

Conference Report

Report of a conference sponsored by the Fogarty International Center for Advanced Study in the Health Sciences, National Institutes of Health, Bethesda, Md., and held in Bethesda on March 27th and 28th, 1972

THE CONTROL OF MOVEMENT AND POSTURE

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SUMMARY

This report attempts to summarize material discussed at a recent conference on the control of movement and posture, held under the auspices of the Fogarty International Center at the National Institutes of Health, Bethesda, Md., on March 27th and 28th, 1972. The Conference was planned to focus on the cross-over between work in animals on muscles and the central nervous system control of movement, and observations in human clinical neurology and neurophysiology. Major emphasis was placed on recent work dealing with the properties of motor units, the role of muscle receptor systems in movement control and with the role of the motor cortex in both 'reflex' as well as 'voluntary' movement.

Attention was also directed to issues of the prospect for and ethical aspects of future experimentation in human subjects.

The participants in the conference were Cosimo Ajmone Marsan, National Institute of Neurological Diseases and Stroke, NIH; Ronald W. Angel, Veterans Administration Hospital, Palo Alto, Calif.; Jennifer Buchwald, University of California, Los Angeles, Calif.; Robert E. Burke*, National Institute of Neurological Diseases and Stroke, NIH; Mahlon R. DeLong, National Institute of Mental Health; Derek Denny-Brown, New England Regional Primate Research Center, Harvard Medical School; Milan Dimitrijevic*, University of Ljubljana, Yugoslavia; W. King

* Invited speakers who delivered major papers at the Conference.

Engel*, National Institute of Neurological Diseases and Stroke, NIH; Edward V. Evarts*, Laboratory of Clinical Science, National Institute of Mental Health; Karl Frank*, National Institute of Neurological Diseases and Stroke, NIH; Sidney Gilman*, College of Physicians and Surgeons of Columbia University, New York; Ragnar Granit*, Scholar-in-Residence, Fogarty International Center, NIH; Sten Grillner, University of Göteborg, Sweden; K. E. Hagbarth*, Academic Hospital, Uppsala, Sweden; Elwood Henneman, Harvard Medical School; Herbert Jasper, Montreal University, Canada; Eric Kugelberg, Karolinska Institutet, Stockholm, Sweden; Yves Laporte*, Faculté de Médecine, Université de Toulouse III, France; C. David Marsden*, The Bethlem Royal Hospital and Maudsley Hospital, London; Peter B. C. Matthews*, Oxford University, England; Grayson P. McCouch, University of Pennsylvania School of Medicine; Vernon Mountcastle, Johns Hopkins University School of Medicine, Baltimore; Ayub K. Ommaya*, National Institute of Neurological Diseases and Stroke, NIH; Charles G. Phillips*, Oxford University, England; Ottavio Pompeiano, University of Pisa, Italy; David A. Robinson, Johns Hopkins University School of Medicine, Baltimore; Ingmar N. Rosén, State University of New York at Buffalo; Pedro Naum Rudomin, Center for Investigation and Advanced Studies, Mexico City; Thomas A. Sears*, The National Hospitals for Nervous Diseases, London; Hans-Lukas Teuber, University of Oxford, England; Wallace M. Tourtellotte, Veterans Administration Center, Los Angeles; John H. Van Buren*, National Institute of Neurological Diseases and Stroke, NIH; Joseph P. Van der Meulen*, University of Southern California Medical Center, Los Angeles; Arthur A. Ward, Jr.*, University of Washington School of Medicine, Seattle; Mario Wiesendanger, Institut für Hirnforschung der Universität, Zurich, Switzerland.

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As it may interest workers in this field to know what particular aspects of motor control were discussed at this Conference, it was decided to publish a brief summary, including a list of participants, in order to facilitate enquiries about the contents of specific contributions. The Conference was planned to bring together pairs of neurophysiologists and clinical neurologists to consider each of a number of topics. The pairs of speakers opened up subjects for discussion by a brief presentation of data and ideas. The Conference essentially became a confrontation of neurophysiological work on man with that on laboratory animals. The material in this report is the authors' view of the Conference discussions and is not intended necessarily to represent definitive statements by the Conference participants.

In order to facilitate presentation in this summary report, the discussions will be grouped under several somewhat artificial headings. These serve primarily as a frame of reference for organization of the material discussed at the Conference and it will be recognized that there are inevitable instances of overlap between sections. It should also be noted that considerable background information and material has not been included, being available in a number of recent reviews on the subject of motor control^{24,25,28,46,48} (and in a recent issue of *Brain Research*, Vol. 40, No. 1, 1972).

Section 1. Motor units and muscles

Burke began the discussion of motor units by summarizing recent work dealing with the interrelation between physiological properties of single motor units in the cat gastrocnemius and the histochemical and morphological characteristics exhibited by the muscle fibers (or muscle unit) belonging to the same units¹⁰. In the cat, the motor unit pool making up the nominally 'fast' gastrocnemius muscle can be divided into three major groups, or types, based on a combination of physiological parameters. Using the method of glycogen depletion developed by Edström and Kugelberg²⁰, the muscle fibers belonging to units in each physiological type were shown to have distinctive histochemical and morphological profiles. Two groups of rapidly contracting units were found. One, called 'type FF', contained units producing large tensions, exhibiting very rapid fatigue during repetitive activation and having muscle fibers which were generally large in size, with high myofibrillar ATPase activity and sparse oxidative enzyme staining. The other group of rapidly contracting units, called 'type FR', produced less tension but were considerably more resistant to fatigue, and had muscle fibers which were smaller in size than most FF unit fibers, with high oxidative enzyme activity. Muscle fibers of FR units also had high myofibrillar ATPase activity but the intensity of ATPase staining differed from FF unit fibers following acidic preincubation. The third major group of gastrocnemius units, called 'type S', were slowly contracting, very resistant to fatigue and produced small tensions. Muscle fibers of S units were small in diameter, relatively poor in myofibrillar ATPase activity and rich in oxidative enzyme activity. There were obvious correlations between the intensity of fiber ATPase staining and unit contraction speed, as well as between relative resistance to fatigue, oxidative enzyme activity and fiber capillary supply.

Early work^{7,8,11} had shown that type S units are innervated by relatively small alpha motoneurons which are specialized by virtue of intrinsic membrane properties for slow repetitive firing. In addition, type S motoneurons are in general more powerfully excited by muscle spindle primary afferents than are the cells innervating fast twitch units. However, some fast twitch motoneurons do receive relatively powerful input from spindles which can drive such cells during muscle stretch and Burke suggested that such units may correspond to the fatigue resistant type FR units.

Henneman discussed the probable usage of motor units of different types, pointing out that the fatigue resistant slowly contracting units and the organization of input to them seem particularly suited for tonic use, as in postural maintenance. The large-tension, easily fatigued units would seem suited only for rapid, powerful contractions which are not sustained and the presence of large numbers of such units in many limb muscles might appear to some extent uneconomical. He raised the question why the motor system should require a third type, both fast contracting and fatigue resistant. Burke suggested that the latter type of motor unit might well be active during repetitive movements such as walking and running, during which there is coactivation of the gamma system, and in which both rapid contraction and fatigue resistance may be essential. Burke mentioned findings from several laboratories

which suggest that motor units may undergo transition between categories analogous to types FF and FR, depending on the exercise history of the animal (*cf.* Barnard *et al.*⁴). Thus, motor units like type FF may be used not only for short term phasic action but may also serve as a reservoir of units which, given appropriate long term demands on the system, convert into more fatigue resistant types.

Kugelberg discussed recent results from his laboratory showing that, while motor unit physiology and histochemistry are closely correlated in the rat as in the cat, the situation in rat muscle appears to be more complex than in the cat. The rat soleus muscle contains three types of muscle fibers, based on the characteristics of ATPase staining. Using the glycogen depletion method developed in his laboratory²⁰, Kugelberg and coworkers have shown that the contraction speed of single units is correlated with the ATPase staining patterns of their muscle fibers. The histochemical profiles of rat soleus motor units are not exactly comparable to those of cat motor units, since all three unit types in the rat soleus have high oxidative enzyme activity and are quite fatigue resistant. Kugelberg pointed out that the utility of having fast contracting, fatigue resistant motor units in the rat soleus may lie in the fact that the rat is a relatively small animal with rapid limb movement in running. He suggested that at least some rapidly contracting units are used in walking and running movements and that these are the motor units with rich oxidative activity in their muscle fibers.

