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INTRODUCTION

Where Anatomy led, Physiology followed: a survey of our developing understanding of the muscle spindle, what it does and how it works

This historical introduction is written for Journal of Anatomy by a long-retired physiologist who spent his professional life personally involved with the muscle spindle. It expresses his gratitude for the dedicated work by anatomists for over a century without which little would or could have been done by physiologists. Denied this fruitful marriage, Anatomy left isolated could only have speculated on function with no hope of achieving proper understanding, while Physiology could not have proceeded without a detailed knowledge of the structures being studied. The present volume illustrates this mutual dependence by celebrating Bob Banks' contribution on his retirement; he was primarily an anatomist, but one who collaborated with physiologists and himself developed their skills. The varied present papers show the continuing need for both approaches in our attempt to understand what remains an enigmatic sense organ upon whose efficient operation we all depend for accurate movement.

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Earliest days

The muscle spindle was noted by histologists in the 1860s, but Angelo Ruffini set the scene in 1898 by providing the first detailed description of its fine structure. Each of its several small elongated striated intrafusal muscle fibres had a large annulospiral or primary nerve ending wrapped upon its equatorial region, and this was normally flanked by one or more smaller secondary or 'flower spray' endings. These were all presumed to be sensory. Further out from the equator he saw 'plate' type nerve endings supplied by small myelinated axons; later observers took these to be motor. Thus, histology by itself had provided enough information to indicate that the 'neuromuscular' spindle was a highly refined sensorimotor organ under central control, though Ruffini himself believed that his 'plate' endings were 'sensorial'. A few years earlier, Sherrington had shown that the spindle was not a 'growth bud', as earlier surmised, but a 'sensory' end organ as large axons were still found terminating inside it after the motor nerves had been forced to degenerate after isolating them from their cell bodies by cutting the motor ventral nerve roots close to the spinal cord. In 1900, Sherrington argued forcefully that the spindle contributed to 'muscle sense' as well as eliciting reflex action. In 1894, he had shown that the rigidity of the decerebrate cat, which provides a model for human spasticity, was instantly abolished when the dorsal, afferent, nerve roots were cut; this demonstrated that such rigidity was crucially dependent upon afferent activity returning from the periphery, with muscle afferents presumed to be responsible, carrying important clinical implications.

Contribution to human rigidity

Physiologists then lacked the tools to carry things further, but in 1924 the neurologist Walshe in effect extended Sherrington's work to man and, in a little-known paper, indicated that muscle afferent activity played an important part in the genesis of the characteristic rigidity of Parkinson's disease in his patients. On injection of the local anaesthetic procaine into the muscles of their upper arm the local rigidity could be abolished without seriously affecting their strength and, dramatically, the patient could then move his arm much more freely than before.

Walshe believed that the procaine had blocked conduction in the muscle afferents while leaving the motor fibres working. Thirty years later, while still a medical student, the present author excited by the new physiological knowledge about the muscle spindle's motor supply started to re-investigate the matter in the decerebrate cat and performed successful pilot experiments in a student classroom; he was then joined by Geoffrey Rushworth who had his own laboratory. The local anaesthetic was applied more controllably to the rigid muscle's nerve rather than into the muscle itself, and duly blocked the muscle's rigidity while preserving its 'strength' as judged by its response to stimulation of its nerve above the block, confirming that the normal large motor axons remained functional. Control experiments showed, as expected, that the large afferent axons from the spindle primary endings actually did have a similar susceptibility to procaine as the ordinary large motor axons while the small motor axons, then recently established as fusimotor (i.e. specifically supplying the muscle spindles), were rapidly put out of action. By then single-unit recording had also shown that in the decerebrate cat the large muscle afferents are being driven to discharge at high resting rates as a result of maintained fusimotor activity, and it was confirmed that the blocking action of procaine abolished this rapid firing. The implication is that some forms of human spasticity and rigidity depend not only upon the spinal cord receiving continuous feedback from the muscle afferents but also that maintained activity in specific fusimotor efferents contributes importantly, possibly aided by an abnormally high level of activity on their part. The therapeutic possibility of selectively damaging small motor fibres chemically in appropriate patients remains to be properly explored, but this could well improve upon partial section of the afferent spinal nerve roots as is still sometimes done by surgeons. In addition, in the light of recent work on sensory vesicles and spindle chemistry, described in the present section on '*Sensory synaptic-like vesicles*', the partial silencing of spindle afferents by drugs acting on the terminals themselves might also be achievable.

Efferent supply

The anatomical foundation upon which all such therapeutic possibilities rests is the histological demonstration that the 'plate' endings are the termination of small axons coupled with the fact that in both the ventral roots and muscle nerves there is a bimodal distribution of the diameters of muscle efferents, some being 'large', some 'small'. This was noted by Langley in 1922 who suggested that the small motor axons might "perhaps form the small nerve endings in the muscle spindles", namely Ruffini's 'plates'. The bimodality was particularly well charted in 1930 by Eccles and Sherrington, who each subsequently won a Nobel prize. However, in a lamentable failure to think widely they refused to draw the obvious conclusion from the anatomical findings, namely that such a gross bimodality could be expected to be coupled with a difference in function; without any supporting evidence they concluded that the small axons simply supplied fewer ordinary muscle fibres than the large ones, with no thought given to the muscle spindle. Three years later, B.H.C. Matthews, my father, found that the firing of some spindle afferents increased when he increased the strength of a stimulus to a muscle's nerve well above that required to elicit a maximal muscle contraction. He suggested that the increased stimulus had excited higher threshold small motor axons that supplied the muscle spindle, over and above exciting the large ordinary motor axons, thereby evoking a contraction of the intrafusal muscle fibres with consequent excitation of the spindle afferent.

