

JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN
1958

THE DISCRETE AND THE DIFFUSE
IN NERVOUS ACTION

DAVID P. C. LLOYD

THE AMERICAN MUSEUM OF NATURAL HISTORY
NEW YORK: 1959

JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN

JAMES ARTHUR LECTURE ON
THE EVOLUTION OF THE HUMAN BRAIN
1958

THE DISCRETE AND THE DIFFUSE
IN NERVOUS ACTION

DAVID P. C. LLOYD

*Member and Professor
The Rockefeller Institute
New York, New York*

THE AMERICAN MUSEUM OF NATURAL HISTORY
NEW YORK: 1959

JAMES ARTHUR LECTURES ON THE EVOLUTION OF THE HUMAN BRAIN

- Frederick Tilney, *The Brain in Relation to Behavior*; March 15, 1932
- C. Judson Herrick, *Brains as Instruments of Biological Values*; April 6, 1933
- D. M. S. Watson, *The Story of Fossil Brains from Fish to Man*; April 24, 1934
- C. U. Ariens Kappers, *Structural Principles in the Nervous System; The Development of the Forebrain in Animals and Prehistoric Human Races*; April 25, 1935
- Samuel T. Orton, *The Language Area of the Human Brain and Some of its Disorders*; May 15, 1936
- R. W. Gerard, *Dynamic Neutral Patterns*; April 15, 1937
- Franz Weidenreich, *The Phylogenetic Development of the Hominid Brain and its Connection with the Transformation of the Skull*; May 5, 1938
- G. Kingsley Noble, *The Neural Basis of Social Behavior of Vertebrates*; May 11, 1939
- John F. Fulton, *A Functional Approach to the Evolution of the Primate Brain*; May 2, 1940
- Frank A. Beach, *Central Nervous Mechanisms Involved in the Reproductive Behavior of Vertebrates*; May 8, 1941
- George Pinkley, *A History of the Human Brain*; May 14, 1942
- James W. Papez, *Ancient Landmarks of the Human Brain and Their Origin*; May 27, 1943
- James Howard McGregor, *The Brain of Primates*; May 11, 1944
- K. S. Lashley, *Neural Correlates of Intellect*; April 30, 1945
- Warren S. McCulloch, *Finality and Form in Nervous Activity*; May 2, 1946
- S. R. Detwiler, *Structure-Function Correlations in the Developing Nervous System as Studied by Experimental Methods*; May 8, 1947
- Tilly Edinger, *The Evolution of the Brain*; May 20, 1948
- Donald O. Hebb, *Evolution of Thought and Emotion*; April 20, 1949
- Ward Campbell Halstead, *Brain and Intelligence*; April 26, 1950
- Harry F. Harlow, *The Brain and Learned Behavior*; May 10, 1951
- Clinton N. Woolsey, *Sensory and Motor Systems of the Cerebral Cortex*; May 7, 1952
- Alfred S. Romer, *Brain Evolution in the Light of Vertebrate History*; May 21, 1953
- Horace W. Magoun, *Regulatory Functions of the Brain Stem*; May 5, 1954
- Fred A. Mettler, *Culture and the Structural Evolution of the Neural System*; April 21, 1955
- Pinckney J. Harman, *Paleoneurologic, Neoneurologic, and Ontogenetic Aspects of Brain Phylogeny*; April 26, 1956
- Davenport Hooker, *Evidence of Prenatal Function of the Central Nervous System in Man*; April 25, 1957
- David P. C. Lloyd, *The Discrete and the Diffuse in Nervous Action*; May 8, 1958

THE DISCRETE AND THE DIFFUSE IN NERVOUS ACTION

Nearly 70 years ago the eminent Spanish histologist Cajal announced a series of physiological inductions concerning the fundamental structure of the spinal cord. Among these were schemata, reproduced here in figure 1, of what have by virtue of the French edition of his monumental work (1909, 1911) come to be called "*les réflexes unilatéraux circonscrits*" and "*les réflexes unilatéraux diffus*." To the left of figure 1 one sees the circumscribed mechanism in which afferent nerve fibers entering the spinal cord make direct connection with motor nerve cells over a limited or localized region of the spinal cord. To the right one finds the diffuse mechanism represented with an internuncial nerve cell intercalated between afferent and motor nerve cells, it extending up and down the spinal cord to bring the afferent influence to a much-extended field of motor nerve cells. Fifty-three years passed before the actual physiological significance of these schemata became apparent, and, in fact, it would seem that they were largely ignored in the interim. In a way it was not too surprising that this should have been so, for the physiological constants of nerve fibers and of nerve cell junctions were insufficiently known, and the apparatus of the physiologist was strained to and beyond its power of resolution in the attempt at analysis of the central machinery of reflex action.

The new era began when Gasser and Erlanger (1922) successfully employed the Braun tube as an inertialess instrument for the recording of nerve impulses. With its use the conduction velocities of various types of nerve fibers have been learned, as has the time consumed in the transmission

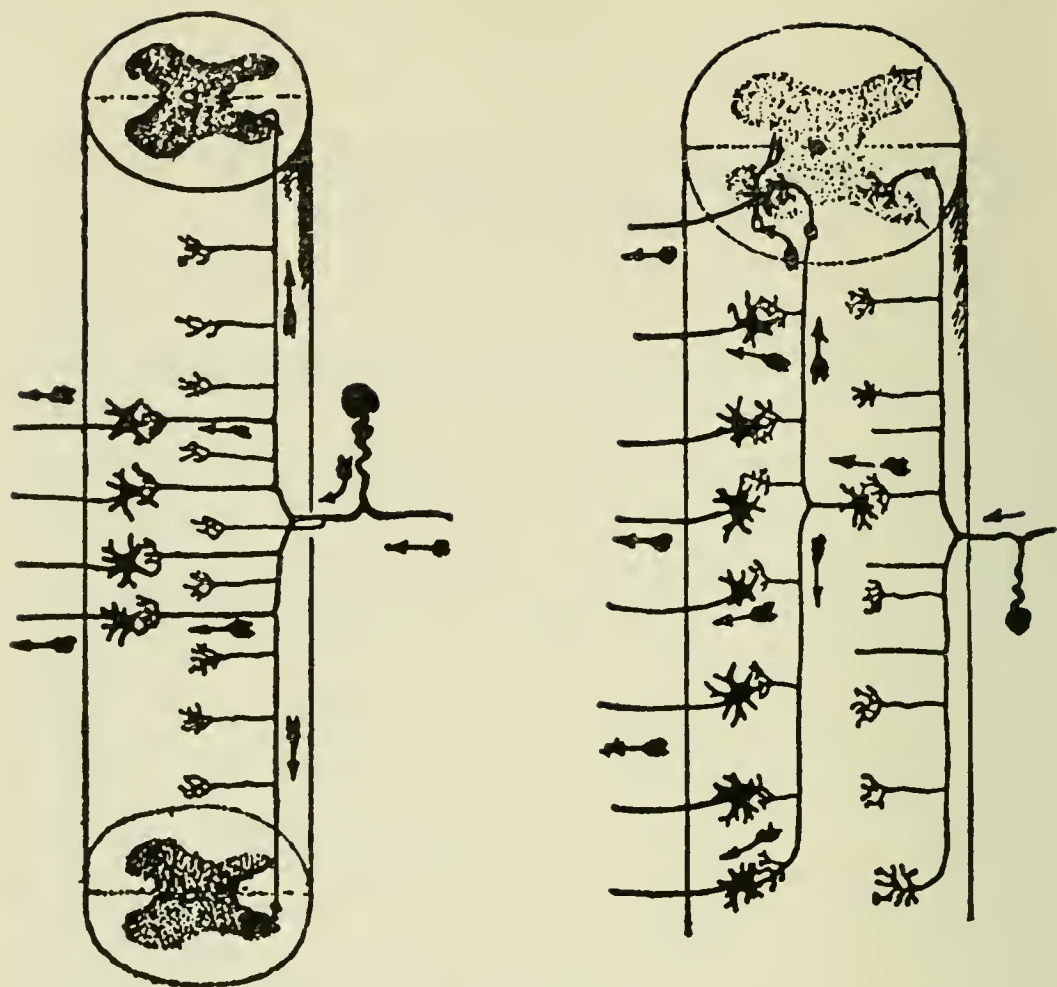


FIG. 1. Diagrams by Cajal, first published in 1890, in which he represented the concepts of the circumscribed and diffuse reflex mechanisms. Arrows indicate the direction of conduction from afferent fibers entering the spinal cord directly to motoneurons and so out again (left diagram), or from afferent fibers to an interneuron and thence up and down the spinal cord to a wide field of motoneurons which in turn conduct outwards (right diagram). Modified from Cajal, 1909.

of excitation from one nerve cell to another. In essence the cathode ray oscilloscope and associated paraphernalia have permitted the physiologist to say not only “where” but “when” with sufficient accuracy to establish the functional significance of the Cajal schemata. And there can be no doubt as to their functional significance.