Engel discussed the histochemical analysis of human muscles in a variety of neuromuscular diseases. Drawing on the information accumulated from work in animals on motor unit organization, he described the complex rearrangements in unit organization which may occur following damage to the motoneuron or to its axonal branches. He pointed out that in normal animal muscle, the muscle fibers innervated by a given motoneuron are scattered through the motor unit territory. When the parent motoneuron is damaged or dies, as in amyotrophic lateral sclerosis, all of the innervated fibers are affected — an *in toto* disorder. It is also possible under some circumstances, as in localized damage to axonal branches, that only some of the motor unit fibers are affected while others remain normal — an *in parte* disorder. Because denervated muscle fibers can accept reinnervation from surviving motoneuron axons, the histochemical mosaic (and the motor unit architecture) in neuromuscular diseases can be markedly altered. An example is the grouping of muscle fibers with identical histochemical profiles, called ‘type grouping’, seen after denervation and reinnervation (*cf.* Kugelberg *et al.*³⁷).

With regard to motor unit usage patterns, Engel described recent work by Warmoltz at NIH with patients undergoing open muscle biopsy. Warmoltz’ results suggest that motor units with fibers having low myofibrillar ATPase activity (called ‘type I’ fibers) tend to show activity in sustained trains at low frequency during states of low tension output. Higher tension demand with brief contraction tended to activate units with high frequency firing in short bursts, and these units had muscle fibers with high myofibrillar ATPase activity (called ‘type II’). In his clinical work, Engel emphasized a dual muscle fiber classification into ‘type I’ and ‘type II’, rather than the multiple groups emerging from experimental work on animals. In other experiments with Campa, Engel has failed to find recognizable histochemical differences between

the alpha motoneurons innervating the different motor unit types in the cat¹².

Engel also emphasized the well documented plasticity of muscle, which can lead to marked alterations in morphology, ultrastructure, histochemistry, biochemistry and physiology, depending on imposed conditions. Such alterations can take place not only in experimental situations such as nerve cross-union, denervation, or cordotomy, but apparently also in human neuromuscular disease as well. He pointed out that in certain disease states, such as the cachexia of terminal carcinoma, there is apparent sparing of type I muscle fibers with concomitant atrophy of type II fibers. Thus the response of muscle to a given condition is to some extent dependent on the initial type, or structural/biochemical profile, of the fibers involved.

Sears extended the discussion of the analysis of muscles as effector systems, using as an example the muscles involved in respiration. He expressed the opinion that neural signals involved in motor control are best understood in the light of the mechanical job the muscles are called upon to perform. Presenting a film of the complex movements of the exposed and marked rib cage in anesthetized cats, from which three-dimensional shape changes had been reconstructed by his colleague de Silva, Sears defined the task of the respiratory muscles as two-fold: (1) moving the rib cage to provide demanded respiratory gas exchange; and (2) adapting simultaneously to the very dynamic problem of assisting movements of the upper limbs connected to the rib cage. In addition, in quadrupeds the rib cage bears a good part of the weight of the animal.

The act of inspiration can be seen to be an elevation of the ribs in conjunction with a downward movement of the costochondral regions, bringing the sternum downwards. The mechanical efficiency of the diaphragm is very much influenced by lung volume. The ring of the diaphragm is inserted into the lower rib cage such that changes in the shape of the latter, as in postural alterations, walking, phonation, arm movements, etc., concurrently alter the length of muscle fibers in the diaphragm and so control its mechanical efficiency. The film made clear also that passive forces perhaps should not be overemphasized in explaining expiration, since both abdominal and intercostal muscles contract actively during the expiratory phase in the cat.

Thus there is in respiration a considerable neural control problem of keeping all the ribs in the right place at the right time and allowing the diaphragm to operate properly. Something of this is reflected in the intracellular records from intercostal alpha motoneurons, in which rhythmically rising slow potentials, generating spikes, can be looked upon as a sort of electrical analogue of the tension development required in a particular demanded movement.

Section II. The question of motoneuron excitability

There were two areas of discussion which can be subsumed under the above heading. The first of these concerned information regarding the way in which the motor unit pool of a given muscle or muscle group may be recruited into activity during movements of varying speed and/or force. Most of this discussion centered around considerations of recruitment patterns related to motoneuron size, which can

be integrated with the preceding material to some extent by virtue of the fact that the smaller motoneurons tend to innervate motor units with slowly contracting, fatigue resistant muscle fibers⁸.

Henneman, who has studied the question of recruitment pattern systematically in decerebrate cats³⁵, stated that in his experience recruitment of motoneurons in response to muscle stretch and a number of other stimulation paradigms always begins with the smallest motoneurons, as judged by the amplitude of extracellularly recorded spikes. He noted that in recent work with human subjects, he and his colleagues had been unable to produce clear variation in recruitment order among motor units activated voluntarily. That is, they were unable to cause an easily recruited unit to cease firing while maintaining discharge in a unit recruited later than the first. Robinson supported the idea of a stereotyped recruitment order among motor units innervating extraocular muscles and noted that the 'threshold' for initiation of unit firing was quite closely correlated with the angular position of the eye. Evarts commented that in monkeys trained to make quick movements for reward, motor units with small EMG spike amplitudes were always recruited before units with larger spike amplitudes, an observation thought to be in accord with the 'size principle' of motoneuron recruitment⁴⁷.

However, Granit and Van der Meulen both offered the opinion that a stereotyped recruitment order based only on motoneuron size might, in some situations, be counterproductive. If very fast action were required in a particular movement, the force-velocity properties of muscle fibers innervated by small motoneurons might be ill-suited to the demands of the moment. Kugelberg pointed out that while a stereotyped order of motor unit recruitment is often observed in electromyographic recordings from human subjects, especially during slow or low tension movements, this is not always the case. In particular, he mentioned recent results of his colleagues Grimby and Hannerz^{31,32} who have observed changes in recruitment order depending on other conditions, such as speed of movement, conditioning afferent input, etc. Marsden described similar observations in studies on hand muscles in humans. It is impossible at the present time to identify the motor units recorded electromyographically in humans in terms of their probable physiological and histochemical characteristics. The relation of such data to the recent results from animal experiments remains speculative. However, both Granit and Van der Meulen suggested that further investigation of this question would contribute greatly to the analysis of motor control in human subjects.

Denny-Brown discussed some results from his experiments in the 1920's on reflex responses of the cat gastrocnemius and soleus muscles. It was a common observation in precollicular decerebrate cats that animals would on occasion make sudden jumping movements, which involved massive activation of the nominally 'fast' gastrocnemius muscle and concomitant silence in the 'slow' soleus. He pointed out that other examples of this apparent reversal of the 'slow to fast' order of recruitment were published in a compendium of results from Sherrington's laboratory¹⁷. Burke reported that, in anesthetized cats with intact neuraxis, electrical stimulation of some skin nerves and of the red nucleus can cause predominant polysynaptic inhibi-

tion in many type S gastrocnemius motoneurons while at the same time producing predominant polysynaptic excitation in a significant proportion of fast twitch cells in the same motor nucleus⁹. Such experimental observations suggest that the nervous system may have available mechanisms which can recruit motor units in various combinations and patterns. It seems possible that the fast twitch motor units capable of producing considerable force might initiate acts characterized by such requirements, while other sorts of movements would begin with mobilization of the small motoneurons, innervating slow twitch muscle and capable of long-lasting tonic activity at low discharge rates. Such slow motor units would be regulated by recurrent inhibition and supported by the gamma loop.

The second area of some discussion centered around the problem of assessment of motoneuron excitability in man and the problems encountered in trying to draw conclusions from such measurements. Both Granit and Van der Meulen took the view that, since motor units operate in motor acts involving both loading and unloading, methods of study which neglected such aspects of motor unit function would be of limited use only. They were critical of the study of the so-called silent period caused by an electrically elicited twitch, taking the view that this test has little in common with the regulation of movement and that its application in the clinic has been of scant service. Too many factors are involved in its interpretation.

