

## INPUT-OUTPUT RELATION IN A FLEXOR REFLEX

By DAVID P. C. LLOYD

(From *The Rockefeller Institute for Medical Research*)

(Received for publication, May 27, 1957)

### ABSTRACT

Observations have been made upon a typical flexor reflex with the aim of disclosing the changes in amount, latency, and temporal configuration of reflex discharge that take place as afferent input is varied from zero to maximal for the band of cutaneous myelinated afferent fibers that extends upward from approximately  $6 \mu$  in diameter (group II fibers). Reflex threshold is reached at 6 to 12 per cent maximal afferent input. From threshold to maximal input the relation between input and amount of output is essentially linear, latency on the average decreases, the shorter central paths in general gain preference, but the known minimum pathway, one of three neurons, does not transmit unless aided by convergent activity. Flexor reflex discharge may occur in several bursts suggesting the existence of closed chain connections in the internuncial pools of the spinal cord. At any given input there is, in successively elicited reflexes, little correlation between latency and amount of discharge, at first sight a surprising result for each variable can be taken as a measure of excitability status of the motoneuron population. However, latency of discharge indicates excitability at the beginning of the reflex event whereas amount of discharge is an expression of excitability over the entire period of discharge. Given a constantly and rapidly fluctuating excitability absence of correlation between these variables would be an anticipated result.

The reflex to be discussed is a flexor reflex for which the afferent limb is confined to the group II fibers of a cutaneous nerve, specifically the sural nerve, and for which the motor limb is the nerve to a flexor muscle, specifically semitendinosus.

Input-output relations of monosynaptic reflexes have been studied intensively in the fifteen years since the relation was first described (Lloyd, 1943 *a*, 1945; Rosenblueth, Wiener, Pitts, and Garcia Ramos, 1949; Rall, 1955 *a*, *b*; Hunt, 1955 *a*, *b*; Lloyd and Wilson, 1957). The relation has been studied, too, in the monosynaptic relay from primary afferent fibers to the spinocerebellar tract (Lloyd and McIntyre, 1950). As a general technique for the identification of the afferent fiber band responsible for a given action, be that excitatory or inhibitory, the coupling of graded, monitored afferent volleys with a suitable monosynaptic test reflex is, indeed, useful (Lloyd, 1943 *a*;

Lloyd and McIntyre, 1948, Figs. 7 and 8; Hunt, 1955 *a, b*). But little is known of the input-output relation proper of a flexor (*i.e.* polysynaptic) reflex (but *cf.* Bernhard and Widén, 1953).

By reason of relative synchrony of input and output, and of relatively fixed latency, study of the relation in monosynaptic reflexes is concerned only with how much output for so much input, the independent and dependent variables being measured as amplitudes of recorded responses. In the study of a polysynaptic reflex because of temporal dispersion one must be concerned not only with amount of output for given input, and this must be measured as a discharge area rather than a discharge amplitude, but also with the temporal characteristics of the discharge. The group II afferent fiber band of skin nerve yields with short conduction distance a spike potential sufficiently synchronous that amplitude measurement is a satisfactory indicator of afferent input.

The preparations were decapitate cats, the sural nerve being fitted with stimulating and recording leads, the nerve of semitendinosus with recording leads. In some experiments the first sacral ventral root was substituted for semitendinosus nerve.

#### *The Relation between Input and Character of Flexor Reflex Discharge*

Fig. 1 presents a series of flexor reflex recordings obtained with the use of incrementing group II afferent volleys. For the top record the afferent volley was below reflex threshold, for the bottom record it was maximal. It is immediately evident that reflex latency is rather variable and that the reflex with incrementing input progressively prefers the shorter central pathways. The not so obvious fact is that flexor reflex discharge is not realized through the minimum pathway which is one of three neurons (*cf.* Fig. 3 B), the anatomical existence of which minimum pathway is easily demonstrated by the observation of facilitated responses (Lloyd, 1943 *b*), or by the use of suitable monosynaptic reflex tests for subliminal excitability change (Lloyd, 1946).

The recordings of Fig. 1 are reminiscent of those obtained by Lorente de Nó from the trochlear nerve following stimulation at the floor of the 4th ventricle (1938), but the preference for shorter paths on increasing input is much more dramatic and there is no evidence, in the form of the strong response being of shorter duration than weak response, that the later part of the flexor reflex discharge suffers by reason of the growing earlier discharge. In other words if motoneurons are prevented from responding late in the discharge period by virtue of moving forward in time with stronger afferent impingement then their place is taken by other motoneurons recruited into the response. It is very unlikely that motoneurons respond twice in the course of a flexor reflex discharge having the character of that seen in Fig. 1 (*cf.* Alvord and Fuortes, 1954).