Today one would refer to the two schemata of Cajal as the monosynaptic reflex arcs and the polysynaptic reflex arcs, respectively—terms that do not contain built into their meaning the notions of discreteness and diffuseness. This, historically, perhaps was unfortunate, for in the end the

qualities of discreteness and diffuseness rather than those of monosynapticity and polysynapticity provided the essential clue to the functional meaning of Cajal's schemata. It was this notion that led to the selection of my title for the present James Arthur Lecture and that prompted the thoughts, musings, reflections, and speculations that comprise a goodly measure of its content. In bringing these before you, I hope that I shall not in any way do injustice to the honor conferred on me by invitation to deliver one in this distinguished series of lectures.

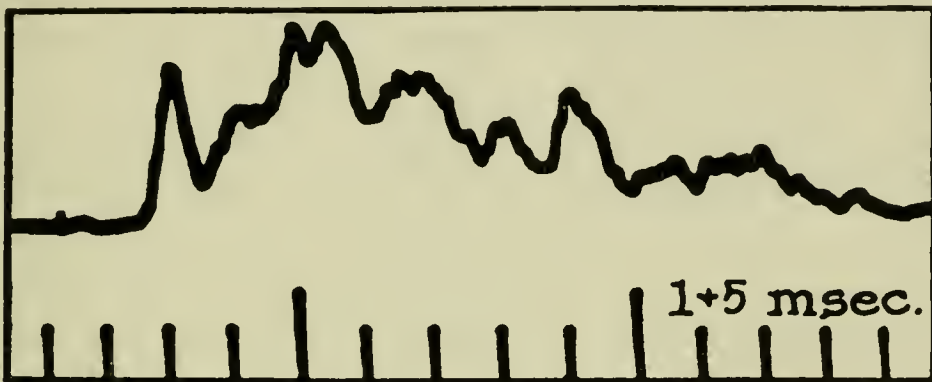


FIG. 2. Segmental spinal reflex discharge evoked by single shock stimulation of a dorsal root and recorded by cathode ray oscilloscope from the ventral root of the same segment. The initial upward "spike potential" denotes transmission of impulses through reflex arcs of two neurons in series: the afferent neuron and the motoneuron. The remaining irregular deflections denote transmission through more complicated (polysynaptic) reflex arcs. From Lloyd, 1955.

Let us consider now a functional picture of the circumscribed and diffuse mechanisms. Figure 2 contains an oscillographic tracing of the reflex output of a segment of the spinal cord thrown into action by a single stimulus to its dorsal or afferent root. The output is recorded from the corresponding ventral or motor root. There is, first of all, a small deflection signaling the instant of stimulation. Next there is a "spike-like" action potential indicating the discharge of a well-synchronized volley of nerve impulses, and finally an enduring irregular wave indicative of a shower of nerve impulses rather than of a volley. Following upon the precise determinations by Lorente de Nó (1935) of the

time required for the transmission of excitation from one nerve cell to another (so-called synaptic transmission), one can state with confidence that the initial spike-like action relates to reflex transmission through an arc of but two neurons in series length (Renshaw, 1939). Employing the same constant of time, one concludes that the remainder consists of discharge through reflex arcs containing more than two neurons in series.

Figure 2 is a functional picture in one sense, but an anatomical one in another. It demonstrates that transmission through the spinal cord of actual nerve impulses does, indeed, occur in the manner predicted by Cajal's diagrams, and in this sense it is functional. On the other hand, from the point of view of reflex physiology it is anatomical, for the dorsal root is an anatomical collection of afferent fibers subserving a variety of reflex functions, and the reflex result from stimulation of it accordingly must be an incoordinate mingling of divers actions. What is more, it says nothing concerning the essence of Cajal's inductions, which lies in the words "*circonscriit*" and "*diffus*."

Some type reflexes

The problem now is to make a functional dissection of the segmental reflex to isolate its components. But before such an analysis is undertaken, it is germane to consider briefly a few of the ipsilateral reflexes that might be represented in the result of dorsal root stimulation as it appears in the recording illustrated in figure 2.

If a limb be flexed passively, it is found to resist the externally applied force by means of extensor muscle contraction that is reflex in origin. This was called by Sherrington the stretch reflex. It was analyzed in terms of muscle contraction by Liddell and Sherrington (1924, 1924) in two papers that are models of scientific thought, execution, and presentation. Pertinent for the present purpose among the findings were that the reflex contraction was confined to the

muscle stretched; that the reflex was "dead-beat," contraction ceasing abruptly with relief from the imposed stretch; and that the stretch contraction was inhibited by traction on the antagonist of the muscle under examination. Liddell and Sherrington concluded that the central pathway must be simple, but the degree of simplicity could not be assessed, nor did they attempt so to do.

If, now, the flexion imposed upon the limb be increased from that which evokes reflex opposition to reach a degree potentially harmful to the stretched muscle fibers, the "over-stretched" muscle, an instant before engaged in strong contraction, suddenly gives way. The giving way is of reflex origin; the stretched muscle is inhibited, its antagonist oftentimes displaying, coincident with its relaxation, a brief contraction. This "inhibitory" reflex is called the lengthening reaction; it is stretch-originated, as is the stretch, or myotatic reflex, it countermands.

If, finally, the limb comes into contact with some source of hurt, it is withdrawn, the action, reflex in nature, being a generalized contraction of the flexor musculature of the limb. This, briefly, is the flexor reflex.

What I have just said concerning these three reflexes, so well seen in the decerebrate preparation, was well known years ago, and it seems at first glance surprising that the rather obvious correlation between the qualities of these reflexes and the anatomical qualities of Cajal's reflex pathways seemingly was not made. What more appropriate mechanism for the stretch reflex than Cajal's "*réflexe circonscrit*"? What more appropriate for the flexor reflex than the "*réflexe diffus*"? But things that may seem so obvious to one generation are not infrequently far from being so to its predecessors. Also, there were road blocks in the way to confuse the issue. I mention but two. Prior to 1939, when physiological experiment confirmed the existence of monosynaptic reflex pathways in the spinal cord, anatomical study had not always done so, and the weight of opinion appears

to have been against the existence of "*collaterales réflexomotrice*" extending from the dorsal root fibers to form direct connection with motoneurons. On the other hand, the most painstaking and careful analysis of the flexor reflex then possible, that by Eccles and Sherrington in 1931, had suggested that its latency, when facilitated, was so short as to indicate transmission by monosynaptic as well as polysynaptic reflex paths. Is it any wonder, then, that the significance of Cajal's inductions was lost? Not until the early 1940's were the road blocks cleared so that the high road to discovery could be resumed.

The spinal mechanisms of elementary reflexes

The first step in dissecting the anatomical segmental reflex into its functional components was to shift one's stimulating electrodes from the dorsal root to peripheral nerves, where the afferent supply from muscle and from skin could be stimulated in isolation, one from the other. When this was done (Lloyd, 1943a) the monosynaptic reflex discharge into a ventral root was found only on the occasion of stimulating muscular afferent fibers, the character of response being exemplified in record A of figure 3. Absent when the cutaneous nerves were stimulated, there was nevertheless a copious polysynaptic reflex discharge, as seen in record B of figure 3.

Once the monosynaptic and polysynaptic reflex discharges had been segregated one from the other, and the former demonstrated clearly to be muscular in afferent origin, the latter largely cutaneous, the major road block was removed and the way open to further experimentation. It was then that a logical hypothesis could be constructed and put to test. If the monosynaptic reflex pathway was indeed that of the stretch reflex, then monosynaptic reflex discharge should, because of the circumscribed nature of the stretch reflex, be found confined to the motor fibers of the muscle nerve subjected to stimulation, and not in the nerves to

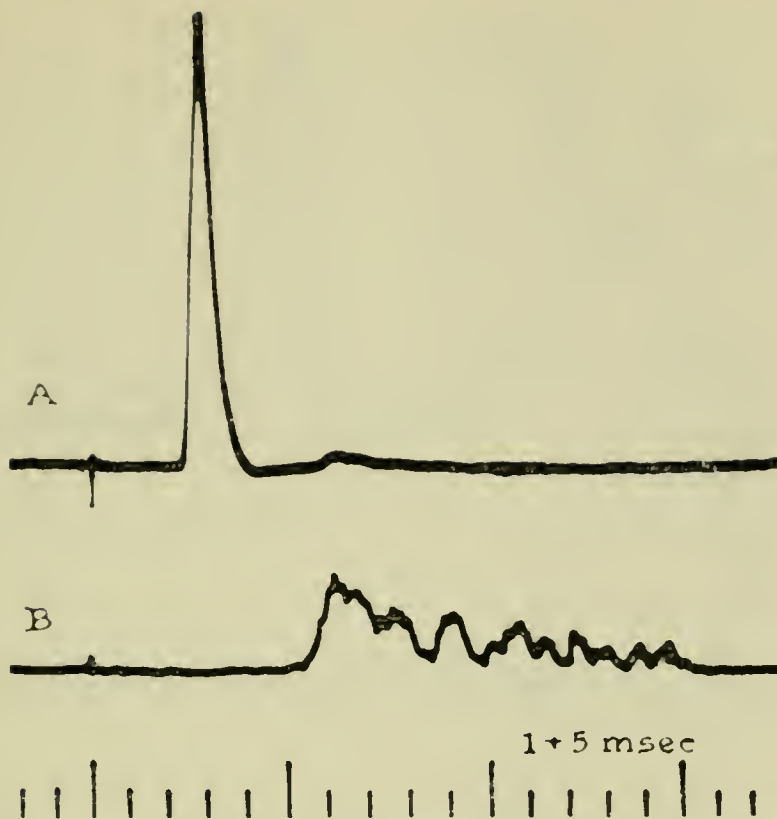


FIG. 3. Reflex discharges recorded in a ventral root following single shock stimulation of afferent nerve fibers from muscle (record A) and from skin (record B). The monosynaptic reflex discharge, yielding a sharply synchronized "spike potential," is seen only in record A. A small polysynaptic reflex results also from stimulation of the muscle afferent fibers, but is much more prominent following stimulation of the cutaneous afferent. After Lloyd, 1943a.

other neighboring muscles. This proved to be the fact (Lloyd, 1943b), as illustrated by figure 4 wherein one sees, indicated by the break in the tracing, a recording of the afferent volley conducted directly in the nerve from stimulating to recording electrodes, followed after a brief interval by the monosynaptic reflex volley, the reflex nature of which is proved (fig. 4B) by the fact of its disappearance following interruption of the central reflex pathway.