Van der Meulen held that the 'H-reflex' has also been over-interpreted in both normal and pathological states. The difficulty in eliciting this response from muscles other than the triceps surae group raises considerable question about the general applicability of the results of this clinical test. The H-reflex activates less than 50% of the available motor unit pool⁵⁵ and is not really reproducible until at least a small M-response has been elicited. Its variability is also great and this aspect of the problem may repay closer analysis, as has been done in animal experiments on monosynaptic reflexes by Rudomin and coworkers⁵¹. The extremely powerful facilitation which occurs in the first 10–15 msec of the cycle has been largely ignored and should be examined more closely. Later in the cycle of excitability changes, long loop supraspinal reflexes may come into play.

Other problems in the interpretation of the H-reflex were brought out by Granit. He pointed out that the H-reflex is strongly influenced by presynaptic inhibition while it has been shown rather clearly that presynaptic inhibition need not strongly influence a steadily firing motoneuron^{16,29}. Steadily discharging motoneurons are, in contrast, highly sensitive to postsynaptic inhibition. Why then use a method which does not distinguish between pre- and postsynaptic inhibition, when the correct information may be contained in the firing patterns of discharging motor units recordable in the electromyogram? Granit emphasized that recent evidence has shown that the monosynaptic terminals of spindle primary afferents, which are responsible for the H-reflex, are widely dispersed over the soma and dendrites of motoneurons⁴⁹. This may mean that postsynaptic potentials produced by spindle primaries can be easily influenced by conductance changes set up by adjacent synapses activated by input systems which normally do not operate in synchrony with spindle primaries. The neurologist interested in functioning muscles and in discharging motoneurons cannot

really interpret changes in the H-reflex in terms of motoneuron excitability alone. In the light of earlier discussions at this Conference, it can be pointed out that, although an increase in the H-reflex will always signify that motoneurons have been made available from the subliminal fringe, it cannot answer whether or not a motor act utilizes the same motoneurons. The actual answers to such questions may come from animal experiments in which intracellular observations can be added to extracellular studies of the monosynaptic reflex.

In terms of further progress in the clinical sphere, both Granit and Van der Meulen agreed that electromyography remains the best method available for neurologists interested in motoneuron excitability and in the premotoneuron mechanisms responsible for much of observed motoneuron excitability fluctuation. Advances in this area will depend partly on technological innovation and partly on development of objective tests for motor performance. For example, Van der Meulen, in collaboration with several biomedical engineers at Case-Western Reserve University, has been developing extremely small wire electrodes that can be inserted into muscles and left in place, in some cases for over 6 months. These electrodes have been designed for multiple-array sequential stimulation but have also been found quite effective as recording electrodes.

Van der Meulen likewise emphasized the need for quantitative evaluation of the deep tendon reflexes which will remain an integral part of the neurological examination. A spring-loaded reflex 'gun' has been developed at Case-Western Reserve University for delivery of constant tendon taps, to be used in conjunction with recording of electrical and mechanical responses in the manner of Dietrichson¹⁸. He believes that comparisons between active and passive movements would be a valuable area for utilization of such techniques.

Finally, Van der Meulen argued that motor abnormalities in patients should be studied as such and not necessarily under a variety of clinical diagnostic headings. He suggested that patients with motor system disorders may exhibit 4 basic dysfunctions, either singly or in combination: (1) inability to move, or weak and ineffective movement; (2) presence of excessive tone which interferes with movement; (3) poor control over voluntary movements; and (4) presence of spontaneous involuntary movements. Such qualitative categories are not new, of course, but one goal for immediate pursuit might well be an attempt to quantitate and isolate each component in patients with motor system disorders.

Section III. The gamma system

Discussion of some recent, and some not so recent, information regarding the role of muscle receptors in movement played an important part in the Conference. The material in this section deals primarily with muscle spindles and gamma motoneurons.

Laporte presented very recent material relating to the innervation of intrafusal muscle fibers by static and dynamic gamma motoneuron axons. In order to ascertain precisely the destination of single fusimotor neurons, he and his coworkers dissected ventral root filaments containing fusimotor axons innervating tenuissimus spindles

until only a single gamma axon to the tenuissimus remained intact. This procedure was performed in anesthetized cats under aseptic conditions. After 7–9 days survival, the same animals were reoperated and in successful experiments, the single fusimotor axon had survived. Its physiological effect on the innervated spindles, either static or dynamic, was then tested and the muscle was removed, fixed and sent to Prof. David Barker in Durham, England, for histological analysis. The surviving gamma axon, its neuromuscular terminal apparatus and the intrafusal fibers innervated by it, could thus be correlated with the physiological responses of the same spindle. Dynamic gamma axons were found to innervate only nuclear bag fibers while axons of static gamma cells innervated both nuclear bag and chain fibers in 8 of 12 cases.

In a variation of this experiment, Laporte's colleagues Bessou, Jankowska and Pagès identified single fusimotor axons to tenuissimus spindles on the basis of their effect on afferent activity and then impaled the intrafusal muscle fibers innervated by the identified gamma axon. They were able to inject the innervated muscle fibers with Procyon Yellow dye and thus Barker could examine the histological characteristics of the innervated fibers. This experiment gave results similar to those obtained in the degeneration work, namely that dynamic gamma axons innervated only nuclear bag fibers, while static axons innervated both bag and chain fibers, including one case in which the two types of intrafusal muscle fibers in the same spindle were innervated by one static gamma axon.

Gilman discussed results from his laboratory dealing with supraspinal control of gamma motoneuron discharge patterns, after citing earlier work on this question by Granit and his coworkers. In Gilman's experience, gamma bias to extensor muscle spindles decreases in cats and monkeys after cerebellectomy or section of the superior cerebellar peduncle. Both the static and dynamic responsiveness of spindle primary afferents is much reduced in this situation but that of the spindle secondaries appears little altered from the control state. Pyramidotomy has much the same effect on spindle gamma bias and there is little further decrease in afferent responsiveness following ventral root section. Several weeks after lesions have been made, there is some partial recovery, or 'compensation'. Gilman compared this effect of cerebellectomy to the extensor hypotonia seen in man following cerebellar lesions.

In Gilman's work, gamma motoneuron firing apparently follows a rather complex pattern on acute cooling localized to the VL nucleus of the thalamus in cats, with ultimate decrease in activity after lesion production. Similarly, after removal of areas 4 and 6 in the monkey, there is an initial stage, lasting 1–2 weeks, of hypotonic paresis accompanied by evidence of decreased gamma motoneuron bias. This is succeeded by a later stage of hypertonic paresis and in this situation, spindle bias appears indistinguishable from that in normal animals. In these results there was no clear distinction possible between dynamic and static spindle bias, but further investigation along these lines may hopefully have direct relevance to studies of muscle tone in patients with various lesions of the central nervous system.

Sears briefly reviewed some of the evidence which suggests that coactivation of alpha and gamma motoneurons plays an important role in the regulation of respiratory movements. He mentioned the load compensating reflexes in the respiratory system,

studied independently by his group and that of von Euler, pointing out that activity of this system is well regulated and automatic but that any mechanical restraint perturbing the predicted input leads to compensatory changes in output. Further, in man such interference is readily perceived. Sears said that while one might have expected the sensation that 'I find it difficult to breathe' to be a wholly chemically based experience, originating centrally, the experiments of Campbell *et al.*¹³ have shown that curarized subjects do not report this sensation. Activation of receptors in the periphery, perhaps including the spindles, appears to be necessary for it. It is becoming increasingly clear that in many movements, the nervous system issues commands in alpha-gamma linkage to bring about predicted movements against predicted loads. When the muscles encounter an unexpected change in load, spindle input clearly signals this and reactions follow which may be organized at many levels, including perhaps that of conscious experience. This latter subject forms a central question in the next section.

To round off the subject of spindle control, Hagbarth presented recent results of his work, and that of his colleague Vallbo, dealing with the behavior of spindle afferents recorded in conscious human subjects through microelectrodes placed in peripheral nerves. They have shown that no resting spindle afferent discharge can be recorded from a 'relaxed, EMG-silent human muscle'. Such findings were checked by blocking gamma efferent discharge with Lidocaine, upon which nothing was altered. To passive stretch, however, the spindle afferents responded in the expected manner, with low discharge frequencies never exceeding 30–40 imp./sec in phasic stretch. Most of the afferents studied were thought to be spindle primaries, but some were tentatively identified as secondary afferents. The maximum firing rates of the latter in maintained passive stretch were of the order of 30 imp./sec.