There the matter rested until 1945 when Leksell showed physiologically that the small motor axons, which he termed 'gamma efferents', must specifically supply the muscle spindles without influencing the main mass of ordinary muscle fibres. On bombarding a muscle with massed gamma efferent impulses no overt contraction occurred while the overall afferent discharge from the muscle increased. Leksell achieved his specific activation by stimulating both large and small fibres electrically, and then selectively blocking conduction in large axons by gently squeezing the nerve so as to block their conduction while sparing that in small ones. Pressure has the reverse of the action of local anaesthetics that preferentially block small axons, providing a further example of the importance of combining anatomical and physiological knowledge. Shortly afterwards, Hunt and Kuffler used a double single-fibre preparation to prove that the gamma efferents provided a segregated motor supply to muscle spindles. They did this by progressively splitting down filaments from the spinal nerve roots for stimulation and recording until, while remaining multi-fibre, the one from the dorsal root was left with only a single one of the spindle afferents from the muscle studied, and the one from the ventral root contained just a single small motor axon to the same muscle and no large ones. Stimulating the gamma efferent then produced no recordable contraction of the muscle, but greatly increased the firing of the muscle spindle afferent. Thus, Physiology followed Anatomy and finally established that the CNS possesses a private motor pathway to enable it to control the muscle spindles without evoking contraction of the main muscle. Combined anatomical and physiological studies have since shown that these specific fusimotor axons may be supplemented by a certain number of so called 'beta' efferents, which primarily supply normal extrafusal muscle fibres. The functional meaning of all this basically anatomical knowledge continues to be hotly debated and investigated, as in several of the following papers.

First afferent recordings

From 1900 onwards, the muscle spindle was confidently presumed to be a stretch receptor, but the physiological determination of how it actually responded had to await the advance of technology. Sensitive valve amplifiers were required to magnify the minuscule external electric signals produced in a nerve trunk by the passage of a single nerve impulse in a single one of its axons, coupled with a recorder capable of capturing and then storing, in correct temporal sequence, the occurrence of such transient events. It took a third of a century after Ruffini before this was achieved. In 1933, B.H.C. Matthews recorded from the central end of a mammalian muscle nerve after partially transecting it distally until the discharge evoked by stretching the muscle had been reduced to that of a single unit, as shown by the constancy of its form and the regularity of its discharge. The unit was identified as that from a muscle spindle by virtue of a pause in its resting discharge when the muscle was made to twitch by stimulating its nerve, thus relieving any pre-existing strain upon it. Such 'in parallel' behaviour contrasts with the 'in series' behaviour of the Golgi tendon organ, which fires a burst of impulses. This fundamental anatomical/physiological fact also underlies our thinking about the function of the muscle spindle and the role of the fusimotor fibres in controlling it.

Matthews' recordings proved that the muscle spindle was indeed a stretch receptor, but one with marked dynamic sensitivity, signalling that the muscle was being stretched, over and above recording simply the absolute amount of stretch *per se*. On stretching the muscle to a new fixed length, he found that the spindle afferent fired much more rapidly while the stretch was being applied than after reaching and 'adapting' to the new final length; at equilibrium, the greater the final amount of stretch the more rapidly it fired. During the period of active stretching the spindle's moment to moment firing rate depended upon both the rate of stretch and the ongoing amount of stretch. The obvious implication is that the muscle spindles are deeply concerned with signalling and helping to control movement, not just absolute muscle length. In retrospect, it has become clear that this classic study was entirely upon the large afferents from the primary endings of the muscle spindle, which are the easiest to record from.

Distinctiveness of primary and secondary endings

Ruffini noted that within the spindle the axons supplying his flower spray secondary endings are smaller than those to the primary annulospiral ending. It is now well established that the difference persists in the main nerve trunk where their conduction velocity can readily be measured in physiological experiments. Small axons conduct more slowly than large ones, permitting single-unit recordings from primary and secondary endings to be distinguished and their responsiveness compared. Important functional differences were then discovered, but this was not until 1961, nearly 30 years after Matthews' recordings. Sybil Cooper, the last ever of Sherrington's collaborators, then found that the secondary ending lacks the great dynamic sensitivity of the primary ending while still responding to the amount of stretch *per se*. It thus approximates to being a receptor for muscle length rather than movement, albeit one whose firing is also dependent upon the level of ongoing fusimotor activity. Any small displacement of a resting muscle normally stirs the primary ending into vigorous action while the secondary ending responds more sedately, needing considerable mechanical change to alter its firing. Thus, it took over half a century for Physiology to be able to follow Anatomy's lead and breathe functional meaning into Ruffini's histological description of two types of sensory ending within the muscle spindle. Put crudely and simplistically, during large movements, covering an appreciable proportion of the physiological range, the primary signals some combination of length and velocity (and possibly acceleration), while the secondary signals length. The spindle thus provides the CNS with two separate but linked channels of information about a muscle's state, with different mathematical transformations of the underlying mechanical parameters.

The primary ending, however, behaves very non-linearly once the movement becomes of appreciable size. Exposed to sinusoidal movement within its small linear range, as when helping to maintain a fixed position, the ratio of its sensitivities to length and to velocity (i.e. phase angle) is not very different from that of the secondary ending, but its absolute sensitivity is usually about 100 times greater. In spite of these complexities, the CNS can be expected to be able to integrate the information derived from these two separate signal channels to improve its performance in achieving its varied purposes, over and above that attainable with a single source of feedback information. As has happened with the histological subdivision of the spindle's nerve endings, further currently recognised features of the spindle's complex internal architecture, neural wiring and ultrafine structure may ultimately prove to have functional meaning. Among these are that the secondary endings lie distally to the primary ending upon a region of the contacted intrafusal fibre that is striated rather than stuffed with an apparently unnecessary number of nuclei .

