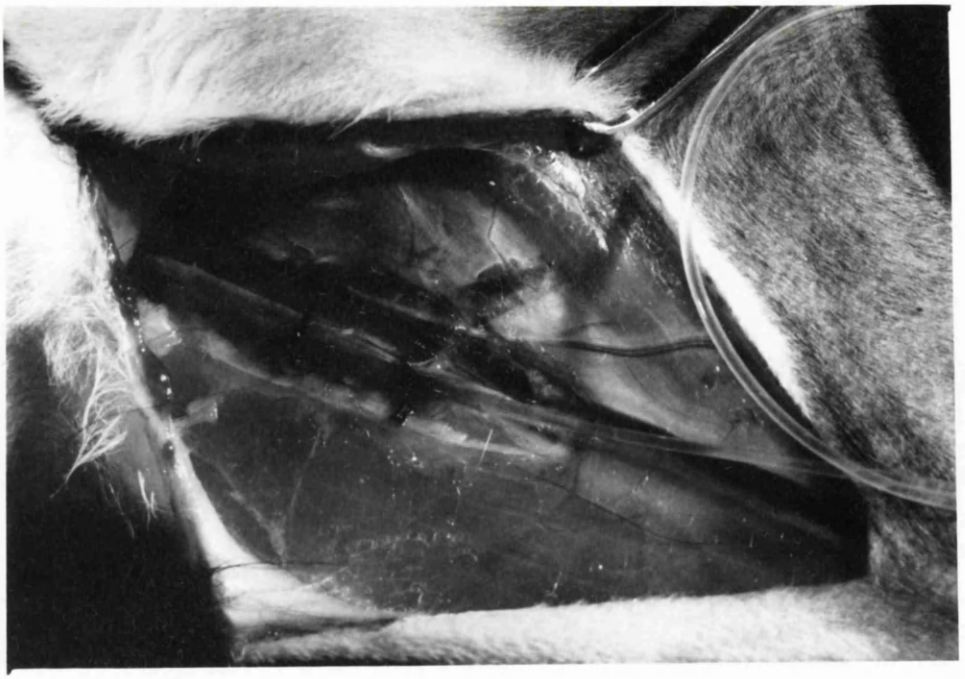

Fig. 3. Medial surface of the right leg, showing the polythene cannula inserted into the femoral artery.

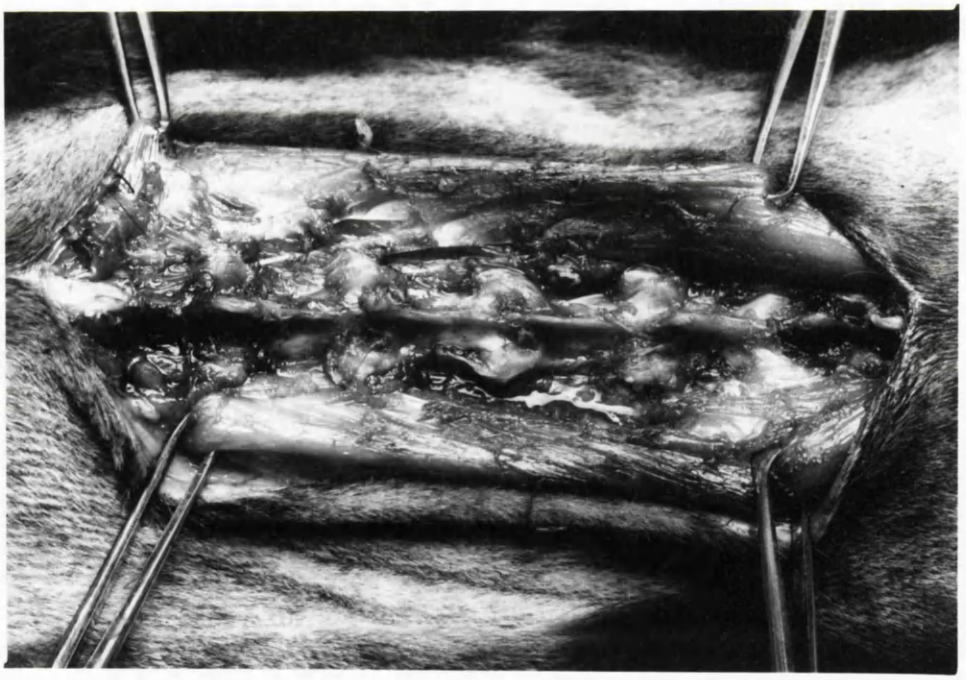

Fig. 4. The exposed vertebral column from L4 to S1.

Laminectomy

The skin on the back of the animal was cleared of fur from the level of the L4 vertebra to the base of the tail, and a midline incision was made in the skin from the level of L5 to S2. The skin on both sides was freed from the underlying fascia by blunt dissection. Cutaneous nerves emerging from the body wall and running to the skin on the left side of the animal were located and cut. Two parallel incisions of the same length as the skin incision were made in the superficial fascia, one incision on either side of the dorsal processes of the lumbar vertebrae. The latissimus dorsi muscles on both sides were separated from the lumbar multifidus muscles of the vertebral column, and held aside by retracting hooks. Dentist's rolls soaked in hot saline were applied to the exposed muscles for about 15 seconds, in order to coagulate their blood supply. The multifidus muscles were then cleared from the vertebral column and removed. Fig. 4 shows the vertebral column from L5 to S1 as exposed by this procedure.

The articular and mammillary processes of the exposed vertebrae were removed using a large pair of bone nibblers. The vertebrae were then removed in the order L7, L6, L5, and finally S1. Removal of the transverse processes of the vertebrae allowed a greater than normal movement of the vertebral joints. To begin the laminectomy the joint between S1 and L7 was opened by grasping the L7 dorsal process in Spencer-Wells forceps and lifting the vertebral column as much as possible. One jaw of a small pair of bone nibblers was inserted into the joint and the bone forming the wall of L7 was cut away. Lifting the vertebral column encouraged the spinal cord to remain on the floor of the vertebral canal, out of the way of the bone nibblers. Once a sufficient portion of the wall of the vertebra had been cut away, a larger pair of bone nibblers was used to remove the rest of the

vertebra. Each vertebra from L5 to S1 was removed in a similar fashion. The walls of the vertebrae were trimmed down and sharp protusions of bone removed (Fig. 5). The edges of the vertebrae were packed with Gel-Foam, which absorbed any slow bleeding from the remaining damaged portions of the vertebral muscles and encouraged coagulation. The spinal cord was covered with moist cotton wool rolls and the skin incision closed with michel suture clips.

Preparation of the soleus muscle

The skin over the muscles of the calf and knee of the left hind limb was cleared of fur, and an incision was made from over the popliteal fat pad to the heel of the foot. The fat pad was grasped in Spencer-Wells forceps and reflected laterally, cutting the blood vessels supplying it between double ligatures. The sciatic nerve which was thus revealed was cleared of connective tissue, and its branches in this area including the aural and peroneal nerves were cut.

The medial and lateral heads of the gastrocnemius muscle were separated and the medial gastrocnemius muscle was reflected aside. The flatter, larger tendon of the soleus muscle was separated from the tendon of the medial gastrocnemius muscle, which was cut. The denervation of the lower leg was completed by cutting the leash of nerves supplying the muscles of the ventral aspect of the calf and the knee joint, the nerves to the medial and lateral gastrocnemi, and the sciatic nerve itself distally to the origin of the soleus muscle nerve. The connective tissue sheath of the central end of the cut sciatic nerve was slit open and a length of approximately 1.5cm of the soleus muscle nerve isolated, so as to allow stimulating electrodes to be placed under it later (Fig. 6). A stout linen thread about 15cm long was stitched into the soleus muscle tendon, which later would be attached to a muscle stretching system.

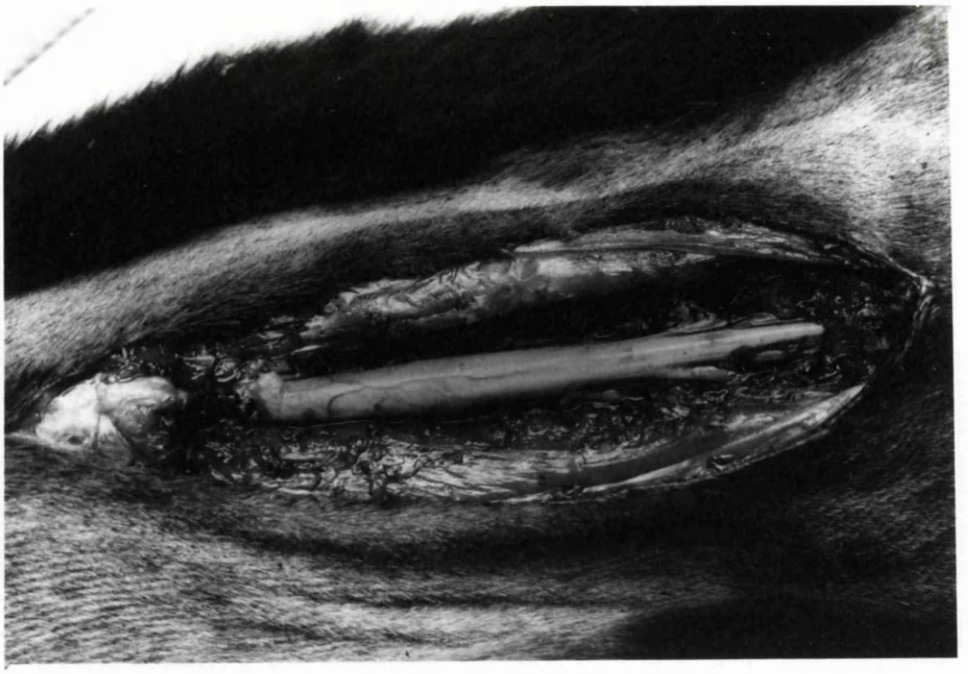

Fig. 5. The spinal cord revealed after the completion of the laminectomy.

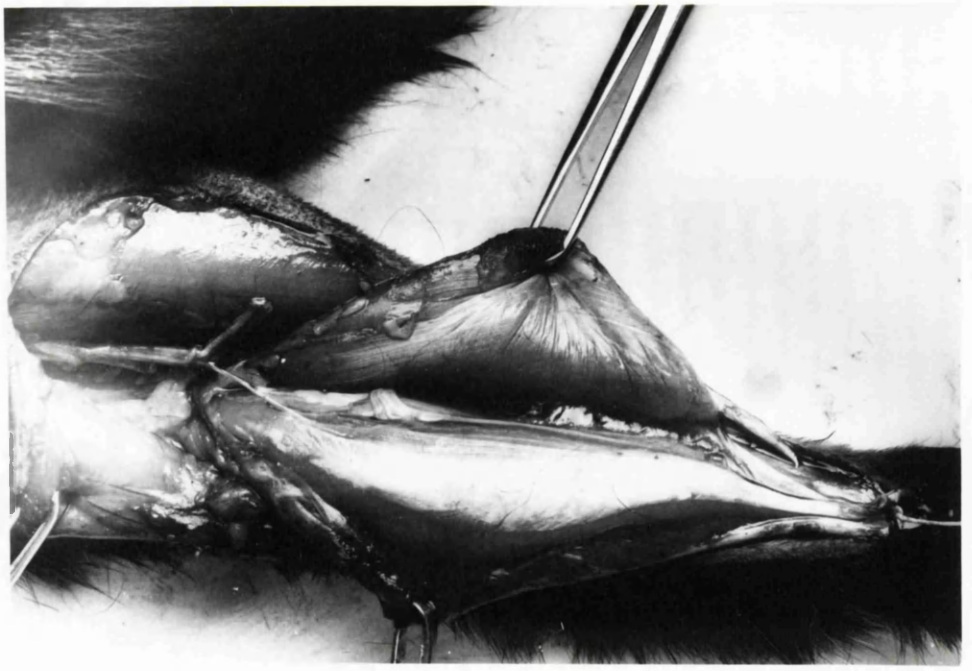

Fig. 6. The dorsal aspect of the left leg showing the soleus muscle and its muscle nerve, after extensive denervation.

A short skin incision was made over the sciatic notch, and by partial reflection of the biceps muscle the sciatic nerve was exposed. The nerve was followed up into the hip region, and the many branches of the main nerve including the cranial gluteal, caudal gluteal, caudal femoral cutaneous, and the pudendal nerves were cut. The nerves from the sacral plexus to the tail were also located in the base of the tail, and cut. The lesser sciatic nerve and the nerve to tenuissimus were revealed by following the main nerve a short distance toward the knee, and cut. This completed the extensive denervation of the left hind limb with the exception of the soleus muscle. The skin incisions were closed with michel suture clips and the cat was moved across to the recording area.

Preparations for recording

For the duration of an experiment the cat was supported in a brass frame fixed to a steel plate of dimensions 64 x 45 x 0.8cm as shown in Fig. 7. The steel plate rested on four 7 x 7cm foam rubber pads, which served to cushion the preparation from vibratory influences in the laboratory. The cat's head was fixed in a head-holder adjusted to a suitable height and inclination. A knitting needle was passed through the muscles of the back about 2cm craniad to the laminectomy, and fixed to the brass frame by means of clamps.

The skin flaps around the laminectomy were raised to make a pool into which paraffin oil at 37°C was poured. The walls of the pool were made by clipping a 1-inch wide strip of exposed X-ray film to the edge of the skin flaps. A similar paraffin pool was constructed over the left hind limb, using an oval brass frame instead of the X-ray film. Two infra-red lamps (250W) mounted on a bracket above the animal and operated by a dimmer switch were used to maintain the rectal temperature of the animal between 35 and 37°C.

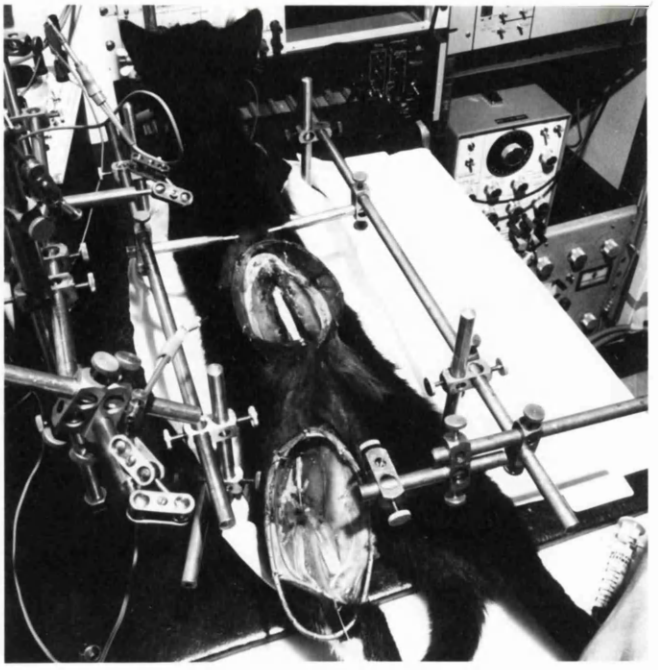

Fig. 7. The animal supported in a brass frame on the experimental table.

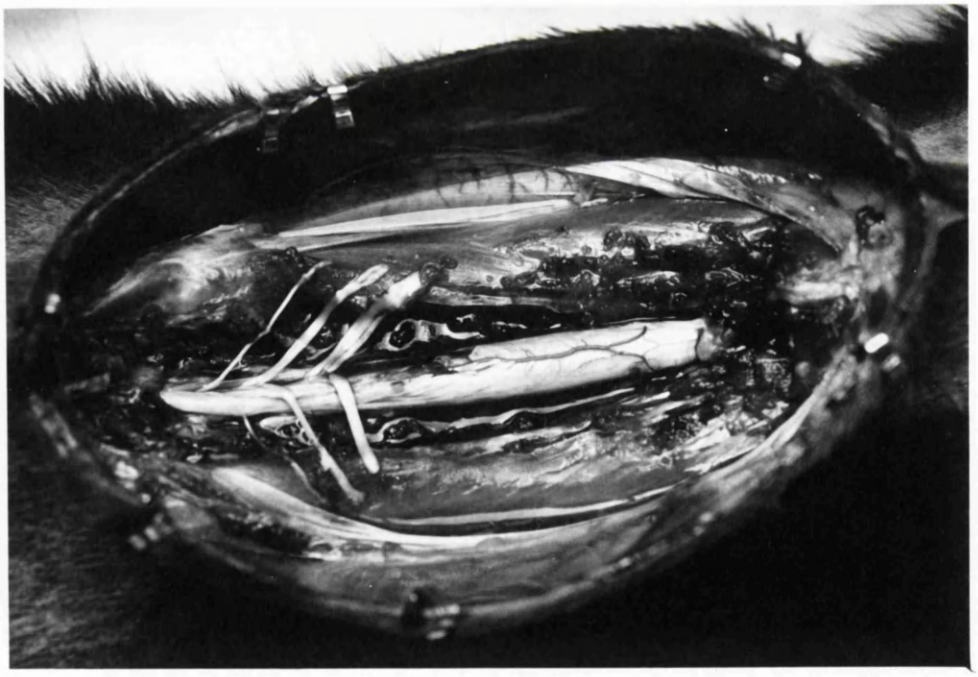

Fig. 8. The extracted dorsal roots (top) and ventral roots (bottom) of spinal nerves S1, L7, and L6.

The remaining procedures were carried out under x6 or x10 magnification provided by a Zeiss binocular dissecting microscope. The dura mater was opened along the midline over the length of the laminectomy. The dorsal and ventral roots of the spinal nerves S1, L7 and L6 were cut close to their points of entry into the spinal cord, and reflected over the muscles on either side (Fig. 8). The dorsal roots were now subdivided to give "single-unit" filaments containing single active muscle spindle and tendon organ afferent axons, as described on page 39.

ELECTROPHYSIOLOGICAL METHODS

Apparatus

Fig. 9 shows diagrammatically the electronic apparatus used in these experiments. Action potentials were recorded from small filaments of the dorsal roots, using shielded bipolar silver wire recording electrodes. The action potentials were amplified 1, 2, 5 or 10 thousand times by a rack-mounted preamplifier, which had been constructed by myself with valuable assistance from the Electronics Unit of the Institute of Physiology.

The amplified action potentials were displayed on the upper beam of a Tektronix 502A oscilloscope. They were also fed into a window-discriminator, which was used to select the relevant spike if there were more than one size of action potential recorded in the dorsal root filament. An audio monitor built into the window discriminator provided an auditory check on the correct triggering of the discriminator. In addition, the discriminator produced one standard - 15V pulse output for each action potential selected. When necessary, these standard pulses were displayed on the lower beam of the 502A oscilloscope, and the correct triggering of the window discriminator was monitored.

The standard pulses provided by the discriminator were fed into an instantaneous pulse-interval meter and the instantaneous frequency of

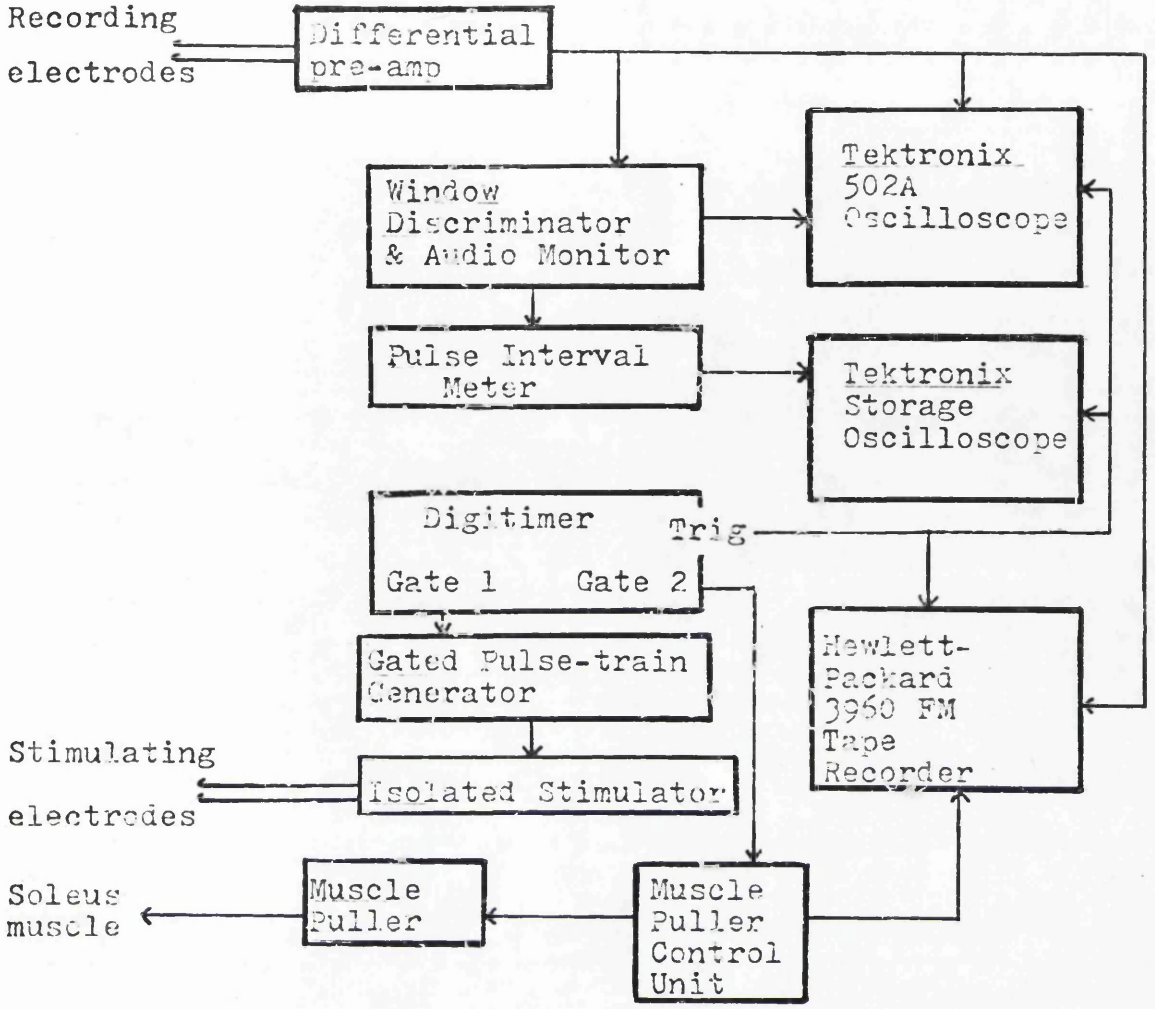

Fig. 9. Diagrammatic representation of the electronic apparatus.

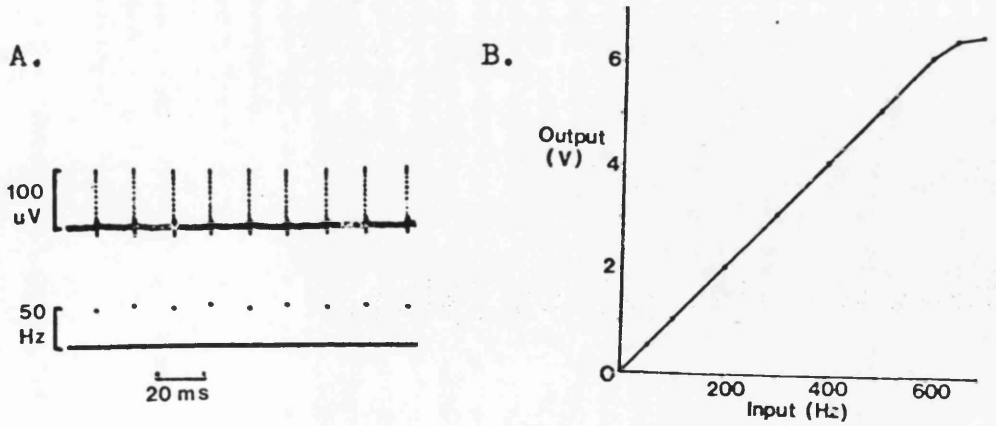

Fig. 10. A. The output of the pulse-interval meter. Upper trace, action potentials. Lower trace, pulses output by the meter. Each dot represents an action potential, and its height above the zero baseline is proportional to the instantaneous frequency. B. Calibration curve for the pulse-interval meter.

discharge was displayed on one beam of a 4-beam Tektronix storage oscilloscope. The output of the pulse-interval meter is illustrated in Fig. 10a, and appeared as a series of pulses above a zero baseline. Each pulse represents the occurrence of an action potential, and the height of the pulse above the zero baseline is proportional to the reciprocal of the time-interval between that action potential and the preceding one. Fig. 10b shows a calibration curve for this instrument. The meter is seen to be linear over the frequency range 5-600 Hz.

By selecting a different mode of operation of the pulse-interval meter, a different form of output better suited to display on a pen-recorder could be obtained. This alternative mode of display consisted of a positive-going DC voltage which varied proportionally to the instantaneous frequency of discharge. However a drawback of this alternative mode of operation was that when a previously discharging sensory ending suddenly became silent, as for example a muscle spindle primary ending following a shortening of the muscle, the DC voltage maintained its last instantaneous value, and did not fall immediately to zero. In some instances, therefore, pen-recorder traces of instantaneous frequency had to be retouched for illustration.

A Devices Digitimer was used to synchronise the various recording and stimulating equipment. A synchronising pulse was available to trigger the two oscilloscopes at the start of each cycle. Two independently variable "gates" were available within each cycle, which were used to operate a Devices gated pulse-train generator and a muscle stretching unit respectively. The gated pulse-train generator was used to provide triggering pulses to an isolated stimulator (Devices Sales Ltd.). Bipolar silver wire stimulating electrodes similar in design to the recording electrodes were used for stimulation.

Fig. 11 illustrates the muscle stretching system used in these experiments. The muscle stretching unit itself consisted of a coil through which a variable current was passed, causing a central armature to move. The muscle to be stretched was attached to a lever which amplified the actual movement of the central armature. The amplitude of displacement of the unloaded stretching lever was variable stepwise from 0.5mm to 5mm, and the time-course of displacement was similarly variable from 0.15 sec to 2 sec. A range of ramp-and-hold stretches of various amplitudes and rise-times could thus be generated.

A significant shortcoming of this stretching system was however that there was no feedback from the moving armature to indicate the true displacement and the rate of displacement that occurred in practice when the stretching lever was attached to the soleus muscle. Since no other more suitable stretching systems were available for use at the time, a photoelectric device was constructed which allowed the displacement of the stretching lever to be followed accurately. I am grateful to the Electronics Unit for advice and guidance in its construction.

Fig. 12 illustrates the principle of operation of the device. A photosensitive potentiometer strip was mounted under clear perspex in a wooden block at a suitable height, so that a small light-emitting diode attached via a short cross-bar to the stretching lever moved close to its surface. A 6V battery was connected across the potentiometer, and the voltage across the circuit with the room lights switched off and the LED in a central position over the potentiometer strip was backed off to zero. The movement of the LED in one direction now produced a positive DC voltage, and in the other direction a negative DC voltage, proportional to the amplitude of movement (Fig. 12b). The LED in fact moved along a slight arc over the photosensitive strip because of the arrangement of the lever, but

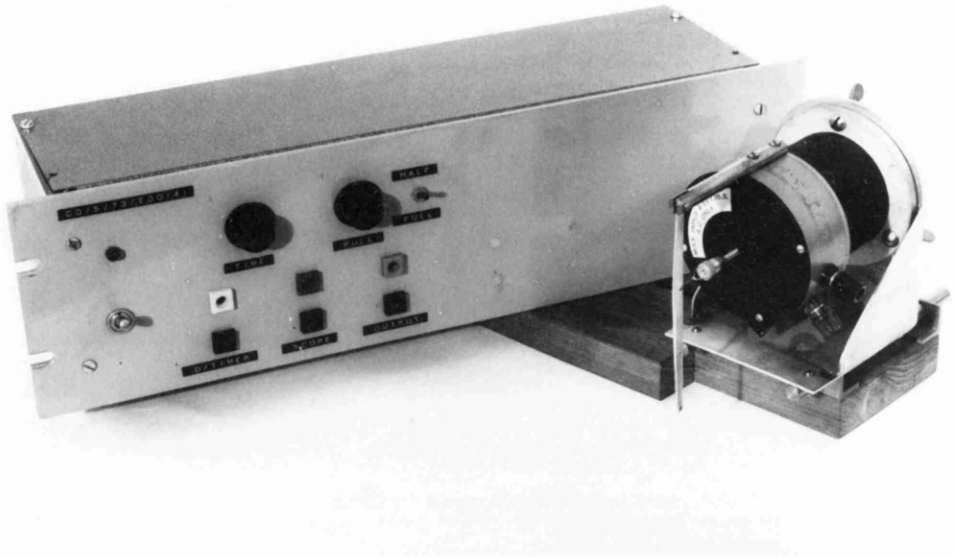

Fig. 11. The muscle puller and its control unit.

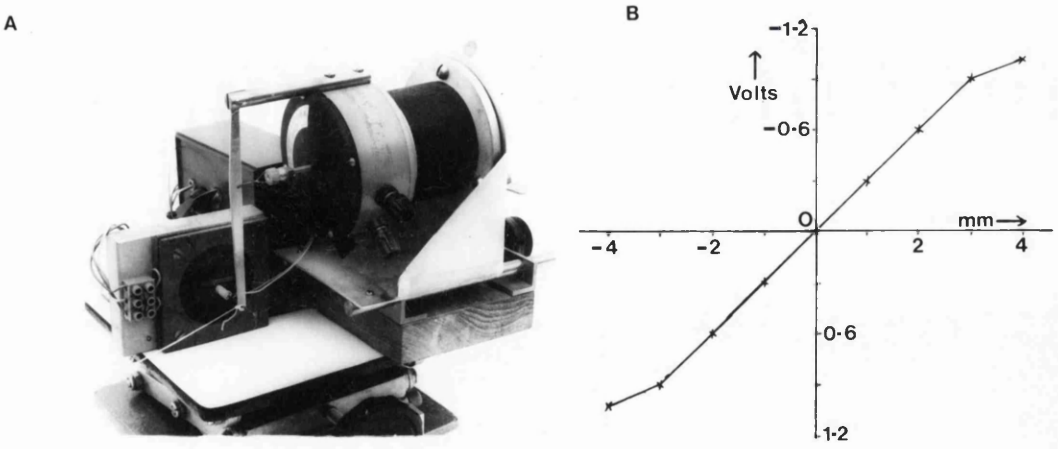

Fig. 12. A: The photosensitive length transducer attached to the puller unit. B: Calibration curve for the length transducer.

its proximity to the photosensitive strip minimised the variation in incident light intensity thus caused.

Examination of the behaviour of the muscle stretching system in several experiments showed that there was a reasonably close matching between the puller drive signal and the displacement actually produced, for stretch amplitudes of up to 3mm starting at moderate initial muscle lengths. Since the photosensitive device could not be used with the main laboratory lights switched on, for the majority of the experiments the puller drive signal was taken to be a close approximation of the actual displacement produced by the stretching unit.

In later experiments (see Results, Section VII) a more advanced muscle stretching system was employed, which had been designed and constructed by Mr. Anthony Auriemma of the Department of Electronics and Biomedical Engineering, University of Southern California. This muscle stretching unit was servo-controlled and an output indicating the actual displacement of the muscle was directly available from a built-in length transducer. The stretching unit was driven by a Servomex wave-form generator, and was capable of applying ramp stretches of 4mm (maximum amplitude) against static loads of up to 1 kilogram.