During the onset of voluntary contraction, Vallbo⁵⁷ found that spindle primaries began firing a few msec after the start of extrafusal EMG activity, and then discharged with frequencies roughly in proportion to strength of the isometric contractions which were 'willed'. Spindle afferent discharge never preceded extrafusal EMG activity. Maximum firing rates were, in this situation, of the order of 75–100 imp./sec. The spindle afferents also fired during voluntary isotonic contractions against moderate loads, showing that the gamma motoneurons coactivated during such movements can maintain spindle primary sensitivity even with shortening muscle. Thus, it is presumed that static gamma motoneurons were involved. Such spindle afferent response during voluntary motion was greatly reduced following partial Lidocaine block of the nerves. In Hagbarth's experiments there was often some apparent reduction in voluntary motor power, but, since maximum power was restored with muscle vibration, the initial reduction did not appear to be due to alpha axon blockade. Rather, this reduction must have been due to the selective removal of spindle support. Although the spindles never appeared to initiate a voluntary contraction, once the motoneurons were brought to firing level by the 'alpha route', the spindle afferents apparently contributed to the maintenance of contractile power in the agonist muscle and to inhibition in the antagonist, as expected with the reciprocal organization of central connections from spindle primaries.

With regard to the question of whether gamma motoneuron discharge may lead or lag the onset of alpha motoneuron activity, Buchwald discussed results of experiments in cats conditioned to produce a hind limb flexion to a tone cue. Recording ventral root filament activity in such animals (unanesthetized with local anesthesia at the recording site), she found tonic ventral root units, presumed to be gamma motoneurons, to increase their discharge rate with latencies around 18 msec after the onset of the tone, while larger amplitude units, presumed to be alpha motoneurons, only began to discharge after some 80–90 msec. Evarts commented that earlier work in man³³ suggested that there was no early increase in monosynaptic reflex before onset of alpha motoneuron activity, indicating that gamma discharge, if it precedes movement, apparently does not lead to much increase in spindle afferent feedback prior to alpha route activation.

Finally, Hagbarth mentioned his preliminary results in studies of Parkinsonian rigidity and states of spasticity. Rigid patients differed from normal subjects in having maintained spindle afferent discharge at rest, with apparent coactivation during movement as in normals. Thus there was evidence for an increased static spindle bias in rigid patients. In spasticity, however, there was no evidence for increased spindle bias in the few patients studied so far and actually such patients gave results little different from normals during stretch. There was in particular no evidence for increased bias of dynamic fusimotor neurons.

Matthews brought up the apparent contradiction between the results of Hagbarth in normal human subjects, in which there was no apparent 'spontaneous' spindle afferent activity suggesting low or absent gamma bias in resting muscle, and the data of Gilman in the monkey, in which spindle afferent activity was present normally with muscles at rest. Matthews asked the question how hypotonia in man, as after cerebellar lesions, could be due to decrease in spindle activity if there is no spontaneous discharge in the normal resting state. Gilman stated that there was no EMG activity in resting muscles of monkeys, just as observed in man. Matthews then asked whether either Hagbarth or Gilman felt that the animal model was comparable to the situation in man, and there was a consensus of opinion that present data lead to no conclusive answer.

Section IV. Central effects of muscle afferents

There was little discussion at the Conference of the well known results of animal experimentation dealing with the central effects of muscle spindle primary afferents. However, Pompeiano introduced the recently controversial question of the segmental effects of muscle spindle secondary afferents by pointing out that, in the decerebrate cat, high frequency vibration of an extensor muscle apparently mobilized virtually all of the primary afferents but produced less reflex tension than stretch of the same muscle. When Matthews first made this observation⁴⁴, he suggested that, under the experimental conditions used, the spindle secondary afferents were excitatory to extensor motoneurons rather than having an inhibitory effect, as had been described in experiments done under different conditions. Such a reversal of sign should be possible

since the secondaries project to motoneurons through polysynaptic interneuronal pathways, which conceivably can change both the magnitude and the polarity of the ultimate effect on motoneurons. The spindle secondaries, being much less sensitive to high frequency vibration than the primary afferents, are thought not to participate in the tonic vibration reflex but are mobilized during relatively slow or steady stretch.

Pompeiano raised this issue as a challenge to Matthews' view and cited recent evidence of members of his group who found that activation of muscle spindle secondary afferents during selective anodal blockade of primaries produced hyperpolarizing potential shifts in intracellular records from cat ankle extensor motoneurons¹⁴. He noted that such records had been obtained only from apparently large gastrocnemius motoneurons (based on the measured duration of afterhypolarization), leaving open the possibility that the effect in smaller cells, which would be more active in the decerebrate preparation, might be qualitatively different. However, he also pointed out that another explanation of the observations was possible, in that vibration apparently produces a significant presynaptic inhibition in spindle primary afferent terminals while static stretch alone does not produce the characteristic signs of presynaptic inhibition¹⁶. Thus, presynaptic inhibition could cause, at least in a qualitative sense, the observations made by Matthews although the question of the 'gain' or magnitude of this presynaptic effect is still unsettled. Grillner³⁰ offered yet another alternative explanation for Matthews' results, having to do with the mechanical stiffness (the length/tension curve) of the cat soleus muscle studied under the same conditions as used by Matthews.

In his reply, Matthews declared himself unwilling to accept the suggested alternative explanations for his findings. His response to Grillner's hypothesis has been published⁴⁵. To Pompeiano, Matthews replied that with selective blocking of group I primary afferents, which he agreed may result in group II spindle secondary inhibition in extensor motoneurons, still does not provide evidence as to what effect a combined input from both primary and secondary afferents may have on spinal segmental mechanisms. He expressed the opinion that the observations are best explained by postulating a complex central interaction activated by the combined effects of primary and secondary spindle afferents.

Turning to the problem of the operation of muscle receptor afferents in human motor control, Marsden discussed recent experiments done in collaboration with Merton. They investigated the response produced by various conditions of loading and unloading during constant velocity flexion movements of the top joint of the thumb⁴³. The subjects were asked to track a constant velocity signal on a monitor screen and during the course of such movements of the thumb 4 different situations were presented in a random sequence of different trials, without warning the subject beforehand. In the control situation, flexion was continued against constant resistance through about 20°, during which both velocity and force exerted were constant. In other trials, after 50 msec the thumb was suddenly driven back by a large force, which produced increased EMG activity as in a stretch reflex. A third condition sometimes imposed was that the load was suddenly removed during the flexion movement, producing a period of EMG silence in the agonist muscle. The fourth condition tested was sudden

halting of the movement during flexion by doubling the resistance to flexion. This situation produced an increase in EMG activity in thumb flexors with a latency of 40–50 msec and continued shortening, suggesting that this response was equivalent to the load compensation servo response predicted to occur with alpha–gamma coactivation. However, quite an unexpected effect was produced by anesthesia of the hand with a wrist cuff, which caused disappearance of all of the above responses to variations in loading, even though the flexion movement was produced by muscles above the wrist whose receptor organs were not interfered with. Marsden and co-workers have interpreted this singular observation to indicate the significant participation of joint receptor afferents, which are presumed to interact with and condition the ultimate motor response to impulses arriving from muscle receptors in the agonist muscle. This conclusion suggests that afferent information other than from muscle receptors can condition the gain of the stretch reflex system and that, therefore, this factor must be taken into consideration when attempting to apply the results of animal experimentation to observations from intact animals or human subjects.

Another observation made by Marsden and coworkers is that all of the EMG responses to variations in muscle loading, recounted above, increased proportionately when the initial load on thumb flexion was increased. This appears to represent another mechanism for adjusting the gain of the feedback loops operating to produce the observed responses. Marsden pointed out that during fatigue, as the EMG activity increased with the attempt to produce the required force for movement, so too did the apparent gain of the stretch reflex. He noted that the responses to load variations occur with a relatively long latency, about 50 msec, which raises the question whether the observed responses might be due, at least in part, to long loop reflexes involving supraspinal centers.

Matthews pointed out that the apparent load compensation responses Marsden obtained with sudden arrest of thumb movement did not necessarily mean that gamma motoneurons increased their firing in response to the arrest of movement but could merely indicate a steady rate of gamma activity initiated by the original movement. Marsden agreed with this comment but noted that his results did apparently necessitate alpha–gamma coactivation in the movement, whether or not there was increased gamma firing at the time of movement arrest.

