Historical analysis of the neural control of movement from the bedrock of animal experimentation to human studies

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Matthews, Peter B. C. Historical analysis of the neural control of movement from the bedrock of animal experimentation to human studies. J Appl Physiol 96: 1478–1485, 2004; 10.1152/japplphysiol.00978.2003.—The history of the investigation of the sensorimotor control of movement is outlined from its inception at the beginning of the 19th century. Particular emphasis is placed on the opening up of new possibilities by the development of new techniques, from chronophotography to magnetic brain stimulation, all of which have exploited developments in technology. Extrapolating from history, future advance in physiological understanding can be guaranteed to require seizing the new tools provided by the physical sciences and refining these to our particular need. The ever-present danger is that these are then deployed with triumphal optimism rather than critical doubt and earlier methods either jettisoned prematurely or used incautiously. The new techniques have enabled experimentation to become ever less intrusive, permitting a progressive shift from animal to human work, thereby offering the prospect of an increasing clinical reward.

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ously, developed their own apparatus to take exactly timed photographs of animals and humans during movement (2, 7); this new technique of “chronophotography” was the precursor of modern cinemography. Both men were born in 1830 and died in 1904 and so came of age along with photography itself. Their beautiful pictures captured for the first time ever what actually happens, with the unexpected observation that during galloping a horse spends much of the time in free flight, quite clear of the ground. But, of course, they were in no position to extend their analyses by making precise biomechanical measurements of the timing and extent of movement for a range of joints or what was happening to the center of mass, as all now attracts increasing attention to help understand the neural programming involved. Whole animal studies then inevitably lapsed, as there must have seemed little that could usefully be done.

Acute experimentation reigned throughout the 19th and much of the 20th century as stimulation, ablation, and, subsequently, electrical recording were all within the range of present technology and had much to show. Clinical neurology made a major contribution throughout, accompanied by limited human studies on “simple” reflexes and their contribution to the central organization of movement. The importance of this latter work did not initially receive the recognition it deserved, as with Wacholder’s (1893–1961) experiments of 1928 on the preparation for movement, whereas Bernstein’s (1896–1966) theoretical contributions and advances in chronophotography only tardily escaped the confines of Russia to influence the Western world (see Refs. 13, 20). Jung (12) has provided a personal snapshot of some of the later contributors.

In contrast, the 21st century is seeing a collapse in acute mammalian experimentation because of considerations of both ethics and cost and an upsurge in the study of natural movement per se, together with the effect of perturbing it. Human work is encouraged by the relative cheapness of each individual experiment once the capital investment has been made in the appropriate complex electronic transducers together with the computers needed to reduce the flood of data to meaningful biomechanical terms and then to model the system studied. This has been accompanied by a resurgence of interest in “cortical localization” made possible by the new cerebral imaging techniques. Chronic mammalian experiments with implanted electrodes and the like also still continue, most notably in North America and Japan. Theoretical understanding has been greatly advanced by work on a variety of invertebrates and lower vertebrates, which, as with the squid giant axon in biophysics, can provide uniquely convenient experimental preparations; fewer neurons are normally involved in mediating any particular act, inter alia permitting refined surgical intervention. General rules of sensorimotor control can thereby be identified, transcending the details of the precise neural “hardware” employed by the particular species studied; this is exemplified in the regulation of gait and posture “where a few general principles can be traced from mollusc to man” (3) and in the development of the concepts of “corollary discharge” and “efference copy” (11). The present introduction has no space to expand on these important matters and deals simply with developments in “classical neurophysiology.”