Preparation of "single-unit" dorsal root filaments

The dorsal roots of L7 and S1 spinal nerves and sometimes of L6 were subdivided to give small filaments containing single active afferent axons from muscle spindles and tendon organs in the soleus muscle. A bipolar silver wire stimulating electrode was placed in a position to stimulate the soleus muscle nerve in the leg pool. The Devices isolated stimulator was set to apply single shocks of 0.1 msec duration, 0.2 to 1.0V as required to elicit a strong muscle twitch. The Digitimer cycle time was set to

trigger the isolated stimulator every 600 msec.

Individual natural rootlets of the dorsal roots were teased free and placed in turn on a bipolar recording electrode in the spinal pool. The electrical activity of each rootlet was amplified and displayed on one beam of the Tektronix 502A oscilloscope. The Digitimer triggered the oscilloscope every 600 msec, 1 msec before the stimulus was applied to the muscle nerve. The oscilloscope sweep speed was set initially to 1 msec/division and rootlets which showed regular evoked potentials 1 to 5 msec following the muscle nerve shock were isolated. These rootlets were then subdivided to give filaments which contained only one active afferent axon, as judged by its evoked potential, spike height and regularity of discharge. When such "single-unit" dorsal root filaments had been prepared, short silk threads of different colours were tied to their ends to identify them.

Muscle spindle afferent axons were distinguished from tendon organ afferent axons on the basis of their differing behaviour during the muscle twitch produced by the supramaximal muscle nerve shock (Fig. 13; Matthews, 1972, Ch.2). Muscle spindle afferent axons were silenced during the contraction of the muscle, while tendon organs fired a burst of several impulses during the muscle contraction. The conduction velocity of the isolated afferent axons was calculated from the delay between the muscle nerve stimulus and the dorsal root evoked potential, and the conduction distance between the recording and stimulating electrodes which was measured in situ at the end of the experiment. Muscle spindle afferent axons conducting at a velocity faster than 80 m/sec were taken to be from primary sensory endings, and those conducting slower than 60 m/sec to be from secondary sensory endings. Spindle afferent axons with conduction velocities between 60 and 80 m/sec were taken to be from "intermediate" sensory endings (Matthews 1972, Ch.4; Rack & Westbury, 1966).

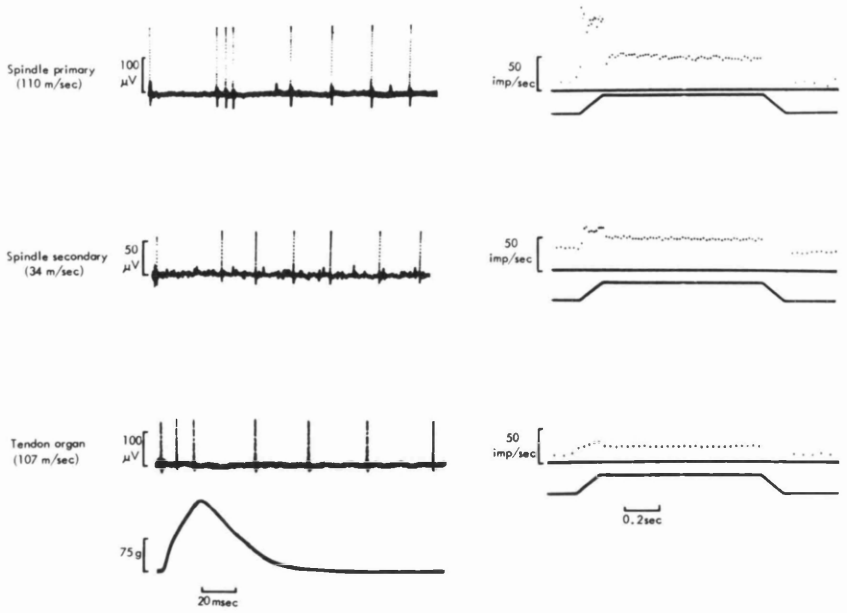

Fig. 13. L.H. column: the discharge of typical primary, secondary and tendon organ sensory endings during a muscle twitch (lowest trace). Each record starts with the stimulus artefact. R.H. column: Impulse-frequency response of the sensory endings to a ramp stretch of 3 m, starting at the same initial muscle length in each case.

Fig. 14. The Watson-Marlow Hi-Flow Inducer and the thick-walled silicone tube used for infusion of SCh.

EXPERIMENTAL PROCEDURE

Suxamethonium (Scoline; Duncan, Flockhart & Co.) was infused or injected either through a polythene cannula in the external jugular vein or through a similar cannula in the contralateral femoral artery. Fig. 14 shows the Watson-Marlow pump used for infusions and the thick-walled 1mm internal diameter silicone tube through which the infusions were made. A polythene three-way tap made the connection between the silicone tube and the polythene cannula. The pump flow rate was adjusted to give an infusion rate of 1 ml/minute (± 0.1 ml) through the silicone tube, and the pump was used at this setting in all experiments.

Solutions of suxamethonium (SCh) for infusion were made up in 25 ml of 0.9% saline by adding the correct amount of the manufacturer's stock solution (5 mg/ml) measured using a 100 µl capacity microsyringe, to produce a concentration of 100 µg SCh/Kg body weight/ml. The pump infusion rate of 1 ml/minute thus delivered 100 µg SCh/Kg/minute into the circulation of the animal.

For injections, the appropriate volume of the stock solution measured by the microsyringe was added to 0.15 ml of 0.9% saline in a 1 ml syringe and injected, followed by 0.5 ml saline to clear the cannula.

When in one animal more than one infusion or a series of injections of SCh were made, a minimum time was allowed to lapse between administrations of the drug. For injections, this ranged from 15 minutes following an injection of 100 µg/Kg SCh or less, to 40 minutes after a dose of 500 µg/Kg SCh (Fehr 1965; Brinling & Smith 1960). The minimum time allowed after an infusion of SCh at 100 µg/Kg/min was determined by the length of time that the infusion was continued. For intravenous infusions of SCh which often continued for 6 minutes or more at an infusion rate of 100 µg/Kg/min, the

minimum recovery time was 45-50 minutes. For intra-arterial infusions of SCh at a similar rate of infusion but which usually were continued for a shorter time, a 25-30 minute recovery period was found to be sufficient. Usually, two to five infusions were made in the same animal, and the results from a given sensory ending were found to be quantitatively reproducible provided that an adequate time was allowed to elapse between successive administrations of the drug (Brinling & Smith 1960).

During administration of SCh, the animal was artificially ventilated by a Palmer respiratory pump connected to the tracheal cannula. The ventilation frequency of the pump was adjusted to be as near as possible to the cat's natural breathing rate, and the stroke volume of the pump was adjusted by eye to produce a normal degree of chest inflation. The pump was disconnected as soon as voluntary breathing returned after the administration of SCh.

Once a suitable number of soleus muscle spindle and tendon organ afferents had been isolated in the dorsal roots, the muscle stretching system (page 38) was set up to apply a series of short-duration ramp-and-hold stretches to the soleus muscle. The instantaneous frequency of the afferent discharge in response to this series of test stretches was displayed on one beam of the Tektronix storage oscilloscope, with the puller driving signal on a second beam. During the experiments the afferent discharge, the muscle puller driving signal, and synchronising pulses from the Digitimer were recorded on a Hewlett-Packard FM tape recorder for subsequent analysis. In some cases, the data was processed off-line by an 8K PDP-8 computer. The object of the computer analysis and the program employed are described fully in Appendix 1.

RESULTS

RESULTS: SECTION I

The response of muscle spindle primary and secondary sensory endings to repetitive stretches of short duration.

In the experiments described here, the effects of SCh on the response of soleus muscle spindle primary and secondary sensory endings to ramp-and-hold stretches of the muscle were studied. The test stretches were of short duration, between 1 and 1.5 sec long. They were applied to the muscle spaced by "rest" intervals of at least 1 sec. In most experiments the stretch applied was of 3 mm at 12 mm/sec; in many experiments different parameters were used, and are indicated as appropriate. This section describes the response of typical primary and secondary sensory endings to repetitive muscle stretching of this kind.

Fig. 15 shows the response of a soleus muscle spindle Ia sensory ending to a single test stretch (2 mm at 8 mm/sec) applied at various starting muscle lengths. At each initial muscle length, the ending discharged at its "resting" adapted discharge frequency for that length before the test stretch was applied. In Fig. 15a, at a short initial muscle length, the ending is silent for about 0.5 sec immediately following the release of stretch. The discharge of the Ia ending then picks up again from the zero baseline, taking about 2 sec to return to its "resting" adapted level.

At longer initial muscle lengths (Fig. 15b, c, d) the depression in the activity of the Ia ending caused by the release of stretch becomes less marked. The period of silence in the discharge of the ending following the release of stretch becomes shorter at longer initial muscle lengths, until eventually the Ia discharge picks up immediately after the shortening of the muscle is complete (Fig. 15d). In addition, at longer initial muscle lengths the Ia discharge rate recovers its "resting" level progressively more quickly following the release of stretch (Fig. 15d cf. 15a).

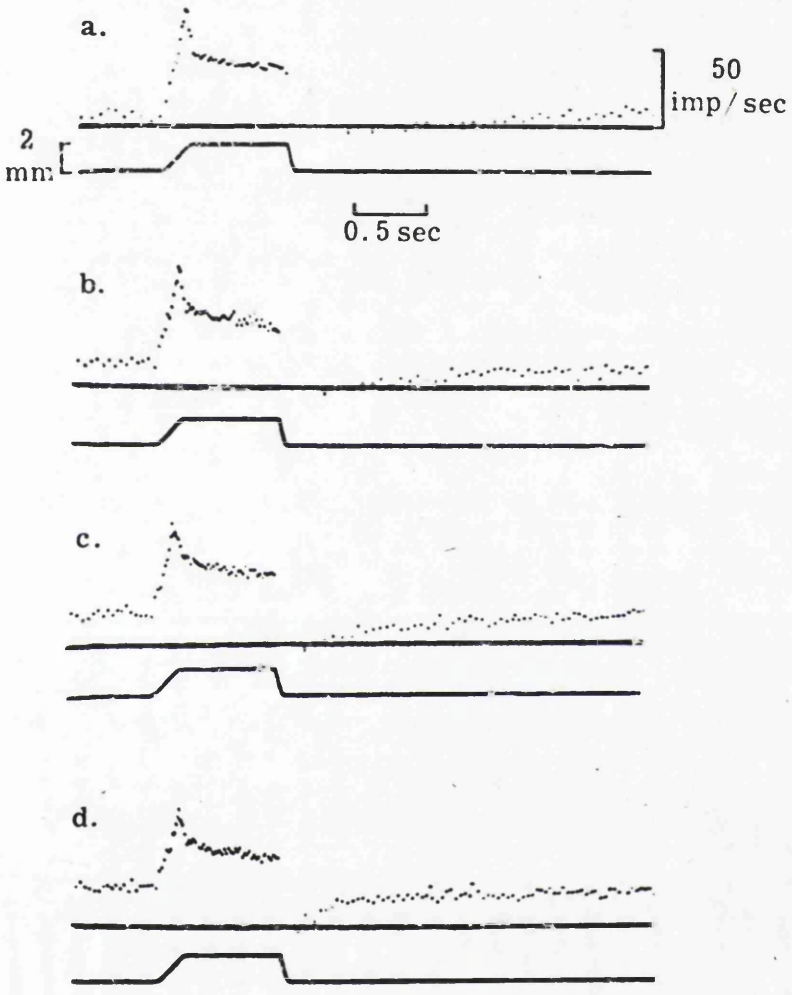

Fig. 15. The response of a soleus muscle spindle primary sensory ending to a single test stretch (2 mm at 8 mm/sec) applied at increasing muscle lengths. In this and following figures, upper trace: instantaneous frequency of discharge; lower trace: muscle puller drive signal. Before each test stretch is applied the primary ending discharges at the adapted "resting" discharge frequency for each initial muscle length. Conduction velocity of afferent, 83 m/sec.

When a series of test stretches are applied at short intervals, the depression in activity of Ia endings following the release of stretch becomes apparent in the rate of Ia discharge between successive test stretches. Fig. 16a shows the response of the same Ia ending to several test stretches of the same parameters as in Fig. 15 applied to the muscle spaced by 1 sec "rest" intervals. Before the start of the stretching sequence, the Ia ending discharged at its adapted "resting" discharge frequency of 14 imp/sec. Between successive test stretches, however, the Ia discharge does not return to its "resting" level, recovering only partially to reach an instantaneous frequency of discharge of 6 imp/sec before the next test stretch is applied. The degree of recovery of the Ia discharge between stretches is quite constant, so that the Ia discharge rate just before the application of each test stretch is close to 6 imp/sec in this particular case.

The response of the Ia ending to the dynamic and the static phases of the test stretches is also constant, after the second stretch of the series. The response of the Ia ending to the dynamic phase of the first stretch is greater than the response to the following stretches (Fig. 16a), probably reflecting an element of stiction within the muscle to be overcome by the first stretch. Nevertheless, following the first stretch of a series of test stretches applied at short intervals, the response of the Ia ending to stretching becomes quantitatively reproducible (Fig. 16a).

In some experiments, Ia endings were found which did not recover to a sufficient degree to be able to discharge at all between successive stretches of a test sequence. These endings had low rates of discharge at the starting muscle length, and could be made to discharge between test stretches by increasing the initial muscle tension. Fig. 16b shows the response of the same Ia ending as in Fig. 16a but at a shorter initial muscle length, as indicated by the lower "resting" discharge rate of the

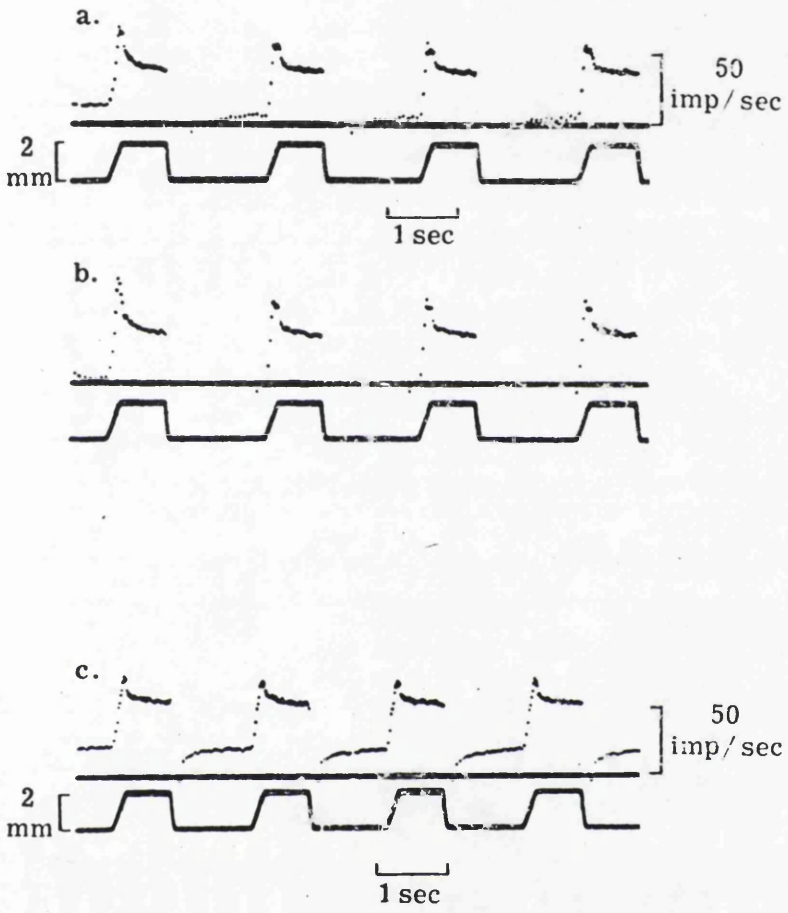

Fig. 16.

a, b: The response of the same primary ending as in Fig. 15 to several test stretches of the same parameters as in Fig. 15. In a, the initial muscle length is the same as in Fig. 15b. In b, the initial muscle length has been reduced to that in Fig. 15a. Before the start of each sequence of test stretches, the primary ending discharges at its adapted "resting" discharge frequency at the initial muscle length.

c: The response of a soleus spindle secondary sensory ending to repetitive test stretching. The initial muscle length is the same as that in a. Before the start of the stretching sequence, the secondary ending discharges at its adapted "resting" discharge rate for this initial muscle length. Conduction velocity of afferent, 40 m/sec.

ending before the start of the stretching sequence. The ending now does not discharge at all between successive stretches. In such cases too, the response of the Ia endings to the dynamic and static phases of the test stretches were quantitatively similar for the stretches following the first test stretch, as Fig. 16b shows. Some Ia endings which remained silent between successive test stretches showed marked "initial bursts" (Matthews 1972) at the foot of each ramp stretch.

Soleus muscle spindle secondary sensory endings also behaved in a similar way during sequential muscle stretching, as shown in Fig. 16c. However, the depression in the activity of secondary sensory endings following the release of stretch was not as marked as the effect on primary sensory endings, with the result that secondary endings as a rule recovered their "resting" adapted discharge rate between the successive stretches of a test sequence (Fig. 16c).

Series of test stretches were often continued for periods of 30 minutes or more, before, during and after administration of SCh. Control recordings from soleus muscle spindle primary and secondary sensory endings show that such series of stretches can be continued for indefinite periods of time, without fatiguing the sensory endings (see also Rack & Westbury 1966).

DISCUSSION: TERMINOLOGY

Bronk (1929) showed in frog muscle stretch receptors presumed to be muscle spindles that the receptors could be "stretched for over a thousand times with only 1 sec intervals of rest without showing appreciable fatigue, provided the successive stretches were of short duration". In the cat, B.H.C. Matthews (1931) found that a long-term after effect could be produced in primary sensory endings in the gastrocnemius muscle, but only if the muscle was held extended for many seconds. This after-effect

(called by him the "adaptation remainder") disappeared after a few seconds of rest. However, Matthews did not study the effects of sequential short duration stretches of the kind used in the present experiments.

The depression in activity of Ia sensory endings following the release of stretch presumably reflects an after-effect of the muscle shortening on the electrical state of the sensory endings. Hunt & Ottoson (1975) have recorded changes in the generator potentials of primary and secondary sensory endings in isolated cat muscle spindles, and showed that while stretch of the muscle depolarised the sensory endings the release of stretch produced hyperpolarisation. The hyperpolarising effects of muscle shortening on the generator potential of primary sensory endings was much greater than on the generator potential of secondary sensory endings. As suggested by Hunt & Ottoson, the silence and gradual recovery of the discharge of Ia sensory endings following the release of stretch must reflect this hyperpolarisation of the endings and their subsequent recovery from it. Increasing the initial muscle length reduces the after-effects of the release of stretch, as shown in Fig. 15, presumably because the greater initial depolarisation of the endings counteracts the hyperpolarising after-effects of the release of stretch.

During a test sequence of repetitive stretches, the fact that the Ia discharge never recovers sufficiently between stretches as to reach the adapted "resting" level, indicates that the Ia endings are still hyperpolarised to some extent when the following test stretch is applied. This is a possible reason for the response of the ending to the dynamic phase of the second and following stretches being lesser than the response to the dynamic phase of the first stretch (Fig. 16a, b). However, since the discharge of the Ia ending during the static extended phase of the ramp

stretches is quantitatively similar for all the stretches, the higher dynamic response to the first stretch may at least in part be due to stiction within the muscle, as suggested above. In either case, soon after the start of sequential test stretching, the response of Ia and secondary sensory endings to stretch became quantitatively reproducible.

The effects of SCh on primary and secondary sensory endings were studied by following three parameters of the behaviour of the endings during repetitive test stretching. These three parameters are defined below and also in Fig. 17.

(i) The initial discharge rate of the sensory ending, defined as the rate of discharge of the ending just before the application of the second or following test stretch of a sequence of stretches;

(ii) The dynamic response of the ending, defined as the rate of discharge at the end of the dynamic phase of stretch;

and (iii) The position response of the ending, defined as the rate of discharge of 0.5 sec after the end of the dynamic phase of the test stretch, while the muscle is held extended.

The initial discharge rate of the ending during a sequence of test stretches is determined by the degree of recovery that occurs between successive stretches from the hyperpolarising after-effect of each release of stretch, as discussed above. Thus it is dependent on the time allowed for recovery between successive stretches, the amplitude of the test stretch, the rate of release of the test stretch, and finally on the inherent rate of recovery from hyperpolarisation of the sensory nerve terminals themselves. The recovery time, the amplitude of stretch and the rate of release of stretch are constant for a particular test frequency of stretches; once a given sensory ending has settled down to give quantitatively similar responses to the sequential test stretches, therefore, the initial discharge rate of the ending then becomes a convenient measure of the rate

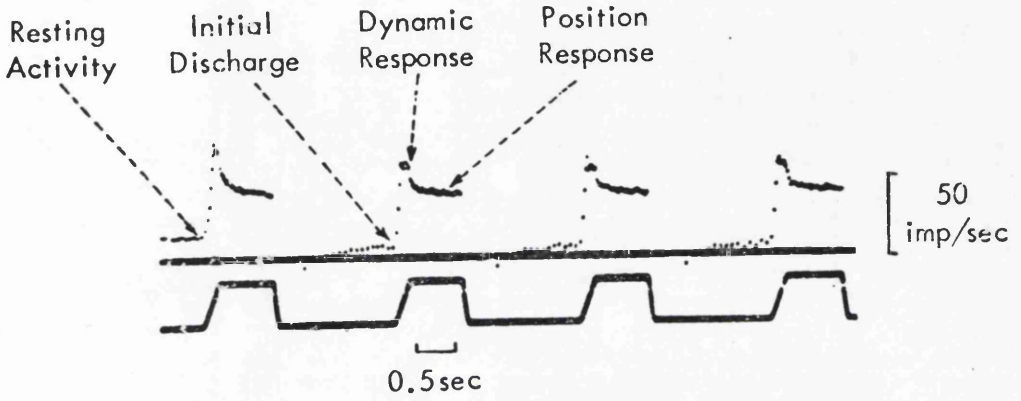

Fig. 17. Definition of the three parameters of the behaviour of muscle spindle sensory endings during repetitive test stretching, with reference to a soleus muscle spindle primary sensory ending.

Initial discharge rate: frequency of discharge of the ending just before the application of the second or following test stretch of a sequence of stretches.

Dynamic response: frequency of discharge of the ending at the end of the dynamic phase of stretch.

Position response: frequency of discharge of the ending 0.5 sec after the end of the dynamic phase of stretch.

of recovery from hyperpolarisation of the sensory ending itself.

The dynamic response defined above is not the "dynamic response" of Jansen & Matthews (1962), which is now termed the dynamic index (Crowe & Matthews 1964). However, the quantitative difference between the dynamic and position responses as defined above is equal to the dynamic index. The effects of SCh on the dynamic sensitivity of the sensory endings in these experiments may therefore be assessed in the conventional way by measuring the effects of SCh on the dynamic index. The position sensitivity of the spindle sensory endings during such sequential test stretching, which determines the change in the discharge rate of the ending caused by the change in muscle length, is reflected in the difference between the initial discharge rate and the position response. However, for Ia endings this measure is not the same as the conventional measure of the true position sensitivity, which is shown in the difference between the adapted "resting" discharge at the initial muscle length and the position response (Matthews 1972). Estimates of the position sensitivity of Ia endings during repetitive test stretching can thus be made by measuring the difference between the adapted "resting" discharge rate and the position response as long as the initial discharge of the ending is below the "resting" discharge rate, or subsequently by measuring the difference between the initial discharge rate and the position response after the action of SCh has increased the initial discharge rate to a value the same as or above the control "resting" activity.

As will become clear in the presentation of the Results, changes in the three parameters defined above during SCh administration provided a useful basis for analysis of the effects of SCh on the sensory endings. This was made easier by the fact that in these experiments it was of interest to examine the changes produced by SCh in the sensitivity of the sensory endings to stretch, rather than to determine the quantitative values for the true

dynamic and static sensitivities of the endings. A fuller treatment of the significance of changes in each of the parameters defined above will be attempted in the General Discussion, in the light of the Results.

RESULTS: SECTION II

Activation of a typical soleus muscle spindle Ia sensory ending by intra-arterial infusion of SCh.

Fig. 18 shows graphically the changes in the initial discharge rate (lowermost curve), the position response (middle curve) and the dynamic response (uppermost curve) of a typical soleus muscle spindle primary sensory ending, during infusion of SCh into the aortic bifurcation (100 µg/Kg SCh/min). In Fig. 19, the response of the Ia ending to the test stretches (3 mm at 12 mm/sec) at various times during the infusion of SCh are shown, to further illustrate the behaviour of the ending.

The "resting" adapted discharge rate of the Ia ending at the initial muscle length in the control condition was 13 imp/sec, but the initial discharge rate of the ending during the repetitive stretching sequence was only 9 imp/sec (Fig. 19a; Fig. 18). The first change to be seen in the behaviour of the ending following the start of SCh infusion took place within 20 sec, when the initial discharge rate began to increase (Fig. 18, "I"). This happened initially without any change in the response of the ending to the test stretches themselves (Fig. 18, stretches 7 to 9). As the initial discharge rate continued to increase, the dynamic and position responses then increased with it, though not to the same extent, so that over about 15 seconds while the initial discharge rate rose from 9 to 20 imp/sec, the dynamic and position responses both increased by only 4 imp/sec (Fig. 18, stretches 7 to 11; Fig. 19b, first two stretches). Thus, the net effect of SCh on the Ia sensory ending in this initial period was to produce a large increase in the initial discharge rate, which first compensated for the discrepancy between the control initial discharge and the "resting" discharge rates (Fig. 17) and then rose to a value above the "resting" discharge rate of the ending. Though the dynamic and position

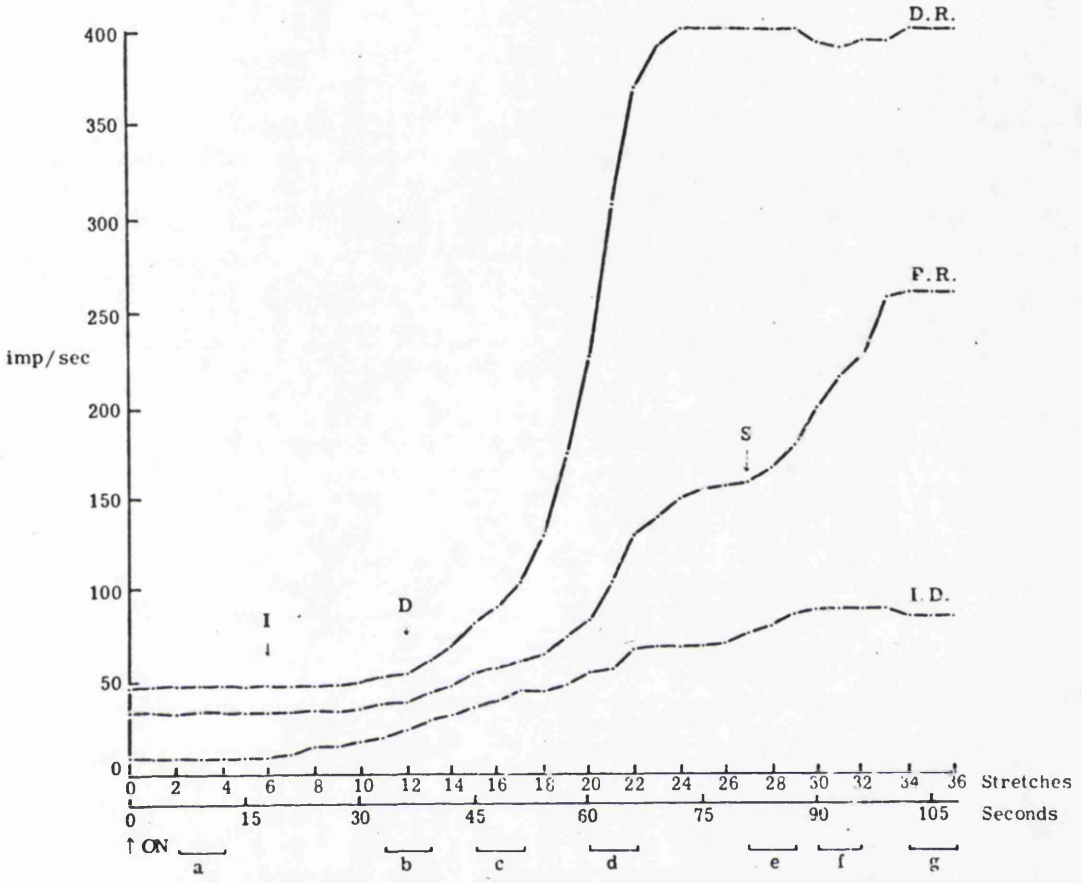

Fig. 18. Changes in the dynamic response (D.R.), position response (P.R.) and initial discharge rate (I.D.) of a typical primary sensory ending during infusion of SCh into the aortic bifurcation at 100 µg/kg/min. Infusion begins at time 0 and continues throughout. a - g indicate times during the infusion when the records illustrated in Fig. 19 were made. "I", "D" and "S" indicate the onset of Phase I, II and III of excitation respectively; see text.

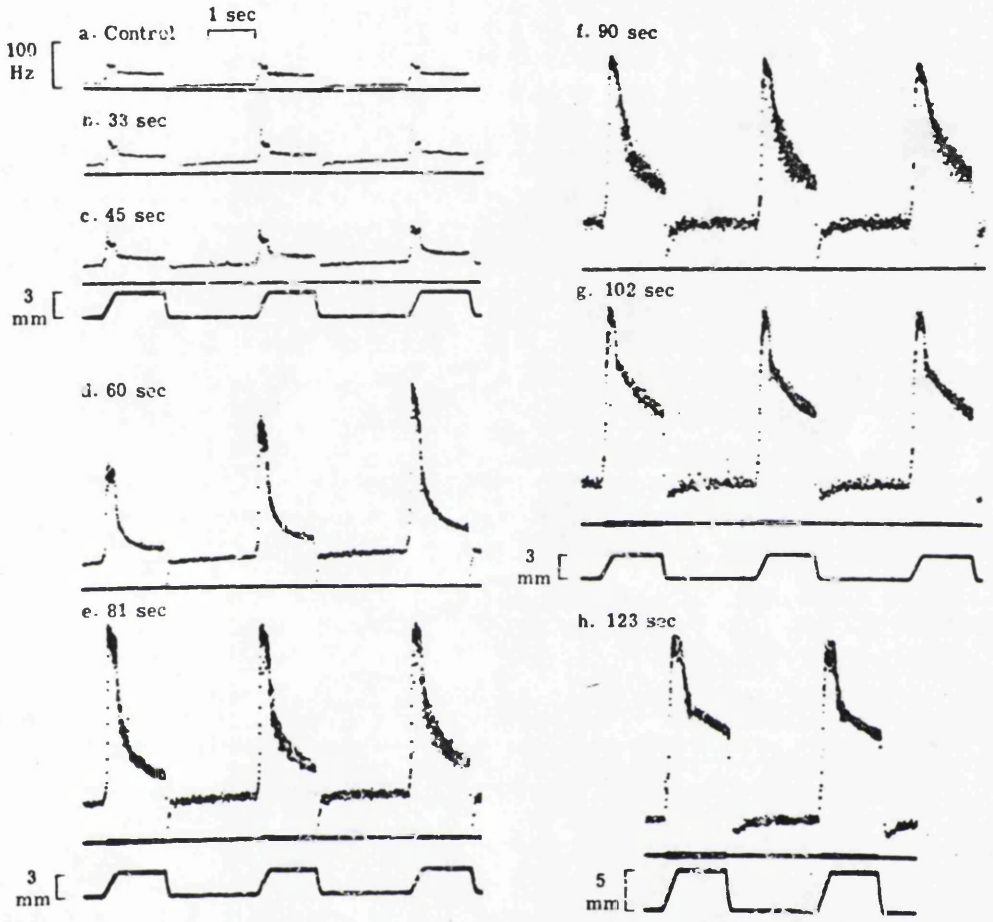

Fig. 19. Changes in the response of the typical primary sensory ending illustrated in Fig. 18 to test stretches (3 mm at 12 mm/sec) during intra-arterial SCh infusion. a - g records taken at the times during the infusion indicated in Fig. 18. h: the response of the maximally activated Ia ending to stretches of 5 mm at 15 mm/sec.

responses of the ending increased with the increase in the initial discharge rate, the dynamic index remained the same as the control value, at 14 imp/sec (Fig. 18). However, the increase in the initial discharge rate above the "resting" discharge rate was greater than the increase in the position response over this period, and as a result the position sensitivity of the ending decreased, from 7.7 imp/sec/mm in the control condition to 6.0 imp/sec/mm (stretch 11, Fig. 18).