Histological distinction between bag and chain intrafusal muscle fibres

During the first half of the 20th century, Physiology advanced while Anatomy produced nothing new. Then, from 1955 onwards, Anatomy once more started to lead,

with new structural findings encouraging major physiological advance. Unusually, this depended not upon technological progress, but upon the refined painstaking application of classical histological methods. From the earliest days it had been recognised that there was a great difference in diameter between the several intrafusal muscle fibres within a given muscle spindle. Then, on the basis of new detailed examination, it was suggested that, as with the spindle's axons, the differences were sufficiently great to suggest a difference in function. Coupled with other distinguishing features, it became rapidly accepted that there were two distinct kinds of intrafusal muscle fibres. The larger 'nuclear bag' fibres were delimited from the smaller 'nuclear chain' fibres by virtue of the arrangement of their nuclei within the spindle's central equatorial region. There ensued a decade of controversy over their motor innervation. The chief protagonists were an anatomist, David Barker, who described a wealth of complicated terminations that defied simple functional analysis, and a physiologist, Ian Boyd, who equally turned his hand to histology. Boyd was a simplifier who forcefully claimed that the 'bag' and 'chain' intrafusal fibres had completely separate motor supplies with morphologically distinct terminals as shown in Thornell's fig. 1, while Barker initially confessed that he "was in the negative position" of "disagreeing with Boyd's thesis without, at this stage, being able to offer any alternative". Time has put order and meaning into many of Barker's complications, with Bob Banks, in whose honour this volume is being published, being a notable contributor to the dedicated work involved. In contrast, Boyd's classification has had to be extensively revised and extended, as can be rapidly appreciated by comparing Fig.1 of Thornell's article with that of Ellaway et al. Yet, Boyd's simplifications encouraged the physiological experiments that demonstrated a functional dichotomy in the spindle's motor supply, namely the subdivision of the gamma efferents into 'static' and *'dynamic'* motor fibres. Once established, this physiological classification existed of its own right and became widely accepted, but its relation to the underlying anatomy took many years to disentangle.

Physiological distinction between static and dynamic fusimotor efferents

The prelude to the establishment of the static/dynamic functional dichotomy came from experiments performed by Jansen and Matthews (myself, not my father) on the decerebrate cat at the time when the new histology had just started to emerge. They studied the effect of the decerebrate's 'spontaneous' tonic gamma motor firing on the primary ending's response to a ramp stretch applied at a low constant velocity and then held at the final length. They used the sudden decrease in the ending's firing rate on completion of the dynamic ramp phase of the stretch as a measure of its responsiveness to movement over and above its response to being simply being held at a new longer length; this was termed the spindle's 'dynamic response'. They compared the primary's dynamic response to stretching while the spindle was being activated by the decerebrate's maintained gamma motor firing with its passive behaviour in the absence of gamma activity, seen after cutting the appropriate motor ventral roots. This showed that the effect of the tonic gamma motor activity was highly variable. Usually the background gamma activity of the decerebrate increased the response to movement, but on some occasions this was decreased; moreover, the changes bore no relation to the level of gamma motor excitation. In line with the emerging histology, Jansen and Matthews argued that this divorce showed that the spindle must be activated by two functionally distinct types of motor fibres, as only thus could fusimotor activity modify the primary's dynamic responsiveness over and above, and independently of, having a direct excitatory effect. They thought that these corresponded to the two types of gamma efferents believed by Boyd to supply the bag and chain intrafusal muscle fibres independently; in addition, they speculatively suggested that the primary endings' terminals on the bag fibre were responsible for its dynamic responsiveness.

Shortly thereafter, the present author used the double single-fibre preparation to demonstrate the existence of functionally distinct 'static' and 'dynamic' gamma motor axons, by stimulating a single gamma motor axon while recording from a single primary afferent. This was done for a wide range of constant-velocity stretches, generated by a newly developed electromagnetic muscle puller, with the analysis of the large amount of nerve traffic vastly facilitated by recording the single-impulse discharge directly as a spike-by-spike analogue display of 'instantaneous frequency' rather than as a sequence of 'spikes' on rapidly moving photographic film; both methodologies subsequently became widely adopted. The dynamic fusimotors behaved uniformly and on being repetitively stimulated had little direct excitatory action to increase the primary ending's resting firing rate, but the moment the muscle started to be stretched the primary's discharge abruptly increased and continued to do so as the dynamic stretching progressively elongated the muscle; these separable afferent responses were both larger than when the spindle was passive, especially that to the continued stretching. The primary ending's 'dynamic response', as measured by the decrease in its firing rate on completion of the dynamic phase of a ramp and hold stretch, was greatly increased. In contrast, the static fusimotors always had a direct excitatory action to increase the resting firing rate and decreased the primary endings' response to being dynamically stretched, sometimes virtually abolishing it; these effects are shown in fig. 1 of Prochazka's article. The patterning of the direct excitation varied considerably. Stimulating some static fusimotors left an ending's instantaneous firing rate approximately constant from spike to spike, as it was at rest, but

other statics made it highly irregular with the immediate genesis of the spikes being dependent upon the arrival of an efferent impulse at the spindle as well as upon the ending's inherent rhythmicity. This suggested that some statically innervated intrafusal muscle fibres contracted rapidly with unfused twitches while others did so much more slowly, as would also the intrafusal fibres innervated by dynamic fusimotors. Such differences in the speed of intrafusal contraction have since been directly observed under the microscope. Static fusimotors also excite secondary endings, increasing their firing rate without affecting their already low dynamic responsiveness; dynamic fusimotors, however, do not influence the secondary endings. The relationship between this new physiological classification and the underlying histology remained unknown and continued in serious dispute for many years; moreover, not all details are even now necessarily finally worked out.