**HISTORICAL ROLE OF ANIMAL EXPERIMENTATION IN DEVELOPING AN INTELLECTUAL FRAMEWORK**

The 19th century terminating in Sherrington’s contribution. The long-established practice of animal experimentation continued throughout the 19th century, with particular emphasis on the study of reflex action and its role in volition. This was all linked with developments in clinical neurology and philosophical speculation and is authoritatively covered in the monographs by Fearing (5), Liddell (14), and Jeannerod (11). Activity was centered in Germany, with major contributions from Setschenow (1829–1905) in Moscow, Pavlov’s “spiritual father.” The initial highlight had been the establishment of the Bell-Magendie law around 1820 by simple surgical experiments on conscious animals, with a cruelty that now seems unimaginable. Sensory and motor function were then shown to be subserved by different sets of nerves, with the dorsal roots of the spinal cord being sensory and the ventral roots motor. Knowledge of reflex action then continued to grow and was finally systematized and a synthesis achieved at the turn of the 19th century by a young professor at Liverpool University, who is now known to everyone as Sir Charles Sherrington. He later moved to Oxford and lived to the ripe age of 94 (1857–1952), having remained in post as head of department just until before his 78th birthday. Despite being personally unprepossessing, he became an inspirational father figure to two generations of neurophysiologists, neurologists, and neurosurgeons (4); one of his pupils was Wilder Penfield, who, working in Montreal in the 1930s, led the world by systematically stimulating the exposed human cortex at operation under local anesthesia. With progressive refinement of technique, Sherrington and his pupils, including the Nobel prize winners Granit and Eccles, continued such studies in Oxford until his retirement in 1935.

**Sherrington’s tools.** Sherrington summarized his early work in his classic *The Integrative Action of the Nervous System*, published in 1906. In addition to the power of his intellectual analysis, Sherrington’s advances were based on three matters of technique; none was wholly original, but their combination was uniquely powerful. First, he worked on “reduced” animal preparations with the cerebral cortex destroyed and thereby reduced to the status of Descartian puppets, with the ethical problem of conscious pain and suffering circumvented; the initial surgery was performed under short-lasting anesthesia. The “spinal” preparation allowed study of the lowest levels of reflex action. Remarkably, it is capable of making rhythmic walking movements, which Sherrington attributed simply to a chain of self-sustaining reflex actions, with each triggering its successor by intraspinal mechanisms as well by its overt effects in stimulating a variety of receptors. However, following Graham Brown (1882–1965), the essential rhythmicity was subsequently established as originating from a spinal “walking center” (central pattern generator), with its timing and strength of action modified by reflex action but not uniquely dependent on it (17). The “decerebrate” preparation, retaining the midbrain and cerebellum as well as the spinal cord, was notable for its rigidity, which was shown to be dependent on reflex action because it vanished on sectioning the sensory dorsal roots. The quantitative importance of the underlying stretch reflex in maintaining postural activity, both at rest and during movement, continues to be studied and debated for humans. The
second factor in Sherrington’s quantitative analysis of reflex action was to take precise control of the stimulus by applying electrical shocks to bared nerves; ingenious pieces of electromechanical apparatus were used to control their timing and magnitude. The third, now quite obvious feature, was to record the magnitude and timing of the reflexly evoked muscular responses with a “transducer” to produce a graphic record, rather than by simply observing them visually. With the technique of the time, this was achieved by connecting the muscle’s tendon to a fine lever whose point rubbed against a rotating “smoked drum” to remove the smoke and produce a plot of magnitude against time.

STUDY OF THE SIMPLEST REFLEX OF ALL, WITH SLOW RECOGNITION OF ITS COMPLEXITY

Tendon jerks. The simple knee jerk was discovered in Germany in 1875 in human subjects. It has continued both to fascinate physiologists and to provide an essential test of neurological function. The initial question was whether it was indeed a reflex or just a direct response of muscle that had become unusually irritable. Estimates of its latency were repeatedly attempted with controversial results, and its reflex origin was only finally agreed on about 1910. The essential refinement of temporal measurement was achieved by recording the muscle’s response electrically, using the newly introduced “string galvanometer,” rather than mechanically. This new technology opened up the recording of the gross electromyogram (EMG), which with successive developments in electronics has become a routine diagnostic test in neurology as well as providing the simplest way of assessing a muscle’s overall activity during human motor activity. The EMG is normally rectified to provide a quantitative measure, but even this is not wholly reliable, and a variety of analytical methods continue to be explored.

H reflex. The tendon jerk’s electrically evoked homolog or H reflex was discovered by Hoffman (1884–1962) in Germany in 1910 just 35 years after the jerk itself; he stimulated the underlying nerves through the skin and recorded the muscle’s response electromyographically. The H reflex was initially sadly neglected, but with the passage of time it has become an invaluable tool in the testing of spinal “excitability” in humans, both in disease and during the course of a variety of motor acts; its name provides an oblique memorial to a remarkable experimentalist whose contributions have been summarized by Wiesendanger (20). The timing and magnitude of the stimulus are easily controlled, and the electromyographically recorded response is likewise readily quantified. As a parenthesis, it must be noted that the full origin and type of the afferent fibers stimulated remain problematical. So also does the quantification of the magnitude of the response, whether before or after rectification, because summing the polyphasic EMGs of different motor units fails to provide a linear measure of the total motor output, particularly when this is slightly staggered in time. Similar considerations apply to the quantification of the tendon jerk recorded electromyographically, with the additional problem that the afferent input continues for a significant time rather than consisting of a single synchronous volley. These complications have only slowly come to be fully appreciated and have bedeviled many studies in which motoneuronal excitability was tested by one or other method during various motor acts in humans. Moreover, because of their differences, it is very hard to interpret experiments in which some maneuver affects the jerk and the H reflex differentially. Every tool has to be critically tested and scrutinized before it can be widely deployed. Every new method provides a wonderful opportunity of probing the unknown but, as with a new drug, carries with it the risk of unwanted and unexpected complications.