Next, in this case 36 sec after the start of SCh infusion, the dynamic response of the Ia ending increased dramatically (Fig. 18, "D"; Fig. 19c, d). Over a period of 36 seconds (stretches 12 to 24 in Fig. 18) the dynamic response rose from 54 to 404 imp/sec, an increase of almost 750%. As the increase in dynamic sensitivity developed, the Ia discharge following the dynamic phase of stretch adapted rapidly and in a curvilinear fashion (Fig. 19d; first stretch in Fig. 19e). The position response, measured 0.5 sec after the end of the dynamic phase of stretch, therefore increased by a much smaller amount, from 38 to 150 imp/sec over the same period. As a result the dynamic index increased rapidly from 16 imp/sec to 254 imp/sec (Fig. 18). This large increase in dynamic sensitivity was accompanied by a smaller increase in the position sensitivity also, which rose from 6.0 imp/sec/mm to 28.6 imp/sec/mm over the same period.

With continued infusion of SCh, the position response of the Ia ending began to increase further, while the dynamic response remained high (Fig. 18, "S"; Fig. 19e, last two stretches; Fig. 19f, g). This was accompanied by a smaller rise in the initial discharge rate, so that the position sensitivity of the ending approximately doubled, from 28.6 imp/sec/mm (Fig. 18, stretch 26) to 58.6 imp/sec/mm (Fig. 18, stretch 35). Since the dynamic response of the ending did not increase further while the position response increased, the dynamic index was reduced from 254

imp/sec before the increase in position response to 143 imp/sec after (Fig. 19e, f, g).

The time course of adaptation of the Ia discharge after the dynamic phase of the test stretch changed gradually over this period, from a curvilinear form of decay to a more linear form (Fig. 19g). During this transition, the discharge of the Ia ending became less regular (Fig. 19f). The dynamic response of the ending decreased by a small amount during this transition but returned to its previous value after it (Fig. 18, stretches 29 to 34). When the increase in position sensitivity had become fully developed, the Ia discharge showed a sharp discontinuity immediately following the dynamic phase of stretch, which had not been present earlier (Fig. 19g, cf. Fig. 19d, e). This discontinuity was made more obvious when a few test stretches of larger amplitude (5 mm at 15 mm/sec) were applied, as shown in Fig. 19h.

No further changes in the behaviour of the Ia ending were observed with continued SCh infusion. Fig. 20 shows graphically the recovery of the Ia ending from the effects of the infusion of SCh, which took place over a period of some 5 minutes following the end of infusion. In Fig. 21, the responses of the Ia ending to test stretches at the indicated times during the recovery are shown.

Within 10 seconds of switching off the SCh infusion, the initial discharge, position response and the dynamic response began to decrease together and at approximately the same rate, so that while the absolute frequencies of discharge of the Ia ending fell, the dynamic and position sensitivities of the ending did not appear to change (Fig. 20, stretches 6 to 12). This was followed by a large decrease in the position response, which decayed from 232 to 162 imp/sec over a period of 24 sec (Fig. 20, stretches 12 to 20). The initial discharge rate decreased by only 16 imp/

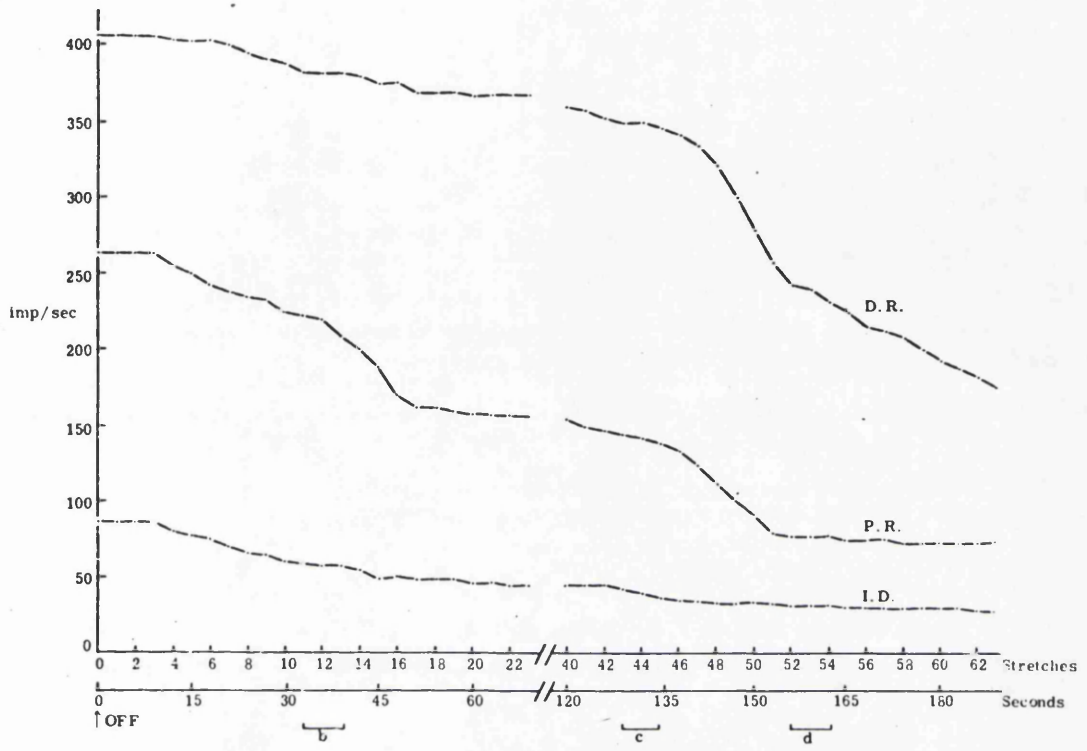

Fig. 20. The recovery of the dynamic response (D.R.), position response (P.R.) and initial discharge rate (I.D.) of the primary ending illustrated in Figs. 18 and 19 from the effects of intra-arterial SCh infusion. The infusion of SCh ceased at time 0. b - d indicate the times when the corresponding records shown in Fig. 21 were made.

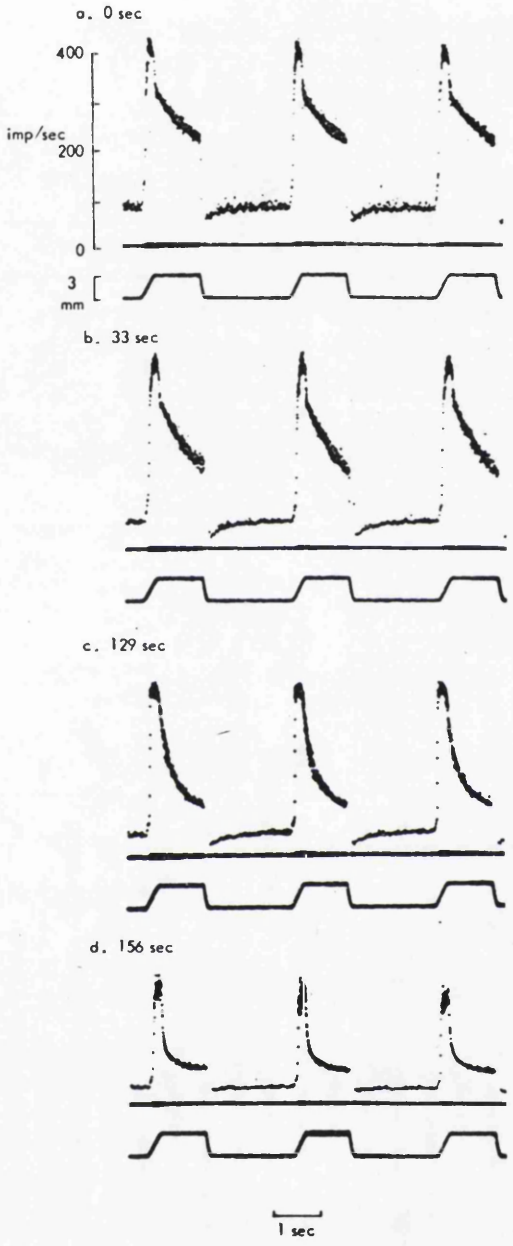

Fig. 21. Changes in the response of the typical Ia ending illustrated in Fig. 20 to stretching during recovery from the effects of SCh infusion. a response of the ending to stretching immediately after the end of infusion. b - d records taken at the times indicated in Fig. 20.

sec over this period, so that the effective position sensitivity of the ending fell from 55.6 imp/sec/mm (Fig. 20, stretch 12) to 37.6 imp/sec/mm (Fig. 20, stretch 20). Since the dynamic response also fell by a smaller amount than the position response over this period, the dynamic index of the ending again increased, from 158 imp/sec to 206 imp/sec. The Ia discharge at the extended length of the test stretch gradually reverted to the more curvilinear form of decay (Fig. 21b, c). Thus, the increase in position sensitivity which took place after the increase in dynamic sensitivity during infusion of SCh, decreased before the dynamic sensitivity during recovery of the ending from the effects of infusion.

The remaining high dynamic sensitivity of the Ia ending was maintained without much change for about 45 sec after the position sensitivity had decayed to its lower value, after which the dynamic sensitivity also gradually decayed (Fig. 20, stretches 40 onwards). The decrease in dynamic response was accompanied by a decline of the remaining position sensitivity of the ending to control values. The dynamic index gradually decreased, to reach control values about 5 minutes after the end of SCh infusion.

To summarise, the activation of this typical Ia sensory ending by SCh appears to take place in three consecutive phases (Fig. 18). Initially, there is a gradual facilitation of the initial discharge rate of the ending, without potentiation of the dynamic or position sensitivities of the ending (Phase I of activation, "I" in Fig. 18). This is followed by a rapid, large increase in the dynamic sensitivity of the Ia ending, accompanied by a smaller increase in the position sensitivity, so that the dynamic index increases markedly (Phase II of activation, "D" in Fig. 18). Finally, there is a further increase in the position sensitivity of the ending, independently of the dynamic response, reducing the dynamic index significantly (Phase III of activation, "S" in Fig. 18). During recovery

of the Ia ending from the effects of infusion, the initial discharge rate falls first (Fig. 20, Fig. 21b) but leaves the ending still with high dynamic and position responses, as in Phase III of activation. The position response then decreases, and the ending returns to a situation where the dynamic sensitivity is high as in Phase II of activation. The response of the ending to the test stretches then gradually returns to normal, as the high dynamic sensitivity decays.

RESULTS: SECTION III

Reproducibility of activation of Ia sensory endings by SCh.

In the course of this work, the activation of Ia sensory endings in the soleus muscle by intravenous (i.v.) SCh infusion as well as intra-arterial (i.a.) SCh infusion was studied. In both kinds of experiment, the rate of SCh infusion employed was 100 µg/kg/min, in order to avoid excessively long recovery times following each infusion (see Methods, page 41).

Infusion of SCh into the aortic bifurcation via a cannula in the contralateral femoral artery was found to be the more reliable means of activating soleus muscle spindle Ia sensory endings in a consistent manner. Of 20 Ia endings studied in 9 cats, 18 were successfully activated by i.a. infusion of SCh at 100 µg/kg/min, through the three phases of excitation described above for a typical Ia sensory ending (Section II). The remaining two cases developed large increases in their dynamic sensitivity to stretch as in Phase II of activation of the typical Ia ending, but this was not followed by a further increase in position sensitivity with continued SCh infusion (Phase III of activation). Fig. 22 shows the times from the start of i.a. infusion of SCh to the start of each of the three phases of activation ("I", "D" and "S" in Fig. 18) for the 20 Ia endings studied in this way.

As can be seen from Fig. 22a, most Ia endings showed a facilitation of their initial discharge rate (Phase I of excitation) within 40 sec of the start of SCh infusion, and all of the endings studied were activated within 60 sec. The difference in lag times between Ia endings is probably not entirely due to differences in circulatory conditions in different animals, e.g. in blood pressure, because in any given animal some Ia

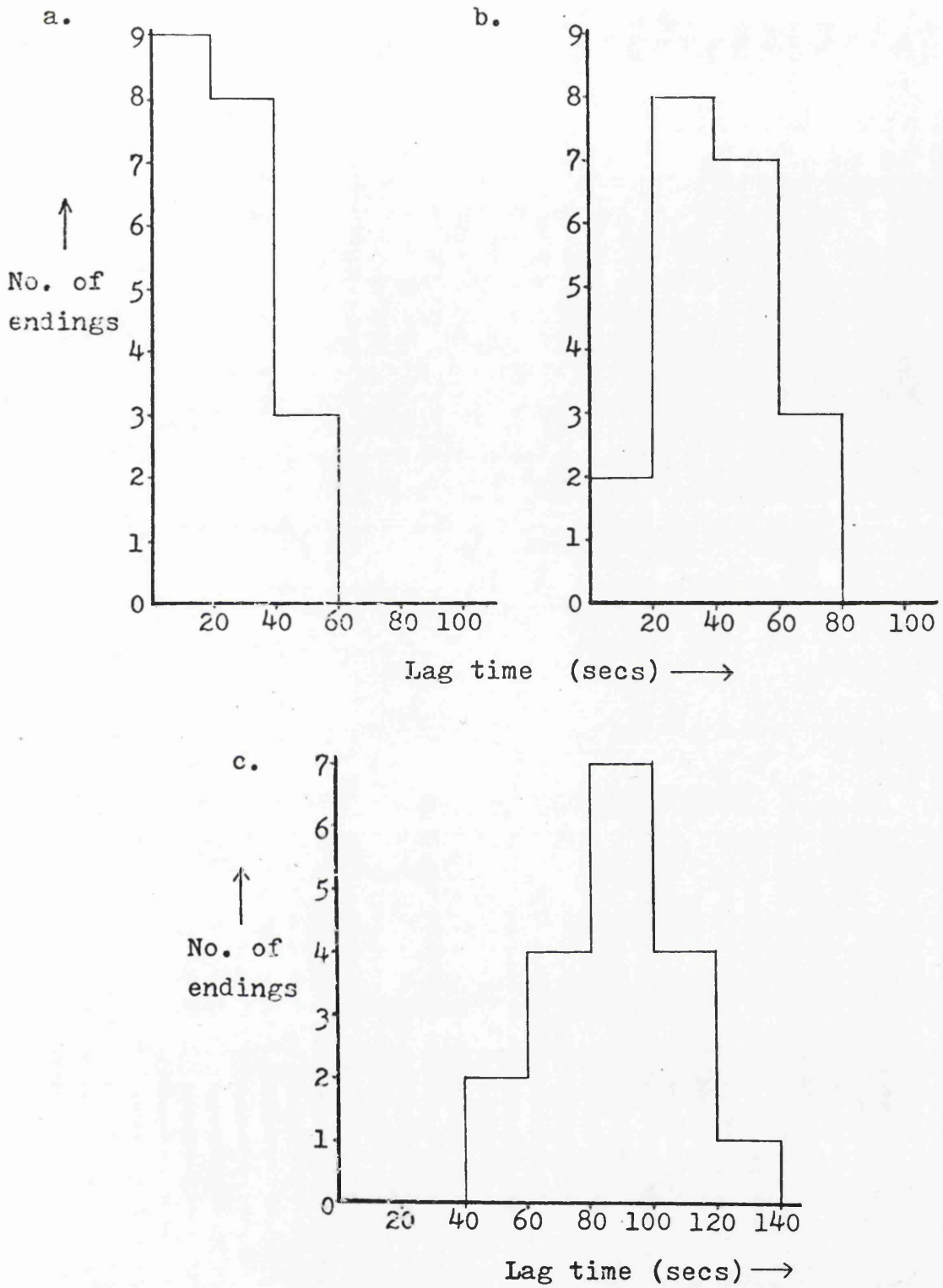

Fig. 22. The lag times from the start of intra-arterial infusion of SCh (100 µg/kg/min) to the onset of Phase I of excitation (a), Phase II of excitation (b), and Phase III of excitation (c) for 20 primary sensory endings studied in this way. Two of the Ia endings did not show Phase III of excitation.

endings were found to be much more sensitive to SCh than others. To give an extreme example, in one experiment one Ia ending showed a rapid, large increase in its initial discharge rate only 6 sec after the start of an i.a. SCh infusion, while a different Ia ending did not respond at all for 46 sec after the start of infusion.

All twenty Ia endings studied during i.a. SCh infusion developed large increases in their dynamic sensitivity to stretch following the initial facilitatory effect (Phase II of excitation), as Fig. 22b shows. Two of the endings showed an increase in the dynamic index between 15 and 20 sec after the start of infusion, while the majority of Ia endings entered Phase II of excitation between 20 and 60 sec after the start of infusion. The two more sensitive Ia endings also had a relatively short lag time between the start of infusion and the start of Phase I of excitation, the first being 6 sec and the second 12 sec.

Eighteen of the twenty Ia endings showed a further increase in their position sensitivity following the increase in dynamic sensitivity (Phase III of excitation). The remaining two endings remained in Phase II of excitation, with a high dynamic index and a characteristic fast adaptation of the Ia discharge following the dynamic phase of the test stretch, until the SCh infusion was stopped when the response of the endings gradually returned to normal. As Fig. 22c shows, the majority of Ia endings studied entered Phase III of activation between 60 and 120 sec from the start of infusion. The two Ia endings which had short lag times to Phases I and II of activation also had relatively short lag times to Phase III, the first being 56 sec and the second 70 sec.

In a different series of experiments, the activation of soleus muscle spindle Ia endings by intravenous infusion of SCh into the external jugular vein was studied. Fig. 23 shows the time-course of activation of 20 Ia

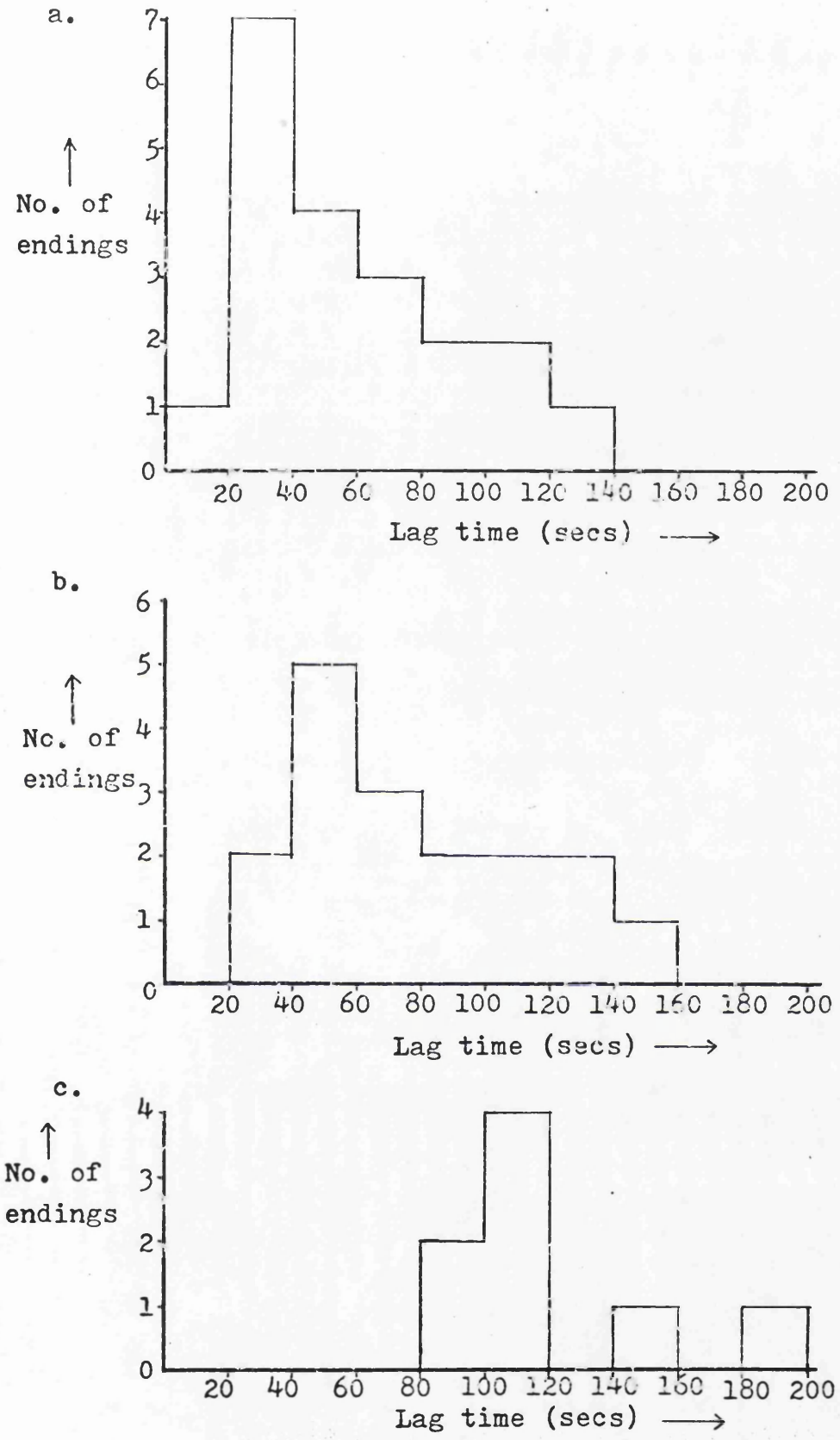

Fig. 23. The lag times from the start of intravenous SCh infusion (100 µg/kg/min) to the onset of Phase I of excitation (a), Phase II of excitation (b), and Phase III of excitation (c) for 20 Ia sensory endings studied in this way. Only 17 Ia endings entered Phase II of excitation, and only 8 entered Phase III of excitation.

endings by i.v. infusion of SCh at 100 μg/kg/min, in a similar format as in Fig. 22. As Fig. 23a shows, all twenty Ia endings studied in this way were activated through Phase I of excitation, but while some of the endings were activated soon after the start of infusion, others required the SCh infusion to be continued for well over 100 sec before showing any effect.

Of the 20 Ia endings, three did not show further changes in their responses to stretch after Phase I of activation, and 17 were activated through Phase II of excitation (Fig. 23b). Again though some Ia endings showed an increase in their dynamic sensitivity within one minute of the start of infusion, others did not do so until the infusion had been continued for a much longer time.

Only 8 of the 20 Ia endings were successfully activated through Phase III of excitation by i.v. infusion of SCh (Fig. 23c). Thus, of 20 cases, 17 showed an increase in their dynamic sensitivity during SCh infusion (Phase II of excitation), and in only 8 of these cases was this followed by a further increase in the position sensitivity (Phase III of activation).

In three preliminary experiments, the activation of three Ia sensory endings by intravenous injections of SCh was studied. The response of one of the Ia endings to test stretches following an injection of 300 μg/kg SCh is shown in Fig. 24. The injection was made 10 sec before the first stretch shown in Fig. 24, and the response of the ending to this stretch is identical to control responses. Following this lag period, the Ia ending was rapidly activated through the same sequence of events as described above for a typical Ia sensory ending during SCh infusion (Section II). First, the initial discharge rate of the ending accelerated quickly ("I", Fig. 24). This was not caused by an increase in the static sensitivity of the sensory ending, however, as the response of the ending

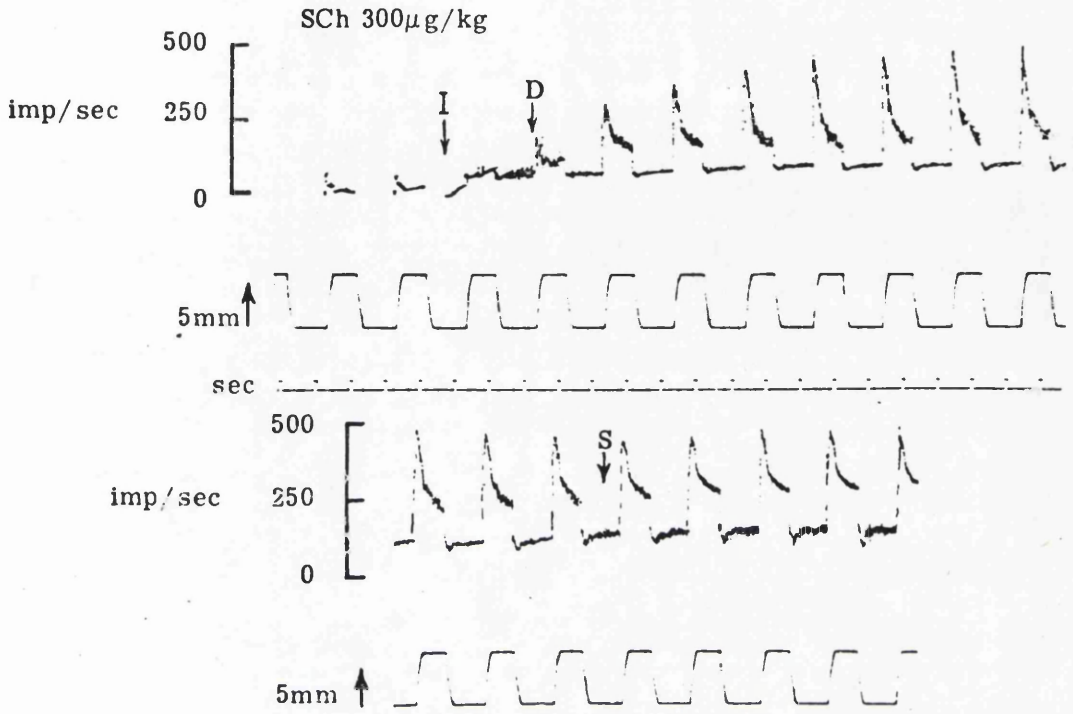

Fig. 24. Response of a soleus muscle spindle primary sensory ending to test stretches (5 mm at 20 mm/sec) following an injection of 300 μg/kg SCh into the external jugular vein. The injection was made 10 sec before the first stretch illustrated; the response of the ending to this stretch is identical to control responses. "I", onset of initial facilitatory effect; "D", onset of dynamic potentiation; "S", onset of later increase in position sensitivity. (Lower trace follows upper).

to the test stretch immediately following "I" in Fig. 24 shows. Instead, this initial increase in the initial discharge rate appeared to be the result of a general facilitation, analogous to Phase I of activation during SCh infusion. The recording was then disturbed by a short period of extrafusal fasciculations. This was followed by a large increase in the dynamic response of the ending, so that the dynamic index increased from about 67 imp/sec at "D" (Fig. 24) to 230 imp/sec 16 seconds later. This is analogous to Phase II of activation of a typical Ia sensory ending during SCh infusion. The position response then increased further while the dynamic response of the ending remained high ("S", Fig. 24), so that the dynamic index decreased from 230 to 135 imp/sec (penultimate stretch in Fig. 24). The dynamic response of the ending decreased by a small amount as the position response increased, but then returned to its previous value. This increase in the position sensitivity is equivalent to Phase III of activation of a typical Ia sensory ending during SCh infusion.

Injection of smaller doses of SCh produced graded effects on the responses of the Ia ending to stretch. Fig. 25 shows the maximum dynamic and position responses and the maximum initial discharge rate reached by the ending following the injection of various doses of SCh. Injection of doses of SCh upto 200 µg/kg produced a related increase in the dynamic response of the ending, but higher doses of SCh did not increase the dynamic response much further. Injection of a dose of 50 µg/kg SCh produced a marked increase in the discharge of the ending between successive stretches, but only a small increase in the dynamic response, as shown in Fig. 26a.

After injections of doses of SCh of 150 µg/kg and above, the position response of the ending increased through two stages, as described for a 300 µg/kg SCh injection (Fig. 24). Following injections of doses below

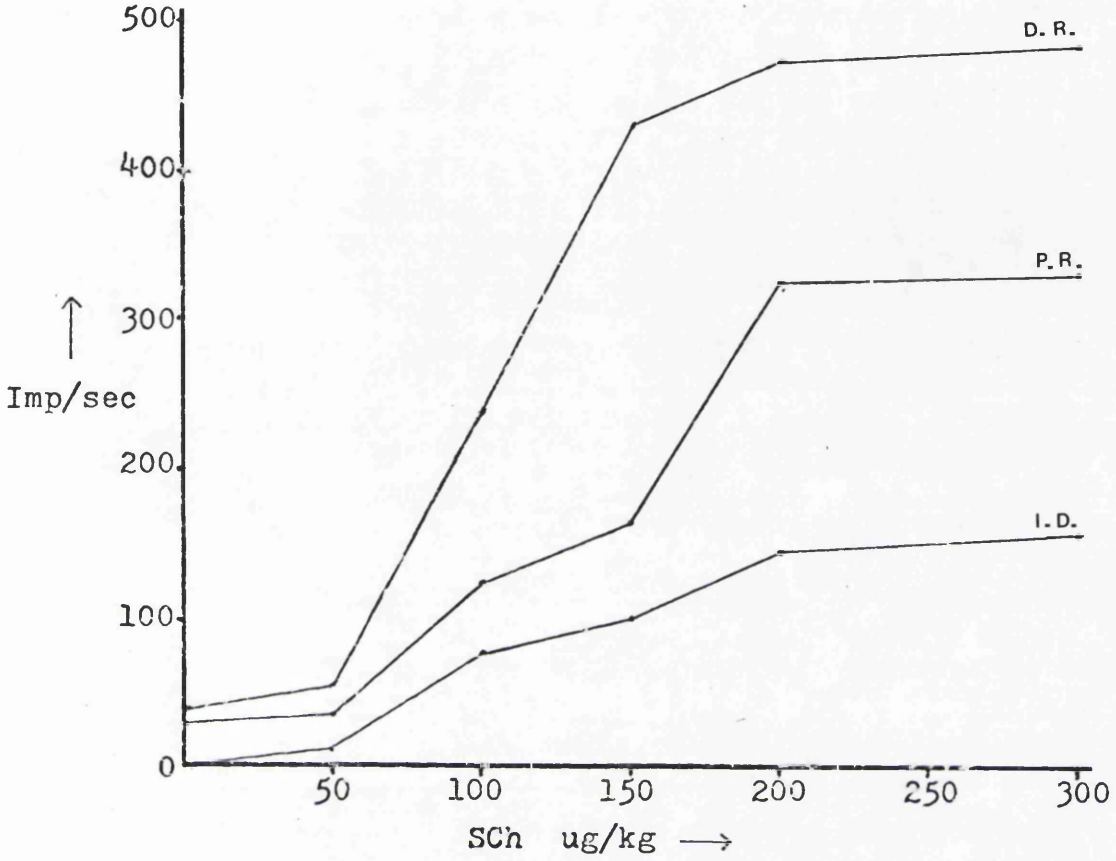

Fig. 25. The maximum dynamic response (D.R.), position response (P.R.) and initial discharge rate (I.D.) of the soleus muscle spindle Ia sensory ending illustrated in Fig. 24 following intravenous injections of various doses of SCh. Test stretches, 5 mm at 19 mm/sec.