But this was not enough really to establish the monosynaptic reflex pathway as that of the stretch reflex. It was necessary to show that the adequate stimulus (muscle stretch itself) provokes a discharge demonstrably monosynaptic in character. Experiments such as that exemplified in figure 5 provided the requisite demonstration. The uppermost re-

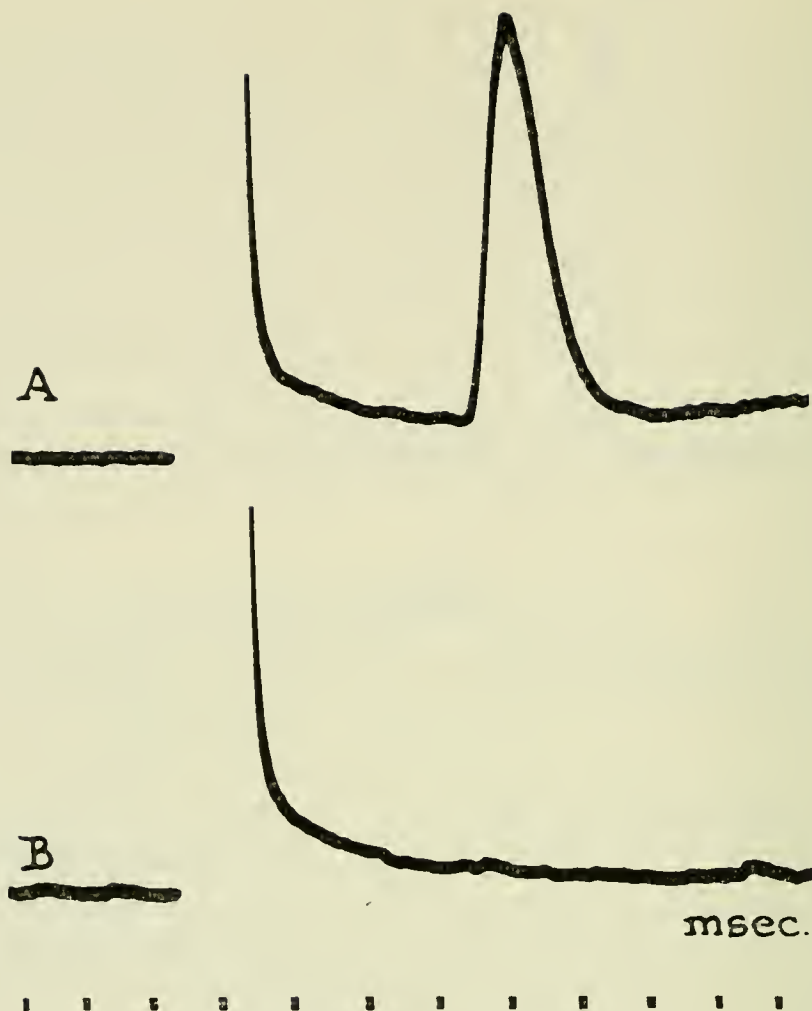


FIG. 4. Reflex result of stimulating and recording from the same muscle nerve. In record A the directly conducted volley is followed, after 4 milliseconds, by a monosynaptic reflex volley. In record B the monosynaptic reflex volley has been abolished following severance of the dorsal roots. After Lloyd, 1943b, 1952.

ording (fig. 5A) contains the afferent response to a brief sudden stretch, comparable to, yet even more restricted in time than, the blow of the physician's reflex hammer upon one's unsuspecting knee-tendon. The next record (fig. 5B) contains a known monosynaptic reflex as it appeared in a ventral motor root in response to electrical stimulation of the afferent path at the exact point from which the afferent response to stretch was recorded. The lowermost record (fig. 5C) contains the stretch-evoked reflex identically recorded. Because the sum of the latencies in the upper two recordings equals the latency in the third, monosynapticity of the stretch-evoked response is proved.

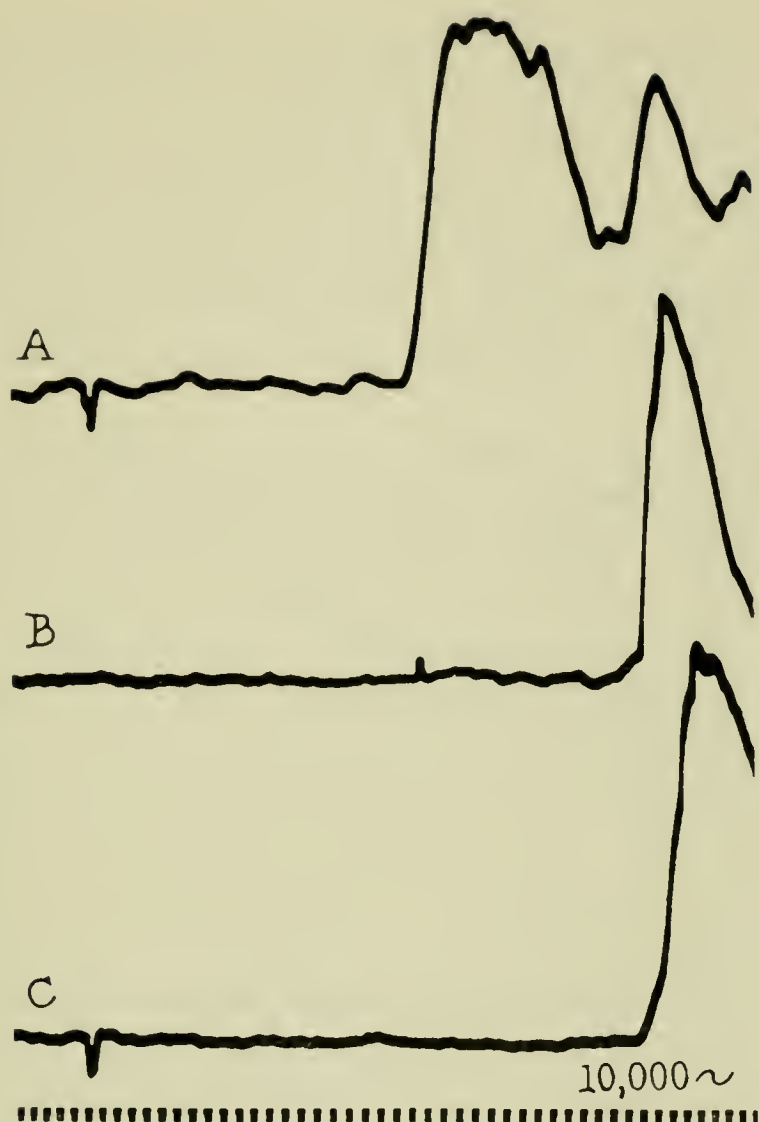


FIG. 5. Proof that the adequate stimulus (stretch) evokes a monosynaptic reflex. Record A, afferent responses to stretch of m. gastrocnemius. Record B, known segmental monosynaptic reflex. Record C, monosynaptic reflex response to stretch. The latencies of A and B equal the latency of C, constituting the proof. After Lloyd, 1943c, 1952.

The myotatic unit

Much action takes place within the nervous system that is, in a manner of speaking, "silent" with respect to the external world. Subliminal excitation and inhibition occur at the motor nerve cell, to be revealed externally only by a change in magnitude of some test of the motor nerve cell's excitability. A monosynaptic reflex can be employed to provide just such a test. Being of a certain amplitude when

elicited in isolation, it is increased if subliminal excitation be present, decreased if inhibition be the influence. As Granit wrote in 1950, "The full theoretical significance of the analysis by means of the monosynaptic volley should not be missed. If, for instance, the test shock finds the motoneurons inhibited, then. . . . This inhibition has ultimately by some central mechanism been applied on to the motoneuron itself."

If one searches through the monosynaptic paths of a variety of limb muscles, as, in fact, was done some 12 years ago (Lloyd, 1946a, 1946b), with the use of them in pairs, one to test what change the other might, or might not, have wrought upon the motoneurons it commands, a pattern emerges. Briefly put, if the pairs are derived from two fractions of a muscle, or are full synergists at a given joint, the action of one upon the response of the other is in the direction of increase. There is facilitation of response indicative of excitatory convergence, by time relations demonstrably monosynaptic. The course of facilitation at the motoneuron level is presented in figure 6, plotted in terms of reflex amplitude on the ordinates and time on the abscissae, zero time being set at coincidence of the convergent volleys. Facilitation is greatest when conditioner and test are coincident at the motor nucleus; it diminishes with time in a characteristic manner.