Monosynaptic action. Despite earlier reasonably documented suggestions, it was not until the 1940s that satisfactory proof was provided that both the jerk and the H reflex were monosynaptic reflexes, with the incoming afferents directly contacting the outgoing motoneurons (MNs). The relevant afferent fibers were shown to be the fast Ia afferents from the primary endings of muscle spindles, which are exquisitely sensitive to dynamic stretching. Much later the slower group II afferents from the spindle secondary endings were also found to contact the MNs monosynaptically, but on a much smaller scale. No other muscular or cutaneous afferents have such a privileged access to the MNs. This was all based on yet more careful timing of the central reflex delay and its comparison with the measured synaptic delay as first shown in the cat by Renshaw and by Lloyd in the 1940s, and then extended to humans by Magladery; all this early work was done with recording of the reflex output from the spinal motor roots. The later discovery of the weaker group II monosynaptic connection awaited the development of the new technique of spike triggered averaging of intracellularly recorded synaptic potentials; this only became possible when small laboratory computers became readily available to permit the massive averaging required to lift a small effect out of the background noise.

Once established as such, the monosynaptic reflex provided a unique way of testing the excitability of the MNs themselves, not just that of the whole spinal cord, and was extensively exploited in both animals and humans. Ingenious ways of using several closely spaced stimuli of various intensities have allowed a good deal of the interneuronal wiring to be worked out for humans, following earlier work on the cat. In humans, the reflex continues to be recorded electromyographically. In the cat, however, the characterization of the reflexly initiated motor discharge from the EMG or the spinal roots was soon largely supplanted by the intracellular recording of synaptic potentials evoked across the MN’s membrane. It bears emphasis that the establishment of a monosynaptic action does not preclude a superadded polysynaptic effect induced by the same afferents. With a synchronized Ia input, the initial monosynaptically evoked motor discharge tends to block, by virtue of MN refractoriness and the like, any further discharge; even so, some such later discharge may occur in humans, with its functional importance yet to be established.

Problems in testing excitability. Despite its successes, monosynaptic testing of MN excitability is, however, no longer felt to be as easily interpretable as it was initially believed. To begin with, synthetically induced presynaptic inhibition of the incoming afferents influences the depolarization evoked in the MNs by a given afferent volley, irrespective of the MNs’ own excitability. Sometimes, however, this can be turned to advantage and the monosynaptic testing used to estimate the amount of presynaptic inhibition itself, whether reflexly evoked or occurring tonically as part of the reflex set. This is, however, further complicated by the phenomenon of “homosynaptic depression” in which the amount of transmitter liberated pre-
synaptically varies with the preceding firing rate of the afferents involved. With the muscle relaxed, increasing the rate of H-reflex testing from once every 10 s to once every second drastically reduces the reflex’s size, whereas when the muscle is contracting tonically and the afferents firing steadily the rate of testing makes rather little difference. H-reflex testing of excitability in humans remains an invaluable tool, shedding light on the great changes in motoneuronal responsiveness during human walking and running, but has to be used with discrimination.