150 µg/kg SCh, however, the second stage of increase in the position response ("S", Fig. 24) did not occur, and the position response remained relatively low (Fig. 25). Fig. 26b shows the response to test stretches of the Ia ending following an injection of 100 µg/kg SCh, to illustrate this point. Thus, doses of SCh of 150 µg/kg and below activated this Ia ending through the equivalent of Phases I and II of activation, while the third and final stage of activation was only seen following injections of doses of SCh above 150 µg/kg.

In the two other experiments where Ia endings were studied following injections of SCh, it was found that while facilitatory and dynamic effects equivalent to Phases I and II of activation could readily be induced by injections of SCh below 200 µg/kg, Phase III of activation was not induced in either case by doses of SCh upto 500 µg/kg. Fig. 27 shows the maximum dynamic and position responses and the maximum initial discharge rate of one of the two Ia endings following injections of various doses of SCh. The dynamic and position responses are seen to increase together, and the marked "step" increase in position response shown by the Ia ending in Fig. 25 between 150 and 200 µg/kg SCh is absent.

Of the three Ia endings activated by i.v. injections of SCh, therefore, two were not activated beyond the equivalent of Phase II of excitation by doses of SCh upto and including 500 µg/kg, and one was excited through all three phases of activation. Thus, as with i.v. infusions of SCh, i.v. injections of SCh readily produced facilitation and dynamic potentiation of the Ia endings (Phases I and II of activation), but produced the final stage of excitation (Phase III) in only one of three cases.

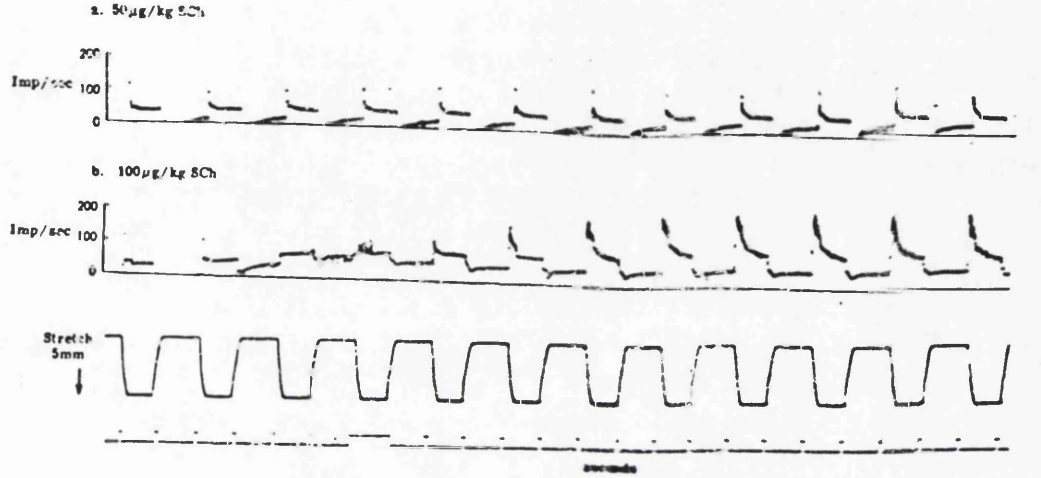

Fig. 26. The effect of intravenous injections of 50 µg/kg SCh (a) and 100 µg/kg SCh (b) on the response to stretching of the Ia sensory ending illustrated in Figs. 24 and 25. The injections of SCh were made 10 seconds before the start of each trace.

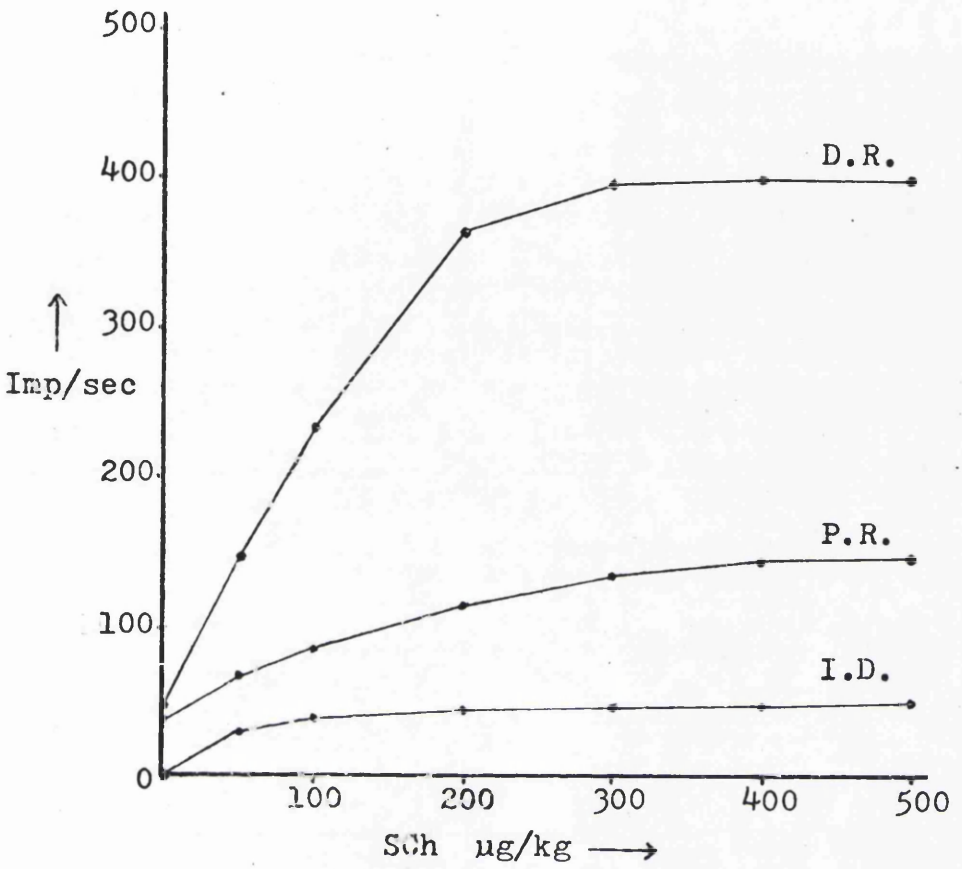

Fig. 27. The maximum dynamic response (D.R.), position response (P.R.) and initial discharge rate (I.D.) of a different soleus muscle spindle primary sensory ending following intravenous injections of various doses of SCh. Compare with Fig. 25.

RESULTS: SECTION IV

The three phases of activation of Ia endings by SCh.

The three stages in which Ia sensory endings are activated during SCh infusion have already been described, with respect to the activation of a "typical" Ia sensory ending (Results, Section II). In this section, the characteristic changes in the response of the Ia endings to stretch during each of the three phases of activation will be further illustrated, using as examples Ia endings activated by i.v. and i.a. infusions of SCh. In general, i.a. infusions of SCh were the more reliable in inducing Phase III of activation, as shown in the previous Section. With i.v. infusions of SCh, however, because the activation of the Ia endings through Phases I and II of activation and, where seen, Phase III of activation took place over a longer period of time, it was easier to distinguish between the successive stages of excitation and to study each in turn.

IV.1. Phase I of activation

All 40 Ia endings studied during i.v. and i.a. infusions of SCh showed an initial phase of excitation in which the initial discharge rate of the endings between successive stretches increased gradually, for the most part independently of the dynamic and position responses of the endings to stretch.

Fig. 28 shows the behaviour of a Ia sensory ending in this initial phase of activation during i.v. SCh infusion (100 µg/kg/min). The Ia ending was silent between successive stretches in the control condition (Fig. 28a), but 20 sec after the start of SCh infusion the ending began to discharge between stretches. At first, the ending fired only a few spikes just before the following ramp stretch was applied (Fig. 28b).

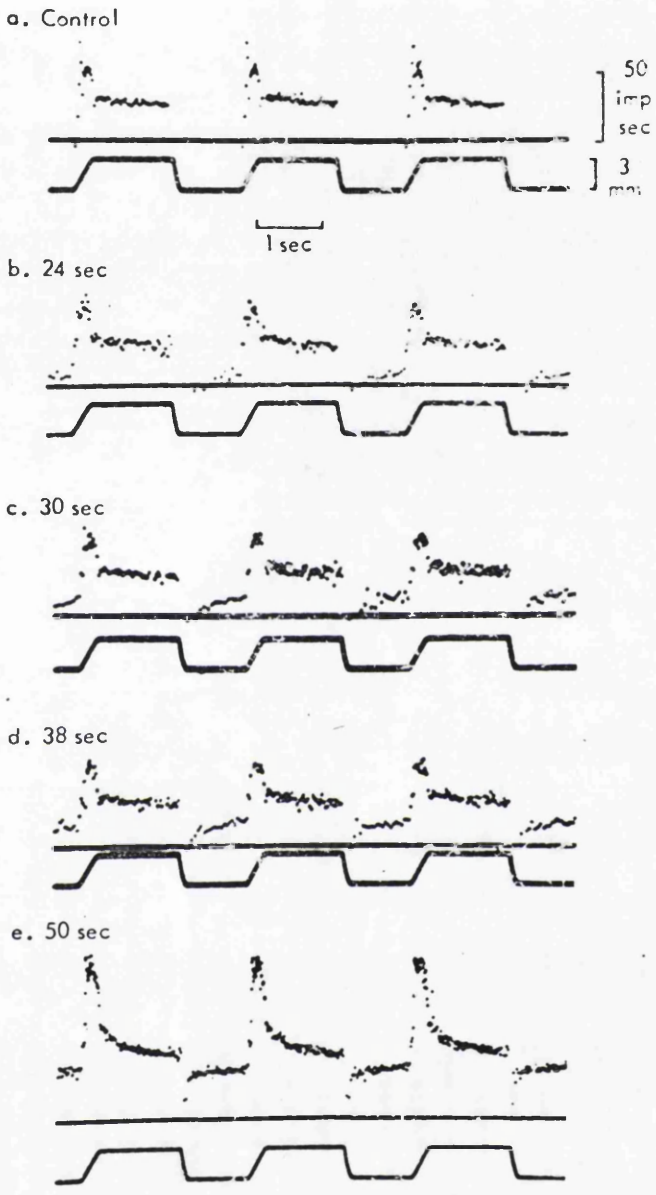

Fig. 28. a - d: The gradual development of Phase I of excitation of a soleus muscle spindle primary sensory ending during intravenous infusion of SCh (100 ug/kg/min). Note the gradual increase in the discharge of the ending between stretches, while the dynamic and position responses remain close to control values. e shows the onset of Phase II of excitation.

Gradually the number of spikes fired by the ending between stretches increased, and the period of silence in the discharge following the release of each stretch became progressively shorter (Fig. 28c), until the discharge of the ending was silenced only during the muscle shortening itself and picked up again immediately after the release of stretch (Fig. 28d).

Throughout this initial phase of excitation, the dynamic and position responses of the Ia ending remained much the same as control values, while the initial discharge rate increased (Fig. 28b, c, d). The effects of SCh on the ending first increased the initial discharge rate to the level of the adapted "resting" activity of about 7 imp/sec (Fig. 28b), and then continued to increase the initial discharge rate further so that about 40 sec after the start of infusion the initial discharge rate was approximately 20 imp/sec, 13 imp/sec above the control "resting" activity. The position response did not increase by a similar amount over its control value, so that the position sensitivity of the Ia ending decreased from 7.5 imp/sec/mm in the control condition to 6.1 imp/sec/mm (Fig. 28d).

The majority of Ia endings showed a substantial increase in their discharge rate during Phase I of activation, usually of the order of 20 to 60 imp/sec above the control initial discharge rate. It was a common finding that during Phase I of activation the initial discharge rate of the activated Ia ending increased to a level well above the "resting" adapted discharge rate of the ending at the initial muscle length, in many cases to double or treble the control "resting" value. Fig. 29 shows as an example a Ia ending in which the initial effects of SCh were more marked than usual. This Ia ending had a "resting" discharge rate of 20 imp/sec at the initial muscle length before the start of the test stretching sequence. During the test sequence in the control condition, the ending was silent for about 0.1 sec following the release of stretch

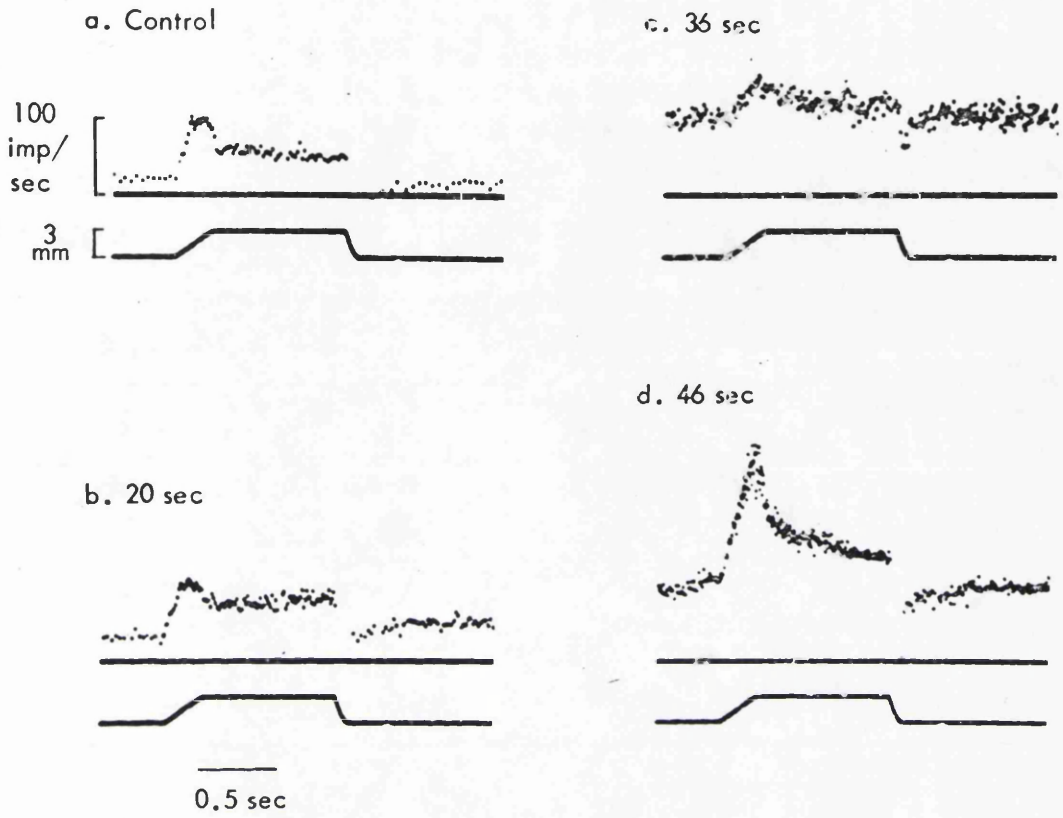

Fig. 29. a - c: Phase I of excitation of a Ia sensory ending during intra-arterial infusion of SCh. Note increase in the initial discharge rate (b, c) and increase in variability (c). d shows the onset of Phase II of excitation.

(Fig. 29a), and the initial discharge rate was 13 imp/sec. Following the start of i.a. infusion of SCh (100 µg/kg/min), the initial discharge rate of the ending increased, and the period of silence after the release of each stretch was abolished (Fig. 29b). The initial discharge rate of the ending then continued to increase, and the instantaneous frequency of discharge of the ending became much more variable (Fig. 29c). The dynamic and position responses of the ending increased with the initial discharge rate, but not to the same extent, so that the dynamic and position sensitivities of the ending decreased (Fig. 29a vs. Fig. 29c). Thus, in this particular case the initial discharge rate of the Ia ending during Phase I of activation reached a value of almost 100 imp/sec, or five times the "resting" adapted discharge rate of the ending. Fig. 29d shows the onset of Phase II of excitation.

In the large majority of cases, Phase I of activation of the Ia endings was soon followed by Phase II, as in the examples given in Figs. 28 and 29. In a few cases during i.v. infusions of SCh, however, Phase I of activation continued for a much longer time before the dynamic sensitivity of the sensory endings began to increase. One such case is shown in Fig. 30. The i.v. infusion of SCh at 100 µg/kg/min began 76 sec before the first stretch shown in Fig. 30 (trace 1), and the response of the ending to this stretch is identical to control responses. The behaviour of the sensory ending over the next minute shows the gradual development of Phase I of excitation ("I", Fig. 30). The silence in the discharge of the ending between successive stretches was gradually filled out as the initial discharge rate increased (Fig. 30, traces 1 and 2). This happened initially without any significant changes in the response of the ending to the test stretches themselves (trace 1), and the dynamic and position response of the ending remained much the same as control values. However, as the initial discharge rate continued to rise, the dynamic and

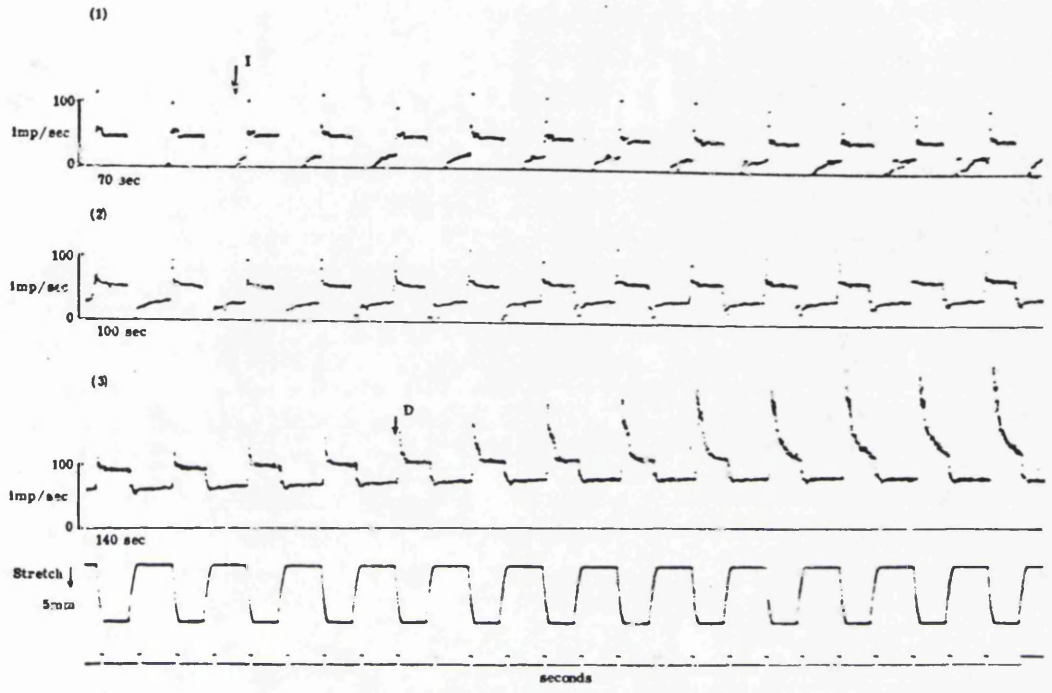

Fig. 30. The development of Phases I and II of excitation of a different Ia sensory ending during intravenous infusion of SCh (pen-recorder traces). The first stretch in trace 1 is identical to control responses. "I", onset of Phase I of excitation. "D", onset of Phase II of excitation. Times below each trace are from the start of infusion.

position responses then increased with it (last half of trace 2, trace 3), so that the position sensitivity of the Ia ending remained much the same as the control value while the dynamic index decreased. In this respect, this Ia ending differed from the more typical cases illustrated in Figs. 28 and 29, where both the dynamic index and the position sensitivity of the Ia endings decreased in Phase I of excitation.

Most Ia endings did not show such a long delay between Phases I and II of excitation, so that soon after the initial effects illustrated in Fig. 28 the endings entered Phase II of excitation, and any further changes in the initial discharge rate on its own could not be followed. However, the possible counterpart of this was often seen during the recovery of Ia endings from the effects of SCh infusion, where soon after the end of infusion the initial discharge rate, the dynamic response and the position response of the endings decreased together (see for example Fig. 20, Section II). Another example of this is shown in Fig. 31. The first stretch in Fig. 31 shows the response to stretch of the Ia ending activated through to Phase III of excitation by i.a. infusion of SCh in the normal way. The SCh infusion was stopped 6 seconds before the first stretch illustrated. The initial discharge rate of the ending is seen to fall from 115 imp/sec (first stretch in Fig. 31) to 63 imp/sec (last stretch in Fig. 31), and the after-effect of the release of stretch on the discharge of the ending gradually becomes more marked. The dynamic and position responses of the Ia ending also decrease with the initial discharge rate over this period, but the dynamic index remains unchanged while the absolute frequencies of discharge decrease. The fall in the initial discharge rate of the ending is however greater than the decrease in the position response, and therefore the position sensitivity of the ending increases slightly. Thus, this initial stage in the recovery of Ia endings from the effects of SCh activation appears to be the counterpart of the first phase of excitation

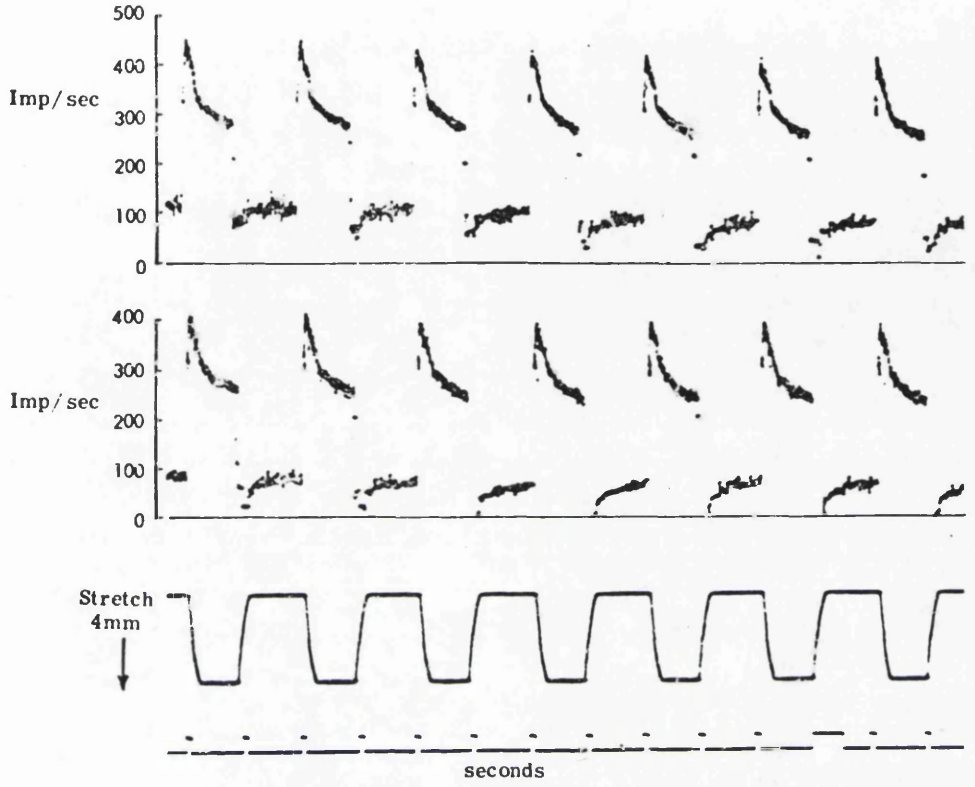

Fig. 31. The behaviour of a typical Ia ending immediately after the interruption of SCh infusion after maximal activation (pen-recorder traces; lower trace follows upper). The intra-arterial infusion was stopped 6 seconds before the first stretch shown. Note gradual decrease in the discharge of the ending between stretches, while the dynamic and position responses remain high.

during SCh infusion, and is the reverse of the sequence of events illustrated in Figs. 28, 29 and 30.

IV.2. Phase II of activation

The onset of Phase II of excitation of Ia endings during SCh infusion was indicated by a progressive increase in the response of the endings to the dynamic phase of the test stretches ("D", Fig. 18; Fig. 19c, d, e). This increase in the dynamic sensitivity of the Ia endings was accompanied by a smaller but significant increase in the position sensitivity also, as described for a typical Ia ending in Results, Section II.

The degree of potentiation of the dynamic sensitivity of the Ia endings during Phase II of activation varied from spindle to spindle. The maximum percentage increase in the dynamic index of the 37 of the total 40 Ia endings which were successfully activated through Phase II of excitation by i.v. and i.a. SCh infusion, is shown in Fig. 32. Most Ia endings experienced large increases in their dynamic index, which typically increased to values between 500 and 1200% of the control dynamic index.

The discharge rates of the activated Ia endings during the dynamic phase of stretch when the dynamic sensitivity of the endings was maximal often reached frequencies of 300 to 500 imp/sec (see for example Fig. 19). The Ia endings were capable of maintaining these high levels of dynamic response apparently indefinitely. For example, in many experiments i.v. infusion of SCh were continued for several minutes after the dynamic sensitivity of the Ia endings had increased to high values, in an effort to induce the later Phase III increase in position sensitivity. In these cases, the Ia endings maintained their high levels of dynamic response without showing signs of fatigue, for as long as the SCh infusion was continued. After stopping the infusion, the dynamic response of these endings gradually decreased to control values.

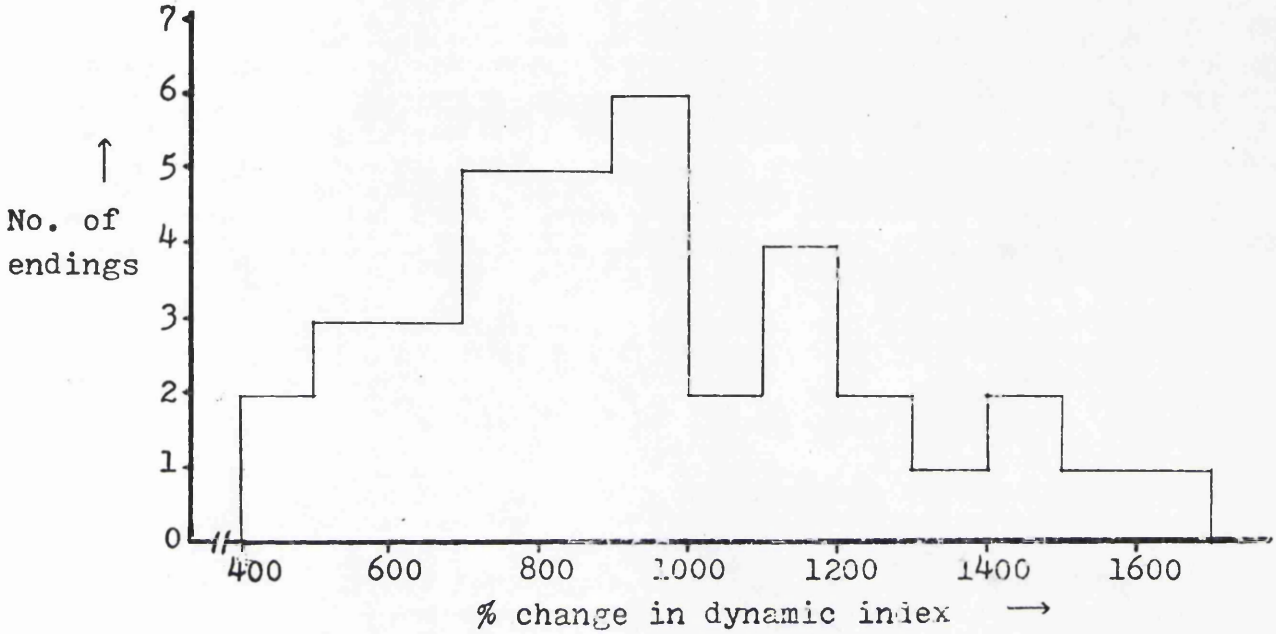

Fig. 32. Maximum increase in the dynamic index of the 37 Ia sensory endings activated through Phase II of excitation, expressed as % age change from the control dynamic index. Data from intravenous and intra-arterial infusions pooled.

During Phase II of activation, the Ia discharge rate immediately following the end of the dynamic phase of stretch adapted rapidly, in a characteristically curvilinear fashion (see for example Fig. 19d, e). This is further illustrated for three separate Ia endings in Fig. 33.

Fig. 34 shows the gradual development of Phase II of excitation during i.v. SCh infusion of the Ia sensory ending whose behaviour during Phase I of excitation was illustrated in Fig. 28. The dynamic index of the Ia ending increases progressively after the onset of Phase II of excitation (Fig. 34b, c), but the curvilinearity in the adaptation of the Ia discharge rate only becomes prominent after the dynamic response has increased severalfold. A similar increase in the curvilinearity of the Ia discharge rate after the end of the dynamic phase of stretch with the increase in dynamic response is also shown in Fig. 19d, e.

The degree and rate of the adaptation of the Ia discharge frequency following the dynamic phase of stretch determines the level of the position response of the ending, and thus the dynamic index. The net increase in the dynamic index of each Ia sensory ending, shown in Fig. 32, is therefore dependent on not only the increase in the level of the dynamic response itself, but also on the degree of adaptation of the Ia discharge rate after the end of the dynamic phase of stretch.

The time-course of adaptation of the Ia discharge rate at the extended muscle length was studied quantitatively, with the aid of a small PDP-8 computer. A program was written (see Appendix I) which calculated the mean interspike interval of the Ia spike train at various times after the end of the dynamic phase of stretch, from data collected over several successive stretches. The time-course of adaptation of the Ia discharge after the end of the dynamic phase of stretch could then be estimated from a plot of the mean Ia interspike interval against the time from the end of the dynamic phase of stretch (cf. Brokensha & Westbury 1976a). It was

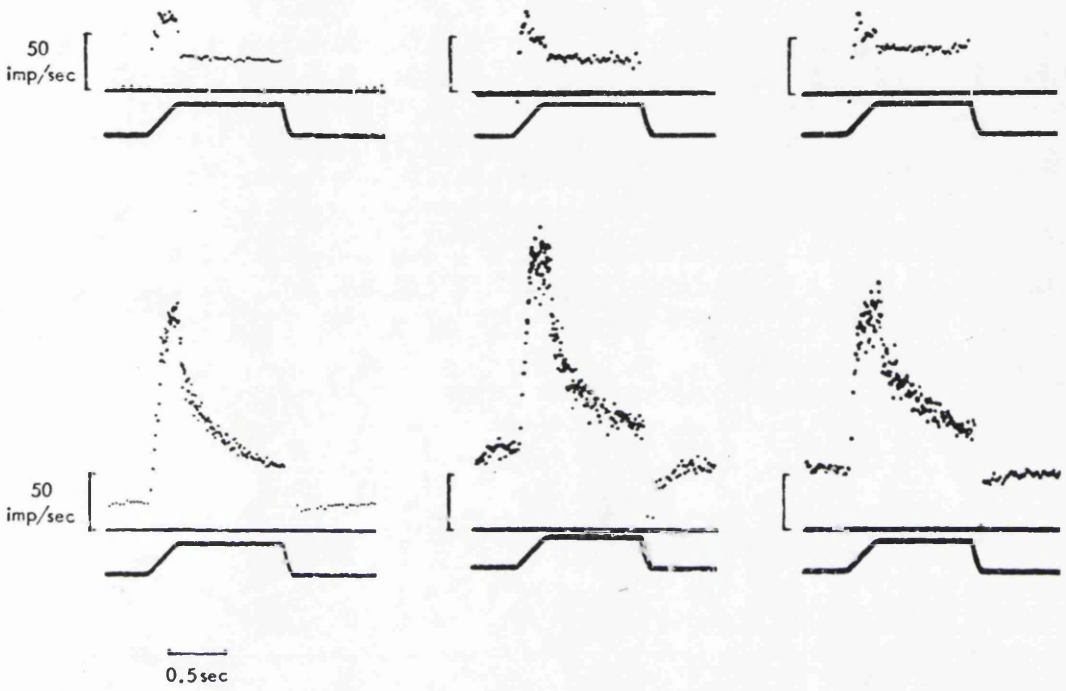

Fig. 33. The response of three separate Ia endings to test stretches (3 mm at 12 mm/sec) in the control condition (upper records) and in Phase II of excitation (lower records). Note the characteristically rapid, curvilinear adaptation of the Ia discharge after the end of the dynamic phase of stretch in Phase II of excitation.