Angel described results obtained in somewhat similar experiments in which the subject was asked to flex the elbow as rapidly as possible against a spring load which could be released by an electromagnet at any point before, or during, the movement (*cf. Angel et al.*¹). In executing such ballistic movements against a spring, there was a double burst of EMG activity, the first serving to accelerate the limb. If the spring is suddenly unloaded after the movement has begun, the limb moves at an unexpectedly high velocity and the second burst is markedly reduced. If, however, the load was removed before initiation of movement the first EMG burst occurred anyway, as if representing the effect of an initial command issued to start the movement. The second burst was much more variable with conditions of loading, suggesting that it might depend on short and long loop effects arising from afferent feedback.

Granit, discussing the subject of loading and unloading of muscles, said that the

silent period observed with unloading of voluntary movements, as discussed by Sears⁵² and by Marsden (above), may not be a pure indication of cessation of discharge in primary spindle afferents. Some time ago, Sommer⁵³ showed that muscles were silenced by unloading during a vibratory contraction that kept the spindle afferents active, since confirmed by Hagbarth. Though not quite conclusive, this result suggests that the silent period at unloading contains an active inhibitory component, possibly from the spindle secondaries. It seems worth investigating why unloading of a rapid voluntary contraction does not cause a silent period. Rather, the silence at unloading seems characteristic of maintained and slow contractions and its presence, together with other evidence, suggests that (1) slow and maintained activity has a substantial spindle component; and (2) the prerequisite for EMG silence at unloading is that the gamma loop has contributed decisively to the depolarization of the motoneurons to firing level.

Unexpected loading of volitional contraction should lead to a load compensating response such as demonstrated by von Euler and coworkers in their study of the motor responses of cat intercostal muscles during occlusion of the trachea (*cf.* von Euler²¹). Work by Hammond³³ and by Sears⁵² has shown an inhibition on loading, interrupting the short latency (presumably monosynaptic) excitatory responses and delaying compensatory excitation by some 50–70 msec. Granit questioned whether this inhibition arose from Golgi tendon organ input transiently overriding the effect of spindle input, or whether it was a centrally organized defense reaction which might be triggered, rather than modulated, by proprioceptive afferent input.

Matthews discussed the subject of conscious sensation arising from muscle afferents, a phenomenon which many, including himself, had regarded as non-existent. A widely accepted view is that muscle afferents function in motor control entirely at subconscious levels. Matthews, with coworkers Goodwin and McCloskey, studied the effect of 100 Hz vibration at the tendon of the biceps brachii in blindfolded human subjects²⁷. This procedure elicits the well known tonic vibration reflex which moves the arm upward, flexing at the elbow. The subjects were instructed to track the movement of the stimulated arm with the opposite limb, which was done with some positional lag. However, when the movement of the vibrated arm was arrested, the tracking arm then extended, indicating that the subject had experienced the illusion of a non-existent extension in the vibrated arm. It was also shown that aberrant sensations can occur whether or not vibration produced a muscle contraction. Such illusions were experienced if the arm was kept in a sling so as to keep it floating sideways, uninfluenced by gravity. One could then adjust the amplitude of muscle vibration to a level below the threshold for contraction, and the subjects had the illusion of movement. In a way, the sensation is one of position but it actually is more adequately described as an aberrant kinesthetic sensation of movement. Such perceptions have generally been ascribed to activity of joint receptors but it seems that muscle receptors may not only contribute, but may succeed in overriding the signals from joint afferents.

Experiments of this kind, controlled and extended in various ways, led Matthews and his colleagues to repeat some earlier experiments which had suggested that large spindle afferents did not give rise to conscious sensation in man, although these were

known to evoke cortical potentials. Some of these experiments consisted of anesthetizing the skin and interphalangeal joints of a finger, which does not paralyze finger movement nor block output from stretch receptors in the long finger muscles. The subjects in such experiments retained the sensation of passive movement of the anesthetized finger, provided it was moved fairly fast through a reasonably large range. Similar studies were repeated using a wrist cuff to make the entire hand anesthetic, with similar results. It would appear that the long flexor and extensor muscles above the wrist must have provided the necessary afferent information for such sensations of passive movement. In the case of abduction and adduction movements of the fingers, there are no long muscles above the wrist and when the hand is anesthetized, passive lateral finger movements cannot be detected.

Hagbarth, citing recent experience in Uppsala, noted that tracking of vibration induced movements in the legs is often inaccurate, as in the arms, but in such experiments the results of arrest of the vibration-produced movements were much more variable and unpredictable than had been Matthews' experience. For example, it was sometimes found that, when the course of vibration-induced movement was arrested, the tracking limb would sometimes proceed further in the original direction rather than reversing.

Matthews' conclusion from the above sorts of experiments on conscious human subjects is that muscle afferents do play a role in forming conscious perception of the results of motor commands, and that when the influence of such afferents is removed, the perceptions formed may give quite inaccurate pictures of the movements which are produced, if any. He discussed this conclusion in terms of an interaction between afferent inflow of information, including spindle input, with the much-discussed corollary discharge which is assumed to accompany motor output commands. He did not feel that internal corollary discharge could, in and of itself, give rise to conscious perception of movement, intended or accomplished, without the additional participation of afferent input to interact with it. Teuber responded to this by pointing out the long history of development of ideas regarding corollary discharge, dating back to Helmholtz and von Holst. (Granit, in a paper in press, has traced the basic notion to Helmholtz' teacher, Joh. Müller, in his *Textbook of Physiology* of 1840.) Teuber spoke of the enormous disorienting effect of a 'mismatch' between output and the expected (reafferent) sensory input in movements taking place under the sort of abnormal situations used in the laboratory. However, the basic question whether or not the postulated corollary discharge can give rise to conscious perception was unsettled.

Discussing the above question in the light of results of animal experimentation, Rosén mentioned that in both cats and primates there is a pathway carrying muscle spindle primary afferent information to the sensorimotor cortex, with sufficient topographic precision as possibly to underlie spatial discrimination of input from individual muscles. Grillner drew attention to recent results from Russian laboratories which suggest that tracts ascending from the spinal cord in cats show activity during movements even when the limbs are deafferented. This would suggest that the spinal cord is one possible site for interaction between motor commands and sensory input.

Burke, pursuing the same point, mentioned recent evidence of Lundberg that spino-cerebellar tract cells receive input not only from primary afferents and segmental interneurons but from axons descending from supraspinal levels as well. Thus, such cells could well be sites of interaction between motor commands and afferent feedback representing the results of those commands (*cf.* Lundberg^{41,42}).

Granit, by no means doubting the existence of numerous afferent feedback circuits and interactions at several levels, nevertheless held that for conscious sensory interpretation, no further 'corollary discharge' was needed other than the gamma loop, through the spindles and back again to the sensorimotor cortex. He regarded the demanded act as being expressed in alpha-gamma linkage to the muscles, and its accomplishment as being checked by the information returning to the cortex, or possibly partly at a thalamic level.

In reply to a question by Engel, Matthews reviewed some information related to the problem of sensations of phantom limbs. His opinion, based largely on the results of Henderson and Smyth³⁴, was that sensation of movement in phantom limbs was often apparently connected with the ability of the patient to produce contractions in muscle stumps still innervated, and that such sensations therefore probably involved some proprioceptive input. Fine finger 'movements' in an arm phantom were not experienced. Teuber brought up the old observation that patients with phantom limb sensations sometimes experience strange 'flexion' illusions, without concomitant 'extension', and mentioned the possibility that such sensations might be produced by abnormal sensory input originating in peripheral neuromas. Denny-Brown noted a patient in whom a spinal cord injury subsequent to amputation converted flexor phantom illusions into feelings of extension, illustrating the possible importance of purely central mechanisms in these phenomena.

Hagbarth closed this portion of the discussion by illustrating the complexity of proprioceptive illusions with the following example. If, in a completely darkened room, a normal subject swings his arm in an arc around the elbow joint and the arm is stroboscopically illuminated only when it is at 90°, the subject has the strong sensation that he is not really moving his arm at all. On closing the eyes, this illusion immediately disappears. Increasingly refined observation and analysis of such illusions may provide ideas which can be tested in more constrained laboratory situations.