Present view on the types of fibre innervated by static and dynamic efferents

The essential of the current position is that for the last 30 years, the 'bag' intrafusal fibres have been subdivided into morphologically and functionally distinct b1 and b2 fibres, with separate motor innervation. The b1 fibres have proved to be supplied by dynamic fusimotor axons, and the b2 by static ones. The chain fibres are only supplied by static axons, sometimes in common with the b2 fibre and sometimes separately. The static axons terminate on the chain fibres in diffuse 'trail' endings rather than discrete plates, and usually likewise on the b2 fibre. Additional motor innervation of the spindle by 'beta' axons that also supply ordinary extrafusal muscle fibres has come to be recognised as commonplace for all types of intrafusal muscle fibres. All this and more is highlighted in Banks' present paper, and illustrated schematically by Ellaway *et al*. in their fig. 1. Thornell presently describes a wealth of newly discovered histological detail about the arrangement and composition of myofibrillar proteins. There are regional variations along the length of a single intrafusal fibre as well as between different fibres; these can be expected to be functionally important. Whether or not there is an ongoing underlying contraction, the precise ongoing visco-elastic properties of these various types of intrafusal muscle fibre must help determine the way the spindle behaves as a stretch receptor. The situation is complex and has yet to be fully explored; few have risen to the challenge of isolating single muscle spindles for study, with partial retention of their innervation. Both b1 and b2 fibres have been seen to contract more slowly than the chain fibres. All types of fibre seem to be activated by local depolarisation evoked by the release of transmitter (namely acetylcholine) at the motor terminal, with or without an all-or-none spike being triggered, and any such spike may well not always be transmitted along the length of the intrafusal muscle fibre. A significant functional effect of both propagated and localised intrafusal membrane depolarisation could well be to change the mechanical properties of the fibre such as its stiffness and viscosity, in addition to frank shortening or the development of tension directly evoking afferent excitation. The daunting microphysiological experiments required to understand the localised mechanical and electrical behaviour occurring within the muscle spindle seem feasible in principle but, with funding scarce, are unlikely to be performed under current conditions; such work is out of fashion and offers no immediate wider reward.

Mechano-electric signal transduction

The neuromuscular spindle's sensory endings are sophisticated mechano-electric transducers that convert mechanical change into pulsed electrical signals that transmit information to the CNS. The spindle applies several separate stages of signal filtering when doing so and transforms the analogue values of the various mechanical parameters of an externally applied stimulus into a frequency code. First, the stimulus is mechanically filtered by the visco-elastic properties of the spindle's intrafusal muscle fibres; in so far as these properties vary along a fibre's length, the waveform of the stretch of its innervated region must differ from that applied to its ends. Contraction of an individual intrafusal muscle fibre will inevitably change its visco-elasticity, with potential effect on its mechanical filtering action and signal transduction. The three types of intrafusal muscle fibres can be presumed each to have its own characteristic behaviour so the overall filtering will be crucially dependent upon the level and nature of the ongoing fusimotor activity. Moreover, the chain fibres are shorter than the bag fibres and will pull upon them so that their visco-elasticity will affect the amount of external mechanical stretch carried through to the bag fibres' central sensorially innervated region. Over and above this complex mechanical filtering, the signal undergoes two stages of electrical filtering. The stretched afferent terminals generate a graded 'receptor potential', which is then transmitted electronically along the axon's membrane to a normally separate 'pacemaker' region where spikes are generated. At each stage the signal waveform can be expected to be transformed, with its dynamics altered. The dynamic behaviours of the variety of molecular channels embedded within the nerve membrane are crucial. Song's present paper presents a mathematical model of this; it contains mechanical visco-elastic springs as well as receptor ion channels, and produces realistic receptor potentials in response to both static and dynamic components of a ramp-and-hold stretch. Her 'white-box' model assigns physiologically possible values to potential real biological variables, and contrasts with a 'black-box' model that would merely fit the observed receptor potential with an arbitrary equation. Importantly, at the next stage of signal transmission, the specialised hemi-nodal pacemaker is able to

respond to a maintained receptor depolarisation with steady firing, rather than just a phasic burst at its onset. As explained in Vincent *et al*.'s present paper, the pacemaker can be degraded to the latter impoverished functionally inadequate state by certain drugs, most notably the chemotherapeutic agent oxaliplatin; this opened up their hunt for the ion channels responsible for tonic firing. Modern methods are beginning to examine the structure and arrangement of such channels by combining genetic modification with imaging on a hitherto unimaginably fine scale. Suslak and Jarman's article reminds us that, as with the study of axonal conduction, much can be learned by spreading our net widely and studying the whole animal kingdom.

Pacemaker location and afferent branching

Reverting to a larger scale, a classical anatomical observation remains at the fore, namely that the afferent axons branch within the spindle before finally terminating in endings upon the intrafusal muscle fibres. The receptor potential must be generated in the terminals, while the site of the spike-generating pacemaker is likely to be further back along the axon, probably at a node of Ranvier, or the heminode where the axon becomes myelinated. Given such branching, the question arises as to whether a given axon has more than one hemi-nodal pacemaker, fundamentally influencing the nature of the signal that the axon transmits to the CNS. With a single pacemaker, the receptor potentials from the numerous terminals would sum so that the resulting spike train would signal a weighted combination of the stretch applied to all the various terminals, with their individual 'static' and 'dynamic' contributions added together. In contrast, if there is more than one pacemaker, the algebra of their interaction will be quite different, with 'the winner taking all'. When two separate trains of ascending spikes collide at an axonal branching point then, due to neuronal 'refractoriness', the higher frequency train will be transmitted onwards while the lower instantaneous frequency is blocked. Thus, the transmitted signal could suddenly switch from one set of terminals to another as their relative firing rate changes. This makes anatomical analysis of the pattern of branching of intense interest with the possibility that the annulospiral terminations on bag and chain fibres, respectively, might interact in this way. In other words, under rapidly changing conditions, as during a cyclic movement, the axon might switch between a dynamic response dependent upon the visco-elastic properties of the b1 fibres while the muscle was being lengthened, to a static response dependent upon chain fibres while the muscle was shortening.