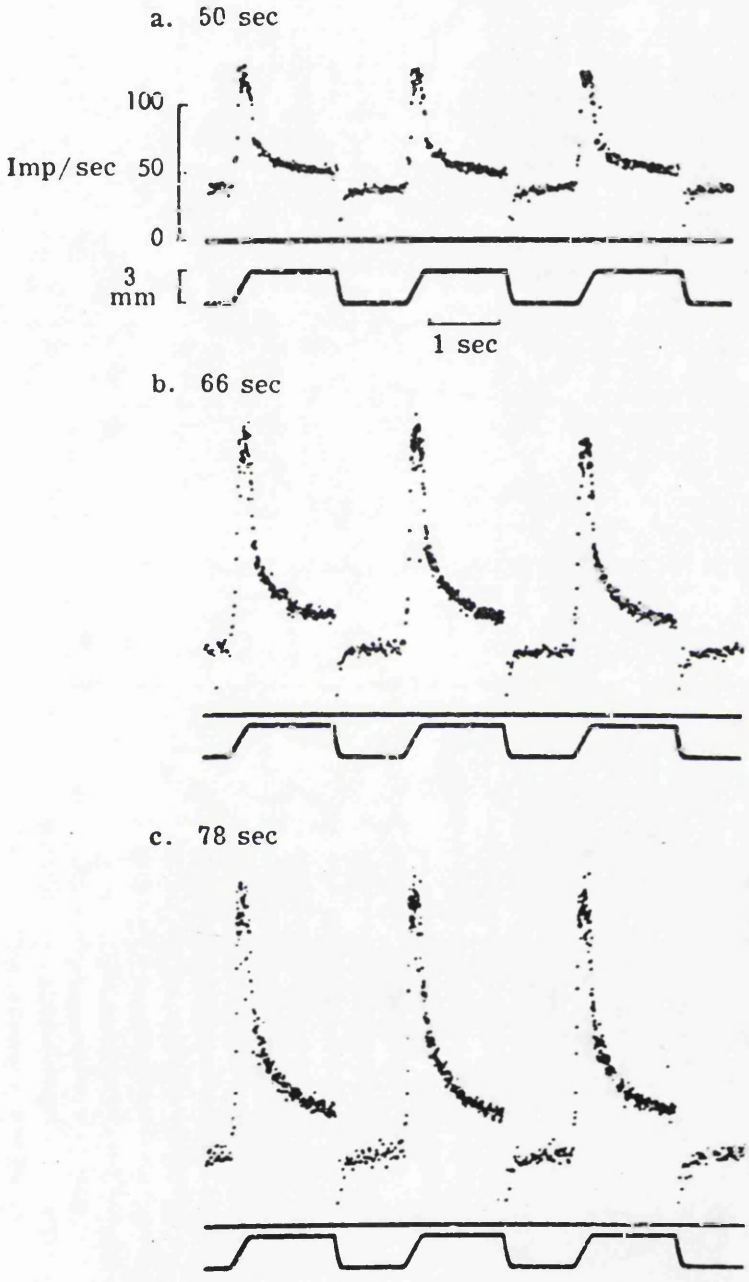

Fig. 34. The gradual development of Phase II of excitation of the Ia ending illustrated in Fig. 28. Times given are from the start of intravenous SCh infusion. Note gradual increase in the dynamic response, and characteristic curvilinear decay of the Ia discharge at the extended muscle length.

necessary, however, that the response of the Ia endings to each of the test stretches to be studied be identical, so that the interspike interval data could be pooled for analysis. Sections of recording were therefore chosen for study which on examination using the pulse-interval meter showed a very similar response of the endings to several successive stretches. Normally during Phase II of activation by SCh infusion, it was difficult to find such sections of recording where the response of the Ia endings to several successive stretches remained the same (see for example Fig. 19d, e). During the recovery of the Ia endings from the effects of infusion, however, the response of the endings to successive test stretches changed much more slowly, as illustrated in Fig. 20 and 21. The analysis of interspike intervals was therefore carried out on data obtained from Ia endings during their recovery from excitation, when their response to stretch was equivalent to that during Phase II of activation (e.g. stretches 41 to 46, Fig. 20).

Fig. 35 shows the mean interspike intervals of the discharge of six Ia sensory endings at various times after the end of the dynamic phase of stretch, measured in this way. The mean interspike interval of the Ia discharge is seen to increase curvilinearily after the end of the dynamic phase of stretch, reflecting the characteristic form of adaptation of the Ia discharge frequency shown in Figs. 33 and 34. The rate of increase of the mean interspike interval is seen from Fig. 35 not to be a simple first-order exponential process. The approximate mean first half-time of the increase in interspike interval after the end of the dynamic phase of stretch was calculated from the data shown in Fig. 35, to be 479 msec, range 297-580 msec.

IV.3. Phase III of activation

In 18 of the 20 Ia sensory endings studied during i.a. infusion of

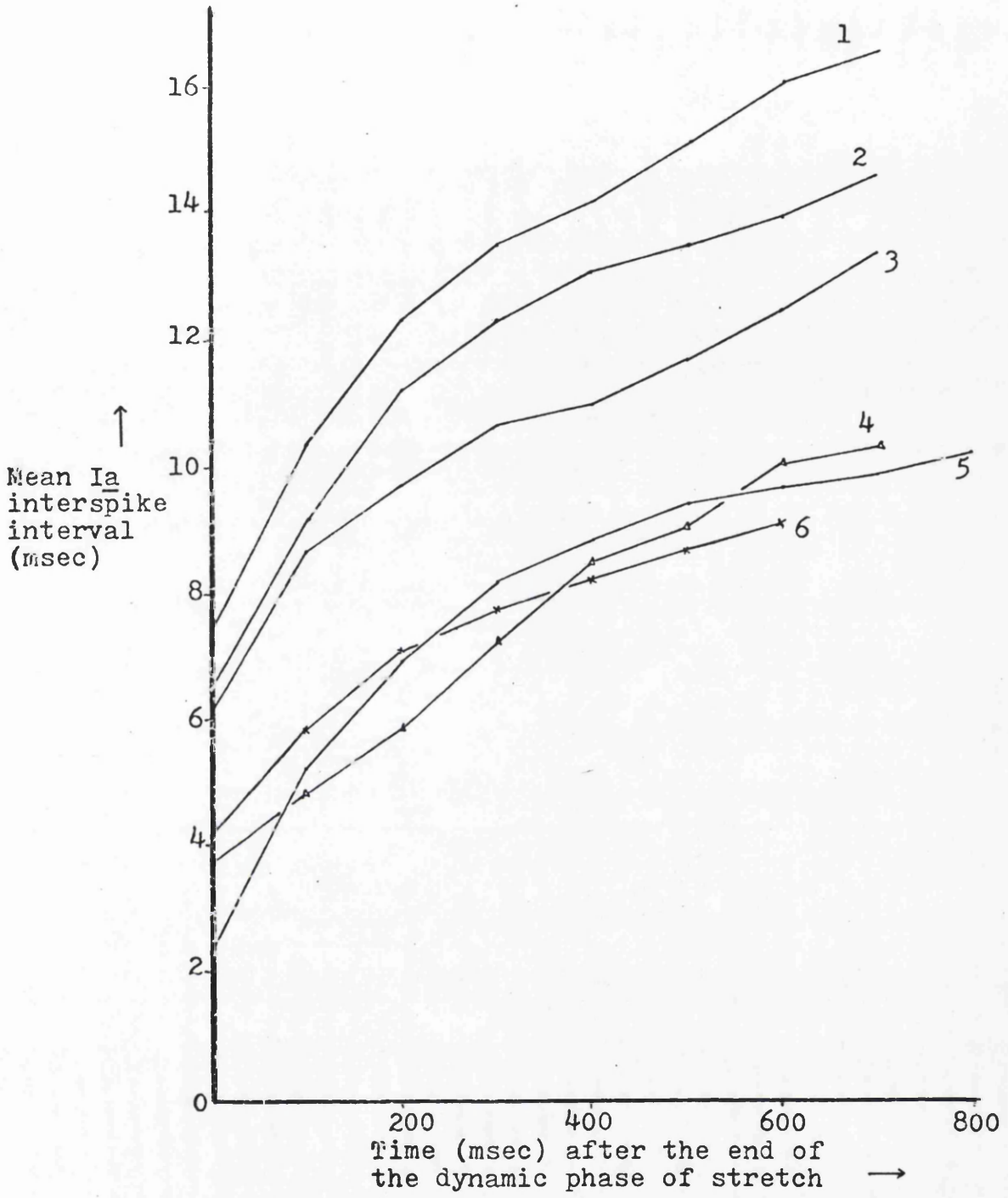

Fig. 35. The time-course of adaptation of the Ia discharge rate after the end of the dynamic phase of stretch in Phase II of excitation, measured for 6 separate endings as the change in the mean Ia interspike interval with time following the end of the dynamic phase of stretch.

SCh, the position sensitivity of the endings, which increased above control values along with the dynamic sensitivity during Phase II of activation, then showed a further large increase while the dynamic response of the endings remained high ("S", Fig. 18; Fig. 19f, g). A similar effect on the position sensitivity after Phase II of activation was also seen in 8 of the 20 Ia sensory endings studied during i.v. SCh infusion. This later increase in position sensitivity which occurred independently of the dynamic response of the endings was the third and final stage in their excitation during SCh infusion.

Fig. 36 illustrates the transition from Phase II to Phase III of activation of three Ia sensory endings during i.a. SCh infusion. The response of the Ia endings to stretch when Phase II of activation was fully developed is shown in the uppermost records, and their response to stretch in Phase III of activation is shown in the lowermost records. The middle records illustrate the response of the endings to stretch during the period of transition from Phase II of activation to Phase III.

The rapid curvilinear adaptation of the Ia discharge rate after the end of the dynamic phase of stretch which is characteristic of Phase II of activation (Fig. 36, uppermost records) is seen to become very much more linear in Phase III of activation (Fig. 36, lowermost records). While in the majority of cases this adaptation of the Ia discharge became so linear as to abolish any trace of the Phase II curvilinear type of adaptation, in a few cases even after Phase III of activation had become fully developed the discharge of the endings after the dynamic phase of stretch showed an initial component of curvilinear adaptation. One such case is illustrated in Fig. 36(3). Some Ia endings showed a marked discontinuity in their discharge immediately after the dynamic phase of stretch which had not been present in Phase II of excitation (see for example Fig. 36(1) and Fig. 19).

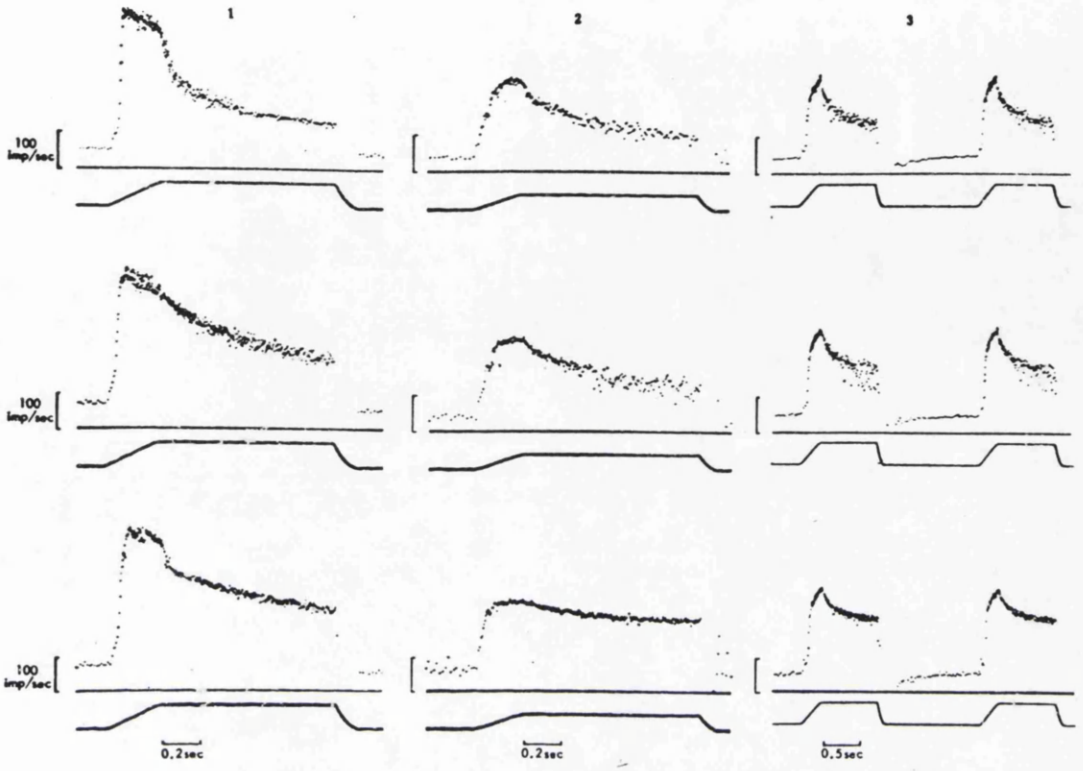

Fig. 36. The transition from Phase II of excitation to Phase III of excitation for 3 separate Ia endings. Top records in each column, response of the Ia endings to stretch in Phase II of excitation. Bottom records in each column, response to stretch of the Ia endings in Phase III of excitation. Middle records, response of the endings to stretch during the transition from Phase II of excitation to Phase III. Stretches in columns 1 and 3, 3 mm at 12 mm/sec; in column 2, 2 mm at 8 mm/sec.

In all cases, the rate of adaptation of the Ia discharge frequency after the dynamic phase of stretch was much slower during Phase III of activation than during Phase II, with the result that the position response of the Ia endings, measured 0.5 sec after the end of the dynamic phase of stretch, increased markedly in Phase III of excitation. Meanwhile, the initial discharge rate of the endings increased by a much smaller amount above the value reached during Phase II of activation (Fig. 36; see also Fig. 19), so that the large Phase III increase in position response represented a large increase in the position sensitivity of the Ia endings, measured as the change in the discharge rate caused by the change in muscle length.

The Phase III increase in position sensitivity of the Ia endings occurred without significant accompanying changes in the dynamic response of the endings (see later), and consequently the dynamic index decreased markedly. This decrease in dynamic index, which was the reverse of the increasing dynamic index characteristic of Phase II of activation, was a good indicator of the onset of Phase III of excitation.

During the transition from Phase II of activation to Phase III, the variability in the discharge of the Ia endings increased and appeared as a greater dispersion of the points on the instantaneous frequency display (Fig. 3b, middle records). This increase in variability was more marked in the discharge of the endings between stretches and during the static extended phase of the test stretch, than during the dynamic phase of stretch. In a few cases however the response of the endings to the dynamic phase of stretch also became irregular, and the dynamic response fell during this transition period (see for example Fig. 19). However, instead of an increase in the variability of their discharge during the transition from Phase II to Phase III of activation, about one Ia ending

in three discharged at two discrete "preferred" frequencies at the extended muscle length. The lower of the "preferred" frequencies of discharge was close to the Phase II position response of the ending, and the higher was close to the Phase III position response. Fig. 36 (3) illustrates one such transition from Phase II to Phase III of activation. The recovery from the effects of infusion of a similar Ia ending is shown in Fig. 39.

The changes in the response of the Ia endings to stretch during the transition from Phase II to Phase III of excitation were reversed during the recovery of the endings from the effects of infusion, as shown for two different Ia sensory endings in Fig. 21 and 39. The initial discharge rate of the activated Ia endings was the first to fall after the SCh infusion was discontinued, as illustrated in Fig. 31 and also in Fig. 39. The dynamic and position responses of the Ia endings remained high as the initial discharge rate decreased. The slow-adapting discharge of the Ia endings then gradually changed as the position sensitivity of the endings decreased, to return to the more curvilinear form of adaptation characteristic of Phase II of activation, leaving the Ia endings with a high dynamic sensitivity to stretch. The Ia discharge at the extended phase of the test stretch usually showed a large increase in variability, often more than in the transition from Phase II to Phase III of activation during infusion.

The changes in the time-course of adaptation of the Ia discharge as the sensory endings recovered from the effects of SCh infusion were followed quantitatively, using the computer program already described. Fig. 37 shows the change in the mean interspike intervals of the discharge of three Ia sensory endings at various times after the end of the dynamic phase of stretch, as the high Phase III position sensitivity of the

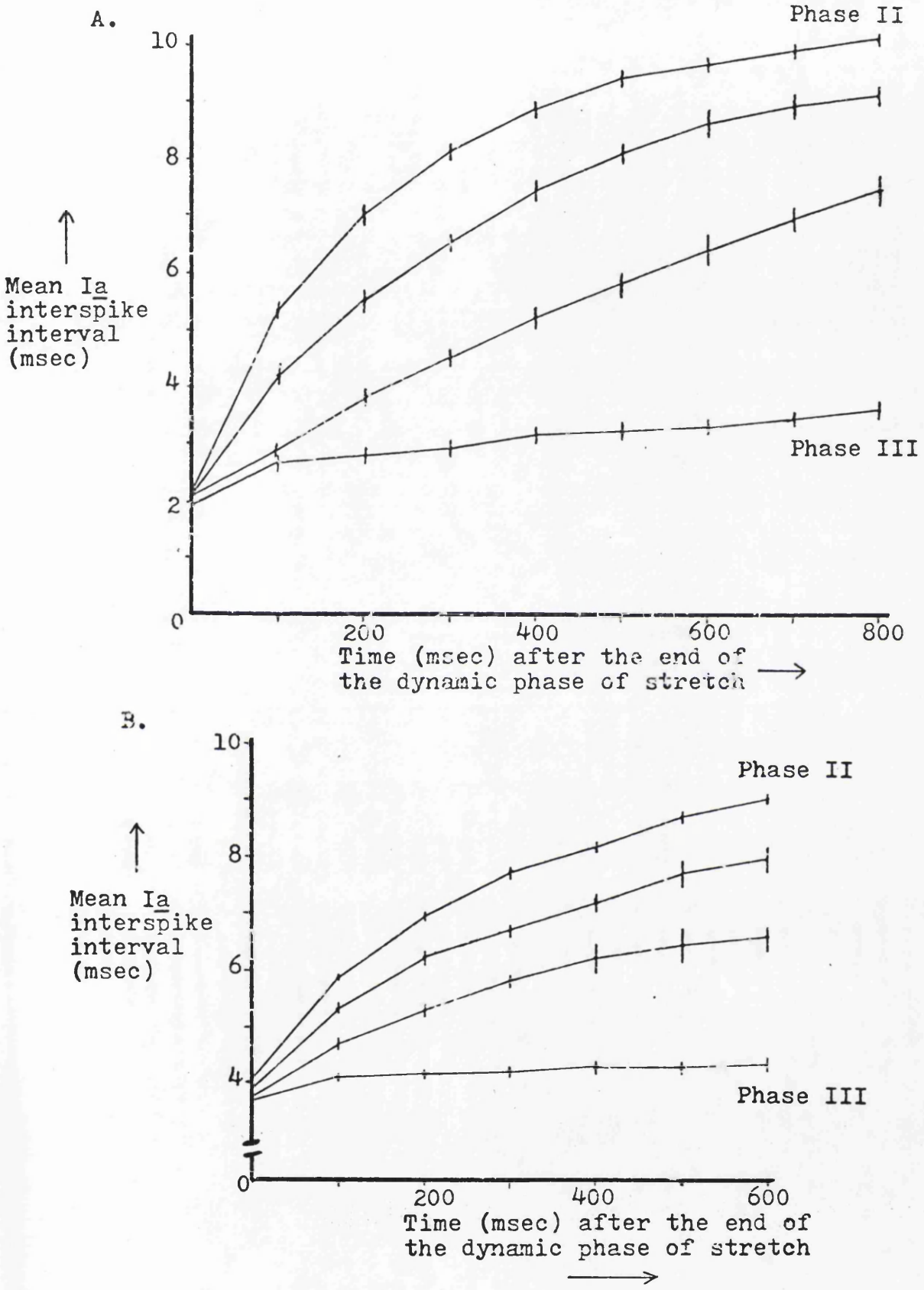

Fig. 37. Continued next page.

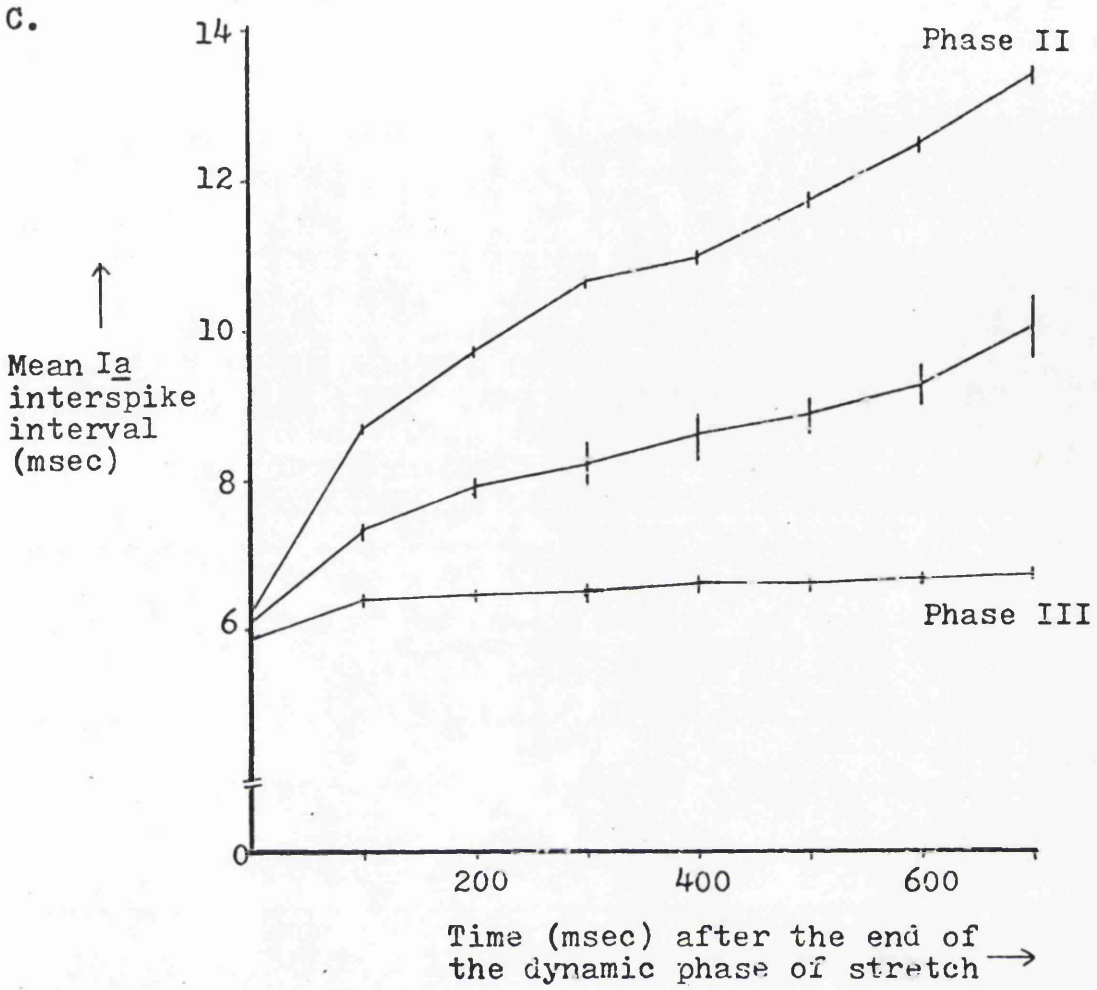

Fig. 37. Changes in the time-course of adaptation of the discharge of 3 separate Ia endings (A,B,C) during their recovery from Phase III of excitation to Phase II, measured as the change in mean interspike interval with time after the end of the dynamic phase of stretch. Vertical bars indicate standard errors. Note gradually increasing curvilinear component in the adaptation during the transition from Phase III to Phase II, and also the transient increase in the variability of interspike intervals seen as an increase in the standard error.

activated Ia endings decayed. In each case, the Ia discharge during Phase III of activation followed an almost linear time-course of adaptation after the dynamic phase of stretch. This linear adaptation rate became progressively more curvilinear, finally reaching the marked curvilinearity characteristic of Phase II of activation (Fig. 37, uppermost curves). The time-course of adaptation of the Ia discharge during this period represented an admixture of the curvilinear and quasi-linear forms of adaptation, with a gradually increasing curvilinear component. During the transition from the quasi-linear to the curvilinear form of adaptation, the variability in the Ia discharge rate usually increased, and then decreased when the transition was complete (Fig. 37, middle curves). The actual increase in the variability of the Ia discharge was pronounced in some cases (Fig. 37b and c), but not as marked in others (Fig. 37a).

During Phase III of activation the increase in the position response of the endings took place in the large majority of cases without a significant accompanying increase in the dynamic response of the endings, except during the transition phase when a transient decrease in the level of the dynamic response was seen in some cases. However, while the dynamic response of the Ia endings at the end of the dynamic phase of stretch in Phase III of activation remained much the same as in Phase II, the Ia discharge rate during the dynamic phase of the test stretch increased more quickly, to reach the peak dynamic discharge frequency sooner than during Phase II of activation (see for example, Fig. 19e, f, g; Fig. 36 and Fig. 39).

Typically, the dynamic response of the Ia endings increased by 5 to 25 imp/sec as the Phase III increase in position sensitivity developed. This increase was however never of a magnitude comparable to the increase

in the position response of the endings. The initial discharge rate of the Ia endings also increased as Phase III of activation developed. Generally, in any one case the increase in the initial discharge rate of the ending was almost exactly the same as the increase in the dynamic response. For example, in the case of the Ia ending illustrated in Fig. 36(1), the dynamic response of the ending increased from 412 imp/sec in Phase II of excitation (uppermost record) to 438 imp/sec in Phase III (lowermost record). The initial discharge rate of the ending also increased by a very similar amount, from 55 imp/sec in Phase II of excitation to 80 imp/sec in Phase III. However, the increase in the position response of the ending, from 149 imp/sec to 267 imp/sec over the same period, is of a different order of magnitude. Fig. 36(3) illustrates another similar case. The dynamic response and the initial discharge rate of this ending increased by 9 and 7 imp/sec respectively as Phase III of excitation developed, while the position response of the ending increased by 68 imp/sec. In the case illustrated in Fig. 36(2), however, the dynamic response of the ending did not increase significantly as the position response increased, but the initial discharge rate rose from 36 to 63 imp/sec in Phase III of excitation.

The possibility that the increase in the position response of the Ia endings during Phase III of excitation occurs without an accompanying increase in the dynamic response, because the Ia endings cannot be made to discharge at impulse frequencies higher than those reached during Phase II of excitation ("saturation") was tested in 11 of the 20 Ia endings activated by i.a. SCh infusion. The ability of the maximally activated Ia sensory endings to discharge at higher frequencies was tested by applying a few test stretches to the muscle at the rate of 25 mm/sec instead of the rate of 8-12 mm/sec normally used in these experiments. Fig. 38 shows the

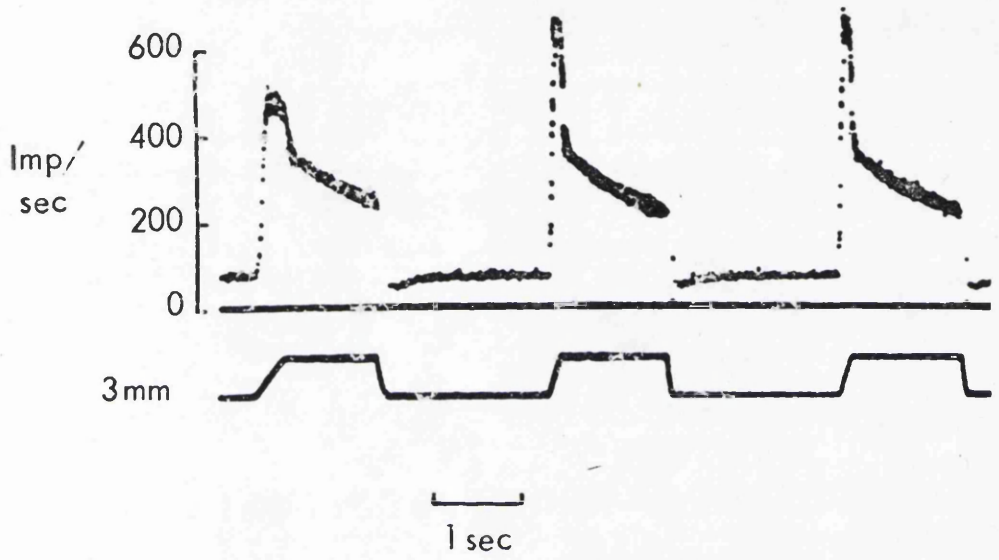

Fig. 38. The response of the Ia ending whose excitation by SCh was illustrated in Figs. 18-21, to a few faster ramp stretches. The first stretch illustrated is the response of the maximally activated ending to a normal test stretch (3mm at 12 mm/sec), and is equivalent to the response shown in Fig. 19f. The two following ramp stretches were applied at 25 mm/sec, in an attempt to evoke a greater discharge from the ending. The higher dynamic response of the ending to the faster stretches clearly shows that the afferent axon was not "saturated" during normal test stretching.

effect of this test on the Ia ending whose activation by SCh infusion was illustrated in Fig. 19. The first stretch in Fig. 38 shows the response of the fully activated Ia ending to the normal test stretch of 3 mm at 12 mm/sec, as shown in Fig. 19f. The following two stretches in Fig. 38 were applied at 25 mm/sec, in an attempt to evoke a greater discharge from the ending. The higher dynamic response of the Ia ending in response to the faster stretches clearly shows that the ending was capable of discharging at higher frequencies than those reached during Phase III of activation. Thus, the Phase III increase in the position response of this Ia ending, which as Fig. 19 shows occurred without a significant accompanying increase in the dynamic response of the ending, did so even though the Ia ending could have discharged at higher impulse frequencies. The onset of Phase III of excitation, therefore, increased the position sensitivity of the Ia sensory ending, but did not significantly alter the response of the ending to the dynamic phase of the test stretch.

Of the eleven Ia endings tested for "saturation" in this way, seven showed a clearly greater dynamic response to the faster test stretches applied when the endings were maximally activated. The remaining four Ia endings, however, could not be made to discharge at frequencies higher than those reached during maximal activation by SCh. These endings were further studied by subsequently re-activating them by i.a. SCh infusion, but at shorter initial muscle lengths and using test stretches with slower rise-times. Fig. 39a shows the response of one of these four Ia endings maximally re-activated in this way to the slower test stretching at 8 mm/sec. As Fig. 39b shows, this Ia ending could now be shown not to be "saturated", by applying a few test stretches at a higher rate of stretch (25 mm/sec).

This Ia ending was unusual in that the discharge between stretches was strongly facilitated after the onset of Phase III of activation (Fig. 39a, b).