If, on the contrary, the pairs are derived from antagonists at a given joint, the influence, similarly monosynaptic according to the dictates of time (Lloyd, 1941, 1946a, 1946b; Wilson and Lloyd, 1956), is inhibitory. The temporal course of that inhibition is illustrated in figure 7, reflex amplitude again being plotted on the ordinates as a function of time plotted on the abscissae.

Finally, if the pairs have any other relation than those described, their routes through the spinal cord are independent, and no change is wrought by the one upon the other.

The description of these interconnections I have given is

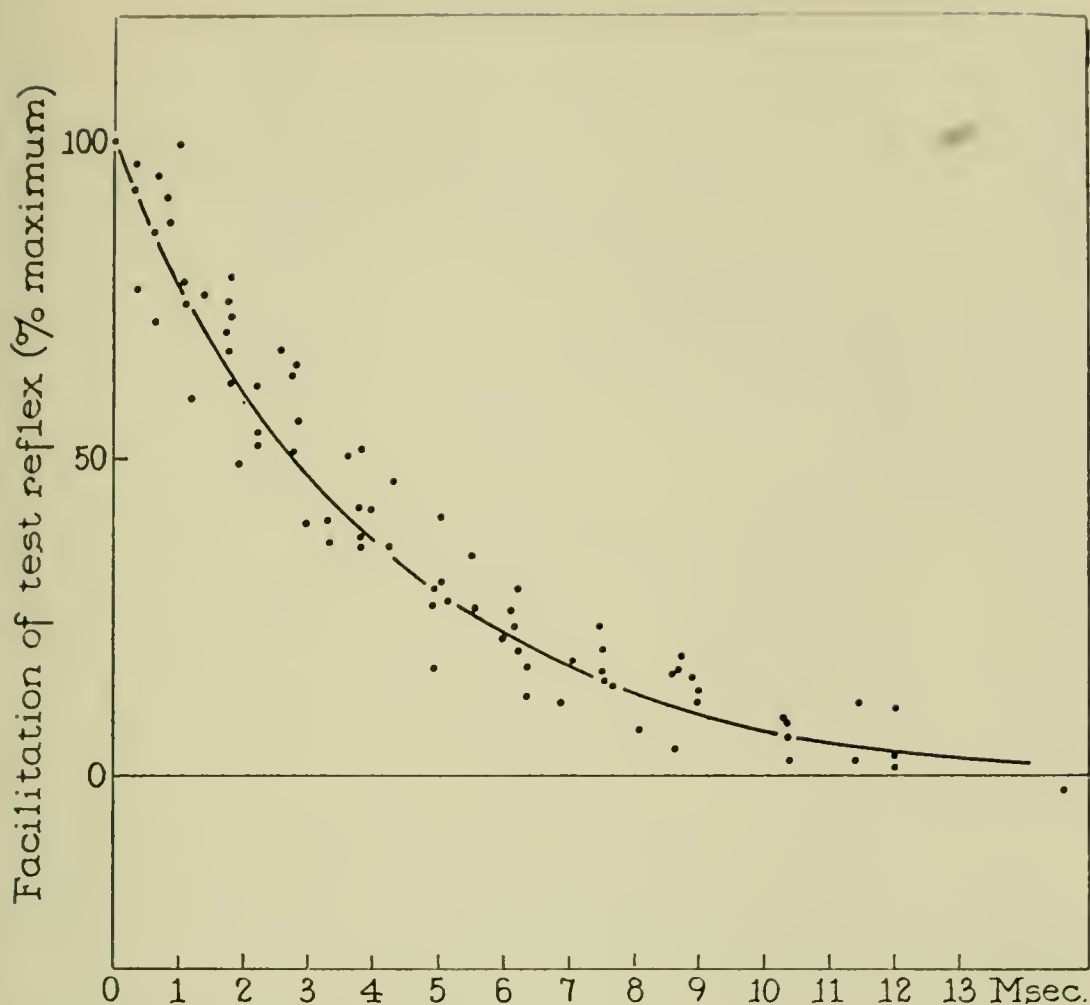


FIG. 6. Temporal course of excitability change (facilitation) caused in a motor nucleus by a synchronous monosynaptic reflex afferent volley as tested by a convergent synergic monosynaptic reflex. From Lloyd, 1946a.

operational; it reveals the facts as experiment discloses them. However, the greater meaning emerges in bolder outline if the facts be restated in different form. A muscle, through its stretch-activated monosynaptic reflex connections, is controlled by itself, by its immediate synergists, and by its immediate antagonists. In turn, through like central connections, that muscle influences its neighbors, synergists, and antagonists. Thus the muscles of a given joint are mutually dependent; nothing in the way of mechanical change can happen to one without influencing the control over the others. In short the muscles of a given joint, together with the monosynaptic reflex connections that bind them, con-

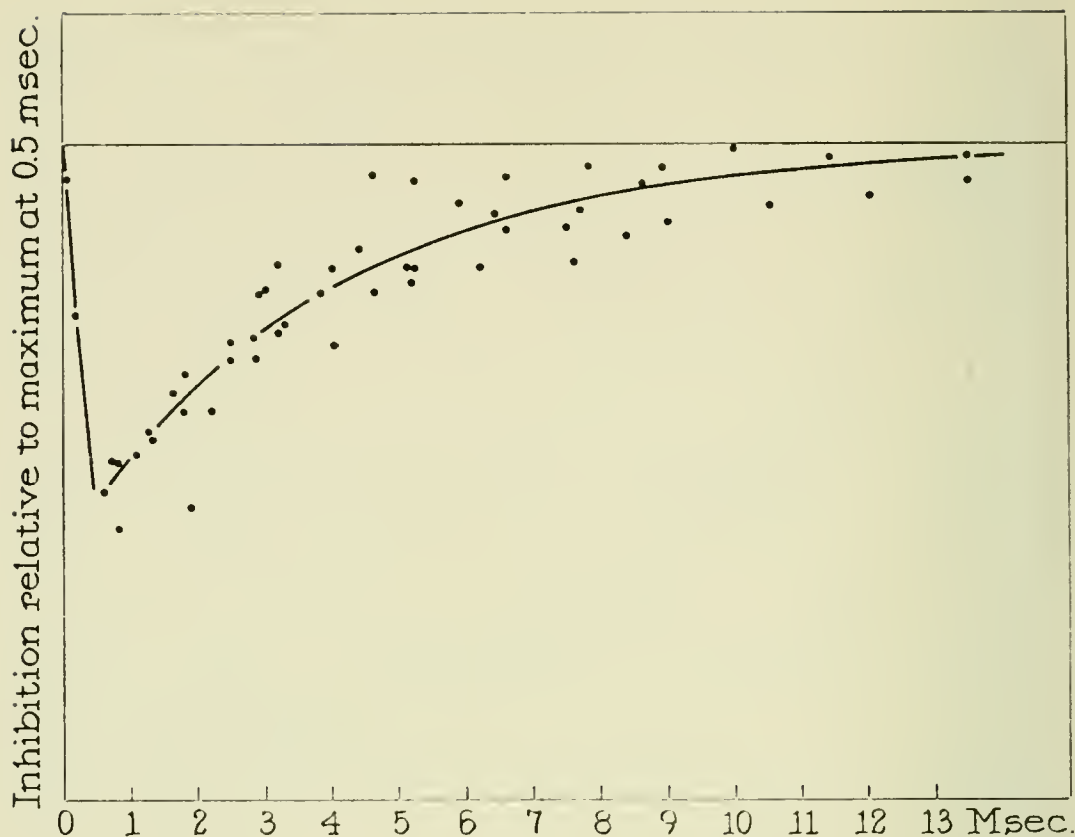


FIG. 7. Temporal course of excitability change (inhibition) caused in a motor nucleus by a synchronous monosynaptic reflex volley as tested by a convergent antagonist monosynaptic reflex. From Lloyd, 1946a.

stitute a unit. This, called the myotatic unit (Lloyd, 1946b), is the elementary unit of postural control.

Mechanism of the lengthening reaction

Mention has been made of the lengthening reaction that in severe stretch comes into opposition to the stretch reflex itself. It too is stretch-activated and in the autochthonous sense is inhibitory. In the intact preparation it finds external expression only because there exists, by the very nature of its origin, an excitatory action, the stretch reflex, upon which it can be written. So in the search after its mechanism, one resorts to the use of monosynaptic reflexes, so useful in revealing the otherwise externally silent actions.