Flexor reflexes do not always consist of a discharge in a single mode, as seen in Fig. 1. They may, not infrequently, take the form of discharges gathered about two or three temporal modes (Lloyd, 1943 *b*; Bernhard, 1945).

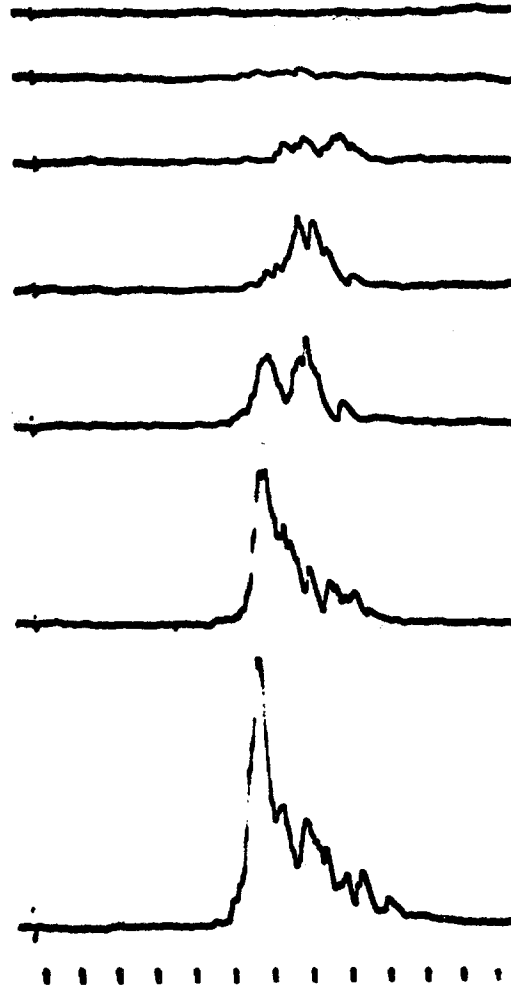


FIG. 1. Flexor reflex discharges in semitendinosus nerve resulting from single shock stimuli of incrementing strength (from above downwards) to sural nerve. Time line at bottom in milliseconds.

One is speaking now of flexor reflex discharges to afferent volleys in group II fibers (*cf.* Lloyd, 1943 *b*, Fig. 6) not of secondary discharges that will appear as stimulation is raised to group III strength (*cf.* Lloyd, 1943 *b*, Fig. 7).

Fig. 2 contains records obtained in the same way as those of Fig. 1, but

from another preparation in which the flexor reflex discharge appeared in two almost completely distinct and separate groupings. Having regard for the difference in recording sweep speeds it will be seen that the first burst of flexor reflex discharge in Fig. 2 is entirely comparable to the entire discharge in Fig. 1, and grows in magnitude with incrementing afferent stimulation in

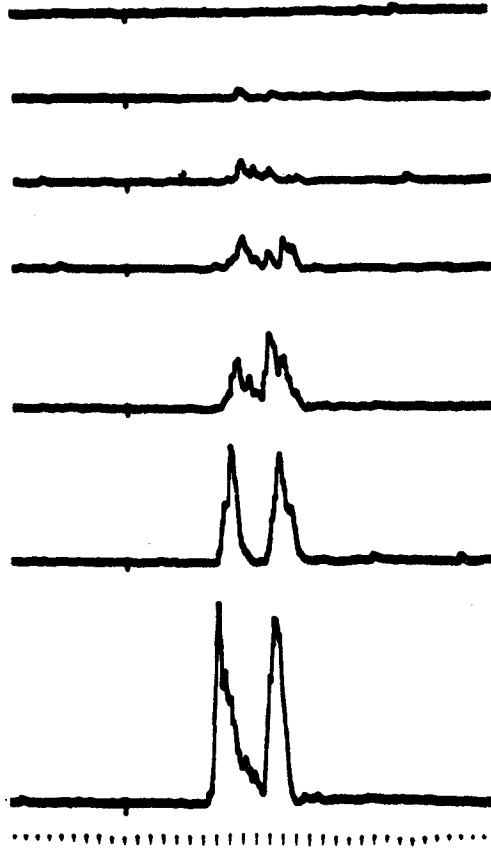


FIG. 2. As Fig. 1 from another experiment. Time in milliseconds.

precisely the same manner. But more interesting is the fact that the second burst of flexor reflex discharge grows *pari passu* with the first. This can only mean that the internuncial barrage is delivered to the motor pool in at least two bursts. Presumably there are in reality three bursts, for the trimodal form of response has been seen (Lloyd 1943 *b*; Bernhard, 1945). Since one must reasonably suppose the machinery for transmission in several bursts to be present in one animal of the species as in another the conclusion would seem to be that success on the part of the later bursts of internuncial activity in

securing motoneuron discharge depends upon "state of the preparation" or some other such factor that has not as yet been brought under experimental control.