Sensory synaptic-like vesicles

Following the first recordings of graded receptor potentials from spindle afferents, it was tacitly assumed that the mechanical deformation of their unmyelinated terminals directly affected the ion channels within the nerve membrane to elicit the potential, leaving no room for chemical intervention. Now, however, the release of glutamate from small synaptic-like vesicles is thought to be also crucially involved. Once again, Anatomy and Physiology have been heavily interdependent in contributing to the emerging story, developed in a close collaboration between Bob Banks, acting both as an anatomist and a neurophysiologist, and Guy Bewick, a synaptic physiologist. Bewick's current article tells all, and conveys the continuing excitement with so much found out and so much remaining to be analysed. After the electron microscope became available, numerous small 50-nm synaptic-like clear vesicles were widely observed within the sensory terminals of spindle primary afferents. Their presence was noted, but any possible functional implications remained ignored and unexplored until, at Bewick's instigation, he and Banks took the matter up some 15 years ago. They undertook this unfundable and unfunded project purely out of scientific curiosity. External support only became available after they had opened an entirely new chapter of sensory physiology, namely that synaptic-like vesicles appear to occur in the sensory nerve terminals of many and probably all mechanoreceptors and, associated with specialised membrane receptors, are involved in the intimate working of these sense organs. The present position for muscle spindles is that their axonal sensory vesicles contain the same chemical transmitter as the synaptic terminals of the same axon within the spinal cord (glutamate), that glutamate is released with vesicle recycling when the primary afferent is excited, that glutamate itself can excite the sensory ending, and that its normal stretch-evoked discharge is blocked by certain specific glutamate receptor antagonists. Glutamate release from the vesicles appears to take an active part in regulating the sensitivity of the spindle afferents to stretch without which transduction fails, complicating understanding of an already complicated situation. Glutamate is essential and operates over a time-scale of tens of minutes as a medium-term regulator of the ionic channels immediately involved in generating a receptor potential, and is not of itself a short-term synaptic transmitter like acetylcholine. The glutamate receptor responsible has unusual properties, and in her article Watson explains how the ability of the new technique of 'click-chemistry' to synthesise highly complex novel organic compounds in a relatively straightforward manner is being exploited to study the receptors further. For this a parent molecule with the appropriate biological properties (in her case kainate) is slightly modified to make it chemically suitable as the initial 'core' molecule for 'click chemistry'; after this, a variety of large molecular sub-units can be readily attached to it using standardised procedures. In addition, Watson discusses her work on the synaptic-like vesicles in hair follicles. Thus, up to the very present, as with branching and with vesicles, anatomical observation and

physiological investigation have continued their happy mutually supportive marriage.

All this new membrane and receptor chemistry has major potential practical relevance. For example, certain highly effective chemotherapeutic agents interact with chemical receptors involved in the muscle spindle's working and interfere with the spindle's normal behaviour, so that a patient's treatment for inoperable cancer of the colon with oxaloplatin may have to be stopped because of an unacceptable failure of proprioception in distal limb muscles. A suitably tailored transient receptor blocker might be able to prevent this. Again, in cats, high doses of pyridoxine chronically damage muscle spindle afferents leaving the animals unable to walk effectively, and this also occurs in humans. Thus, advances in the understanding of receptor chemistry also conversely offer new hope for the pharmacological alleviation of human spasticity and rigidity by reducing muscle spindle activity without inducing complete spindle failure.

Single afferent recording during movement

Everything shows that the muscle spindle must always be thought of as an organ primarily concerned with signalling and controlling active self-induced movement. Examining its response to artificially applied stretches and electrical stimulation of motor axons can only be a prelude to the infinitely more demanding task of observing and understanding how it behaves in real life. The spindle is part of the peripheral 'hardware' required to control active movement, and its basic functioning as such can be determined in anaesthetized animals. The CNS's 'hardware' holds and runs the essential 'software' that determines how the spindle is actually deployed in real life movements, and this can only be examined while movement is being generated physiologically. As reviewed in Prochazka's present article, this has been successfully achieved over the last 30 years with metal microelectrodes painstakingly deployed to examine the afferent signals being sent back to the CNS by muscle spindles during normal, centrally induced, movements. Most strikingly this has been done for forearm muscles of human subjects making a variety of voluntary movements and for leg muscles of fully conscious cats; yet more has been learned by recording from both afferents and fusimotor efferents in decerebrate cats induced to walk on a treadmill (presently reviewed by Ellaway *et al*. who, like Prochazka, discuss the functional meaning of their findings). This was a purely physiological achievement requiring great technical expertise and personal dedication and, uncommonly, owed nothing to Anatomy. Two separate kinds of questions were primarily addressed. First, the pattern of afferent firing has been correlated with the phase of the ongoing movement to attempt to deduce the ongoing level of fusimotor activity, on the basis of knowing the afferent response to external stretch applied during various patterns of electrical fusimotor stimulation. This has confirmed that static and dynamic fusimotor axons can be controlled by the CNS independently, both of each other and of the ordinary large motor axons; appreciable co-activation also commonly occurs. Significant functional questions were how far the static fusimotor actions served to maintain the spindle's firing when it might otherwise fall silent, as when a muscle is actively shortening, and how far the spindle's response while the muscle was being lengthened was accentuated by dynamic fusimotor action. In addition, the physiological significance of the anatomical duality of the static fusimotor fibres was examined.