**ADDITIONAL BIOPHYSICAL PROPERTY OF THE MOTONEURON**

*The plateau potential.* Over the last 20 years or so, a fascinating phenomenon has been progressively realized to complicate matters yet further. For the quarter of a century following the initial successful microelectrode impalement of MNs in 1951, their excitability at any moment was seen as simply as the final outcome of the interplay of short-lasting excitatory depolarizing potentials and inhibitory hyperpolarizing potentials converging onto the MN’s trigger zone or “initial segment.” This essential idea survived the second-order complications introduced by the local interaction, within the MN’s dendritic tree, of these opposing potentials, together with their underlying conductances; such interaction was emphasized by Rall 50 years ago, and understanding is now underpinned by a formidable amount of mathematical modeling. However, the belief that all this provided a full description of normal mammalian MN behavior was based on a hidden assumption, namely that MNs would lose nothing by being studied in anesthetized or acute spinal preparations, as was the common practice. In more normal preparations the mammalian MN is both more lively in itself and exposed to a number of chemical neuromodulators, as can be reproduced for a variety of neurons in a tissue bath. This has now demonstrated the widespread existence of an additional phenomenon, called the plateau potential, which depends on long-acting voltage-sensitive conductances that are facilitated by slow chemoreceptors. Its functional role for the MN in acting as the “final common path” for all motor activity has yet to be fully established (9).

*Accidental recognition of importance of plateau potential for reflex action.* As so often happens in science, the way in which plateau potentials came to the attention of reflexologists started with an accidental finding and the story then got off on the wrong foot. The initial finding was that exciting Ia afferents for some seconds by vibration in the decerebrate cat sometimes initiated a prolonged motor discharge that continued long after the afferent stimulation had stopped (sometimes many minutes), but which could be abruptly shut off by an inhibitory stimulus. Following classical thinking, this was attributed to starting up an interneuronal pool into self-reexciting reverberatory activity, rather as can occur in a fibrillating heart. However, it was soon shown that the continued activity was intrinsic to the MNs themselves, each acting on its own, and due to the plateau potential. Concurrently with the initial reflex work, quite independent voltage-clamp MN recordings, especially in drug-induced “spinal epilepsy,” had discovered the MN’s plateau potential and analyzed its underlying changes in conductance, reproducing what was already known for certain invertebrate neurons. The prolonged activity usually depends on the slow activation, by prolonged depolarization, of an L-type voltage-sensitive calcium conductance, which then produces an inward current that, once activated, maintains the depolarization after the triggering depolarizing input has been withdrawn (slow inward sodium currents probably sometimes contribute). In the cat, a gross overt reflex effect was first noticed in the decerebrate preparation, serendipitously, because the L-type conductance is then facilitated by metabotropic receptors acted on by neuromodulators (especially by norepinephrine and serotonin), which, in the decerebrate, are steadily liberated around the MNs by tonic activity in a descending pathway from the midbrain.

*Putative role in normal function.* Initially, attention was concentrated on the “bi-stable” behavior of the MN as it switched between firing during the plateau potential and silence on its cessation, after a brief inhibitory input. This is now seen as an extreme case, depending on a gross excess of neuromodulatory drive, and attention is shifting to the effect of the L-type conductance in regulating the responsiveness of the MN under normal conditions. The story is evolving rapidly, with strong evidence of a major role in the decerebrate cat in controlling its reflex responsiveness to monosynaptic and other inputs, and there is suggestive evidence that the same may be happening in humans. In due course we can hope for a much better understanding of the role of neuromodulators in regulating the input-output characteristics of the MN and thus the higher control of movement and posture. In due course, all this can be expected to produce a spin-off in the understanding and treatment of human spasticity and other pathological derangements of tone.

**CLASSICAL BREAKTHROUGH: RECORDING FROM SINGLE MOTOR UNITS**

*Single unit recording in humans.* Unitary recording from single motor units became readily feasible with the introduction of the valve amplifier, and its widespread use was initiated in 1928 by Adrian and Bronk; Wacholder’s earlier string galvanometer recordings seem to have passed largely unnoticed (20). They probed human muscles with a “needle electrode” consisting of hypodermic needle threaded with an insulated wire as is still done today; a variety of related electrodes have since been developed. The early interest was to see the “all-or-none” impulses and to find that their firing rate increased with the strength of contraction, thereby helping to establish the “frequency code” as the mode of signaling in the peripheral nervous system. Interest then moved on to the study of the differences between different motor units, with the firing properties, “refractory period,” and recruitment threshold found to be linked with the speed, strength, and fatigability of their constituent muscle fibers and their use in different types of contraction (especially speed vs. postural tasks). The recognition that the contractile properties of the muscle fibers of a given motor unit are all much the same and are related to the properties of the MN that supplies them is of great interest for developmental biology and has led to an exhaustive analysis of how far this depends directly on “trophic” chemical signals from nerve to muscle and how far it arises indirectly as a result of the rate and pattern of firing of the MN. A similarly enduring thread in “motor control” has been whether Henneman’s “size principle” is universally applicable, that is to say whether
motor units are invariably recruited in a fixed order, related to their size and speed of contraction (from small and slow to large and fast), or whether the recruitment can be varied to fit the task in hand. Spike-triggered averaging allows the contractile properties of individual human motor units to be readily determined and the duration of a MN’s relatively refractory period (postspike afterhyperpolarization) can be suggestively determined from the statistical properties of its pattern of tonic firing.