Without entering into great detail concerning the lengthening reaction, one may state that the action upon the motoneuron is exerted disynaptically, which is to say that inter-

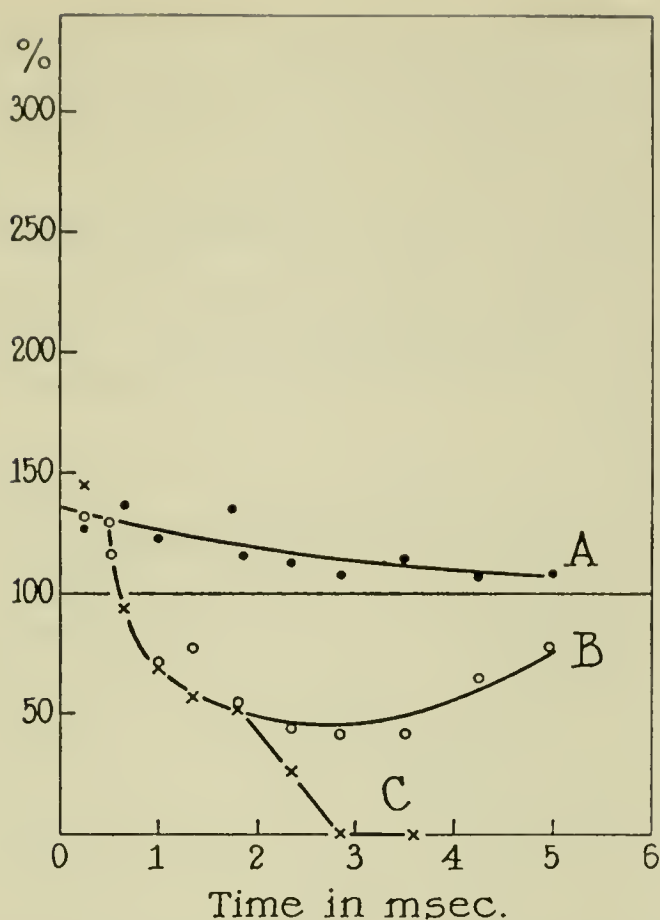


FIG. 8. Excitability changes caused in a motor nucleus by synchronous afferent volleys in incrementing strength. Curve A plots the monosynaptic reflex facilitatory change similar to that seen in figure 6. Curve B shows the disynaptic inhibitory action that is superimposed on the facilitatory change after slight increase in strength. Curve C shows the occurrence of a further inhibitory change after considerable strengthening of the stimulation. This last is, in fact, the inhibitory concomitant of a flexor reflex. From Laporte and Lloyd, 1952.

nuncial neurons, or connector cells as they are sometimes called, are placed between the afferent fibers and the motoneurons (Laporte and Lloyd, 1952). Figure 8 exemplifies the sort of evidence upon which this conclusion is based. Curve A of figure 8 plots the course of monosynaptic stretch reflex conditioning of a synergist test reflex recapitulating, in effect, the experiments illustrated in figure 6. Curve B, obtained with the use of conditioning volleys but slightly enhanced, shows the stretch reflex facilitatory action to be cut off abruptly after approximately one two-thousandth of a second (the time required to pass through an internuncial relay; Lorente de Nó, 1935), there being subsequently a

net inhibition of the motoneurons. The third curve, C, does not concern us at the moment. It is, in effect, a control showing the result dependent upon still further enhancement of the conditioning action. A similar result is to be found whenever action in a pair of synergist muscular afferent channels is combined, and not infrequently the two actions, monosynaptic excitatory and disynaptic inhibitory, cannot be segregated one from the other in the type of experiment under discussion.

Throughout the myotatic unit the action of lengthening reaction afferent fibers is precisely the opposite of the stretch reflex afferent fibers and in all instances equally delayed in time. The lengthening reaction, then, is in reality one part of an integrated pattern of action the totality of which might well be called, according to its nature, the inverse stretch reflex. Intercalation of an interneuron in the inverse myotatic reflex mechanism I believe to be highly significant from a functional point of view, although its functional role in this instance is not one of diffusion of action. I shall return to this question below, but first let us consider the mechanism of flexor reflexes.

Mechanism of the flexor reflex

When, with one's recording electrodes placed upon the nerve to a flexor muscle, one stimulates any other nerve in the vicinity, there appear action potentials indicative of a shower of reflex discharges. Figure 9 illustrates a typical flexor reflex discharge, the afferent limb of the reflex pathway being a cutaneous nerve (the sural, to be specific), the motor limb being the nerve to semitendinosus (a flexor of the knee-joint). The successive records were obtained with the use of stimuli incrementing in strength. Little mensuration is needed to convince one that the discharge was mediated in the spinal cord by polysynaptic connections, or that the multiple, and even the closed, chains of interneurons described by Lorente de Nó (1933), and illustrated diagrammatically here in figure 10, were involved. To the left

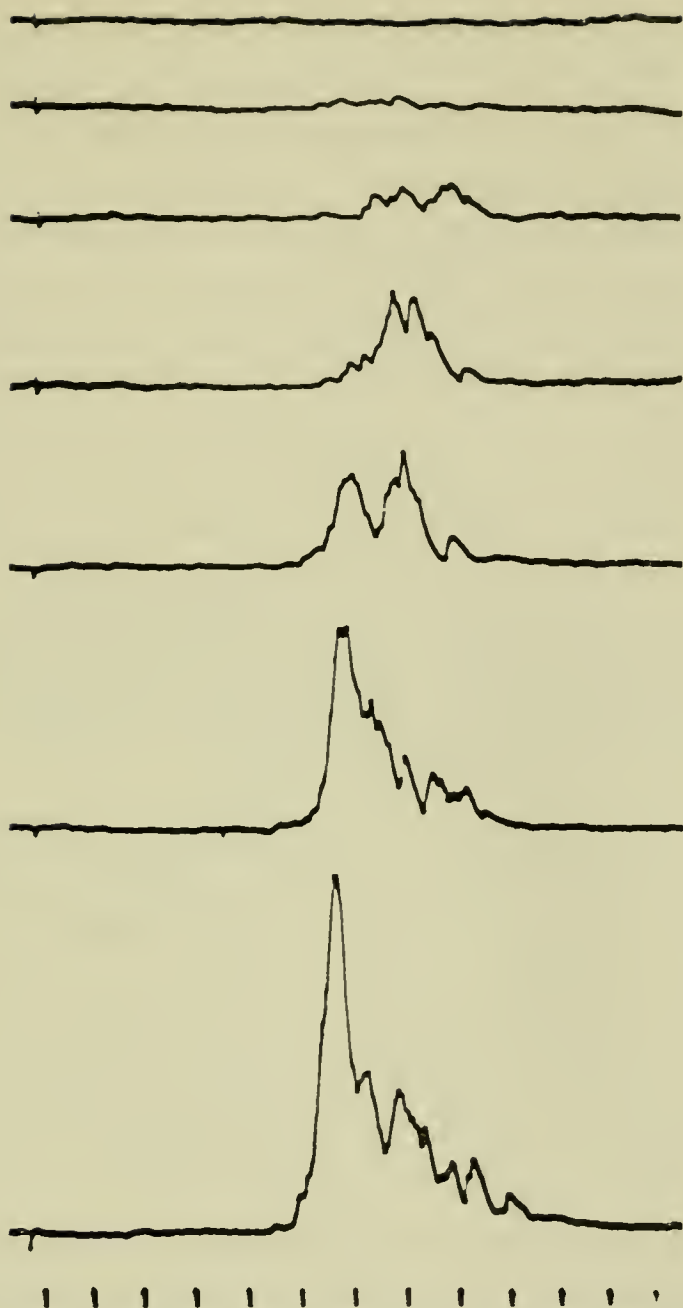


FIG. 9. Typical flexor reflex discharges evoked by afferent volleys of graded intensity. The responses were recorded from semitendinosus nerve following single shock excitations of the cutaneous sural nerve. The topmost record resulted from stimulation at strength below reflex threshold, the bottommost from maximal stimulation for the reflex in question. From Lloyd, 1957.

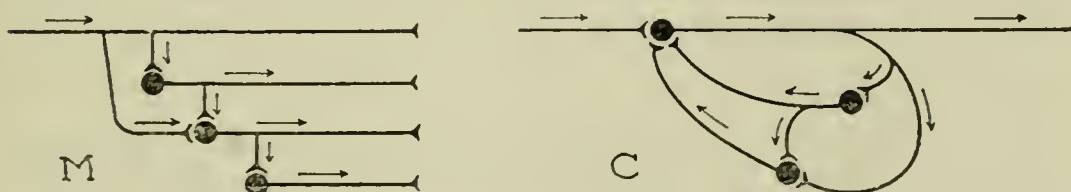


FIG. 10. Diagrams of Lorente de Nó to illustrate the two fundamental types of internuncial circuit. On the left is the multiple chain; on the right, the closed, self-reexciting chain. After Lorente de Nó, 1938, from Lloyd, 1955.