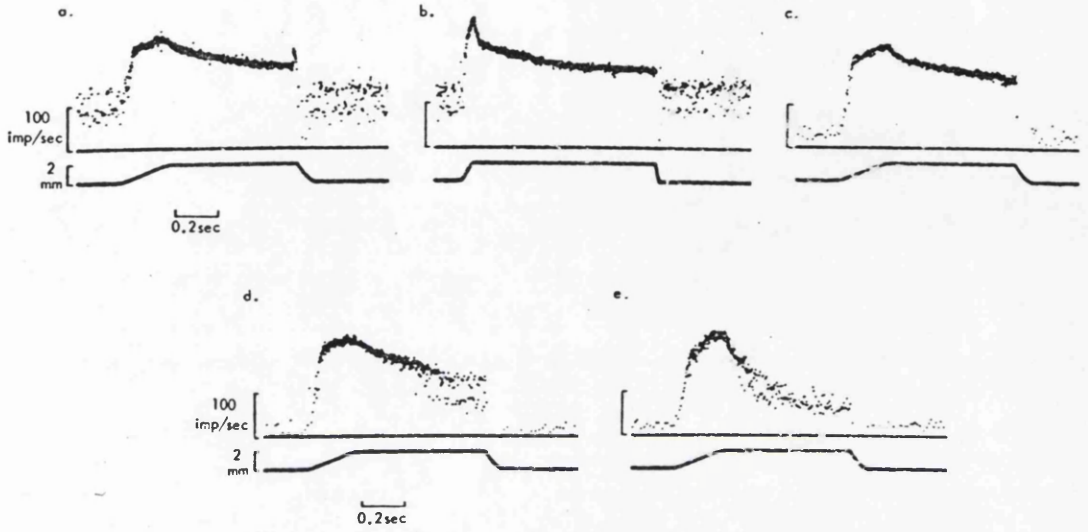

Fig. 39. The recovery of a soleus muscle spindle Ia sensory ending from the effects of SCh infusion. a. The response of the maximally activated ending to stretch after 100 sec of i.a. SCh infusion. b. A faster stretch applied to the muscle shows that the Ia ending is not "saturated" (see text). c. 11 seconds after the SCh infusion ceased, the discharge of the ending between stretches has decreased (compare with Fig. 31). d. As the high Phase III position response decays, the ending discharges at two "preferred" frequencies of discharge at the extended muscle length. e. The high Phase III position sensitivity has decayed, leaving the Ia ending with a high dynamic sensitivity.

Fig. 39c shows the response of the ending to the normal test stretches 15 sec after the end of SCh infusion, when the discharge of the ending between stretches has decreased but the dynamic and position responses of the ending remain high. Fig. 39d and e show the decay of the Phase III position sensitivity of the ending as the recovery from the effects of infusion progresses. In this particular case, in place of the increase in the variability of the Ia discharge after the end of the dynamic phase of stretch, the Ia ending discharged at two "preferred" frequencies (Fig. 39d). The higher of the "preferred" discharge frequencies of discharge of the ending is close to the position response of the ending with maximum position sensitivity (Fig. 39c), while the lower of the "preferred" discharge frequencies is close to the position response of the ending after the high Phase III position sensitivity has declined (Fig. 39e). Eight of the 28 Ia sensory endings successfully activated to Phase III of activation by SCh infusion behaved in a similar manner to the Ia ending illustrated in Fig. 39. The remaining Ia endings showed an increase in the variability of their discharge, as the Phase III effect on position sensitivity was induced during infusion, and as it declined after the end of infusion. Where one Ia ending preferred to discharge at two distinct levels of instantaneous frequency, it did so at the onset of Phase III of excitation during infusion, and also during the recovery from activation as the Phase III increase in position sensitivity declined.

In all of the four Ia endings tested for "saturation" at the shorter initial muscle lengths and with stretches of slower rise-times, it was possible to show that the frequencies of discharge reached by the endings during Phase III of activation were not the maximal discharge frequencies attainable by the endings, as shown for example in Fig. 39. Thus, the possibility that "saturation" of the Ia afferent axons prevents the dynamic

response of the Ia endings from increasing further while the position response of the endings increases in Phase III of activation, can be discounted for all of the eleven Ia sensory endings specifically tested for this. Therefore it would appear that no significant algebraic interaction between the dynamic and position responses of the Ia endings occurs at the onset of Phase III of excitation, except for the small increase in the dynamic response and the initial discharge rate illustrated in Fig. 36.

Nevertheless, a significant interaction between the dynamic and position responses was seen in one of the 28 Ia sensory endings successfully activated to Phase III of activation by SCh infusion. This case is illustrated in Fig. 40. Fig. 40a shows the response of the Ia ending to stretch when Phase II of excitation was fully developed. The two stretches shown in Fig. 40b show the response of the ending to stretch during the period of transition from Phase II of excitation to Phase III, and illustrate the high degree of variability of the discharge after the end of the dynamic phase of stretch. The response of the ending to stretch when Phase III of activation had developed fully is shown in Fig. 40c. The dynamic response of this Ia ending decreased markedly, from 388 imp/sec to Fig. 40a to 345 imp/sec in Fig. 40c, as the position response of the Ia ending increased. Figs. 40d, e and f show the recovery of the ending from the effects of infusion. The decrease in the dynamic response as Phase III of excitation developed during SCh infusion, was reversed as the high Phase III position sensitivity of the ending decayed. Thus, in this singular case, there appeared to be a significant interaction between the dynamic and position responses of the Ia ending during Phase III of activation. In all other respects, however, this exceptional Ia ending behaved like the "typical" Ia ending described in Results, Section II.

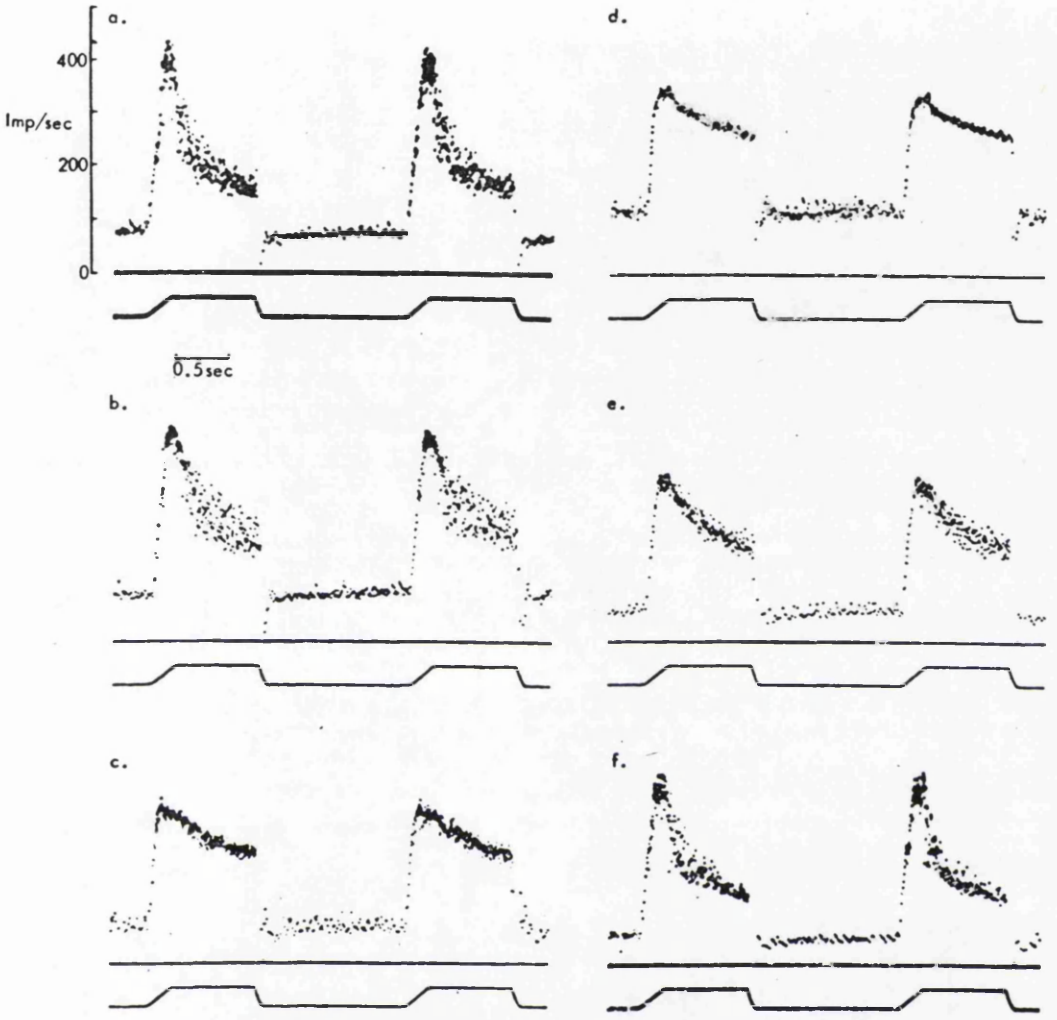

Fig. 40. a - d: transition from Phase II of excitation (a) to Phase III (d) of a Ia ending in which a marked interaction between the dynamic and position responses was observed. Note large increase in variability of discharge after the dynamic phase of stretch in b, and marked decrease in the dynamic response when Phase III of excitation was fully developed (d).

e,f: The i.a. SCh infusion ceased after d. e and f show that as the Phase III increase in position sensitivity decays, the dynamic response increases (f) and the Ia ending returns to a similar state as in (a). (Stretches, 3 mm at 12 mm/sec).

RESULTS: SECTION V

The excitation of soleus muscle spindle secondary sensory endings by SCh.

Muscle spindle afferent axons with conduction velocities below 60 m/sec (35-37°C) were taken to be from secondary sensory endings (Methods, page 40). A total of 19 secondary sensory endings were studied in the course of these experiments, ten during intravenous infusion of SCh and 9 during intra-arterial infusion.

Fig. 41 illustrates the behaviour of a typical secondary sensory ending during an intravenous infusion of SCh at 100 µg/kg/minute. In the control condition, the discharge rate of the secondary ending fell to zero during the release of each test stretch (Fig. 41a), and then recovered rapidly so that the initial discharge rate of the ending was the same as the adapted "resting" discharge rate, at 26 imp/sec.

Forty seconds after the start of SCh infusion, the initial discharge rate of the secondary ending began to rise, and the ending discharged a few spikes during the release of stretch (Fig. 41b). As the initial discharge rate increased, the after-effects of the release of stretch on the discharge of the ending gradually became less marked (Fig. 41c, d), eventually becoming almost completely abolished (Fig. 41e). The position response of the ending increased with the initial discharge rate so that the position sensitivity of the ending, measured as the change in the discharge rate caused by the change in the muscle length, remained much the same at about 9 imp/sec/mm (Fig. 41a vs. Fig. 41e). The dynamic response of the ending also increased with the initial discharge rate and the position response, but by a smaller amount, so that the dynamic index gradually decreased from 12 imp/sec in Fig. 41a to 6 imp/sec in Fig. 41e.

The gradual increase in the initial discharge rate, accompanied by

Soleus muscle spindle secondary sensory ending during I.V. infusion of suxamethonium (100 µg/Kg/min)

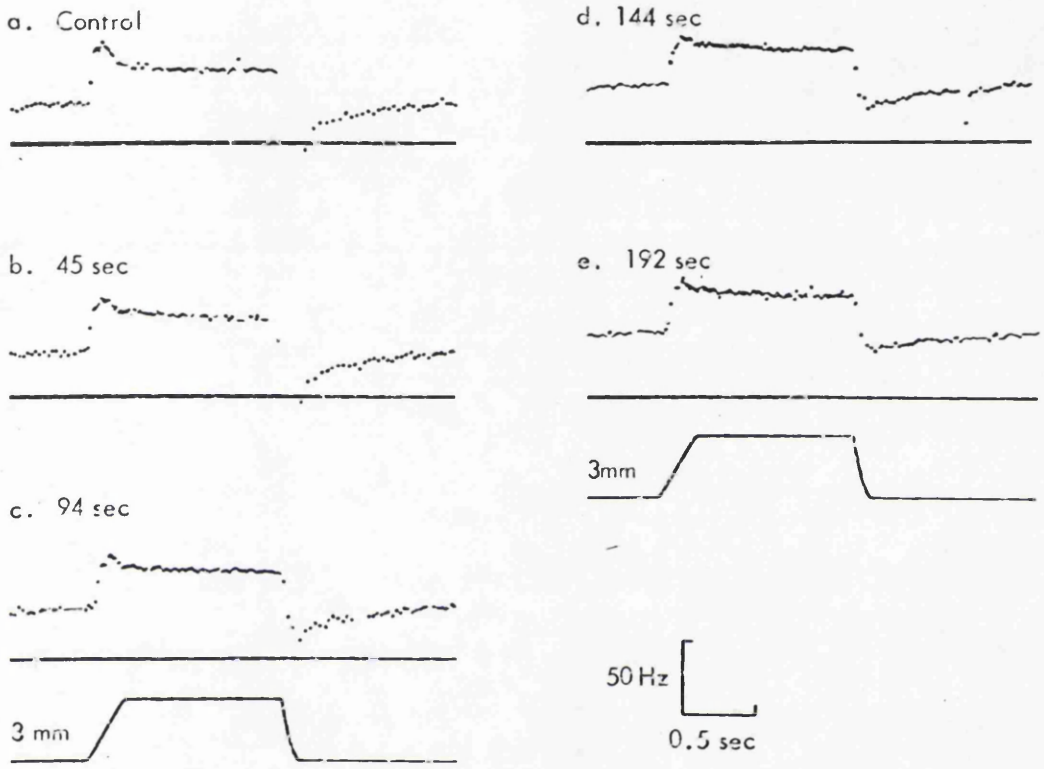

Fig. 41. The response of a soleus muscle spindle secondary sensory ending to test stretches at the indicated times during an intravenous infusion of SCh.

the progressive reduction of the after-effects of the release of stretch on the discharge of the ending, was reversed during the recovery of the secondary sensory endings from excitation. This is illustrated for a different secondary ending in Fig. 42. Fig. 42a shows the response of this secondary ending to a test stretch when strongly activated by intra-arterial infusion of SCh. The SCh infusion was stopped just after this test stretch was applied. Figs. 42 b-d illustrate the response of the ending to test stretches at the indicated times after the end of SCh infusion. The initial discharge rate and the dynamic and position responses of the secondary ending gradually decreased as the ending recovered from the effects of SCh. The after-effects of the release of stretch on the discharge of the ending became progressively more marked, until the response of the secondary ending to stretch returned to normal (Fig. 42d).

The lag times from the start of SCh infusion to the onset of excitation of the 19 secondary sensory endings studied in these experiments are shown in Fig. 43. As with Ia endings (Figs. 8 & 9) the lag times to excitation of secondary sensory endings were shorter during intra-arterial infusion of SCh (Fig. 43a) than intravenous SCh infusion (Fig. 43b). The majority of secondary endings were activated within 60 sec of the start of an intra-arterial SCh infusion, and within 100 sec of the start of an intravenous infusion. Most secondary sensory endings showed a substantial increase in their initial discharge rate during their excitation by SCh, often reaching frequencies of discharge twice their control "resting" discharge rate (see for example Fig. 41). However, in three of the 19 cases, the initial discharge rate of the activated secondary endings increased by only a few impulses/sec above the control "resting" discharge rate, after several minutes of SCh infusion into the external jugular vein.

The activity of five of the nine secondary sensory endings studied

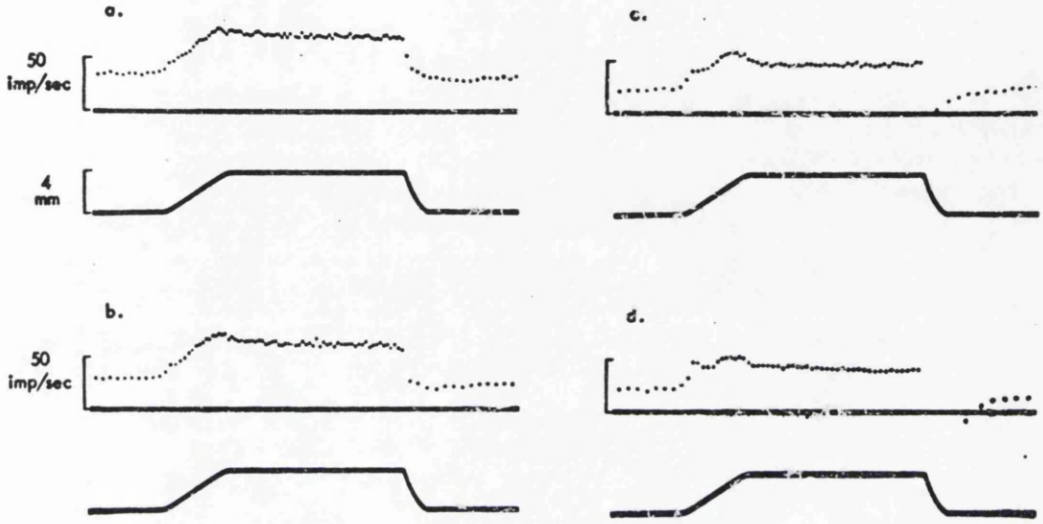

Fig. 42. The gradual recovery of a secondary sensory ending from excitation by SCh. a shows the response of the ending to a test stretch when strongly activated by i.a. SCh infusion. b, c and d show the response of the ending to stretch 18, 40 and 108 seconds respectively after the end of SCh infusion. The response of the ending to stretch in d is identical to control responses before the start of SCh infusion.

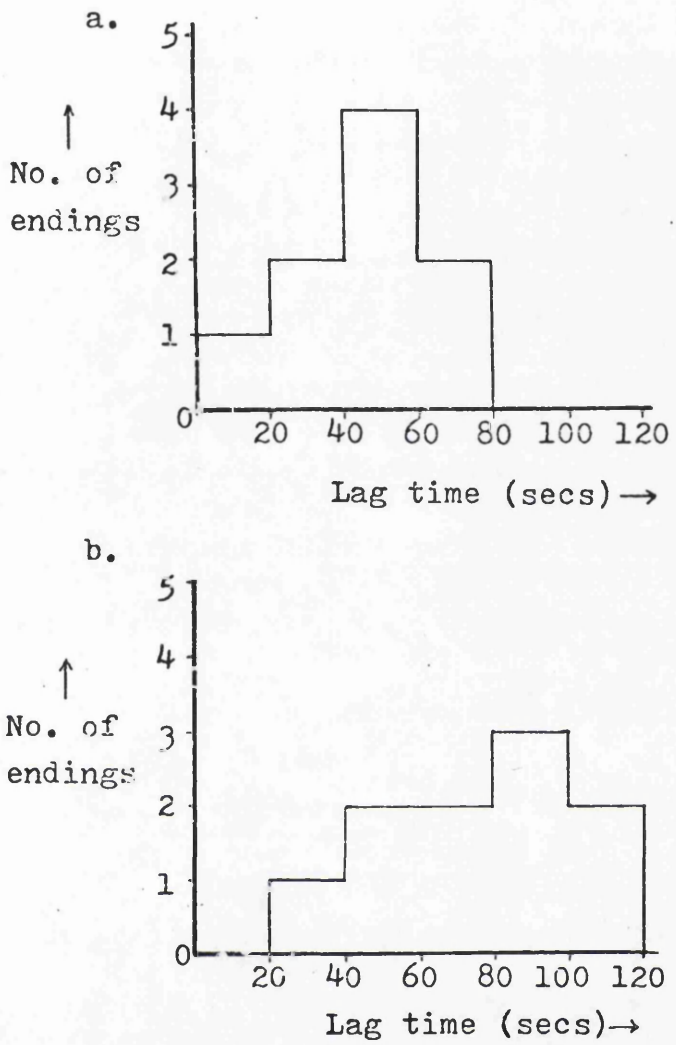

Fig. 43. a The lag times to the onset of excitation of the nine secondary sensory endings studied during intra-arterial infusion of SCh (100 µg/kg/min).

b The lag times to excitation of ten secondary endings activated by intravenous infusion of SCh (100 µg/kg/min).

during intra-arterial SCh infusion was recorded simultaneously with that of spindle Ia afferent axons, so as to allow comparison of the time-course of activation of the two types of sensory ending. In Fig. 44, the time-course of excitation of a secondary sensory ending is compared with that of the Ia sensory ending whose activation is illustrated in Fig. 18. The activity of the secondary sensory axon was recorded simultaneously with that of the Ia axon, using a duplicate system of electrodes and amplifier. The onset of excitation of the secondary sensory ending, which in all probability was located in a different spindle than the Ia ending, occurred in this case 6 sec after the onset of excitation of the primary ending. After the onset of activation, the total extent of excitation of the secondary sensory ending was much less than that of the primary ending, so that while the initial discharge rate of the Ia ending increased from 3 imp/sec to 86 imp/sec over 90 sec of SCh infusion, the initial discharge rate of the secondary ending increased from 13 imp/sec to 21 imp/sec over the same period. In addition, the large increase in the dynamic and position sensitivity of the Ia ending at "D" and in the position sensitivity at "S" (Fig. 44), which caused related increases in the initial discharge rate, were not reflected in the discharge of the secondary sensory ending. Instead, the dynamic index and the position sensitivity of the secondary ending decreased significantly during SCh infusion.

Thus, secondary sensory endings, unlike primary sensory endings, did not experience increases in their dynamic and position sensitivities during their activation by SCh. On the contrary, the dynamic index of the secondary endings normally decreased during SCh infusion, while the position sensitivity either remained much the same as control values or decreased fractionally. The salient effect of SCh on the secondary sensory endings

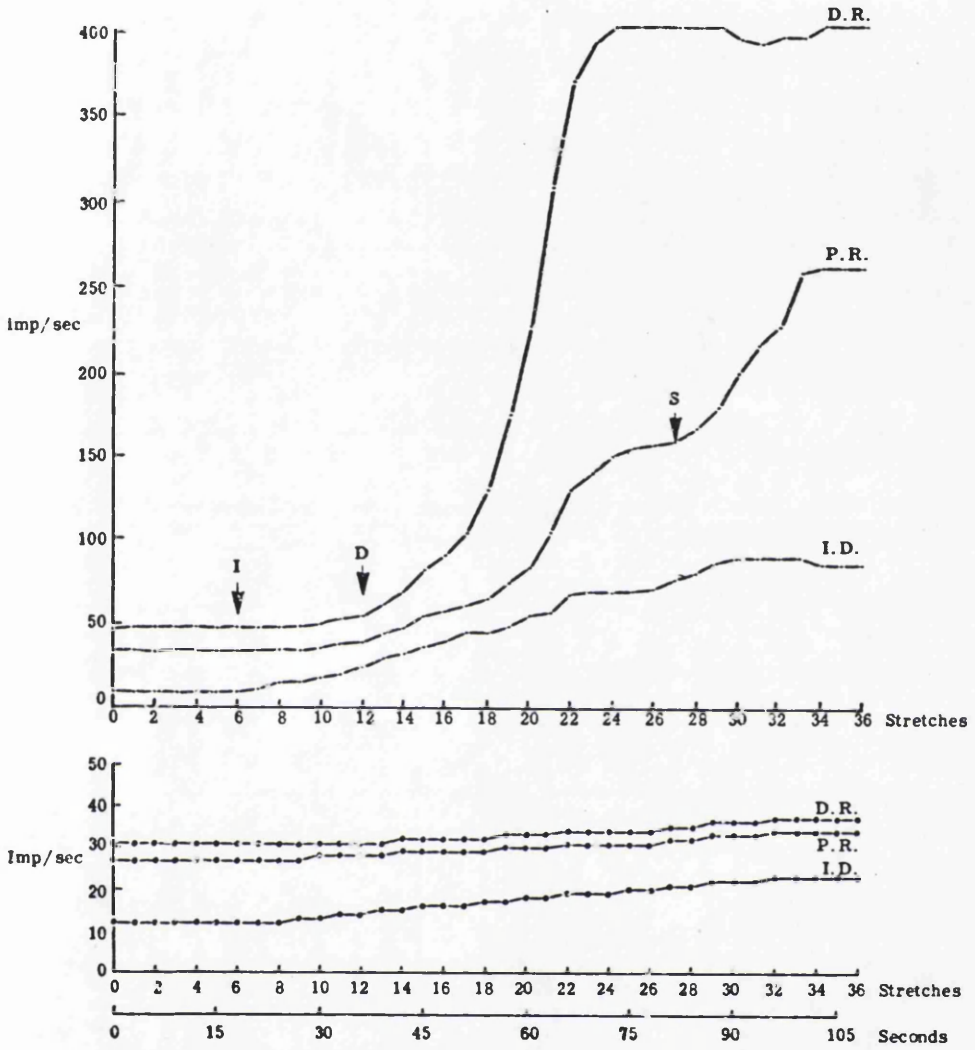

Fig. 44. Comparison of the time-course of excitation during i.a. SCh infusion of a primary sensory ending (upper graph) with a secondary sensory ending (lower graph). The activity of the primary and secondary endings was recorded simultaneously. D.R., dynamic response; P.R., position response; I.D., initial discharge rate. "I", "D", and "S" indicate the onset of Phases I, II and III of excitation of the primary ending, which is also illustrated in Figs. 18-21.

therefore consisted of a facilitation of their discharge between successive test stretches, with a simultaneous reduction in their sensitivity to the release of each stretch. The activation of secondary sensory endings by SCh was in this way very similar to the Phase I excitation of Ia sensory endings. However, while Ia endings subsequently experienced large changes in their dynamic and position sensitivities to stretching in Phase II and III of excitation, secondary sensory endings did not show similar effects with continued infusion.

RESULTS: SECTION VI

The excitation of soleus muscle spindle "intermediate" sensory endings by SCh.

Muscle spindle afferent axons with conduction velocities between 60 and 80 m/sec (35-37°C) were taken to be from "intermediate" sensory endings, which could not be clearly classified as primary or secondary sensory endings on the basis of the conduction velocity of their afferent axons (Matthews 1972, Ch. 4; Rack & Westbury 1966). The behaviour during SCh infusion of fourteen such "intermediate" sensory endings was studied in the course of these experiments. Five of the "intermediate" sensory endings were studied during intravenous infusion of SCh, and the remaining nine during intra-arterial SCh infusion at 100 µg/kg/min.

The effects of SCh on the majority but not all of the "intermediate" sensory endings closely resembled either those on typical primary sensory endings (Results Section IV) or those on typical secondary sensory endings (Results Section V). Thus, three of the "intermediate" endings studied during intravenous SCh infusion and two of the endings studied during intra-arterial SCh infusion, showed only the gradual facilitation of their discharge without potentiation of their dynamic or position sensitivities to stretch, and therefore behaved in a similar way to spindle secondary sensory endings. On the other hand, two of the "intermediate" sensory endings studied during intra-arterial SCh infusion, and the remaining three endings studied during intravenous SCh infusion, experienced marked increases in their dynamic and position sensitivities after an initial facilitation of their discharge, in a similar way to the excitation of a typical Ia sensory ending during SCh infusion.

However, the four remaining "intermediate" sensory endings behaved in an apparently intermediate manner during infusion of SCh. The excitation

of one of these "intermediate" endings during intra-arterial infusion of SCh is illustrated in Fig. 45. In the control condition (Fig. 45a), this "intermediate" ending was silent for almost 0.3 sec following the release of each test stretch. The discharge of the ending then picked up again to reach an initial discharge rate of 6 imp/sec, a little below the resting adapted discharge of the ending at 10 imp/sec. After the start of SCh infusion, the initial discharge rate of the ending began to rise (Fig. 45b), and the silence in the discharge caused by the release of each stretch became progressively shorter (Fig. 45b, c, d). The dynamic index and the position sensitivity of the ending gradually decreased as the initial discharge rate was elevated (Fig. 45b-e). Thus far, this "intermediate" sensory ending behaved like a typical secondary sensory ending during SCh infusion (see for example Fig. 41).

About 120 sec from the start of the infusion of SCh, however, there was a large increase in the initial discharge rate and the position response of the sensory ending (Fig. 45f, g, h). The position response increased by a greater amount than the initial discharge rate, so that the position sensitivity of the ending increased from 9.5 imp/sec/mm (Fig. 45e) to 14.9 imp/sec/mm (Fig. 45h). The dynamic index remained at about 9 imp/sec while this happened. No further change in the response of this ending to stretch occurred with continued SCh infusion.

Four of the five remaining "intermediate" sensory endings experienced a gradual facilitation of their discharge followed by a significant increase in their position sensitivity during SCh infusion, in a similar way to the example illustrated in Fig. 45. The increase in position sensitivity of each of these "intermediate" endings occurred between 80 and 120 sec from the start of SCh infusion into the aortic bifurcation. The remaining "intermediate" ending was also activated in a similar manner, but instead

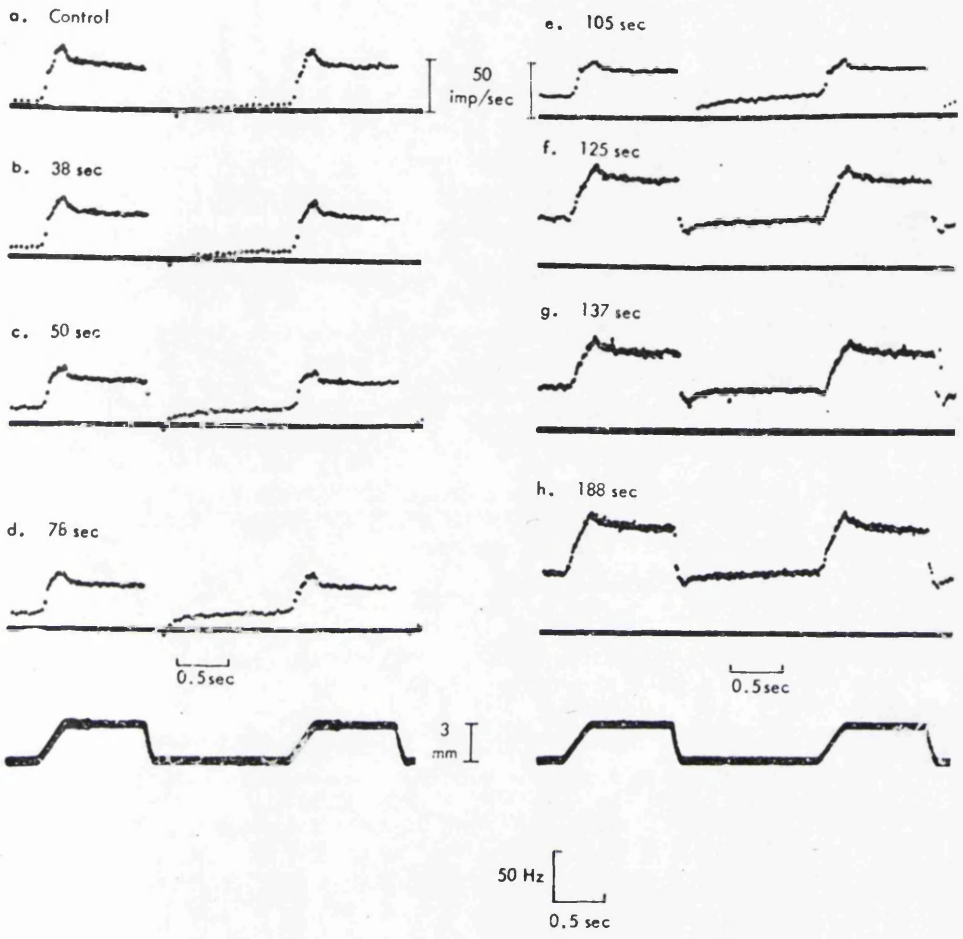

Fig. 45. The behaviour of a "truly intermediate" sensory ending (afferent conduction velocity, 69 m/sec) during intra-arterial SCh infusion. Note initial stage of excitation similar to the action of SCh on typical secondary endings (b - e) followed by a significant increase in the position sensitivity of the ending (f - h).

of an increase in its position sensitivity after the initial facilitatory effects of SCh, this ending experienced a gradual increase in its dynamic sensitivity to stretch. The response to stretch of this "intermediate" ending at various times during its activation by SCh infusion are illustrated in Fig. 46. The initial action of SCh on this ending consisted of a gradual facilitation of its discharge between stretches (Fig. 46b), but 48 sec after the start of SCh infusion the dynamic index of the ending began to increase (Fig. 46c, d), eventually reaching a maximum value 130 sec after the start of infusion (Fig. 46e). The position sensitivity of the ending also increased with the increase in the dynamic index (Fig. 46c vs. Fig. 46e).