The second, wider question, leading on from this is: What does it all mean for the spindles' role in the control of movement? Obviously, fusimotor action is doing far more than overcoming a supposed 'design fault' and maintaining the spindle's afferent firing and sensitivity to stretch during muscle shortening as would not otherwise occur with its 'in parallel' relation to the main muscle fibres. *Inter alia*, this could be achieved by having just 'beta' axons; these are the sole route for fusimotor action in the frog but co-exist with specifically fusimotor axons in mammals. An early extreme suggestion was that fusimotor drive provided the sole command signal in a 'follow-up length servo' mediated by a powerful spinal stretch reflex. This is no longer tenable; static fusimotor action can still be suggested to provide some measure of such servo-assistance, but dynamic action is too weak to contribute significantly. Next, fusimotor activity has been seen as a way of the CNS controlling the spindle's sensitivity as a measuring instrument, adjusting its dynamic range by setting its gain to an appropriate level for the ongoing motor act; this could better enable it to signal what is going on by avoiding saturation for large signals without small signals being lost in the noise. The sensitivity of the primary ending to small movements might usefully be set high by dynamic action during holding and then decreased by static action when movement was required. In thinking about all this the role of the secondary ending remains enigmatic; uninfluenced by dynamic action it is never particularly sensitive to dynamic movement while equally excited by static fusimotor action. It is inconceivable that its distinctive messages should be ignored by the CNS.

The challenge to the CNS requires it to model the situation

Returning to a global view, the difficulties faced by the CNS in controlling movement are extraordinarily challenging. The CNS has to shape the outgoing motor discharge, in both space and time, to produce the desired movement when relying upon a series of non-linear motors with complex dynamics (the muscles) acting upon mechanically variable loads. In part, these lie in the external environ-

ment, and in part internally, in the moved limb with its inertia depending upon the angular position of its component parts and its visco-elasticity varying with the contractile state of all of its mechanically linked muscles. Biomechanical principles spell out that during natural self-generated movements the spindle's behaviour must be far more complex than that found when a passive muscle is pulled upon by an external device. During active movement the immediate effect on spindle length of applying an external disturbance to a limb (whether a resistive force or a fixed displacement) will vary with the ongoing contractile state of all muscles involved. Visco-elastic muscle fibres connect to bone via an elastic tendon so that, when the force is changing, the angular displacement of a joint and limb position cannot, on their own, determine the length of a muscle, as measurable by its muscle spindles. Moreover, the essential excitatory deformation of the afferent terminals depends not only upon a muscle spindle's stretch but also upon the ongoing state of the intrafusal muscle fibres; first, their contractile shortening may directly deform the sensory terminals; second, any change in their visco-elasticity with contraction will affect the way in which they help filter the waveform of a stretch extrinsically applied to the whole length of the spindle. Muscle spindles undoubtedly provide useful feedback to help the motor control centres in their challenging task, but it is private from each muscle involved. It reflects but does not directly signal the state of any particular variable for the moved part as a whole. However, it must help to do so when the outputs from several muscles, both agonists and antagonists, are consolidated with other sources of information.

It is now widely believed that the CNS learns to produce and control accurate movement by creating internal models of the whole situation, including features both internal to the body and those of the external world, and then using these to generate the appropriate motor commands. The model has to be predictive so that it can 'look ahead' to the expected outcome of commanding a given motor output under the current conditions, not only externally in the outside world but also internally, muscle by muscle to set their particular performance. Proprioceptive feedback from the contracting muscles can be expected to play a crucial role both in originally building the model during learning, and then while running it to achieve a desired motor act; such a model needs to be able to predict future sensory states by integrating knowledge of the present state with that of the motor output. Any deviation from planned performance reported by sensory feedback during a movement could be used initially to apply immediate corrective action, as by reflex action, and then, more slowly, to update the model continuously. A major problem when making an ongoing comparison of actual with desired performance is that, given the limited speed of axonal conduction, afferent feedback only reaches the various control centres in the CNS after a significant time delay. Correction for this can be achieved peripherally as well as centrally by the afferent feedback being generated so as also to 'look ahead' in time. It has long been recognised that with an applied sinusoidal stretch the primary ending's dynamic 'velocity' sensitivity does this by providing a signal that is phase-advanced upon the actual degree of elongation. Additionally, it has been suggested that during certain voluntary movements the CNS actively improves upon this and, in effect, incorporates the spindle into the model by using the fusimotor system to adjust both the length and velocity components of the spindle discharge to that expected sometime in the future. If the appropriate command centres (whether located spinally or higher) should find a deviation from the desired value then action can be taken. In making such comparisons, the control centres need to receive 'efferent copy' of the outgoing motor messages modified appropriately for the centre in question; the spindle can even be suggested to be an elementary such control centre receiving its private 'efferent copy' via the fusimotor system, thereby allowing a certain amount of computation to be performed locally 'on site' before information is transmitted back to the main control centres; any such distributed computation would require less long-distance transmission of information via signal channels of limited capacity and reduce the computational burden on higher centres along with those in the spinal cord.