Section V. Movement in deafferentation

Discussion of the role of sensory input to motor control must include consideration of the quantity and quality of movement possible following removal of all sensory feedback from the moving limb. The subject of deafferentation was taken up by Ommaya, who reported results of experiments done in collaboration with Bossom⁵ on prism adaptation in monkeys, both normal and with cervico-thoracic deafferentation (C2 through Th4). Normal animals, placed in a situation in which food was visible through a hole in an otherwise obstructing plate, easily reached the food without being able to see their arms. When vision was distorted by prism glasses fitted to a hood which prevented the monkey from seeing his arms, there was apparently no

'adaptation' to the situation and the monkeys consistently missed getting the food as long as they never caught sight of their arms or fingers. However, if the animals were permitted to see their fingers through the hole ('terminal display'), there was very rapid adaptation to the visual distortion and the number of successful trials went up rapidly. After extensive deafferentation of the arms by dorsal rhizotomy, exactly the same results were obtained as in the normals, in terms of the ability to correct for visual distortion given a visual clue as to the position of the reaching arm. Ommaya concluded that visual information as to the results of movement were paramount for adaptation in this situation and that proprioceptive input apparently contributed little to solving the problem.

Ommaya discussed the point that animals with deafferented limbs can certainly move them, given time for 'reintegration' and sufficient encouragement and retraining. This is particularly true of bilateral rhizotomies, as also emphasized by Taub⁵⁶. Although movement in such monkeys is not normal and there are usually considerable deficits in finger movements, some movements can be rather precise. Ommaya discussed recent results of experiments done in collaboration with David Levine at NIH in which monkeys with bilateral rhizotomy from C2 through Th4 were trained to squeeze a rubber bulb taped into one hand in order to obtain a juice reward. Restraints were designed such that only finger squeeze produced the required output and animals were trained to produce pressures maintained within specified pressure 'windows'. It was found that such deafferented animals could produce very accurately controlled finger pressure and in fact were as good at the task as normal monkeys. The animals had no feedback as to the amount of pressure being produced; they simply were rewarded or not depending on their success at maintaining the specified pressure. Such results suggest that, in some situations, quite precise control over muscle activity is possible without any feedback graded in terms of the results of the contraction. Frank, however, mentioned the possibility that finger muscle output might be tightly coupled with some other action such as jaw muscle contraction (*e.g.*, 'gritting the teeth') and, if so, the animal could gauge his hand effort via the uncut afferents from the jaw muscles.

Wiesendanger did not doubt that deafferented monkeys could be trained to do a great deal, even to producing finger apposition after prolonged retraining, but noted that a persistent deficit in such animals is an apparent inability to maintain constant activity or posture of the affected limb. In EMG studies of cervico-thoracic deafferented monkeys, Wiesendanger and coworkers noted that the normal sustained firing of motor units was replaced by bursts of activity resulting in small ballistic movements. Movement deficits in such animals are more noticeable in extensor muscles than in flexors, in just those muscles which Phillips and coworkers¹⁵ have found to possess motoneurons richly supplied with both spindle primary afferent and corticomotoneuronal connections.

Denny-Brown thought the results of such work to be of great theoretical importance but questioned the completeness of deafferentation by the methods used by Ommaya and others. He and Kirk had shown that the dermatome distribution of afferent inflow from a particular part of the body surface apparently becomes en-

larged after a subconvulsive dose of strychnine or after cord section. Such observations imply that the distribution of afferents in dorsal roots may be more extensive than is demonstrable under the usual experimental conditions. He noted that all work with deafferentation has shown that even very limited surviving afferent inflow greatly reduces the deficits produced by the operation. Denny-Brown noted that the finger movements in monkeys after deafferentation were not simple grasps but rather clawing movements involving projection of the whole limb, including shoulder musculature. Such animals, however, can place and walk more or less naturally on all four limbs. He recounted earlier results with Gilman, showing that abnormal postures and changes in muscle tone after cortical lesions and unilateral decerebration are unmodified by deafferentation, implying that such changes depend primarily on influences directly impinging on alpha motoneurons.

Taub suggested that incomplete deafferentation such as postulated by Denny-Brown could not really explain the observations made since complete deafferentation in monkeys, done in several stages and eventually involving all of the dorsal roots, left movements in the initially deafferented forelimbs essentially unchanged. Taub noted that, in his experience, individual finger movements were possible, including opposition of thumb and forefinger⁵⁶. Such results depend very much on intensive and prolonged retraining, a point also made by Ommaya. Taub said that deafferentation of infant monkeys on the first day of extrauterine life produced animals which developed all of the movements exhibited by older monkeys deafferented in adolescence, so that proprioceptive feedback did not appear necessary for formation of motor patterns. However, these animals did have visual feedback of limb position.

Taub discussed his own recent experience with prism adaptation in deafferented monkeys. His results were basically similar to those of Ommaya and Bossom but Taub found that after adaptation had taken place and the prism glasses were removed, there was persistence of misdirected movements in deafferented animals which lasted up to 5 times longer than in normal animals. He interpreted this result to mean that since the animals were primarily dependent on visual feedback for success, this modality of input dominated performance to such an extent that persistent aftereffects were quite marked. Taub also recounted experiments dealing with force gradation in deafferented limbs and noted that in situations in which the animal had to flex a limb against increasing loads to avoid shock, normal animals learn quickly to flex but deafferented animals do not, as long as there is no clue to successful performance. However, when a buzzer is sounded at the point when the animal has flexed sufficiently to avoid shock, it adapts quickly. He noted that this result, and that of Ommaya and Levine, suggest that animals can compensate for various loadings during voluntary movements given very tenuous clues as to the results of effort, but that such clues must be present in some form, although they need not be graded with effort.

Teuber, commenting on the prism experiments of Ommaya and Bossom, pointed out that with enough persistence the intact monkey will adapt even in the absence of the 'terminal display' visual feedback. He also drew attention to the 'functional' deafferentation which appears to occur in some situations, such as rearing monkeys in padded chairs in which they cannot see their hands. Fine reaching and

finger movements do develop but when the animal first sees his hand, he is incapable of using it in visually guided movements. However, visually guided activities then develop in 7-9 days.

Both Marsden and Ward questioned whether the results of animal experimentation really applied to man with regard to deafferentation, since it had been their experience that the rare patients with dorsal rhizotomies had never been known to recover motor function in the fingers of the affected limbs. Taub pointed out that such cases invariably involved unilateral deafferentation in which the animal results also showed little return of function without special conditions. Ommaya affirmed the view that the retraining of such patients must be not only intensive but also directed specifically at making the affected limb do the work, rather than trying for most effective use of the entire motor apparatus which is the philosophy underlying much of rehabilitation of patients with motor deficits.

Section VI. Cortical mechanisms in motor control

In discussing his experiments, Marsden had raised the following questions: What exactly is the motor cortex asking of the muscles? How accurate are the instructions it issues to the spinal cord? What is the role of the cerebellum? Phillips pointed out that, with techniques of recording neuronal activity during voluntary movements in monkeys (*cf.* Evarts²³), it has been shown that the motor cortex, the cerebellum, the basal ganglia, thalamic nuclei and other structures all possess neurons which are active in advance of movements. It is therefore impossible to remove the motor cortex from its neurophysiological context in seeking answers to the many questions now clamoring for attention.

Phillips nevertheless decided to isolate the motor cortex for discussion and did so in order to ask whether there is anything it may uniquely contribute to movements and whether it has anything in terms of functional mechanisms which other structures do not possess. Reviewing results from one of the classic approaches to these questions — that of lesion making — Phillips noted that the results of pyramidotomy are relatively clean-cut. The hand loses its normal reactions to contact and placing, and precise finger movements and independent activity of fingers and thumb are also lost. Speed of motor reaction in a reaction task is very much slowed⁴⁰. Such observations are not only found in adult animals deprived of pyramidal tract but also in animals developing motor patterns after pyramidotomy in infancy^{40a}.

Denny-Brown noted that the grasp lost after pyramidotomy is the 'instinctive grasping' response to contact stimulation of the palmar surface of the fingers. Gilman further noted that this sort of grasp depends on cutaneous contact, and that the 'traction' response elicited by slight pulling or stretch of the fingers is preserved after pyramidotomy.

Denny-Brown described results of ablation of sensorimotor cortex in infant monkeys on the development of motor behavior. Bilateral ablation of area 4, or of both pre- and postcentral cortex, leads to no grossly observable deficit in motor

patterns in the first 3 months of life. Later, however, development of normal patterns of reaching and palpation is delayed but not abolished, and such movements are entirely visually guided: blindfolded animals show none of them. Wider ablations lead to spasticity of the lower limbs but not the upper, which are still used in visually guided movements. However, when lesions include the most posterolateral portion of the parietal lobe, spastic quadriplegia results, suggesting that the posterior parietal cortex, a region of strong visual projection, somehow 'protects' the upper limbs from spasticity at least when the eyes are open. Denny-Brown also described another vision-associated mechanism related to extrapyramidal motor control. Localized bilateral lesions in the posterior putamen lead to a state in which the animal has no visually guided placing or reaching, no optical righting in a fall, and yet appears acutely aware of his visual surroundings.