**Shared input to MNs.** Over the past 20 years, the development in the power of simple laboratory computers has allowed single-unit recordings to be analyzed in ever more detail. In consequence, a side issue has been exhaustively studied to little enduring purpose, namely the idea that the amount of shared presynaptic innervation impinging on a pair of MNs can be quantitatively determined by cross-correlating their firing moment by moment. Appreciable such shared input undoubtedly occurs, but its extent can only be determined from the cross-correlogram when the MN’s multitudinous inputs lack all temporal correlation (i.e., pure white noise input). Unfortunately, it is now well recognized that the neurons of the motor cortex tend to fire in synchrony at a variety of frequencies and that this produces a temporal correlation in the descending discharges impinging on the MNs. This “error” could have been suspected from the outset, because it was found that during a single task the value of the index of correlation between a pair of motor units could vary from moment to moment; such behavior is unlikely to occur if fixed hard-wiring were responsible but is to be expected with the fluctuating cerebral rhythms. Present interest is focused on the weakly synchronized MN firing occurring at a variety of “tremor” frequencies (10 Hz and above), some of which are driven by the cortical synchronization. Thus the EMG may provide a window for observing crucial rhythmic cortical activity, possibly related to briefly binding groups of cortical neurons together into a coherent functional unit.

**PROBLEM OF HOW BEST TO ANALYZE AND QUANTIFY THE MOTOR OUTPUT**

**Comparison of unitary and massed EMG.** Recordings of the gross EMG continue to be of inestimable value, both for the analysis and quantification of normal motor activity and for neurological diagnosis. A particular example of the latter is in measuring the conduction velocity of human motor nerves, because the EMG is so much easier to record than the electro-neurogram. The endplate delay is of course readily eliminated by taking the difference in latency on stimulating the nerve at two separate sites, as was done by Helmholtz 150 years ago when he made the first-ever measurements of axonal conduction velocity, using the frog and recording the muscular conduction. With modern averaging devices, the electro-neurogram can, of course, be readily measured for large sensory nerve fibers, which, unlike motor axons, can be stimulated repetitively without upsetting the subject. Recording from single motor units, rather than just the summed EMG, provides a more accurate level of analysis. Temporal measurements can be made more accurately, because there is no spread of conduction velocity of different motor axons, which matters in a large animal like humans, and magnitude estimates are no longer complicated by the interference produced by overlapping positive and negative waves of different motor units. The disadvantage of single-unit recording is that it is much more laborious to perform, and an appreciable number of units have to be studied to build up the population response that is immediately available from the gross EMG.

**Peaks and troughs in the EMG.** The unitary response to a randomly delivered stimulus is normally quantified by determining a poststimulus time histogram (PSTH) giving the number of spikes per unit time after a number of trials. Small effects can be brought out by determining a cumulative sum by taking a running average of the excess or deficit of spikes from the preexisting baseline firing. The size of the initial deflection provides a useful, but highly nonlinear, measure of the evoked change in membrane potential. However, any later deflections need to be treated with the greatest caution because the MN fires rhythmically rather than at random; classical, elementary considerations show that an initial “excitatory” wave in the PSTH is inevitably followed by a period of reduced firing, giving a trough in the PSTH, leading into a second peak separated from the first peak by the MN’s firing interval; put more concisely, the PSTH contains features that reflect the MN’s autocorrelation function as well as its direct response to the stimulus. A similar succession of peaks and troughs also inevitably occurs in the gross EMG after an abrupt stimulus or other excitatory input. Thus knowledge of the MN’s basic biophysical behavior is essential for analyzing the central programming underlying the “triphasic EMG” found in a rapid voluntary movement when the agonist shows two bursts of activity separated by silence; this was first noted by Wachholder in 1928 and then forgotten for many years (20).