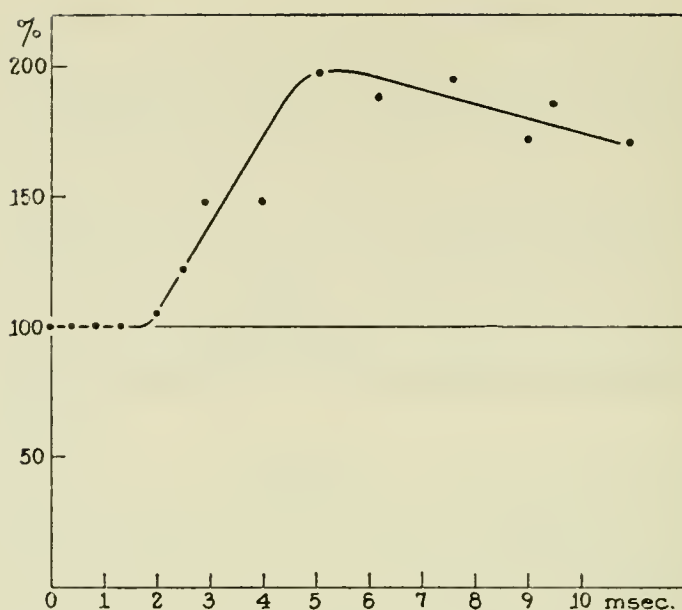


FIG. 11. Excitability change in a flexor nucleus during the course of a flexor reflex evoked by single shock stimulation of a cutaneous nerve. The latent period of some 2 milliseconds proves the minimum flexor reflex pathway to be one of three neurons in series. Modified from Lloyd, 1946b.

of figure 10 is depicted a multiple chain by means of which an action initially synchronous becomes dispersed in time by virtue of passing through neuron chains of different lengths. To the right is depicted the closed self-reëxciting chain. But such a discharge as is seen in figure 9 does not reveal the minimum pathway available to flexor reflex action. To determine this one resorts again to use of monosynaptic reflex tests for change at the motoneuron level. When this is done in a variety of situations, the result in one of which is seen in figure 11, there is always a period in which no change is seen, in duration something less than one five-hundredth of a second, before flexor reflex action is signaled by increase in excitability in the flexor motor nucleus. When an accounting is made of time for conduction and for delay at nerve cell junctions, one cannot avoid the conclusion that the minimum flexor reflex pathway is one of three neurons in series.

If one places recording electrodes upon a number of flexor nerves in the limb, confining the stimulation to a single cutaneous nerve, then discharge is found in greater

or lesser degree in all. The flexor reflex is diffuse, indeed, in its field of action.

In this brief account of several spinal mechanisms I have hoped to show the justification for equating monosynapticity with circumscription of action and polysynapticity with diffusion of action. If it required more than 50 years to validate the physiological inductions of Cajal, it is perhaps not so very surprising that more than 30 years were required to stamp "valid" upon this sentence written in 1911 by Jolly, which I quote: "The relation between the synapse times suggests that the knee-jerk mechanism involves one spinal synapse or set of synapses, while the flexion reflex involves two." And those "synapse times" of Jolly's were off only by a factor of two, which is not by much when one considers the small magnitudes involved, and yet enough, once the synapse time had been measured accurately, to suggest that Jolly's conclusion might not have been correct.

Mass action, giant fiber systems, and internuncial pools

We turn now to more general considerations of neural organization, moving, as it were, from solid ground to shifting sand—from the realm of relative certainty and a measure of proof into one of speculation, uncertainty, and purposivism.

Although some animals may curl up in defiance, presenting a forbidding aspect to some potential marauder, while others adopt protective coloring to prevent detection, it is in general true that animals are equipped for sudden withdrawal and flight away from a source of harm, and in a sense the withdrawal and flight are mass actions. The mechanisms for withdrawal and flight are of interest from an evolutionary point of view. Withdrawal is the more primitive reaction and certainly all that is available to the sessile forms, for example, the sea anemone. Among the free-moving invertebrates there may be localized withdrawal, but the striking action is one of flight. It is among these free-moving forms

that a special system of giant nerve fibers has evolved and, apparently, evolved several times over to serve the purpose of mass action. As one moves up the scale, it does seem rather unlikely that the fish, properly speaking, withdraws from potential danger. Its mechanism, too, is one of flight, but some difference may exist between the squid and the fish, for the fish in flight very clearly uses his ordinary means of locomotion, thrown, as it were, into high gear. But among the higher vertebrates, quadruped and biped, withdrawal and flight are both possible; they are integrated functions and yet separate. Whereas the lobster, or the squid, removes himself forcibly and as a whole, and the fish swims vigorously away, the higher vertebrate need not do likewise. A part may be withdrawn when hurt, with the organism as a whole maintaining its ground. On the other hand it may take to flight, then using, as does the fish, its normal means of locomotion. Two patterns of action are present: one for withdrawal, one for flight. The reflex capabilities of the decapitated cat in this respect were described in a delightful manner by Sir Charles Sherrington (1910) whom I quote, "Under these stimuli and in these forms the flexion-reflex is evidently protective. It is often accompanied by stepping of the crossed hind-limb and, though less commonly, of the other limbs as well, but not of the limb itself stimulated. The irritated foot is withdrawn from harm and the other legs run away."

The flexion reflex of the mammal is often considered to be primitive, for it is in a sense a mass action, and because of its nociceptive character. But it may not be so primitive as it seems at first glance despite these apparent evidences. The truly primitive withdrawal would be the spreading reaction seen in coelenterates dependent in its degree of involvement upon the degree of facilitation in the nerve net. In this withdrawal the extent to which "local sign" is in evidence varies roughly inversely with the stimulation, ultimately to disappear altogether with maximal withdrawal.

This is a fact observable by any small boy who has watched and played with anemones along the rocky shore. The anemone, of course, cannot take flight. A flight mechanism based upon a giant fiber system is an evolutionary development grafted upon the primitive withdrawal system. In it there is no local sign. The central giant fibers of the lobster, for instance, connect at each segment directly with motor giant fibers. If a central giant fiber is active, all the motor fibers become so, and a resulting mass flexion of the tail serves for rapid escape. Interestingly enough, and I suppose to confound the argument, the lobster's close relative, the crab, has lost its motile tail, has no giant fiber system, and must scurry off on eight of his 10 legs, which, to judge by the ghost crabs, he does very successfully.

The giant fiber system is carried over into the chordates. *Amphioxus* apparently has no localized movements. The axons of its giant fibers course backward from the anterior part of the body and forward from the posterior part. Young (1950) suggests that stimulation at the oral end would cause *Amphioxus* to retreat into the sand, and at the caudal end to emerge and escape. This may represent local sign of a sort, although it is in fact nothing more than what the squid achieves by altering the angle of its funnel.

As a generalization, the giant fiber system begins to disappear as more elaborate mechanisms of locomotion develop that can, among other things, take over the functions of flight. But then animals are left without a withdrawal mechanism. This latter develops anew, apparently, as legs are developed, and it is unlikely to be the direct descendant of any withdrawal mechanism that went before.

The main features of the withdrawal mechanism of higher vertebrates, in particular mammals, that makes use of the highly organized internuncial systems are the fixity of pattern and the degree of local sign that are exhibited. Presumably the entire flexor-directed internuncial system of the region is reached by afferent action consequent upon

hurtful stimulation, but the action is distributed throughout the system according to patterns, rather than spread through it, as occurs in the coelenterate. All parts are not equally affected even by the strongest afferent influx. The point is nicely exemplified by table 1, which is taken from

TABLE 1
(After Creed and Sherrington, 1926, from Creed *et al.*, 1932.)

AFFERENT NERVE	HIP FLEXOR (TENS. FASCIÆ FEM.)	KNEE FLEXOR (SEMITENDINOSUS)	ANKLE FLEXOR (TIBIALIS ANT.)
Internal saphenous. .	100	56	87
Popliteal (Tibial). . .	3 or less	42	100
Peroneal (distal to Tib. Ant. N.)	14	100	69

the classical work of Creed and Sherrington (1926) on concurrent contraction in flexor muscles. One sees that stimulation of the saphenous nerve produced its greatest flexor reflex response in the hip flexor, whereas stimulation of the tibial nerve was almost, but not quite, ineffective at the hip while producing its greatest effect at the ankle. Finally, stimulation of the peroneal was most effective at the knee-joint. From this one can appreciate the fact that hurtful stimulation at various loci on the limb will cause the limb to assume different final positions. Fixity of pattern and local sign, then, are the key distinctions between the primitive withdrawal mechanism that was lost in evolutionary advance and that which was gained at a later stage. From the point of view of mass action in reflex performance it is the fact of local sign that differentiates the primitive mass action system of the giant fibers and the finely integrated mass action of an internuncial system.

Other functional roles of interneurons

In addition to their well-established roles as distributors of action in the nervous system, the interneurons may serve other important needs of an integrative mechanism. The

surface of the motoneuron is limited (Eccles, 1957, estimates it at $5 \times 10^{-4} \text{ cm}^2$), and the motoneuron is the final common path upon which all the myriad influences ultimately must play, either directly or indirectly, if they are to find any expression in the external world. In this vein I digress, but only slightly, to express this thought in the words of Sir Charles Sherrington (1924), "These, the skeletal muscles, are the motor machinery for all that life of the animal which the older physiologists were wont to call the 'life of external relation.' Of the importance of that life of external relation the moralist has written that even in man the crown of life is an action, not a thought. Should we demur to this distinction, we can still endorse the old adage that to move things is all mankind can do, and that for such the sole executant is muscle, whether in whispering a syllable or in felling a forest." I would add to this only that muscle awaits the command of the motoneuron, and faithfully executes that command when given.