Phillips reviewed Kuypers' descriptions of the anatomical destination of projections from the sensorimotor cortex in primates (*cf.* Kuypers³⁸; Kuypers and Brinkman³⁹), pointing out that such evidence suggests that quite a large portion of the cortical outflow is directed to regions involved in processing afferent information, both in the brain stem and in the spinal cord. This appears to be a phylogenetically old system. Turning to the projections which appear to be organized for more direct control of motor output, Phillips noted the existence of phylogenetically old bilateral projections to the midline pontine reticular formation, which projects in turn bilaterally to the most medial parts of the ventral horn and thus appears organized for control of the trunk and of proximal segments of the limbs. Then, there is a bilateral but predominantly contralateral projection to the lateral reticular formation and to neurons of the intermediate region of the spinal cord, an anatomical organization which may underlie cortical control of reflex transmission such as has been extensively studied by Lundberg. Lastly, Phillips described the direct corticomotoneuronal projection from precentral cortex, connecting bilaterally with trigeminal motor nuclei, unilaterally to the contralateral facial nucleus and also contralaterally to the lateral groups of spinal motoneurons which innervate distal muscles of the limbs. In particular, he stressed the dense corticomotoneuronal projection in primates to cells innervating musculature of the hand. This system has been shown to increase rapidly in ascending the phylogenetic scale in the primates, and in the higher primates such as gibbon and chimpanzee the direct corticomotoneuronal fibers make up about half of the pyramidal endings in the spinal cord. In man, the figure may be even higher.

In physiological experiments on the direct corticomotoneuronal system in the monkey, Phillips and coworkers noted that cortical colonies of cells projecting to single motoneurons were of two types, one relatively diffuse and the other quite localized into narrow columns of cells (*cf.* Phillips⁴⁸). The former appear to be activated most effectively by surface stimulation while the latter have been investigated with great profit by intracortical microstimulation, such as used by Asanuma and coworkers³. Briefly reviewing the results of Asanuma and his colleagues, Phillips noted that restricted columns of cells projected to specific muscles or to synergist groups and that such groups were especially evident with finger muscles. Colonies of cells projecting to elbow or wrist were much fewer. Of particular importance is the finding that

such motor cell columns, concerned with a given specific movement, receive afferent input from skin, joint and probably muscle spindle secondary afferents with localized receptive fields clearly related to the direction of movement produced on micro-stimulation. Some columns appear organized to produce only one movement, for example, thumb abduction. In other cases, several movements of a given finger may be produced by stimulation of different regions in a given cortical column. Phillips noted that the afferent pathway from periphery to motor cortex appears to be quite direct, with latencies corresponding to trisynaptic organization. Thus, a relatively powerful and direct pathway exists carrying afferent information spatially organized in accord with the movements produced by a particular column of cells in the motor cortex.

Rosén agreed with the above summary of his results with Asanuma^{2,50} and provided further documentation. He noted, as had Phillips, that there is no evidence for a significant input from muscle spindle primary afferents to cells in area 4 in the primate, while spindle secondaries do seem to project there. Rather, spindle primaries project to area 3a and the evidence was reviewed by Phillips. Wiesendanger confirmed this conclusion with observations from recent experiments employing succinylcholine to activate spindle primary afferents selectively in the baboon. Wiesendanger noted that there is multimodal convergence of afferent input onto cells in the motor cortex, including both skin and muscle afferent input, and this point was also evident in the results of Asanuma and Rosén. The observations concerning cortical motor columns were summarized by Phillips using the old analogy of the 'upper motor neuron', considering cell columns with very specific muscle activation to be rather like spinal cord elements 'transplanted' to the motor cortex.

Finally, Phillips discussed motor control of the two hands and the problem of eye-hand coordination. He mentioned especially the results of Brinkman and Kuypers⁶, who studied the problem in complete split-brain monkeys. Blindfolding one eye, they restrained the ipsilateral arm and tested the dexterity of movement in the arm governed by motor cortex in the hemisphere opposite to that receiving visual input. They noted apparently normal visually guided arm movements, picking food from a board. However, when using a special food board on which food could be seen but not palpated, the hand groped dextrously about the board without being able to pick up the food. Releasing the arm controlled from the hemisphere with visual input led to immediate grasp of food pellets. This shows a bilateral organization of arm control by visual input but an apparent unilateral system for control of the distal finger muscles, which appears to be dependent on the direct corticomotoneuronal connections.

Evarts discussed recent observations dealing with the latency of pyramidal and non-pyramidal cell activity related to ballistic arm movements in the monkey. In previous experiments, with monkeys trained to perform a change of force or position in response to a visual signal, Evarts²² had found activity beginning in some motor cortex cells about 100 msec after the onset of the cue light, and the first EMG response occurred at an average latency of about 150 msec. There was little difference in patterns of response between pyramidal and non-pyramidal cortical neurons and thus

the pyramidal neurons cannot be said to be exclusive 'prime movers'.

Evarts then began a variation of this experiment, this time using a sudden movement of the handle grasped by the monkey as the cue to trigger the rapid movement required for reward. Now, with the stimulus applied to the same set of muscles, joints, etc. which also produced the output response, Evarts found that pyramidal tract neurons began to discharge about 25 msec after the stimulus and the EMG response in the activated muscles occurred at about 35 msec latency after the stimulus. He also noted that these remarkably brief latencies occurred only when the monkey appeared to be attending to the task at hand. If the animal's attention wandered, the latencies for both cortical neuron and muscle activation were prolonged. Also visible in the short latency response was a muscle activation at about 15 msec delay, which Evarts attributed to monosynaptic activation of motoneurons by spindle primaries. Evarts noted the evidence for short latency pathways from arm afferents especially to post-central cortex in the monkey and suggested that such pathways were probably utilized in producing the very fast response seen in his experiments.

Evarts then discussed observations of Hammond³³ in which a human subject held his arm in a certain position until it was suddenly and unexpectedly subjected to a pull. The subject was instructed either to resist the pull or to let go. In both cases there was a muscle response at about 20 msec after the stimulus, attributed to spindle primary afferents. If the subjects had been instructed to resist the pull, a strong muscle response occurred after about 50 msec. If the subject had been instructed to let go, a smaller response occurred. Therefore, Hammond concluded that the response at 50 msec was determined by the 'set' of spinal reflex mechanisms based on the verbal instructions given to the subject. Evarts concluded, based on his results with the monkey, that the response to sudden stretch (which was 'plastic' in the sense of being modifiable by instruction of the subject) might have involved pyramidal and motor cortical mechanisms as well as some reflex 'set' localized at the spinal segmental mechanism. He considered that one possible locus for 'setting' the system to respond differently to a given input might be found in the connections between the cortical areas receiving short latency afferent input and the output pyramidal cells.

Sears, commenting on the above, noted that Hammond demonstrated clearly that there was no difference in the monosynaptic 'true' reflex response to the stretch occurring 20 msec after the stimulus, comparing the discharge in the 'resist' *versus* the 'let go' situations. Thus, there did not seem to be any evidence for increased motoneuron excitability in the 'resist' situation, either of alpha or gamma cells. Matthews commented that the latencies seen in Evarts' recent results were perhaps so short as to make pyramidal mechanisms unlikely to contribute, especially since, in the visually triggered task, Evarts had found a 50 msec interval between onset of pyramidal neuron discharge and the onset of EMG activity. Evarts agreed that the latencies were very brief but said that perhaps the difference between the visual and tactile stimulus experiments might partly be explained by an additional spinal 'set' mechanism which could make the motoneurons quite excitable and therefore subject to rapid activation with pyramidal tract input even though such was not apparent in Hammond's human subjects. Sears noted that Phillips and coworkers had observed considerable temporal

facilitation during repetitive activation of corticomotoneuronal synapses (*cf.* Phillips⁴⁸) and brought up the point that motoneurons do considerable integration of synaptic input before discharging. This unusual property of corticomotoneuronal synapses might well be related to the relatively long (50 msec) delay seen between pyramidal discharge and motoneuron activation under the earlier conditions used by Evarts.