**Problem of deriving an MN’s input from its unitary discharge.** Despite appreciable study, both mathematical and experimental, there seems to be as yet no reliable way of deducing the waveform of an underlying net depolarization of appreciable duration from the PSTH and its derivatives. Some simplification with increase in sensitivity to small signals can be achieved by triggering the testing stimulus at a constant time after a preceding “spontaneous” spike, because the MN’s excitability is then always tested at the same stage of the MN’s relatively refractory period (afterhyperpolarization). The direct count of the number of spikes fired per unit time can then be improved on by converting it into an “interval death rate” or “hazard function”; this provides a more direct measure of the underlying depolarization, albeit still a nonlinear one (16). The best way of extracting the maximum information from the PSTH or gross EMG remains an important question, with major implications for the study of motor control in humans with its widespread need to deduce the level of underlying nervous activity impinging on the MNs. This all awaits further study; the present author’s conviction is that the way forward lies in making a model of the MN with its nonlinearities and using this iteratively to determine, step by step, the input required to produce the observed waveform in the PSTH.

**VERSATILITY AND COMPLEXITY OF REFLEX ACTION**

**Reflex integration.** The electrophysiological analysis of individual reflexes with its emphasis on the precise value of the central delay, as required to characterize the number of synapses involved and their pattern of connectivity, is powerful but limited. Overall function is then too easily lost sight of in
the pursuit of detail. The tendon jerk has no simple “function” per se but is a “fractional manifestation” of a more comprehensive stretch reflex, accidentally triggered by a stimulus more abrupt than anything occurring in nature. The overall stretch reflex, however, can readily be recognized as having functional meaning. It assists posture by helping to prevent a muscle yielding under gravity, with its phasic role in walking and running now coming to the fore; extrapolating slightly, the stretch reflex is widely believed to provide a measure of servo-assistance to almost any voluntary movement. It can also be triggered by an unnatural stimulus, namely high-frequency vibration that powerfully excites the primary endings of muscle spindles.

But there are probably real differences between this “tonic vibration reflex,” which depends simply on the Ia afferents, and the stretch reflex proper in which the group II afferents from the secondary endings of the muscle spindle probably sometimes contribute, as may also the Ib afferents from the Golgi tendon organs. On the basis of work on barbiturate-anesthetized or acute spinal preparations, the Ib afferents were classically considered to produce autogenetic inhibition, but in high-decerebrate preparations with walking afferents were classically considered to produce autogenetic inhibition, but in high-decerebrate preparations with walking they are now thought able to produce autogenetic excitation at times when the “central set” is suitable (3). Tendon vibration has also proved to be a powerful tool for demonstrating the sensory effects of Ia activation. At the lowest integrative level, it elicits an illusory sensation of the limb movement that would occur if the vibrated muscle were to be being grossly stretched, but localized to the appropriate joint rather than to the muscle itself. Integrated into higher percepts, however, the abnormal afferent input can also produce illusions of the body image and of localization in space.

Transcortical reflexes. The stretch reflex as seen in the decerebrate cat is undoubtedly a spinal reflex, probably facilitated by the occurrence of “plateau potentials.” It was thus a considerable surprise when, some 25 years ago, the major reflex resistance to stretching of the small human hand muscles was found to occur with an unduly long latency. There is now excellent evidence that for muscles of the hand the “stretch reflex” is a “transcortical reflex” mediated by the motor cortex and the pyramidal tract and superimposed on any initial short-latency spinal response. A dramatic example of this is provided in the Klippel Feil syndrome, in which a given unilateral cortical area has direct bilateral connections with the MNs and an attempted unilateral voluntary movement occurs bilaterally. The stretch reflex elicited by unilateral stretching then also occurs bilaterally. The rationale for such roundabout routing of the stretch reflex up to the cortex and back again is perhaps partly to allow the size of the reflex to be modulated according to present conditions, and more particularly to allow it to “irradiate” or spread to other muscles that under voluntary drive happen to be acting in temporary synergy with the muscle that is stretched. Different muscles probably differ in their stretch reflex control, so even this simplest of reflexes shows considerable variability.