Importance of the spinal cord

Jankowska's presently described 'wiring diagrams' show that the information from the spindle primary endings is sent to five separate discrete regions of the spinal cord, distinguishable both anatomically and functionally. Much signal processing with 'integration' of different inputs can be expected to occur in this parallel computing network and used for a number of different purposes; for example, the primary afferent's direct monosynaptic excitation of the motoneurones of its own muscle provides for the immediate correction of an unwanted 'stretch'. Such parallel processing at multiple sites is quite unlike the serial processing done by many present-day computers in a single CPU (central processing unit). All this requires to be explored by extensive computer modelling of the biologically engineered system, systematically based upon all types of experimental data; yet more anatomical, biomechanical and electrophysiological experimentation will undoubtedly be required for this. Much analysis of sensorimotor control by the brain is currently concentrated on trying to discover the basic principles of the computing algorithms employed, such as the spatial co-ordinates used in the body maps created for various particular circumstances. This valuable theorising is supported by employing complex instrumentation to see what hap-

pens when a subject performs a movement under changing conditions. What is avowedly missing is any serious attempt to link all this to the brain's available hardware, as the running of the requisite neural software for these high-level voluntary tasks is probably widely distributed, with the cerebellum and cerebral cortex both involved. As a limited more tractable goal, the amount of integrative computation achieved within the spinal cord could be modelled and studied more thoroughly, taking as a starting point the laboriously-established hardware described in Jankowska's article. The spinal cord both filters the sensory messages before they are sent upwards and decodes the brain's descending commands into a pattern of motoneuronal firing, as well as itself directly initiating co-ordinated motor action by responding reflexly to signals from the periphery. Moreover, when suitably primed, the neural networks within the spinal cord are by themselves capable of generating organised motor outputs with fusimotor involvement, patterned in time as well as space, to produce rhythmic movement, as required for walking and scratching. What requires emphasis is the fact that the ability to make accurate movements is a remarkable skill, demanding a high level of neural computation at all levels of the CNS. As a corollary, in accordance with its complex structure, the mammalian muscle spindle can be presumed to provide sophisticated types of information over and above that which could be obtained by a sensor recording simply joint angle. Tendon organs can also be confidently presumed to contribute importantly, as discussed along with much else in Prochazka's fully referenced present article.

Efference copy and the 'sixth sense', proprioception

For the first half of the 20th century, it was generally believed that the afferent discharges from muscle spindles contributed to conscious sensation, providing a 'sixth sense' of awareness of the position and movement of our limbs, and so on. This was in addition to their helping to regulate movement, automatically and unconsciously, via spinal reflexes and higher centres like the cerebellum. This view was then largely abandoned on the basis of limited experimentation coupled with a deep conceptual problem. The problem is that the level of spindle firing depends upon the ongoing fusimotor discharge as well as upon the mechanical state of an individual muscle. Spindle firing thus cannot provide a direct measure of limb position, which is all that we are conscious of; apart from the debatable 'sense of effort' we have no independent awareness of what is going on in muscle *per se*. For a time, the dilemma was sidestepped by abandoning the spindle and allocating the prime responsibility for conscious proprioceptive sensations to the joint receptors, which had always been believed to be involved. However, after 10–15 years of this heresy the original belief was revived, largely due to the experiments by Goodwin, McCloskey and myself in 1972, especially those using vibration. In these a human subject flexed one arm isometrically against a steady load, and a 100-Hz physiotherapy vibrator was pushed against the tendon of the main contracting flexor muscle (biceps brachii). The subject then experienced a strong sensation that their arm was steadily and continuously being extended at the elbow, although no such movement was occurring; the sensation was one of moving, referred to the arm as a whole, not to the muscle itself, and not of an abrupt change of position. The experiments were initiated because animal recordings had shown that the spindle primary endings with their high dynamic sensitivity were powerfully excited by vibration, often being driven to fire an impulse on every successive cycle of vibration. Thus, 100-Hz tendon vibration could be expected to excite many of biceps' spindle primary endings to fire at a rate that would normally only be produced by appreciable dynamic stretching. Spindle secondary endings and tendon organs are very much less sensitive to vibration. It was concluded that the sensation of limb movement evoked by vibration of biceps was due to the excitation of spindle primary endings, with the essential corollary that spindle afferents do contribute to conscious proprioception as originally believed, with the spindle secondaries also likely to take part and contribute positional information. Subsequent work has consolidated this view. The sensation is always referred to the limb as a whole with the antagonistic contributions from flexors and extensors compounded. McLoskey dramatically confirmed that stretching of a single muscle can produce a sense of joint movement by personally experiencing this when the tendon to one of the muscles to his own big toe was pulled upon, after being exposed under local anaesthetic.

The question then forcibly arises: How do the sensory centres avoid mistakenly interpreting a purely fusimotor-induced increase in afferent firing as due to movement? Such firing has been recorded during an isometric contraction in man, without any sense of movement. This is a restatement of the classical problem as to how CNS centres handle sensory traffic to distinguish between 'ex-afference', evoked by an external stimulus, from 're-afference', evoked by a motor act commanded by the CNS with quite different behavioural significance; the effect of eye movement on the visual scene provides the oldest example. It is usually presumed that the sensory system can, and does, make this discrimination by virtue of receiving an 'efference copy' of the outgoing motor command, delivered by a 'corollary discharge' from a motor centre, whether by axonal branching or specific interneurones. Histological studies have long shown that the anatomical substrate for this exists, with various sensory and motor centres being interconnected rather than comprising totally separate pathways from 'the brain' to the spinal cord. Such central processing of spindle afferent messages seems entirely possible in principle, with the

'expected' and 'actual' returning signals being suitably integrated, as by an appropriate algorithm such as subtraction, before being acted upon and used to create a 'body image', which is compounded from both this and other sources of information. Among these, the signals from specialised cutaneous receptors, especially those in the human hand, undoubtedly contribute to 'proprioceptive' awareness. Proske's present mini-review makes the case that, as with vision, the brain creates multiple maps of the 'body image' for its varied purposes, with spindle information, from both its primaries and secondaries, contributing more importantly to some than others; moreover, when competing with sight proprioception is the junior partner. Precise knowledge of the location and nature of the requisite central processing can be expected to be slow in coming, and much remains controversial. Static 'position' sense with the body at rest is inaccurate and unreliable; the muscle spindle's province is movement requiring advanced technology for its study.