Ward began by discussing observations made on patients during electrical stimulation of the brain which produces movement. Stimulation of the motor cortex may lead to movement but the patient always has the clear impression that an external agent provoked it. However, in Ward's experience, stimulation at the thalamic level can produce complex, even semi-purposive movements accompanied by a feeling that something within the individual produced the movement: 'The arm wanted to move.' Such effects are produced by stimulation of the nucleus ventralis lateralis. Ward discussed earlier experiments in cats in which stimulation of this structure leads to cessation of spindle afferent discharge⁵⁴. In man, similar stimulation produces complete inhibition of the contralateral knee jerk. Despite this, however, Ward noted that ventralis lateralis stimulation in the cat can be shown to produce enhanced alpha motoneuron activity and, in the human, accelerated motor movements. Both the effects on gamma motoneurons as well as those on alpha cells apparently depend on the integrity of the motor cortex.

Ward described recent results of Fetz and Finocchio²⁶ which relate to the question of cortical control of muscle groups. In these experiments, monkeys were rewarded for producing different combinations of increased or decreased discharge of motor cortex neurons coupled with either increase or absence of EMG activity in muscles normally associated positively with increased activity in the studied cortical neuron. It was relatively easy to reinforce cortical cell discharge during silence of EMG activity in the apparent target muscles. However, it was apparently more difficult to produce EMG activity in the target muscles and at the same time decrease firing in the associated cortical neurons. At best, the animals showed some decrease in cortical cell firing rate but complete silence was not observed. Ward noted that one interpretation of such data is that cells in the motor cortex are not 'soldered onto' spinal motoneurons but rather there must be some gating mechanism (or mechanisms) permitting some disconnection between pyramidal cell activity and motoneuron response. Evarts concurred and noted that this conclusion was already manifest in the observation that pyramidal and non-pyramidal cells in the motor cortex usually show some spontaneous activity without any muscle activity, especially during sleep.

Frank brought up the point that the functional interrelation between observed cortical cells and the muscles recorded in experiments like those of Fetz and Finocchio has not really been demonstrated. The observation of apparent disconnection may be due, at least theoretically, to the possibility that the cortical cell recorded is actually doing something quite different than controlling the muscles observed. To consider that in such cases the animal has 'learned' to control a single cortical cell would be a considerable overstatement. Teuber questioned whether a conditioned motor behavior can be considered in the same sense as a spontaneous or 'voluntary' movement. This question is clearly related to the question of the influence of the 'set' of the system

discussed by Evarts. The participants agreed that, in making interpretations of results from the experiments of Evarts, Fetz and others, one must be cautious in interpreting temporal correlations between neuronal activity and muscle activity as final evidence of functional relation. Obviously, cells in the motor cortex play an important role in hand and arm movement in primates, but the available evidence indicates that these 'upper motor neurons' operate on lower motoneurons as statistical collections of active cells, projecting their functional control in concert with, and perhaps through, other mechanisms operating at other levels of organization which are only beginning to be investigated in awake, behaving animals.

Section VII. Prospects and ethical aspects of experimentation in man

As should be clear from the preceding material, a good deal of discussion at the Conference centered around results obtained from experiments performed on human subjects. Such procedures included recording muscle activity during contraction or stretch at one end of the scale, to stimulation as well as recording in the brains of conscious human patients during craniotomy at the other. In calling for ideas on fruitful future pathways for research in motor control, the Organizing Committee felt it important to deal with the problem of the ethical aspect of human experimentation, in addition to technical questions of the scientific merit of certain approaches and the methods available to pursue them.

Dimitrijevic discussed the results of his group, studying patterns of reflex activity and their modification with repetitive stimulation in chronic spinal human subjects (*cf.* Dimitrijevic¹⁹). These studies were done with a highly selected group of patients with clinically complete cervical or thoracic spinal lesions leading to spastic paraplegia. Dimitrijevic discussed the rigid criteria used for selecting patients and the care with which their differing situations must be evaluated so that reasonable conclusions can be drawn from observations on members of the group. He emphasized the essentially innocuous nature of the experimental procedures used, with skin stimulation and recording techniques and mechanical evaluation of muscle responses. Using standardized techniques, these experiments have yielded considerable data on the habituation of reflex responses in spinal man.

Van Buren discussed the ethics of human experimentation, dividing experimental situations into 3 categories: (1) innocuous procedures; (2) definitely noxious procedures; and (3) borderline cases. He noted that our society prohibits procedures which are obviously noxious to the subject. The problems arise with the 'borderline' situations. He noted that we really have no medico-legal basis for doing research on man at all. However, we must not therefore cease investigative work but it should be clear that, in its most basic aspect, the ethical responsibility for human experimentation lies with the conscience of the investigator. The investigator can, however, use certain procedures to share some of this burden. One is the so-called 'informed consent' of the subject, a matter which still depends very much on the actions and the conscience of the investigator involved. Another mechanism for sharing responsibility is the peer review system, and Van Buren detailed the levels of review presently operative within

the NIH with regard to human experimentation. However, he pointed out that even with this partial sharing, ultimate responsibility still rests with the investigator.

Frank began his contribution by discussing developments currently in use or in advanced stages of development by which neural control is exercised on an external device. This area of discussion contains some clear examples of the carry-over of information from basic research into applied developments. He spoke of 'functional neuromuscular stimulation', in which externally generated electrical currents are delivered to weakened or denervated muscles in order to cause contraction. Functionally useful contractions can be achieved through proper system design, as in the heel switch device developed in Ljubljana, Yugoslavia for aiding stroke patients with gait disturbance. An interesting sidelight from this work is that, after a period of walking with the artificial assistance of the heel switch device, many patients note an increased facility even without it. This may relate to the changes which can occur in the morphological and histochemical characteristics of muscle fibers with long term electrical stimulation of paretic muscles, leading to increasing fatigue resistance and concomitant biochemical changes in the muscle fibers. Studies are underway, for example in Cleveland, to determine the optimum schedule for stimulation of paretic muscles which will hopefully lead to further refinement of techniques for effective utilization of muscles which patients may have but cannot control.

Frank dealt at some length with the problem of obtaining signals from the nervous system with which to control external devices, such as prostheses or neuromuscular stimulation apparatus. For many years, simple 'on-off' control, using an existing muscle contraction as a trigger, has been used to control one function of a device, such as opening and closing a pincer prosthesis. More sophisticated control is possible using patterns of electrical activity directly recorded from several active muscles. For example, the Moss Rehabilitation Hospital group in Philadelphia has for some time been developing an arm prosthesis which is controllable through patterns of activity in the remaining shoulder musculature of an upper limb amputee. The very important point with this device is that an inexperienced individual can learn to control the complex prosthesis quite readily, since the designers have constructed the system to respond appropriately to patterns of shoulder muscle activity which normally occur during arm abduction, flexion, etc. Frank noted that an important rule in thinking in this area is: 'Use everything you can about the organization of the nervous system which is already there.'

Going further with the idea of outward transfer of information from the nervous system, Frank discussed the possibilities for direct recording of usable signals from the central nervous system itself, citing the experiments of Evarts and others as possible models. In work at NIH in Frank's laboratory, a group has been exploring the possibility that the firing patterns of multiple cortical cells might be used to control a device and have shown that such spike trains, suitably processed, do contain information which can be used to predict the position and force of arm movement in the monkey (Humphrey *et al.*³⁶). Coupling this with the results of Fetz and Finocchio described by Ward (above), Frank suggested that an animal, or a man, might be able to control the firing patterns of cortical neurons so as to control external devices even

if the interface system were imprecisely matched. He suggested further that this direction of development of applied neurophysiology is both necessary and inevitable. For this reason, careful consideration must be given to the ethical consequences of such development and the human experimentation possibilities contained.

When asked about his ideas on the ultimate goals of such technological developments in the area of neural control, Frank noted that what we must be considering now are probable outcomes at some time in the relatively distant future. There is little question that applied neurophysiology directed toward improved rehabilitation of hand-capped patients is a socially useful goal at the present time. With regard to other developments, one may conceive of devices to extend the physical and mental capacities of normal individuals. Although such goals smack of science fiction at the moment, he felt it legitimate to consider that future societies may well require such developments. To negate such a possibility would in his view imply an ability to predict future conditions beyond our present capacity.

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