The behaviour of these four "intermediate" sensory endings during SCh infusion clearly differed from that of typical primary or secondary sensory endings, and also differed from the behaviour of the other "intermediate" endings which were activated by SCh in a primary-like or secondary-like manner (page 79). For convenience, therefore "intermediate" endings which behave in the manner illustrated in Fig. 45 and 46 will be termed "truly intermediate" sensory endings, while the other intermediate endings will be termed "primary-like" or "secondary-like" intermediate endings according to their behaviour during SCh infusion.

Fig. 47 illustrates the relationship between the conduction velocity of the "intermediate" afferent axons and the type of behaviour exhibited by their sensory endings when activated by SCh. All "intermediate" endings which behaved in a primary-like manner during SCh infusion had afferent axon conduction velocities above 74 m/sec. Similarily, all the "intermediate" endings which behaved in a secondary-like manner had afferent axon conduction velocities below 71 m/sec. The conduction velocities of the afferent axons of the four "truly intermediate" sensory endings, however, lay between 69 and 77 m/sec.

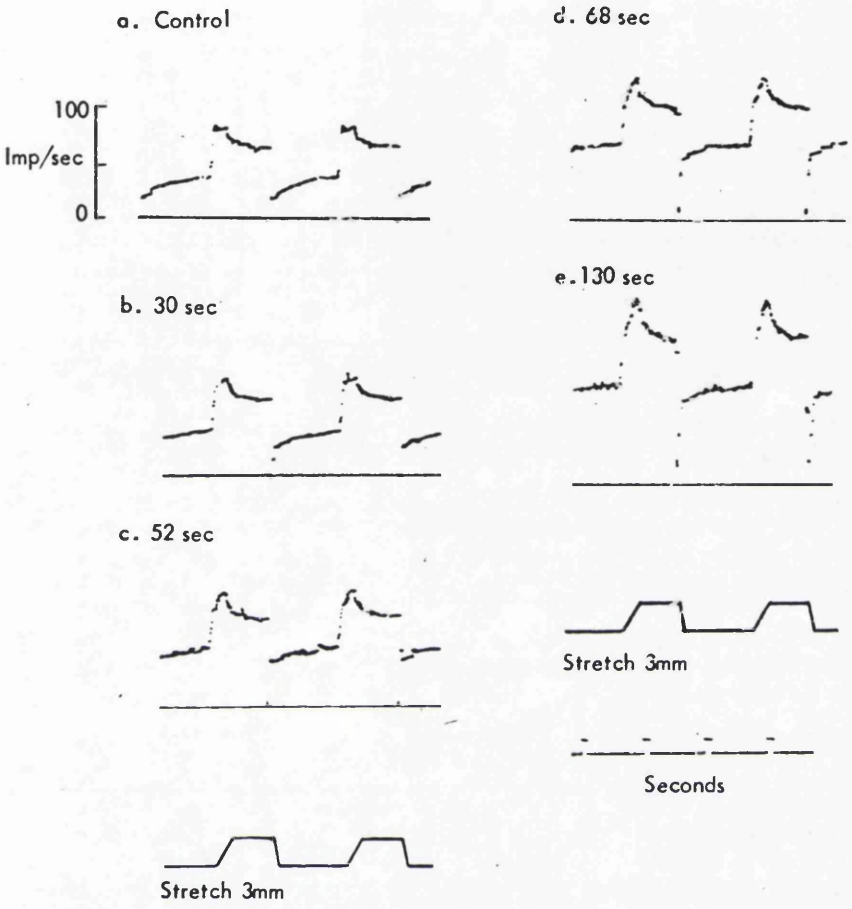

Fig. 46. The behaviour of a different "truly-intermediate" ending (afferent conduction velocity, 74 m/sec) during intra-arterial SCh infusion. Pen-recorder traces. Note initial facilitation in (b) followed by an increase in the dynamic sensitivity of the ending (c, d, e).

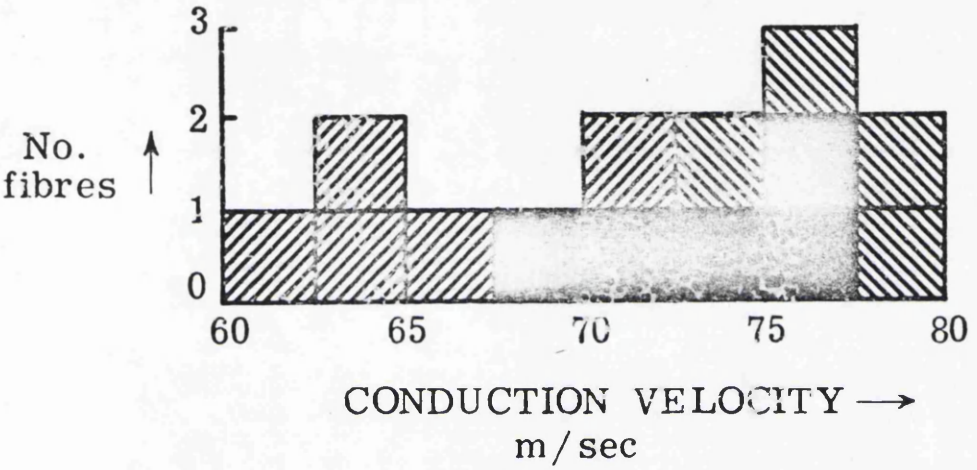

Fig. 47. Histogram relating the type of behaviour shown by the 14 "intermediate" endings when activated by SCh with the conduction velocity of their afferent axons.

/// "secondary-like" intermediate ending.

\\\ "primary-like" intermediate ending.

■ "truly-intermediate" ending.

RESULTS: SECTION VII

The effects of SCh on the response to stretch of Golgi tendon organs in the soleus muscle.

These experiments were carried out in collaboration with Dr. W.R. Ferrell, and represent an extension of the preceding study of the effects of SCh on muscle spindles in the soleus muscle (Results Sections I-VI). It had become apparent in the experiments of Ferrell (1977; Ph.D. Thesis, University of Glasgow, 1977) that injections of SCh given intravenously to the whole cat had an excitatory effect on the discharge of some of the mechanoreceptors located in the cruciate ligaments within the knee joint. Earlier, Burgess & Clark (1969) had recorded an SCh-sensitive discharge from the posterior articular nerve (PAN), and attributed its presence in the joint afferent nerve to afferent axons from muscle spindles in adjoining muscles. However, Ferrell (1977) showed that there was no significant contamination of the PAN by afferents of muscular origin, and found that the sensory endings responsible for the SCh-sensitive discharge were instead spray-type endings in the cruciate ligaments, very similar in structure to Golgi tendon organs. These results indicated that SCh in the intact animal could have a direct excitatory action on the discharge of some sensory endings which unlike spindle endings were not associated with muscular structures. The object of the present experiments was therefore to re-examine the earlier negative findings of Granit et al (1953) that SCh did not excite Golgi tendon organs in the cat soleus muscle, using the same protocol of test stretching as used in the spindle experiments (Results Section I) combined with intra-arterial infusion of SCh at 100 µg/kg/min.

In the course of these experiments, a total of 59 tendon organ afferent axons were isolated in filaments of the dorsal roots of 9 cats. The degree

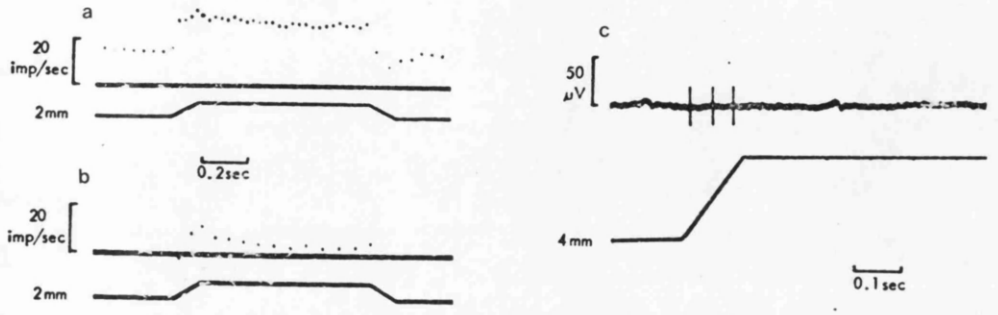

Fig. 48. The response of three different Golgi tendon organs to muscle stretch. a and b: upper traces, instantaneous frequency of afferent discharge; lower traces, muscle length. c: upper trace, action potentials recorded from dorsal root filament; lower trace, muscle length. Note different time-scale in c. Records from one experiment; each test stretch was applied starting at the same initial muscle length.

of passive stretch of the soleus muscle required to elicit a tonic discharge from each of the tendon organs varied widely (Jansen & Rudjord 1964; Stuart, Goslow, Mosher & Reinking, 1970), so that while some tendon organs exhibited a maintained discharge at moderate static muscle tensions (75-100 g) and responded readily to the ramp test stretches, others did not discharge tonically even at high muscle tensions and fired only during the dynamic extension of the muscle. The behaviour of three typical tendon organs with different thresholds to passive stretch is illustrated in Fig. 48. In each case, the initial muscle tension was adjusted to be approximately 75 g, and a servo-controlled muscle stretcher (see Methods) was used to apply a series of ramp-and-hold test stretches. Fig. 48a illustrates the behaviour of a "low-threshold" tendon organ, which was tonically active at the set initial muscle tension and responded readily to the ramp stretch. The tendon organ shown in Fig. 48b was of "intermediate" threshold, responding only to the muscle stretch and remaining silent between stretches. Fig. 48c shows the response to a larger ramp stretch of a "high-threshold" tendon organ, which responded only to the dynamic phase of stretch and could not be made to discharge tonically even when the initial muscle tension was increased to 500 g.

In these experiments, the initial muscle tension was always set at the start to a moderate value (75-100 g), and our observations have concentrated mainly on the effects of SCh on the discharge of "low-threshold" tendon organs which were then tonically active. A detailed statistical analysis of the tension thresholds of different tendon organs similar to that carried out by Stuart et al (1970) was however felt to be outside the scope of this investigation. Of the total of 59 tendon organ afferent axons isolated in the course of these experiments, therefore, the effects of SCh were studied only in 21 cases. Fourteen of these cases were "low-threshold" tendon organs

which discharged tonically at the set initial muscle lengths. The remaining seven tendon organs were of the "intermediate" type (Fig. 48b), which responded only to muscle extension.

Fig. 49 shows the changes in the dynamic and position responses and the initial discharge rate of a typical "low-threshold" tendon organ during and after intra-arterial SCh infusion, in a similar way to the behaviour of a primary ending illustrated in Fig. 19. As Fig. 49 shows, the initial discharge rate and the dynamic and position responses to stretch of the tendon organ began to increase within one minute of the start of SCh infusion, and continued to rise as the infusion progressed. The dynamic index remained at about 3 imp/sec while this happened, and the position sensitivity of the ending also did not change significantly. The facilitation of the discharge of the tendon organ was accompanied by a gradual reduction of the effects of the release of stretch on the discharge of the ending, in a similar way to the effects of SCh on secondary endings (Results Section V) and on primary endings during Phase I of excitation (Results Section IV.1). However, the actual increase in the rate of discharge of the tendon organ over a five-minute period of SCh infusion was much smaller than the increase observed in the discharge rates of typical primary and secondary sensory endings during shorter periods of SCh infusion. Unlike spindle sensory endings, the discharge rate of the tendon organ continued to increase after the infusion of SCh ceased, and reached a maximum about ten minutes after the end of infusion. This was followed by a very prolonged recovery as the discharge rate of the ending gradually fell, to reach control values nearly two hours after the end of SCh infusion.

Infusion of SCh was found to facilitate the response to stretch of all of the fourteen "low-threshold" tendon organs studied in these experiments,

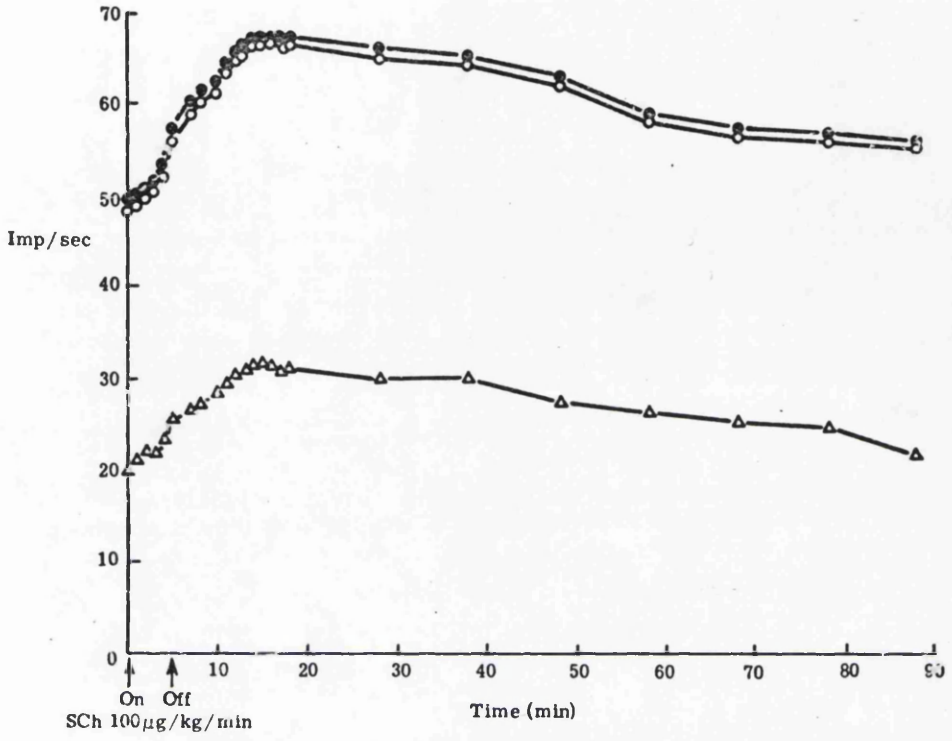

Fig. 49. Changes in the dynamic response (•) position response (o) and initial discharge rate (∧) of a typical low-threshold Golgi tendon organ during and after a 5-minute intra-arterial infusion of SCh. Ramp test stretches, 4 mm at 16 mm/sec.

in the manner illustrated in Figs. 49 and 50. The actual extent to which the discharge rates of the tendon organs increased above control values during their activation by SCh however varied from only a few impulses/sec in some cases to a doubling of the initial discharge rate value in others. Generally, the extent of activation of the tendon organs by SCh appeared to depend on their thresholds to passive stretch, so that tendon organs which were tonically active at low muscle tensions and which readily responded to ramp stretches were most affected by SCh, while others which had higher thresholds to passive stretch were less affected by SCh. This is illustrated for three tendon organs in Fig. 50. The two tendon organs shown in Fig. 50a and 50b (upper records) were both of "low threshold" type and discharged tonically at the set initial muscle tension, but one had a lower threshold to passive stretch than the other, and discharged at a higher rate at the initial muscle length (Figs. 50a vs. 50b). The third tendon organ illustrated in Fig. 50c was of "intermediate" threshold, and discharged only in response to the test stretches. The lower records in Fig. 50 show the maximal effects of a 3 minute infusion of SCh on each of the tendon organs. It can be seen that the effects of SCh on the tendon organ with the lowest threshold (Fig. 50a) were significantly greater than those on the tendon organ with the higher threshold (Fig. 50b), while the "intermediate" type tendon organ (Fig. 50c) appeared not to be affected at all by the infusion of SCh. Of the seven "intermediate" type tendon organs studied in the course of these experiments, only one showed a detectable degree of activation following SCh administration. The response to stretch of the other six "intermediate" type tendon organs remained unchanged during periods of SCh infusion of two to six minutes, and in this they differed significantly from "low-threshold" tendon organs whose activity was recorded simultaneously.

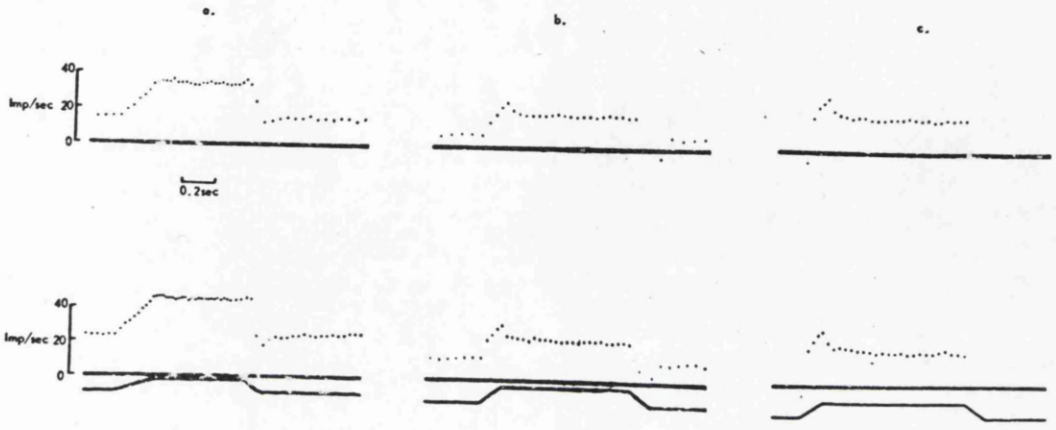

Fig. 50. The effects of a 3-minute infusion of SCh on the response to stretch of three separate Golgi tendon organs (a, b, c). Upper records, control responses; lower records, responses of the tendon organs to stretch after SCh. Records are from different experiments, but the initial muscle tension in each experiment was set at approximately 75 g. Ramp test stretches: in a, 3 mm at 8 mm/sec; in b and c, 3 mm at 12 mm/sec.

Fig. 51 compares the maximal effects of a 3 minute infusion of SCh on the discharge of a low-threshold tendon organ (Fig. 51c) with the maximal effects on a spindle primary ending (Fig. 51a) and a secondary ending (Fig. 51b), and illustrates the relatively small facilitatory effects of SCh on the response of the tendon organ to stretch. The maximum activation of the spindle sensory endings occurred during the period of SCh infusion, but the peak excitation of the tendon organ occurred about 10 minutes after the end of the SCh infusion. Unfortunately, the primary sensory ending whose activity was monitored in this experiment did not develop a typical Phase III type increase in its position sensitivity (see Results Section IV.3).

These results clearly show that SCh given to the whole animal does excite Golgi tendon organs which have low thresholds to passive muscle stretch (cf. Granit et al 1953), in a similar way to the effects of SCh on some mechanoreceptors in the cat knee joint (Ferrell 1977; Ph.D. Thesis). The gradual facilitatory effects of SCh on the discharge of these sensory endings which are not associated with muscle structures are probably due to a direct action of SCh on the afferent nerve terminals (see Discussion), and similar direct effects of SCh on muscle spindle sensory endings may also occur (cf. Fehr 1965).

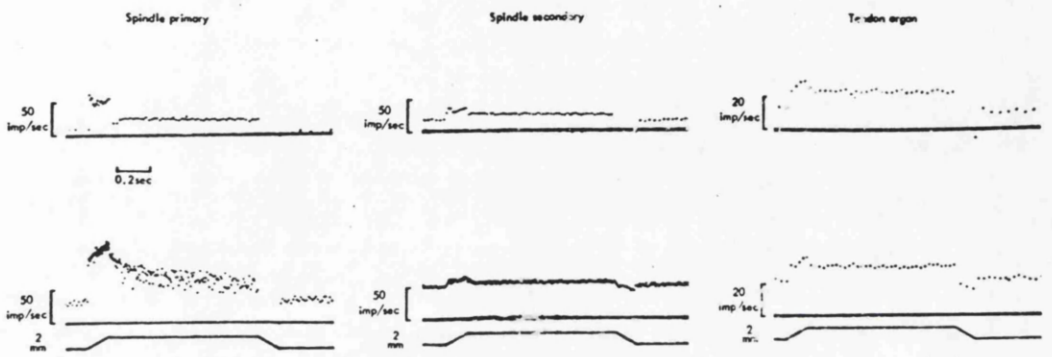

Fig. 51. Comparison of the effects of a 3-minute SCh infusion on the response to stretch of a spindle primary ending, a spindle secondary ending and a "low threshold" Golgi tendon organ. Records obtained simultaneously in the same animal. In each case: upper record, control response to stretch; middle record, response of activated endings to stretch; lower record, muscle length. Note different vertical scale for tendon organ.

DISCUSSION

The present study of the action of SCh on the discharge of muscle spindles in the cat employed a new combination of the experimental approaches used by earlier workers. Thus, while Brinling & Smith (1960) studied the effects of intravenous infusions of SCh on the discharge of gastrocnemius muscle spindle sensory endings, they did so only at fixed muscle lengths. On the other hand, Rack and Westbury (1966) described the effects of SCh on the response of spindle sensory endings to dynamic stretching of the muscle, but concentrated their observations on the effects prevalent at various times at least 30-60 sec after single bolus injections of SCh were given intravenously. The experimental approach employed in the present work, which combined repetitive test stretching of the soleus muscle with continuous infusion of SCh, enabled the gradual development of the effects of SCh on the discharge of the spindle sensory endings to be studied in detail.

The three parameters chosen for the purpose of the analysis of the effects of SCh on the spindle sensory endings, namely the initial discharge rate, the dynamic response and the position response (Results, page 47) allow changes in three aspects of the response of the endings to stretch to be studied during SCh infusion. The difference between the dynamic response and the position response of a sensory ending at a given time is the same as the conventional measure of the dynamic sensitivity, the dynamic index (Crowe & Matthews 1964a, b). Similarly, the difference between the position response and the adapted discharge rate at a given time is a measure of the change in the discharge rate of the ending caused by the change in muscle length, in effect a measure of the position sensitivity of the sensory ending (see Matthews (1972) Ch. 4). The third aspect of the behaviour of the sensory endings which is of interest is reflected in the initial discharge rate itself, and is a direct result of the repetitive

test stretching technique employed in the present study. The discharge of the sensory ending after the release of each test stretch (Fig. 15) reflects the gradual recovery of the sensory nerve terminals from the hyperpolarisation caused by the muscle shortening during the release of stretch (Hunt & Ottoson 1975; Results page 45). The initial discharge rate of a sensory ending during a sequence of test stretches, therefore is determined by the degree of recovery from the hyperpolarisation of the sensory nerve terminals that takes place between successive test stretches. During a sequence of test stretches of constant amplitude and duration applied at set intervals, the initial discharge rate attained by a sensory ending between successive stretches depends directly on the rate at which the ending is capable of recovering from the hyperpolarising after-effects of each release of stretch. The initial discharge rate is thus a convenient indirect measure of the electrical state of the sensory nerve terminals, before each test stretch is applied.

Under the experimental conditions of the present study, the excitation of spindle primary sensory endings during SCh infusion occurred in three consecutive stages, as described in Results Sections II-IV. Marked changes in the dynamic and position responses of the Ia endings were only seen in Phases II and III of excitation. In Phase II of excitation, the sensitivity of the Ia endings to the dynamic phase of the test stretch increased dramatically, accompanied by a smaller increase in position sensitivity, as described in Results Section II and IV.2. Phase III of excitation in the present experiments was characterised by a large increase in the position sensitivity of the Ia endings, while the dynamic response of the endings remained high, as described in Results Sections II and IV.3. The increase in the dynamic sensitivity of the Ia endings in Phase II of excitation was very similar to the behaviour of the Ia endings following intravenous

injections of SCh as described by Rack & Westbury (1966). In Phase II of excitation, the response to a ramp stretch of the Ia endings was very similar to that of Ia endings under strong simultaneous dynamic and static fusimotor stimulation (Crowe & Matthews 1964a; see for example Emonet-Denand et al 1977, Figs. 6, 7, 8). Rack & Westbury (1966) in their experiments occasionally observed a similar "early response to a large dose (of SCh).....quite similar to the effect of combined stimulation of powerful static and dynamic fusimotor fibres" (their page 704). This combined static and dynamic pattern of response of the Ia endings then changed usually within one minute of the injection of SCh, to give way to the markedly dynamic behaviour upon which Rack & Westbury concentrated their attention. Because in their experiments this Phase III-like effect was seen only occasionally after intravenous injection of SCh, Rack & Westbury suggested that it was caused by a transient contraction of some of the intrafusal muscle fibres, in a similar way to the fasciculation of the extrafusal muscle fibres before the onset of paralysis. The main effect of SCh on the muscle spindles, they felt, was to produce a sustained contraction of the intrafusal muscle fibres which mediate the dynamic fusimotor activity on the Ia sensory endings.

In the three preliminary experiments of the present study where Ia endings were tested following intravenous injections of SCh (Results Section III), two Ia endings experienced only the large increase in the dynamic index characteristic of Phase II of excitation, in a similar way to the effects observed by Rack & Westbury (1966). Only one Ia ending showed a Phase III-like increase in position sensitivity. Intravenous infusions of SCh were successful in inducing the Phase III increase in position sensitivity in only 8 out of 20 cases (Fig. 23). However, intra-arterial infusions of SCh induced Phase III of excitation in 18 out of 20

cases (Fig. 22), presumably because of a more efficient delivery of the drug to the muscle spindles. Once induced, the Phase III effects on the position sensitivity of the Ia endings persisted for as long as the infusion of SCh was continued, and only declined after the infusion ceased (Figs. 18 and 20).

It is thus unlikely that this later increase in the position sensitivity of the Ia endings is caused by the transient occasional contraction of some of the intrafusal muscle fibres as suggested by Rack & Westbury (1966). On the contrary, the Phase III potentiation of the position sensitivity of Ia endings appears to be a further stage in their activation by SCh, which has a significantly higher threshold to SCh than the dynamic potentiation characteristic of Phase II of excitation. Thus, whilst the Phase II dynamic effects on the Ia endings can be readily induced by intravenous administration of SCh to the whole animal (Results Section III; Rack & Westbury 1966), the characteristic Phase III effects are seen only in approximately 1 out of three cases under those conditions, presumably only in those spindles which are as a whole more sensitive to intravascular SCh (Rack & Westbury 1966). However, by infusing SCh into the aortic bifurcation and thus restricting its delivery mainly to the appropriate leg, the Phase III effects on the position sensitivity of Ia endings can regularily be induced in the majority of cases (Results Section III).

The characteristic changes in the dynamic and position sensitivities of Ia endings in Phases II and III of excitation during SCh infusion are entirely as would be expected from the work of Gladden (1976) on the sensitivity of the intrafusal muscle fibres of isolated muscle spindles to ACh. These experiments showed that the two nuclear bag fibres, and not the nuclear chain fibres, were made to contract by ACh, and further that

the dynamic nuclear bag fibre (DNB) was more sensitive to topically applied ACh than the static nuclear bag fibre (SNB; see page 29). Subsequent experiments (Boyd & Gladden, Personal Communication) have demonstrated that the DNB also has a lower threshold to topically applied SCh than the SNB, and have confirmed the original observation of Boyd that the nuclear chain fibres are not made to contract by SCh.

The large changes in the dynamic and position sensitivities of the Ia endings during Phase II and III of excitation are presumably caused by the recruitment by SCh of the dynamic and static nuclear bag fibres respectively. Thus, the strong similarity between the effects of dynamic fusimotor stimulation and the Phase II dynamic effects of SCh on Ia endings (Results Section IV.2; Rack & Westbury 1966) is no doubt caused by the activation of the DNB, which has the lower threshold to SCh in vitro (Gladden 1976) and which is made to contract by dynamic fusimotor axons (Boyd, Gladden, McWilliam & Ward 1977), when the concentration of SCh at the muscle spindle rises to a level above its threshold. The subsequent Phase III increase in the position sensitivity of Ia endings is presumably caused by the contraction of the SNB, which has the higher threshold of the two nuclear bag fibres in vitro (Gladden 1976), when the concentration of SCh at the spindle is sufficiently high. The characteristic form of the response to stretch of Ia endings in Phase III of excitation, which is very similar to the effects of combined stimulation of strong dynamic and static fusimotor axons (see for example Crowe & Matthews 1964a), is thus the result of the simultaneous contraction of the DNB and the SNB, after the concentration of SCh at the muscle spindle has exceeded the threshold of the SNB.

After the end of SCh infusion, the Phase III effects on the position sensitivity of the Ia endings decay first, leaving the endings with a high dynamic sensitivity to stretch (Figs. 21 and 39). This is no doubt

caused by the relaxation of the higher-threshold SNB, as the concentration of SCh at the muscle spindle falls. The Ia endings revert to a situation similar to that in Phase II of excitation, when the DNB is the only intrafusal muscle fibre in contraction. The remaining high dynamic sensitivity of the Ia endings then gradually decays, when the DNB also relaxes as the levels of SCh at the spindle continue to fall.

The evidence for the recruitment of the dynamic and static nuclear bag fibres by SCh infusion in the present experiments is admittedly indirect, and relies on the interpretation of changes in the dynamic and position sensitivities of the Ia endings rather than the observation of the actual contraction of the intrafusal fibres themselves. Alternative explanations of the behaviour of Ia endings in Phases II and III of excitation are, however, difficult to envisage. This is so precisely because it is the dynamic sensitivity of the sensory endings that change, in a characteristic sequence. The only alternative means of increasing the dynamic and position sensitivities of the Ia endings in a similar manner is via the stimulation of dynamic and static fusimotor axons, which themselves are known to produce contractions in the intrafusal muscle fibres (Boyd 1976b; Bessou & Pages 1975).

The behaviour of Ia endings in Phase I of excitation during SCh infusion, however, appears not to be related to the contraction of the two nuclear bag fibres. Phase I of excitation in the present study was characterised by a gradual increase in the discharge of the Ia endings between successive test stretches, which occurred without potentiation of, and usually a decrease in, the dynamic and position sensitivities of the sensory endings (Results Sections II, IV.1). As observed earlier (page 45), the discharge of the sensory endings between successive test stretches reflects the gradual recovery of the endings from the hyperpolarisation

caused by the release of each stretch. The action of SCh on the Ia endings in Phase I of excitation thus appears to greatly facilitate the process of their recovery from the hyperpolarising effects of muscle shortening. This is seen most clearly in those Ia endings which were silenced for some time after the release of each test stretch, as for example in the case illustrated in Fig. 28. In the control condition, this Ia ending was not able to recover sufficiently from the after-effects of each release of stretch to be able to discharge at all between successive stretches (Fig. 28a). As Phase I of excitation developed, however, the silent period following the release of each stretch gradually shortened, and the initial discharge rate of the Ia ending increased, until eventually the discharge of the ending picked up again immediately after the release of stretch (Fig. 28d). The hyperpolarising after-effects of the release of stretch on the discharge of the ending were thus almost completely abolished by SCh in Phase I of excitation.

The initial discharge rate of Ia endings in Phase I of excitation normally increased to values higher than the "resting" adapted discharge rate of the endings at the initial muscle length (see for example Fig. 29). Thus, the action of SCh on the Ia ending in Phase I of excitation not only counteracts the hyperpolarisation caused by the release of stretch which initially prevents the Ia discharge from recovering fully between stretches (Figs. 15 and 16), but also facilitates the discharge of the Ia endings to such a degree as to allow the initial discharge rate to increase to values above the control "resting" level.