Quantitative anatomy

Careful counting suffices to demonstrate the functional importance of afferent feedback from muscle, with the muscle spindle being pre-eminent. A typical muscle is supplied with more myelinated axons of appreciable size concerned with the regulation of movement than with its actual production; the large motor axons providing the 'final common path' to the main muscle fibres are outnumbered by nearly two to one by the sum of the number of afferent axons to the primary and secondary spindle endings and tendon organs together with the spindles' small efferent fibres. Evolution would not permit such apparent profligacy unless it served a major purpose. Next, except for the extraocular muscles of some species, nearly every mammalian striated muscle contains muscle spindles. Their complexity and relative numbers have long been known to vary from muscle to muscle, offering an as yet inscrutable clue to spindle function. This must always be to signal what is going on in the muscle, but the uses to which it is put by the CNS could well vary widely depending upon the muscle concerned and the task involved. Nearly all the early experimentation was upon major limb muscles, so that attention was initially unduly concentrated upon the role of the primary endings in producing a stretch reflex that helped maintain posture by immediate monosynaptic action within the spinal cord. This limited view of the stretch reflex has had to be substantially modified; the secondary endings and higher centres are now both considered also likely to be involved. More importantly, not all muscles seem likely to have a stretch reflex, least of all a spinal one. The small intervertebral muscles of the neck probably do not, while the information that their signals convey seems to be crucial in helping to stabilise the head in space and provide a reliable platform for stable vision; the ability of many long-necked birds to do this while flying is quite remarkable.

In a computer-controlled system, a single sensor with a wide-band transmission line could well be all that was required to measure each particular mechanical variable of interest. In a biological system, however, the signal transduction is inevitably more noisy, and the pulsed axonal transmission line is of severely limited capacity, signalling magnitude simply by firing frequency. The body has compensated for this in the obvious way by equipping every muscle with an appreciable number of muscle spindles (detailed in Banks' article) and averaging their output at multiple functionally distinct receiving centres within the spinal cord (described in Jankowska's paper). Both papers emphasize that over and above systematic trends, and unlike an engineered system, foetal development introduces considerable randomness in the connectivity of individual units of one and the same kind, such as in the number of both afferent and efferent axons received by an individual muscle spindle. The mammalian nervous system operates statistically using an ensemble of functional units, not just one or two particular neurones dedicated to a specific task, as in some invertebrates. Functional understanding has also been sought by anatomists painstakingly counting every spindle in a number of different muscles. Their absolute number increases with a muscle's size, which would not be required if all that the CNS needed was a measure of the length of each individual muscle, suggesting that spindles must do much more. Indeed, whatever they are doing, when a muscle is acting across a single joint as a single functional unit the CNS might seem to need much the same amount of information from a large muscle as a small one making it unnecessary for the body to increase spindle numbers with muscle mass, beyond ensuring that sufficient are available to effectively sample regional differences and produce a reliable ensemble average applicable to the muscle as a whole.

The question then arises: Are some muscles richer in spindles than others, due to a special need for accurate control? Spindle richness has classically been assessed by calculating a muscle's 'spindle density', or number per gram of muscle. On this count the small muscles of the hand and neck score highly. However, without being validated, spindle density has hitherto been uncritically accepted as a reliable measure of spindle richness. In his article, Bob Banks explains how he set out to question the matter, statistically examining the data from first principles, and found that this simple measure was misleading and needed to be replaced by a more analytical approach. On collating the values for a large ensemble of human muscles, he showed that the absolute spindle count increased approximately as the square root of muscle mass (more specifically as a fractional power function, yielding a straight line when the data were plotted logarithmically).

A muscle that contained more spindles than expected from this relation could then safely be judged to be spindle rich. On this measure small muscles of the neck continued to show a high need for accurate spindle control; in contrast, the minute 'high-density' 4th lumbrical of the hand did no better than the massive 'low-density' gluteus maximus of the behind! Discussion continues, while leaving it abundantly clear that spindles meet a universal need for the CNS to receive feedback from all types of muscles, with the classical stretch reflex of postural muscles providing a specific example of its many uses.

Conclusion

The long-standing partnership between Anatomy and Physiology has already carried us far, but the game is not finished. We can expect to profit from continuing to analyse the spindle's underlying peripheral mechanisms, from the molecular level upwards. However, the overwhelming challenge remains to understand how the CNS deploys the spindle during active movement, regulating its fusimotor drive and integrating its two separate afferent signal channels with those from tendon organs to achieve precise movement. The controlling centres need muscle feedback both for immediately counteracting an unexpected disturbance and for learning to adjust their 'programming' to deal with changing mechanical conditions. Direct study of the control centres themselves is difficult and is not currently widely in prospect. Meanwhile, it might be possible to deduce much about the central programming by continuing to correlate patterns of afferent and efferent firing, for a variety of muscles performing a variety of tasks, with the underlying biomechanical situation. This needs doing both while a movement is proceeding smoothly as planned and also when the unexpected happens. Furthermore, it would be interesting to know what happens when the central programme is adjusted to allow for changing circumstances, whether external (such as gravity in space travel) or internal (such as muscle strength with training, growth and disease).

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