Reflex modulation and patterning. As recognized by Sherrington, purely spinal reflexes can show a remarkable complexity. They can be turned “on and off” or adjusted in magnitude by varying the level of reflex “set,” with the ongoing reflex responsiveness adjusted to be appropriate for the task in hand. A striking example is the response to a stimulus on the dorsum of the foot, applied during different phases of walking; during the swing phase this betokens being obstructed by an obstacle and the limb is raised by flexor action, whereas during the stance phase little or nothing happens. The stretch reflex likewise undergoes huge changes in responsiveness during walking and running. A yet more sophisticated mode of action was recognized classically in the scratch reflex of the spinal dog and the wiping reflex of the spinal frog and turtle, which attract continuing attention. Both have a dual requirement, first to steer the requisite limb so it lies over the “itchy” area of skin, second to generate a rhythmic series of movements to deal with the offending itch. The first demands an accurate transition from “sensory space” organized topographically to “motor space” with the appropriately graded contraction of a range of muscles. The second requires temporal as well as spatial coordination between a number of muscles. This utilizes a rhythmic “spinal generator” akin to that involved in walking that, as with the latter, can be expected to be under continuous reflex control. Moreover, two quite different kinds of reflex are involved in walking: resistance-type reflexes that tend to boost muscle power as required by the environment and “trigger”-type reflexes that help determine the transition from the swing to the stance phase of walking. This phylogenetically old spinal generator behavior lends itself to intensive investigation in simple animals with relatively few neurons involved, notably the lamprey, with a rich harvest in basic understanding. In higher animals with their nervous system intact, then, except for those of shortest latency, it is often impossible to decide whether an apparently simple reflex response is purely spinal or is being mediated partially or even entirely by a higher center.

Hope for “intelligent” neural prostheses. The clinical challenge raised by all this is how best to harness the reflex action of the spinal cord in making prostheses to overcome motor disabilities arising from central motor failure while the periphery remains intact. The crude approach of producing a range of movements by implanting a separate stimulating electrode cuff on each of a wide range of motor nerves makes massive demands on computing power with considerable difficulty in achieving precise adjustment of stimulus strength in the face of potentially varying thresholds. Triggering the appropriate reflex by sensory stimulation offers a much subtler and more natural approach.

BYPASSING THE “WILL” BY DIRECTLY ACTIVATING THE HUMAN MOTOR CORTEX

Cortical stimulation: the animal background. One of Sherrington’s triumphs was to expand on earlier work and show the detailed topography of the motor cortex of humans’ closest relatives, namely various anthropoid apes, by systematic stimulation of the exposed brain with surface electrodes. Penfield later made essentially the same observations in humans, with progressive shift of the electrode along the motor strip activating movement of a different part of the body with a systematic topographic shift. The inherent uncertainties about what was happening on activating such a complex structure electrically then progressively came to the fore. The current spreads significantly through an appreciable volume of tissue containing a mass of different neurons with potentially antagonist effects and different topographical arrangement. Moreover, early workers used repetitive stimulation, thereby favoring...
neuronal interaction, both excitatory and inhibitory, and with temporal summation, cumulative fatigue, and so on. Much discussion became focused on the essentially simplistic controversy as to whether muscles or movements were “represented” in the cortex. The muscle proponents hoped that sufficiently focal stimulation would activate just one anatomical muscle, whereas the movement school correctly recognized that this was not so without being able to give any precision as to what they meant by “a movement” being focally represented. The tools available were quite inadequate to set out de novo to try to discover how the motor cortex actually worked, with massive interaction between nearby neurons. The more recent use of genuinely focal stimulation and recording, with tungsten microelectrodes driven into the neuronal layers of the cortex, is now the preferred method and has revealed a wealth of detail, including localized sensory feedback onto the outgoing motor elements; this all continues to be explored, especially in conscious animals trained to perform a particular task. Given that every movement involves an array of muscles, it is hardly surprising that an array of cortical neurons is now thought to be involved, generating the statistically appropriate patterns of firing in even a simple movement; there is no sign of the “columns” that are such a prominent feature of the visual system.

*Stimulation of motor cortex in humans.* Having flourished through the first half of the 20th century, gross electrical stimulation of the brain became an outdated method, with its indiscriminate action on a variety of disparate elements; it had apparently little left to offer and seemed about to pass into history. It is thus quite a surprise that it has suddenly been resurrected on a massive scale for use in humans for a variety of purposes (18). The starting point was provided by Merton, experimenting on himself some 20 years ago, who realized that the discharge of a single high-voltage shock with a very small total charge, as from a condenser, should suffice to excite the underlying neurons even when applied to the outside of the skull. By placing a stimulating electrode over the motor cortex, he was thereby able to produce a “twitch” type of contraction of a variety of muscles. Unfortunately, the electric shock also activates large numbers of cutaneous nerve fibers running in the scalp, including nociceptors, producing a violently unpleasant sensation. Volunteers for experimentation are thus very hard to come by, clinical applications are largely impossible, and even experimentalists dedicated enough to work on themselves become reluctant to continue.