Since the contraction of either the dynamic or the static nuclear bag fibres of the muscle spindles would increase the dynamic or position sensitivity of the Ia endings, as happens during fusimotor activation, the fact that the Phase I effects of SCh take place without such changes in the

response of the Ia endings to stretch indicates that the facilitation of the Ia discharge in Phase I of activation is independent of the later contraction of the two nuclear bag fibres. Instead, the gradual abolishment of the effects of hyperpolarisation on the discharge of the endings, and the simultaneous increase in the initial discharge rate to values above the control "resting" level, must be the result of a progressive depolarisation of the afferent nerve terminals by SCh, either directly or indirectly. In an analogous manner, the after-effects of the release of stretch on the discharge of the Ia ending become less marked when the initial muscle length is increased (Fig. 15), no doubt because of a greater initial depolarisation of the sensory nerve terminals at the longer muscle lengths (cf. Hunt & Ottoson 1975).

The facilitation of the discharge of low-threshold Golgi tendon organs during SCh infusion (Results Section V), which was similar in effect to the Phase I action of SCh on the discharge of Ia endings, is probably also caused by a similar depolarising effect of SCh on the Ib sensory nerve terminals. Excitation of the Golgi tendon organs by an increase in muscle tension can be excluded as an alternative explanation, since SCh rapidly induces paralysis of the extrafusal muscle fibres. However, the effects of SCh on the discharge of tendon organs were much less marked than those on the discharge of muscle spindle Ia endings in Phase I of excitation, and in general also had longer lag times to excitation from the start of SCh infusion. The low sensitivity of most tendon organs to SCh, and the comparatively small overall effects of SCh on their discharge which might not be readily apparent without the aid of a pulse-interval meter, may account for the earlier negative findings of Granit et al (1953).

The prolonged time-course of activation of tendon organs during and after SCh infusion, which differed significantly from the faster time-course

of activation and recovery of muscle spindle sensory endings, may suggest that the concentrations of SCh at the sensory terminals of the Ib axon equilibriate with the plasma levels of SCh at a much slower rate than in the muscle spindles, perhaps because of differences in the local blood supply, the permeability of the connective tissue capsules around the sensory nerve terminals, and the amount of pseudo-cholinesterase associated with the sensory nerve terminals.

The facilitatory effects of SCh on the discharge of Golgi tendon organs and on the response of muscle spindle Ia sensory endings to stretching in Phase I of excitation may be the result of a direct depolarising action of SCh on the sensory nerve terminals themselves, as first suggested for Ia endings by Granit et al (1953). ACh given intra-arterially appears to depolarise directly the sensory nerve terminals of cutaneous Group A, B, and C axons (Douglas & Gray 1953; Douglas & Ritchie 1960). It is thus possible that SCh also acts directly on other afferent nerve terminals in a similar way. Kidd & Kucera (1969) have shown that SCh does act directly on the sensory nerve terminals of Group III afferent axons in the rat, but only in high concentrations. Ferrell (1977; Ph.D. Thesis) found that some of the knee joint receptors of the cat were excited by intravenous injections of SCh, which suggests that the direct action of SCh on the muscle spindle and tendon organ afferent nerve terminals also extends to these sensory endings. Nevertheless, in the only direct study of its kind so far, Ottoson (1961) showed that ACh, SCh and other cholinesters do not have such a depolarising action *in vitro* on frog muscle spindle sensory endings whose intrafusal muscle fibres have been destroyed.

An alternative, and perhaps more attractive, possibility is that the facilitatory action of SCh on the discharge of Ia and tendon organ sensory endings is an indirect result of the depolarising blocking action of SCh

on the extrafusal motor end-plates. In the presence of SCh, significant amounts of intracellular K^+ are released from the extrafusal muscle fibres into the interstitial spaces (Paton 1956). Injection or infusion of low doses of SCh into an isolated perfused gastrocnemius muscle causes a large increase in the K^+ concentration of the perfusate (Paton 1956). Klupp & Kraupp (1954; see Paton 1956) have shown that in dogs, an intravenous injection of 200 µg SCh/kg is sufficient to raise the K+ levels of the plasma by 30%.

As pointed out by Smith (1966), it is possible that "the magnitude of the potassium release after SCh might alone be sufficient to induce an appreciable change in spindle receptor function" (his page 229). Excess potassium in the Krebs' solution bathing an isolated cat tenuissimus muscle spindle produces a marked increase in the afferent discharge frequency (Lippold, Nicholls & Redfearn, 1960b). Kidd & Vaillant (1974) have shown that increasing the K+ concentration in the solution bathing an isolated rat muscle spindle has a series of effects on the response to stretch of the primary sensory ending, which range through "facilitation of the effects of stretching, frank excitation summating with stretching, a preclusion of stretch evoked discharge, to complete inexcitability" with increasing K+ concentration. The facilitation of the response of the spindle sensory endings to stretch was seen when the K+ concentration was increased from the normal 5 meq/l to 8 meq/l, and the summation effects at 10 meq/l.

An additional, and possibly more potent, source of K+ in the muscle spindle may be the nuclear chain fibres, which experimental evidence to date shows are also paralysed by ACh and SCh (Gladden 1976; Boyd & Gladden, Personal Communication; Smith 1966). Assuming that the blockade of the gamma motor terminals on the nuclear chain fibres is also a depolarising

one similar to the extrafusal blockade, then K+ must also be released from the nuclear chain fibres directly into the muscle spindle capsule. The fact that the in vitro effects of high concentrations of K+, consisting of a preclusion of the stretch evoked discharge and the complete inexcitability of Ia endings (Kidd & Vaillant 1974) were not seen in the present experiments, indicates that the intramuscular concentrations of K+ were never sufficient to reach the required concentrations. Previous workers, however, have recorded abnormal responses to stretch from spindle Ia endings following large doses of SCh, or observed inexcitability of the sensory endings after large injections of SCh (Rack & Westbury 1966).

Thus, the behaviour of muscle spindle Ia sensory endings during Phases I, II and III of excitation in the present experiments can be related to the sequence of intrafusal events that take place as the concentration of SCh at the spindle gradually rises. The initial Phase I facilitatory effects of SCh on the discharge of the Ia endings occur without potentiation of the dynamic or position sensitivities of the endings to stretching, and probably reflect a gradual electrical depolarisation of the afferent nerve terminals by SCh, either directly or indirectly. With continued infusion, the concentration of SCh rises to a level above that required to induce the contraction of the DNB fibre, which has a lower threshold to SCh than the SNB. The Ia endings enter Phase II of excitation when the DNB contracts, and their response to stretch is then very similar to that of Ia endings under strong dynamic fusimotor activation. As the SCh infusion is continued, the concentration of SCh at the muscle spindle continues to rise until the threshold of the SNB is also exceeded, when the Ia endings enter Phase III of excitation. The response of Ia endings to stretch in Phase III of excitation is very similar to that of

Ia endings under strong combined dynamic and static fusimotor activation, and is no doubt the result of the simultaneous contraction of the DNB and the SNB fibres. The excitation of muscle spindle Ia sensory endings by SCh thus appears to be the result of a combination of an electrical effect of the drug on the sensory nerve terminals, and a further action on the dynamic and static nuclear bag fibres, in a manner similar to that originally suggested by Granit et al (1953).

In contrast, the effects of SCh on soleus muscle spindle secondary sensory endings with afferent axon conduction velocities below 60 m/sec were limited to a gradual facilitation of the discharge of the endings, similar to the Phase I effects of SCh on the Ia endings and to the effects of SCh on the discharge of low-threshold tendon organs (Results Section V). While spindle Ia endings subsequently experienced marked changes in their dynamic and position sensitivities to stretch as a result of the recruitment of the two nuclear bag fibres by SCh, secondary sensory endings did not show similar effects (Fig. 44), and their rates of discharge remained much lower than those of activated Ia endings, as reported by Fehr (1965). The finding of Rack & Westbury (1966) that following SCh injections the "sensitivity of the secondary afferent to static and dynamic stretching increased together, and the general shape of the record remained unchanged", agrees well with the results of the present study.

Presumably, the gradual facilitatory action of SCh on the discharge of secondary sensory endings is also caused by a progressive depolarisation of the afferent nerve terminals either directly or indirectly by SCh, in a similar way to the facilitatory effects of SCh on the discharge of Ia endings and Golgi tendon organs. The excitation of muscle spindle secondary sensory endings by SCh therefore appears to be entirely the result of a gradual electrical depolarisation of the sensory endings, with no apparent

contribution from the contraction of the nuclear bag fibres.

Histological studies of muscle spindle structure have shown that spindle "secondary" sensory endings, classified as such on the basis of their afferent axon diameters and the location of their sensory nerve terminals on either side of the primary sensory spirals (Boyd 1962), lie mainly on the nuclear chain bundle but may also have collateral terminations on the nuclear bag fibres. However, the fact that in the present study all the sensory endings with afferent axons of conduction velocity below 60 m/sec were apparently unaffected by the SCh-induced contraction of the nuclear bag fibres, indicates either that none of these secondary sensory endings had collateral sensory terminals on the nuclear bag fibres, or that if present, such terminals did not contribute significantly to the generation of the secondary afferent discharge.

Rack & Westbury (1966) were able to characterise all spindle sensory endings with afferent conduction velocities between 60 and 80 m/sec ("intermediate" sensory endings) as either primary-like or secondary-like, according to the effects of SCh on their dynamic sensitivity to stretching. In the present study, the majority of "intermediate" sensory endings did fall into two groups in a similar way, but some sensory endings were encountered which behaved in a significantly different manner (Results Section VI; Fig. 47). The differences in the effects of SCh on the primary-like, the secondary-like and the remaining "truly intermediate" sensory endings, must reflect differences in the intrafusal distribution of the sensory nerve terminals of the afferent axons. Thus, "intermediate" sensory endings which behave in a secondary-like manner and are unaffected by the SCh induced contraction of the two nuclear bag fibres, presumably innervate the nuclear chain fibres alone, and have no functional input from the nuclear bag fibres. Similarly, "intermediate" sensory endings which

behave in a primary-like manner probably innervate all three types of intrafusal fibre, like a typical primary afferent axon.

However, the behaviour of the "truly intermediate" sensory endings in the presence of SCh indicates that these endings have a functional input from one, but not both, of the nuclear bag fibres. The change in the sensitivity of the endings to stretching following the initial facilitatory effects of SCh (Figs. 45 and 46) is presumably the result of the contraction of this nuclear bag fibre. Such sensory endings therefore appear to correspond to those "secondary" sensory endings observed histologically which lie on the nuclear chain fibres but also have collateral terminals on the nuclear bag fibres (Boyd 1962; see also Banks et al 1976). The fact that in four of the five such "truly intermediate" sensory endings the position sensitivity, and not the dynamic sensitivity, increased after the initial facilitatory action of SCh (Fig. 45), suggests that these "intermediate" endings had collateral terminals innervating the SNB rather than the DNB. The fifth "truly intermediate" sensory ending experienced an increase in its dynamic sensitivity to stretch (Fig. 46), in a similar way to the Phase II effects of SCh on Ia endings. This suggests that the collateral terminals of this "truly intermediate" afferent axon innervated the DNB, which is the nuclear bag fibre activated in Phase II of excitation of Ia endings by SCh.

In summary, the results of the present study indicate that typical secondary sensory endings, with afferent axon conduction velocities below 60 m/sec, appear not to receive a functional input from the nuclear bag fibres and thus probably lie only on the nuclear chain fibres of the muscle spindle. In addition, all the afferent axons with conduction velocities in the intermediate range but below 65 m/sec (Fig. 47) were from spindle sensory endings which were apparently unaffected by the

recruitment of the nuclear bag fibres by SCh, and which therefore behaved like typical secondary sensory endings. This finding agrees well with that of Rack & Westbury (1966), who also found that all the "intermediate" conduction velocity afferents studied in their experiments which behaved in a secondary-like manner in the presence of SCh had conduction velocities below 65 m/sec. However, while Rack & Westbury were able to classify all the intermediate afferents in their experiments as either primary-like or secondary-like when activated by SCh, in the present study a significant minority of "intermediate" sensory endings clearly did not fall into either category (Fig. 47). From their behaviour during SCh infusion, these endings appear to have a functional input from one but not both of the nuclear bag fibres, and thus probably represent a "truly intermediate" form of spindle sensory ending.

As a means of studying the internal working of the mammalian muscle spindle, the reproducible activation of the dynamic and static nuclear bag fibres of soleus muscle spindles by SCh administration to the intact animal (cf. Gladden 1976), provides a useful experimental alternative to the activation of the intrafusal muscle fibres by stimulation of dynamic and static fusimotor axons in the conventional manner. The true intrafusal destinations of fusimotor axons isolated in the ventral spinal roots are normally unknown, and can only be determined either by direct observation of the relevant muscle spindle (Boyd 1976b; Boyd et al 1977) or by means of complex glycogen-depletion studies (Barker et al 1973). Thus, though the majority of fusimotor axons may be clearly classified as "dynamic" or "static" in their action (cf. Emonet-Denand et al 1977), the nature of the intrafusal muscle fibres they activate may be uncertain, particularly for static fusimotor axons as outlined in the Literature Review. This uncertainty limits to some degree the use of combined dynamic and static

fusimotor activation as a means of studying the contribution from each of the individual sensory spirals of the Ia sensory ending to the Ia afferent discharge (cf. Lennerstrand 1968; Hulliger et al 1977a, b, c).

In contrast, the selective activation of the static and dynamic nuclear bag fibres of the soleus muscle spindles by SCh, enables the role of the two nuclear bag fibres in the generation of the Ia discharge to be examined. The effects of the contraction of the two nuclear bag fibres on the afferent discharge of primary, secondary and "intermediate" sensory endings has been discussed above. The remaining discussion will be concerned with a detailed examination of the changes in the response to stretch of Ia endings after the contraction first of the DNB, and then of the SNB, during intra-arterial infusions of SCh.

The contraction of the DNB in Phase II of excitation causes a dramatic increase in the response of the Ia endings to the dynamic phase of stretch, which is seen as a large increase in the dynamic index (Results, Sections II and IV.2). However, it is apparent from the cases illustrated in Figs. 33, 34 and 35, and from the analysis of interspike-interval data (Figs. 35, 37), that the degree and rate of the adaptation of the Ia discharge that occurs after the end of the dynamic phase of stretch varies from spindle to spindle, being rapid and regular in some cases (Fig. 34), or slower and less regular in others (Fig. 33c). The analysis of interspike intervals during this adaptation shows that while the Ia discharge frequency decayed with a mean approximate half-time of 479 msec (n=6), the individual observed values ranged from 297 to 580 msec (Results Section IV.2). As a result of the different rates of adaptation of the Ia discharge in different spindles, the maximum percentage change in the dynamic index of the Ia endings caused by the contraction of the DNB can also vary considerably from spindle to spindle, as shown in Fig. 32.

Presumably, this difference in the adaptation rates of Ia endings in Phase II of excitation reflects differences in the rate and extent to which the poles of the activated DNB fibre give way, and the Ia spiral on the DNB shortens, after the end of the dynamic phase of stretch (Boyd 1976b, c; Boyd, Gladden & Ward 1977). This finding, which suggests that the "creeping" behaviour of the activated DNB fibres of different spindles may vary considerably in amplitude and duration, should be taken into consideration when comparing the actions of dynamic fusimotor axons in different spindles, as was done for example in the survey of fusimotor actions carried out by Emonet-Denand et al (1977). In making such a comparison, it is possible that some of the fusimotor axons which seem to have a "dynamic action modified by a weak static action" on Ia sensory endings (Category II, Emonet-Denand et al 1977) appear as such not because some other intrafusal muscle fibre in addition to the DNB is activated by the fusimotor axon, as suggested by Emonet-Denand et al, but because the "creeping" behaviour of the activated DNB fibre in these cases may be significantly different from that seen in the "pure dynamic" Category I responses. On this basis, it would be interesting to carry out a detailed study in which the effects of dynamic fusimotor stimulation on the response of Ia endings to stretch are compared with the effects produced in the same spindles by the selective SCh-induced contraction of the dynamic bag fibre. However, such a study would be complicated by the fact that many dynamic fusimotor axons activate only one pole of the DNB fibre (Boyd, Gladden & Ward 1977), which SCh causes contraction at all the end-plate zones on the DNB (Gladden 1976). Consequently, it may prove difficult to interpret differences between the effects on the Ia discharge of stimulating such "single-pole" dynamic fusimotor axons and the effects of the full activation of the DNB by SCh

(see Boyd, Gladden & Ward 1977).

At the onset of Phase III of excitation of Ia endings during SCh infusion, when the SNB is made to contract in the presence of DNB contraction, the changes in the response to stretch of the Ia endings provide an insight into the manner in which the two nuclear bag fibres interact in the generation of the Ia afferent discharge. In all cases where Phase III of activation was successfully induced by SCh infusion except one, it was apparent that the dynamic response of the Ia endings was not significantly altered as a result of the contraction of the SNB, and remained close to the level attained during Phase II of excitation when the DNB was the only intrafusal muscle fibre in contraction (Results Section IV.3). In the one exceptional case, however, the onset of Phase III of excitation was accompanied by a significant reduction in the dynamic response of the Ia ending, as illustrated in Fig. 40. The recruitment of the SNB in this singular case significantly modified the influence of the activated DNB fibre on the Ia discharge, indicating the occurrence of a competitive occluding interaction between the Ia sensory spirals on the SNB and the DNB fibres of this particular spindle. However, in the much greater majority of cases, such an occluding interaction of the SNB Ia terminal with the DNB Ia terminal was not seen. Further, the fact that the dynamic response of the Ia endings remained unchanged after the contraction of the SNB in Phase III of excitation, even though the Ia afferent axons were not "saturated" and could be made to discharge at a higher frequency by applying a faster muscle stretch (Results Section IV.3), indicates that the alternative form of interaction, that of complete or partial summation between the Ia sensory terminals on the two nuclear bag fibres, also did not occur.

It appears, therefore, that the contraction of the SNB in Phase III of

excitation does not contribute significantly to the dynamic response of the Ia endings, which continues to be determined by the Ia sensory terminal on the activated DNB as in Phase II of excitation.

Nevertheless, the small increase in the level of the dynamic response seen in many cases when Phase III of excitation was fully developed, and the more rapid increase in the frequency of discharge of the Ia endings during the dynamic phase of stretch (see page 70), may either reflect a small contribution from the SNB Ia terminal to the dynamic response of the Ia ending, or may be caused by a change in the rate of transmission of the overall spindle extension to the equatorial region of the DNB when the adjacent, stronger SNB is made to contract.

The curvilinear form of adaptation of the Ia discharge after the end of the dynamic phase of stretch, which was characteristic of the activated DNB in Phase II of excitation, (Figs. 33, 34 and 35), was substituted in the majority of cases by a regular more linear form of adaptation when the SNB was activated in Phase III of excitation (Results Section IV.3; Figs. 36 and 37). During the transition from Phase II of excitation to Phase III, the variability in the discharge of the Ia endings after the dynamic phase of stretch increased (see for example Fig. 36), and in some cases the Ia endings discharged at two discrete "preferred" frequencies (see for example Fig. 39). In many cases a sharp discontinuity became apparent in the discharge of the Ia endings immediately after the dynamic phase of stretch, when Phase III of excitation was fully developed (see for example Fig. 36c).

The fact that in the majority of cases the discharge of the fully-activated Ia endings showed no remaining trace of the curvi-linear form of adaptation characteristic of the activated DNB, seems to indicate

that the DNB Ia terminal no longer made a significant contribution to the discharge of the Ia axon, and was over-ridden and replaced by a greater response to the change in muscle length from the Ia sensory terminal on the activated SNB fibre. However, in many cases the adaptation of the Ia discharge in the static extended phase of stretch continued to show a component of curvilinearity, even when Phase III of activation was maximal (see for example Fig. 39). In such cases, it would appear that the Ia sensory spiral on the DNB fibre continued to contribute to the Ia afferent discharge after the end of the dynamic phase of stretch, and that its contribution was modified but not occluded as a result of the contraction of the SNB fibre.

These findings strongly suggest that a complex form of interaction, which is different from the straightforward summation of generator potentials, occurs between the individual Ia sensory terminals on the dynamic and static nuclear bag fibres of the cat spindle. The response to stretch of Ia endings when both nuclear bag fibres have been made to contract by SCh, may best be explained using the concept of "pacemaker switching" (Crowe & Matthews 1964a; Matthews 1972). The increase in the variability of the Ia discharge after the dynamic phase of stretch, and particularly the fact that some Ia endings are capable of discharging at two separate "preferred" frequencies during the transition from Phase II of excitation to Phase III, indicates that the Ia sensory spirals on the two nuclear bag fibres are each capable of generating a train of action potentials, which then interact competitively to determine the discharge of the Ia afferent axon. At any given moment, the discharge of the Ia axon is dominated by that sensory terminal which has the higher instantaneous frequency of discharge (Matthews 1972, Ch. 6; Eagles & Purple 1974). As a result, in Phase III of excitation when both nuclear bag

fibres have been activated by SCh, the dynamic response of the Ia ending continues to originate in the Ia terminal on the DNB fibre, which because of the viscoelastic properties of the DNB has the greater dynamic sensitivity of the two bag fibres (see Boyd 1976b, c; Boyd, Gladden & Ward 1977). The position response of the majority of Ia endings in Phase III of activation is however dominated by the Ia sensory terminal on the SNB, which occludes the contribution from the DNB, presumably because the SNB Ia terminal has the greater static sensitivity than the DNB Ia terminal. In response to a ramp stretch, therefore, the sensory terminal governing the discharge of the Ia afferent axon switches from the DNB Ia spiral during the dynamic phase of stretch to the SNB Ia terminal in the static extended phase of stretch. This switching of the site of the pacemaker governing the discharge of the Ia axon presumably causes the sharp discontinuity in the discharge of some Ia endings immediately after the dynamic phase of stretch.

However, since in a significant minority of cases the curvilinear form of adaptation characteristic of the DNB is still apparent in the Ia discharge in Phase III of excitation and also since the form of the dynamic response of the Ia ending may change after the activation of the SNB, it appears that in some cases at least the pacemaker which dominates the discharge of the Ia afferent axon at a given time is not completely immune from the effects of the alternative pacemaker on the other nuclear bag fibre. This may be because the dominating pacemaker is unable to suppress the activity of the alternative pacemaker by means of antidromic spikes in its branch of the Ia axon ("non-simultaneous reset", Eagles & Purple 1974). This is unlikely, however, since Ito (1968) and Brokensha & Westbury (1978) has shown that in the frog muscle spindle that antidromic spikes in the afferent axon can invade and reset all the spike-

initiating areas of the axon; presumably the cat Ia sensory ending is similar in this respect. An alternative explanation is that the currently dominating pacemaker does reset the alternative pacemaker on the other nuclear bag fibre, but continues to be influenced by the electrotonic spread of the generator potential from that sensory spiral, as a consequence of the close proximity of the two bag fibres in the spindle. The precise pattern of branching of the Ia axon inside the muscle spindle capsule (Banks et al 1977), and the distance of each of the pacemaker regions from the sensory spirals on the intrafusal muscle fibres, may thus determine the extent to which the Ia afferent discharge can be exclusively dominated by the output of one of its sensory spirals.

APPENDIX I

In later experiments on muscle spindles, it became of interest to examine quantitatively the rate of adaptation of the discharge of primary endings following the dynamic phase of the test stretch, at various times during their excitation by SCh. This could readily be done for the response of the endings to single test stretches, by displaying the instantaneous frequency of discharge obtained from the pulse-interval meter on the Tektronix storage oscilloscope and making the appropriate measurements on the oscilloscope screen. However, since a PDP-8 computer was accessible, a short FOCAL program was written (page 111) which carried out the required analysis much more efficiently.

A machine-language subroutine (FSPI) written by Dr. V.A. Moss was available which measured and stored in sequential memory locations the time-intervals between successive pulses of a train of pulses presented to the computer via a suitable interface. This subroutine differed from other conventional ones in that it could be used to digitise a variable number of trains of pulses of given length. The FSPI routine was employed in the program to measure the interspike intervals of Ia spike trains in response to several sequential ramp-and-hold stretches. The number of stretches which could be digitised was limited by the available storage capacity to a maximum of five. The digitised interspike intervals were stored in a two-dimensional array, with the start of each rank of the array corresponding to the start of a train of Ia spikes.

The mean interspike interval of the Ia discharge at various times after the end of the dynamic phase of stretch was then calculated from the stored data. For example, the Ia intervals collected between 250 and 350 msec after the end of the dynamic phase of stretch were retrieved from the array for each of the digitised stretches, and pooled together. The mean interspike interval and the standard error of the retrieved sample

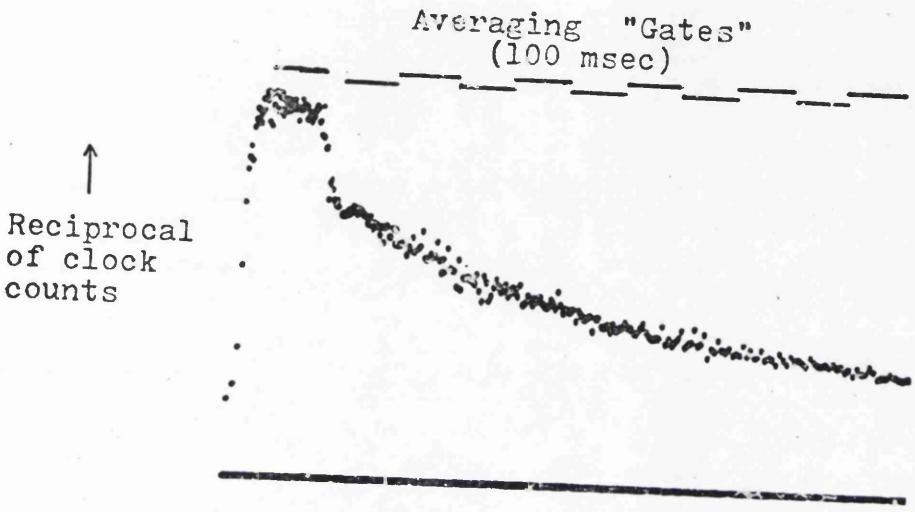

Fig. 52. The interspike interval data collected during one stretch displayed by the computer program during the analysis procedure. Each dot represents one interspike interval, and its height above the baseline is proportional to the reciprocal of the number of clock-counts accumulated in that interval. The clock frequency was set (using lines 5.1 to 5.6 of the program, page 110) at 20 KHz. The digitisation of data was initiated by a trigger pulse at the start of the dynamic phase of stretch, and continued for the following 1.3 seconds in this example. The program then waited for another trigger pulse to start collection of data during a second stretch, and so on until the set number of stretches had been digitised. The interspike intervals collected in the first stretch were then displayed on the Tektronix oscilloscope (above), and the "gate" periods for the averaging procedure were set up (lines 1.08 to 1.2 of the program). One "gate" was set up during the dynamic phase of stretch, and the following ones during the subsequent adaptation. The program then went through each digitised stretch in turn, plotting the data on the oscilloscope, and calculated the mean interspike interval, the standard error, and the coefficient of variation of the Ia discharge during each of the set "gate" periods.

was calculated, and taken as the mean Ia interspike interval at 300 msec after the end of the dynamic phase of stretch. Similar calculations were made for data collected at various times after the end of the dynamic phase of stretch, always using a "gate" sampling period of 100 msec. During this process, the reciprocal of each retrieved interspike interval was plotted on a Tektronix oscilloscope, and horizontal bars marked the span of each "gate" period (Fig. 52). The rate of adaptation of the Ia discharge could then be estimated from a plot of the mean interspike interval against the time from the end of the dynamic phase of stretch (Figs. 35 and 37; Brokensha & Westbury 1976a).

The pooling together of data from several test stretches enabled a reasonable sample size to be achieved in each "gate" period ($n > 30$). However, in doing this it was assumed that the response of the primary ending to each test stretch remained unchanged. In order to justify this assumption, sections of recording were chosen for study which on initial examination using the pulse-interval meter showed the response of the Ia ending to the successive stretches to be almost identical.

The working of the program tested using a square-wave generator set at various repetition frequencies as the source of the trains of pulses to be digitised, before using the program to analyse the recorded Ia data. I am grateful to Dr. V.A. Moss for his constant interest and help with the computer during the development of the program.

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C-8K FOCAL 01969

01.01 C PROGRAM ORIGINATOR-M.DUTIA
01.02 C ANALYSIS OF SCH DATA, VERSION OF 10/9/77
01.06 A !"MODE: C,A, OR CAL? "A;I (3-A)5.1,7.2,1.07
01.07 S SE=FAR(2,'D,1,1);S DU=FAR(2,'D,1,2);S D=500/DU;D 7.3;D 6
01.08 A !"NO GATES "G,"AUTO? "A;I (A-0Y)1.2,A "START "Y," STEP "T,!
01.09 F P=1,G;S SA(P)=Y;S Y=Y+T;S EA(P)=Y;D 2.03;D 2.04
01.10 I (Y-DU)1.21;T "";G 1.08
01.20 F P=1,G;T %2!P;A "-GATE "SA(P),"TO "EA(P);D 2.03;D 2.04
01.21 F P=1,G;S TO(P)=;S TA(P)=;S C(P)=
01.40 D 7.3;F NS=1,SE;D 2
01.50 F P=1,G;D 3
01.60 A !!"RPT? ",A;I (A-0Y)1.7;D 6;G 1.08
01.70 0

02.01 S SU=;S Y=;S P=1;T %2 NS;A A;I (-A)2.02;R
02.02 D 8;I (SU-SA(P))2.02;
02.03 S T=100+5*FSGN(P-2*FITR(P/2)-.1)
02.04 S A=FDIS(SA(P)*D,T);S A=FNEW(EA(P)*D,T)
02.05 S TO(P)=TO(P)+N;S TA(P)=TA(P)+1;S C(P)=C(P)+N*N
02.06 D 8;I (-N)2.07;T "*
02.07 I (SU-EA(P))2.05;S P=P+1;I (P-1-G)2.02,2.3
02.30 D 8;I (-N)2.4;T "/";R
02.40 I (SU-DU)2.3

03.10 S ME=TO(P)/TA(P)
03.20 T !!"GATE"%6.02,SA(P)," TO",EA(P)," MSEC
03.40 T !"SAMPLE"TA(P),!"MEAN  "ME
03.50 S A=FSQT(<C(P)-TO(P)*TO(P)/TA(P)>/<TA(P)-1>)
03.60 T !"ST ERR"A,!"CO VAR"A/ME

05.10 A !!"RC ",T,!
05.20 D 7.3;T %4,C;I (FABS<T-C>-T/5)5.4;A X;G 5.2
05.40 D 7.3;I (C-T)5.5,5.6
05.50 S X=FDIS(,);S X=FNEW(500,250/<C-T>);G 5.4
05.60 T "";G 5.4

06.10 S Y=;S SU=;S NS=1;F ME=1,501;D 8
06.20 S NS=;S Y=;S SU=
06.30 F ME=,100,DU;S X=FDIS(ME*D,);S X=FNEW(ME*D,550)

07.20 A !"DATA: NO SEG "SE," DUR SEG "DU;S D=500/DU;T !!"READY"!
07.21 S X=FAR(3,'D,1,3);S X=FAR(1,'D,1,1,SE);S X=FAR(1,'D,1,2,DU)
07.30 S C=FX(1000,)/10
07.40 S X=FAR(3,'I,SE,500);S X=FX(SE,500,DU/C);T "EOJ"!;A X
07.50 D 6;G 1.08

08.05 S Y=Y+1;I (Y-511)8.1;R
08.10 S N=FAR(2,'I,NS,Y);I (-N)8.2;S ME=511;R
08.20 S N=(N*C)/1000;S SU=SU+N;S X=FDIS(SU*D,500/N-250)

09.10 S X=FDIS(,250);S X=FNEW(,-250);S X=FNEW(500,-250)
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