As the nervous system has advanced along the road of evolution, the influences multiply, as do the tracts that mediate them, all aiming at the motoneuron already encrusted with synaptic knobs—those points of contact for the delivery of excitatory and inhibitory direction. How can all these new influences be accommodated? On the one hand the old order could break down, leaving room for the new. This would imply that the nerve cell origins of the synaptic knobs covering the motoneurons might differ, for instance, in cat and in monkey, which in fact they do. On the other hand influences of like sort, in terms of their ultimate action upon the motoneuron, could converge upon an interneuron, making of it a common path of communication to the motoneuron and greatly alleviating the space problem on the motoneuron surface. The notion that is advanced is depicted diagrammatically in figure 12, in which a large number of sources of influence is represented by fibers convergent upon an interneuron which in turn connects to the motoneuron at

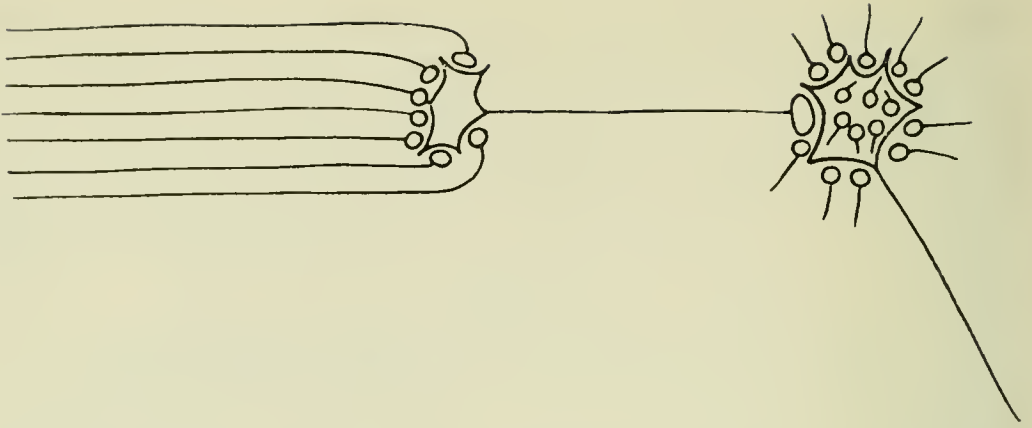


FIG. 12. Diagram to indicate the manner in which interneurons serve as a focus of convergence and, by acting as a common path for a variety of influences, reduce the spatial requirements on the soma surface of motoneurons.

the right already heavily encrusted with fibers from yet other sources. The pyramidal system, from one point of view, might exemplify this function of interneurons, for in its development it serves as the common path to the motoneuron for willed movement. Convergent upon it are those influences that culminate in its direction to the motoneurons to execute the desired movement.

Another function with which interneurons have been endowed is that of changing the nature of chemical transmitter at a given step of a neural pathway. In its original form the hypothesis was proposed by Feldberg (1950) who, noting that the pyramidal tract and dorsal roots were low in choline acetylase, while the enzyme was abundant in motoneurons and other cell masses in which these paths terminate, suggested that cholinergic and non-cholinergic neurons alternate in series.

More recently Eccles (1957), mindful of Sir Henry Dale's suggestion that it is unlikely that different branches of one and the same neuron would elaborate different chemical transmitters, and supposing that a single transmitter substance could not have both excitatory and inhibitory functions at different loci, has proposed that an interneuron should be intercalated into the monosynaptic inhibitory path, the interneuron having no function other than that of

switching from an excitatory transmitter to an inhibitory transmitter. This is not the occasion to follow all the finely spun argument advanced to support Eccles' assumption or the chain of evidence against it. Sufficient to say that it is not a necessary assumption (Grundfest, 1957) and that the most careful study of time relations precludes the possibility that there is an intercalated interneuron in at least some of the inhibitory connections. So, at best, this proposed function of interneurons is highly controversial.

One final function for interneurons is deserving of mention. It is what might be called "the valve action." To illustrate this, one returns to consideration of the stretch reflex and the lengthening reaction, with their respective monosynaptic and disynaptic pathways shown in figure 13. Not enough difference exists between the stretch threshold of

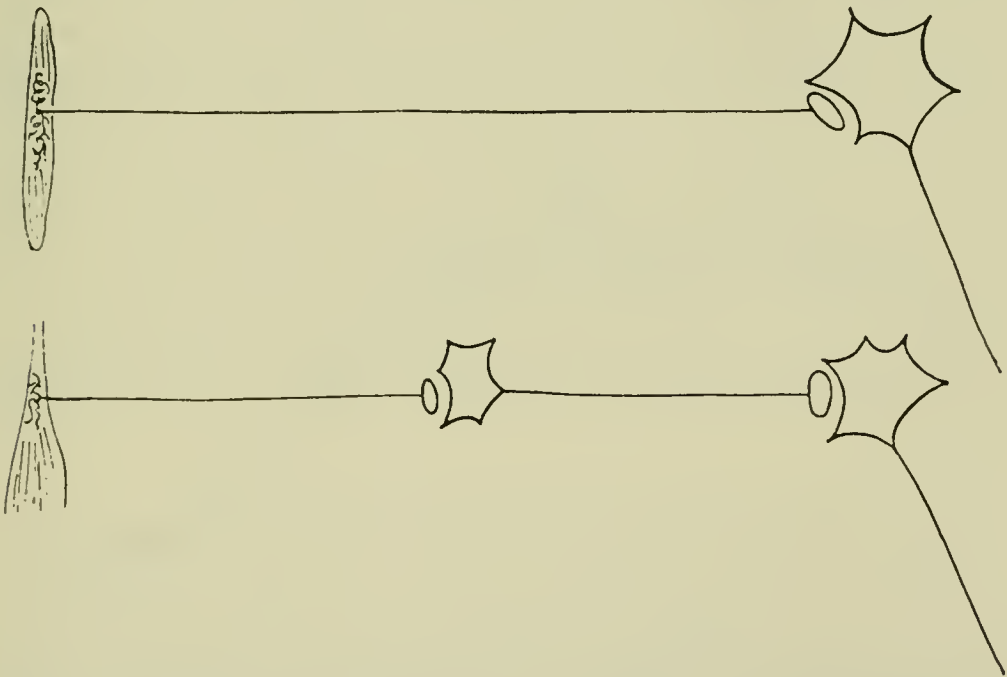


FIG. 13. Diagram of the monosynaptic reflex pathway from muscle spindle afferent fiber to motoneuron (above) and of the disynaptic reflex pathway from Golgi tendon organ through an interneuron to motoneuron (below). Somatic reflex action inevitably involves tension changes in muscle, which means that myotatic afferent impulses inevitably arise, and, because of the direct connection to motoneurons, these last inevitably are influenced. Thus myotatic reflex activity plays a part in all reflexes of the intact animal. On the contrary, inaction of the interneuron, as by inhibition, leaves the motoneuron free from influence. The interneuron thus can act as a valve.

the muscle spindle, afferent end-organ for the stretch reflex, and that of the tendon organ, afferent for the lengthening reaction, to account for the great difference in reflex threshold of the two reflex effects in the decerebrate animal. Furthermore, in the spinal animal, it is the inhibition of the lengthening reaction rather than the excitation of the stretch reflex that is the presenting feature (Henneman, 1951), unless one is dealing with highly synchronized brief stretch, in which case the excitatory impulses, so to speak, beat out the inhibitory impulses in point of time.

That stretch excitation of autochthonous motoneurons is present at all degrees of stretch follows from the fact that monosynapticity of action implies inevitability of action. That the inhibition may dominate in the spinal animal and yet be held in check in the decerebrate means that the internuncial link of the disynaptic path is open in the former and closed in the latter. This, indeed, is the action of a valve. It would seem that there is, collateral to the stretch reflex pathway, a connection, inhibitory in character, to the internuncial relay of the lengthening reaction, which holds the latter in abeyance until such time as the input from tendon organs becomes overwhelming. For these responses to be coördinated in appropriate manner, it is essential that an interneuron be present in the pathway for the lengthening reaction.

Monosynapticity as an evolutionary development

Because all that is neural in the central nervous system, save the primary afferent projections and the motoneurons, is internuncial in character, it is self-evident that proliferation of the interuncial system is a cardinal feature in evolution of the human brain. This means that there has been an enormous increase in complexity of the liaison between perception of, and action in, the external world. Coupled with this is the suggestion by implication that directness of connection is therefore primitive. If we compare the giant fiber

systems for flight (paradigms of directness) with the elaborate flight mechanism of higher animals, the point would, indeed, seem well taken. But if we were to explore a less obvious facet of evolutionary development we might find just the opposite to be true. Indeed, there is some evidence to suggest that short-latency, direct connection to motoneurons stands at the very pinnacle of evolutionary development of the nervous system.