*Magnetic stimulation.* The breakthrough for human application came with the use of the entirely painless “magnetic stimulator,” which had already been developed for stimulating human nerve trunks percutaneously. The stimulator is a simple application of Faraday’s principles of electromagnetism, discovered at the beginning of the 19th century, and consists of a small coil of thick wire through which a brief but very strong current is passed. As the current rises and falls, it produces a transient magnetic field that spreads into the surroundings, and the changing magnetic field induces electrical potentials that then elicit a brief flow current through any spatially distributed conductor lying inside the field. This current is what provides the neuronal excitation, and the degree of excitation will depend on the thresholds and orientation of the nervous elements concerned; small cutaneous afferents would appear to be unfavorably situated, thereby freeing the subject from pain. Responses are typically recorded electromyographically so, as with much of human neurophysiology, the technique and the collection of data are easy but the interpretation is fraught with pitfalls. To begin with, quantifying the brief EMG response shares many of the uncertainties of interpreting the H reflex, with the added complexity that the descending cortical discharge typically consists of a brief burst of impulses (direct and indirect waves) rather than a single volley. The later indirect waves are undoubtedly due to the initial excitation of interneurons rather than the descending neurons themselves. With electrical stimulation, the initial direct wave is due to excitation of the descending axons, often an appreciable distance below the cortex, whereas its origin with magnetic stimulation has been the subject of considerable debate. Thus any idea that the summed response to transcranial stimulation measures a supposedly simple entity entitled “cortical excitability” represents a sad neglect of the underlying complexities.

Nonetheless, this new and exciting tool of cortical stimulation in humans continues to be applied on an increasing scale. The problem is how best to deploy it to produce genuinely new knowledge about “how the brain works” rather than simply phenomenology, or concluding the obvious such as that the cortex contains inhibitory as well as excitatory circuitry. Inherent in the method is that spatial localization is rather poor, whereas temporal measurements are excellent. This contrasts with the even more striking advance of cerebral localization by the new imaging techniques; here localization is good but temporal measurements are bad. Both rest on fundamental uncertainties, namely what precise aspect of neural activity is being imaged, or just what neural elements are actually being stimulated. The long march to the present advanced level of the study of human motor control has been dependent throughout on the tools provided by physicists and engineers, with their fine tuning by physiologists who have to deploy them in the field. The danger is that as the tools become more complex and progressively more incomprehensible in their inner workings then the ordinary biologists and clinicians who use them will cease to think sufficiently critically about their limitations and errors.

**CONCLUSION, WITH FUTURE HOPES FOR THE BENEFIT OF HUMANKIND**

New techniques are opening new horizons in the study of sensorimotor control and much can be hoped for in the next decade, provided that the work is conducted in a spirit of self-critical enquiry rather than triumphal optimism; the limitations as well as the advantages of every new method need to be properly assessed. Basic understanding of the periphery and the spinal circuitry is well advanced, having become ever better understood from animal experimentation and then applied to humans, where the prime tool of the EMG opens a window for the quantitative analysis of neural activity. This is an essential prelude to understanding how the higher motor centers operate, because they evolved subsequently and have to “talk” to the spinal cord in a language that it can understand with everything finally channeled onto Sherrington’s “final common path” of the MN.

The Western world’s aging population has much to gain from better understanding, because motor disabilities feature large in limiting their activity and thus their quality of life; in
the long term, hope focuses on producing local neural repair and regeneration, including with implanted tissue. At the simplest level, the failure of sensorimotor control leads to falls in the elderly, thereby producing a massive amount of disability, and even death, through fractures of weakened bones; some of this suffering might be prevented by better understanding of postural mechanisms. Humankind’s love affair with the car leads to ever more paralysis in the young; their plight could be greatly alleviated by the development of neural prostheses to activate their intact muscle machinery and make it obey the commands of their will. In the late middle aged, the merciless progression of Parkinson’s disease occurs in those with intact mental capacity and cries out for remedial action. The rehabilitation and retraining of the numerous elderly who suffer motor disabilities after a stroke likewise should be improved by better understanding, as well as by the development of neural prostheses. Thus there is much waiting to be done, and only basic research can lead the way. This will require ever newer tools to hack into the jungle of the unknown, but they must be wielded with care to avoid falling into the pitfall of faulty interpretation.

SELECTED READINGS