The monosynaptic reflex pathways so highly developed in the cat (Lloyd, 1943a) and in man (Hoffman, 1918; Magladery and others, 1952) are present only in a rudimentary form in the frog, and have not been seen to be capable of transmission even with the most massive afferent input, although many have observed the slow potential change, a post-synaptic potential so-called, indicative of monosynaptic connection. An example of this is presented in figure 14. In recording from a ventral root of the frog while stimulating the dorsal root of the same segment, one finds a blaze of late

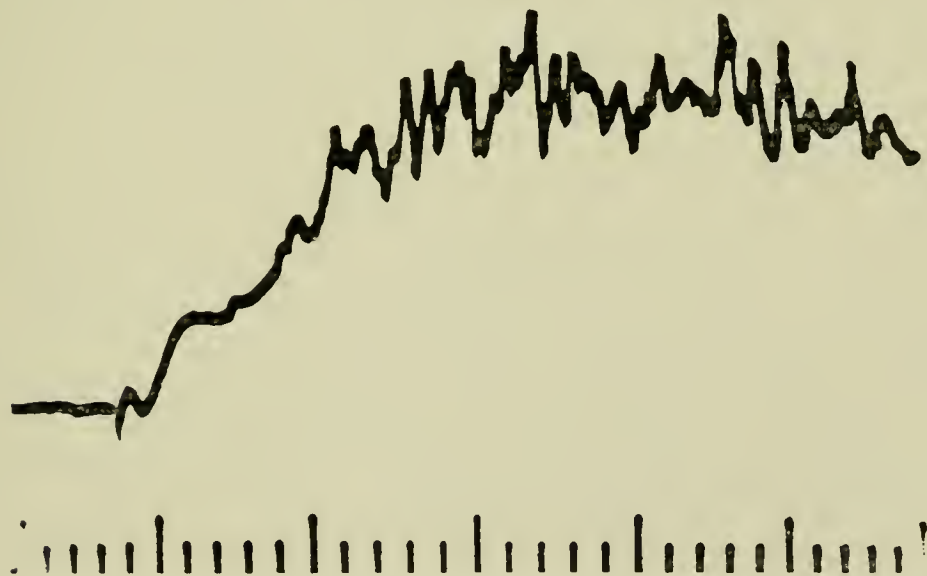


FIG. 14. Synaptic potential and reflex discharge of bullfrog motoneurons in a segmental reflex. The potential change beginning 1 millisecond after stimulation bespeaks the presence of monosynaptic reflex connections of a sort, however, that do not give rise to reflex response. It is probable that this results from the fact that the primary afferent connections are located on the motoneuron dendrites rather than on the cell body. Time 1 and 5 milliseconds. From an unpublished experiment of D. P. C. Lloyd and A. K. McIntyre, University of Otago, Dunedin, New Zealand.

reflex discharge (proof that stimulation has engaged all the myelinated afferent fibers), and yet in the monosynaptic reflex position, at the beginning of electrical change, there is no reflex, the only indication of connection being the above-mentioned subthreshold excitatory potential.

But it is in consideration of the pyramidal system that we find the strongest evidences of the preëminent role of direct connection. The cat possesses a pyramidal tract for encephalized control of its musculature, all the fibers of which end not upon motoneurons, but rather in the internuncial pools from which activity is relayed to the motoneurons (Lloyd, 1941b). When watching a cat in action, one may see it fanning the toes, extending the claws to scratch, flexing the paw, and so on, all mass movements of the sort to be expected, in the light of present-day knowledge, of action mediated through an internuncial pool.

The monkey, on the other hand, has the ability to move its fingers in a discrete manner, and it is in this animal that we find, in the studies of Bernhard, Bohm, and Petersen (1953), for the first time physiological evidence for the existence of direct connection from pyramidal tract to the motoneuron.

Thus in both stretch reflex pathway and in the primate pyramidal system the emergence of a short-latency, direct connection seems to be correlated with the emergence of a discrete, finely localized control over motor performance. Interesting it is, indeed, that in its first evolution the direct connection from ganglionic mass to motoneuron should be a mechanism for superimposing a massive diffuse action upon actions of a more or less local nature, whereas in its second evolution it should be precisely the reverse, a mechanism for superimposing discreteness of action upon a nervous system geared to mass actions. In assessing the importance of this recurrence in a new form of a system of direct impingement upon the motoneuron, let us not forget that it is the possession of discrete control of his fingers and op-

posable thumb that has made man the forger of tools to forward his own destiny and the player of musical instruments for the soothing of his soul.

LITERATURE CITED

BERNHARD, C. G., E. BOHM, AND I. PETERSEN

1953. Investigations on the organization of the corticospinal system in monkeys (*Macaca mulatta*). Act. Physiol. Scandinavica, vol. 29, suppl. 106, p. 79.

CAJAL, S. R.

1909. Histologie du système nerveux de l'homme et des vertébrés. Paris, Maloine, vol. 1.
1911. Histologie du système nerveux de l'homme et des vertébrés. Paris, Maloine, vol. 2.

CREED, R. S., D. DENNY-BROWN, J. C. ECCLES, E. G. T. LIDDELL, AND C. S. SHERRINGTON

1932. Reflex activity of the spinal cord. Oxford, Clarendon Press.

CREED, R. S., AND C. S. SHERRINGTON

1926. Observations on concurrent contraction of flexor muscles in the flexion reflex. Proc. Roy. Soc., sect B, vol. 100, p. 258.

ECCLES, J. C.

1957. The physiology of nerve cells. Baltimore, the Johns Hopkins Press.

ECCLES, J. C., AND C. S. SHERRINGTON

1931. Studies on the flexor reflex. Proc. Roy. Soc., sect. B, vol. 107, p. 511.

FELDBERG, W.

1950. The role of acetylcholine in the central nervous system. Brit. Med. Bull., vol. 6, p. 312.

GASSER, H. S., AND J. ERLANGER

1922. A study of the action currents of nerve with the cathode ray oscillograph. Amer. Jour. Physiol., vol. 62, p. 496.

GRANIT, R.

1950. Reflex self-regulation of muscle contraction and autogenetic inhibition. Jour. Neurophysiol., vol. 13, p. 351.

GRUNDFEST, H.

1957. Electrical inexcitability of synapses and some consequences in the central nervous system. Physiol. Rev., vol. 37, p. 337.

HENNEMAN, E.

1951. Excitability changes in monosynaptic reflex pathways of muscles subjected to stretch. Trans. Amer. Neurol. Assoc., p. 194.

HOFFMAN, P.

1918. Über die Beziehungen der sehn Reflexe zur Willkürlichen Bewegung und zum Tonus. Zeitschr. Biol., vol. 68, p. 351.

JOLLY, W. A.

1911. On the time relations of the knee-jerk and simple reflexes. Quart. Jour. Exp. Physiol., vol. 4, p. 67.

LAPORTE, Y., AND D. P. C. LLOYD

1952. Nature and significance of the reflex connections established by large afferent fibers of muscular origin. Amer. Jour. Physiol., vol. 169, p. 609.

LIDDELL, E. G. T., AND C. S. SHERRINGTON

1924. Reflexes in response to stretch (myotatic reflexes). *Proc. Roy. Soc., sect. B.*, vol. 96, p. 212.

1925. Further observations on myotatic reflexes. *Ibid.*, sect. B, vol. 97, p. 267.

LLOYD, D. P. C.

1941a. A direct central inhibitory action of dromically conducted impulses. *Jour. Neurophysiol.*, vol. 4, p. 184.

1941b. The spinal mechanism of the pyramidal system. *Ibid.*, vol. 4, p. 525.

1943a. Reflex action in relation to pattern and peripheral source of afferent activity. *Ibid.*, vol. 6, p. 111.

1943b. Neuron patterns controlling the transmission of ipsilateral hind-limb reflexes in cat. *Ibid.*, vol. 6, p. 293.

1943c. Conduction and synaptic transmission of the reflex response to stretch in spinal cats. *Ibid.*, vol. 6, p. 317.

1946a. Facilitation and inhibition of spinal motoneurons. *Ibid.*, vol. 9, p. 421.

1946b. Integrative pattern of excitation and inhibition in two-neuron reflex arcs. *Ibid.*, vol. 9, p. 439.

1952. On reflex actions of muscular origin. *Res. Publ. Assoc. Nerv. and Ment. Dis.*, vol. 30, p. 48.

1955. Principles of nervous action. *Section I in* Fulton, John F., *Textbook of physiology*. Philadelphia and London, Saunders.

1957. Input-output relation in a flexor reflex. *Jour. Gen. Physiol.*, vol. 41, p. 297.

LORENTE DE NÓ, R.

1933. Vestibulo-ocular reflex arc. *Arch. Neurol. Psychiat.*, vol. 30, p. 245.

1935. The synaptic delay of motoneurons. *Amer. Jour. Physiol.*, vol. 111, p. 272.

1938. Analysis of the activity of the chains of internuncial neurons. *Jour. Neurophysiol.*, vol. 1, p. 207.

MAGLADERY, J. W., A. M. PARK, W. E. PORTER, AND R. D. TEASDALL

1952. Spinal reflex patterns in man. *Res. Publ. Assoc. Nerv. and Ment. Dis.*, vol. 30, p. 118.

RENSHAW, B.

1940. Activity in the simplest spinal reflex pathways. *Jour. Neurophysiol.*, vol. 3, p. 373.

SHERRINGTON, C. S.

1910. Flexion reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *Jour. Physiol.*, vol. 40, p. 28.

1924. Problems of muscular receptivity. *Nature*, vol. 113, pp. 892, 929.

WILSON, V. J., AND D. P. C. LLOYD

1956. Bilateral spinal excitatory and inhibitory actions. *Amer. Jour. Physiol.*, vol. 187, p. 641.

YOUNG, J. Z.

1950. *The life of vertebrates*. Oxford, Clarendon Press.