Although there is no reason to suppose that the type of response depicted in Fig. 1 requires of its mediate system anything more complex than the multiple chain arrangement described by Lorente de N6 (1933, 1938), the type of response found in Fig. 2 is suggestive of reverberation through a reentrant pathway (the delay paths of Forbes, 1922; reverberating circuits of Ranson and Hinsey, 1930; or the closed chain of Lorente de N6, 1933, 1938).

The alternative notion, that a multiple chain is so constructed that the paths of increasing length are distributed with respect to transmitter potentiality in several peaks, seems rather implausible.

One might suppose that operation of a reentrant pathway would involve repetitive response of the motoneurons. True, by definition the internuncial impulses, having circulated, would return to the same motoneurons, but the response they yield could well concern only such motoneurons as are left in the subliminal fringe by antecedent bursts. Thus the observation of Alvord and Fuortes (1954) that individual motoneurons rarely respond twice in a single shock flexor reflex is accommodated easily on two counts. In the first place, as just noted, action in a reverberant circuit need not lead to repetition in motoneuron response. In the second it would appear that the reflexes studied by Alvord and Fuortes compared with those here shown in Fig. 1 rather than those of Fig. 2. Clearly the latter type of reflex should be studied in terms of individual motoneuron response.

#### *The Relation between Input and Amount of Flexor Reflex Response*

Fig. 3 A presents the input-output relation for a semitendinosus flexor reflex. It is essentially linear from reflex threshold to maximal group II input. In other experiments a slight upward convexity or concavity appeared, but the deviation from linearity being inconsistent in direction and small in degree may be considered as error. Reflex threshold in individual experiments varied from 6 to 12 per cent of maximal group II input. In the experiment illustrated by Bernhard and Wid6n (1953) threshold was slightly above 10 per cent maximal input.

Each plotted point in Fig. 3 A represents the mean value for reflex discharge area in a number of trials. This fact quite naturally raises the question of reflex variability which in the case of polysynaptic reflexes is a matter not only of amount of output, but also latency of output. The question also arises as to what degree of correlation there may be between these two variables. The over-all relation, that is the relation between mean reflex response and latency as input is varied, can be seen in conjoint study of Fig. 3 A and B. In 3 B each plotted point represents the latency of one or more individual

responses, plotted on the ordinates, as a function of afferent input, plotted on the abscissae. Several points of interest emerge. As input is increased, and so too output, minimum latency decreases within limits as does variation in

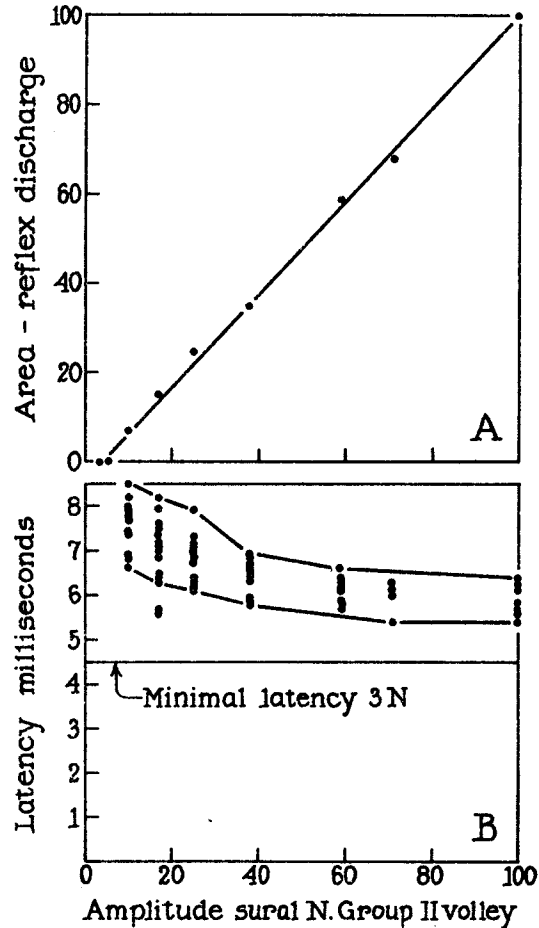


FIG. 3. A, input-output relation in a flexor reflex. B, input-latency relation in a flexor reflex. Minimal latency 3 N at approximately 4.5 milliseconds represents the calculated reflex time for a pathway containing a single internuncial relay.

latency. Theoretical minimum latency for the pathway including a single internuncial relay is not reached and as far as one can tell is only reached in facilitated responses (Lloyd, 1943 *b*; Alvord and Fuortes, 1954; *cf.* also Eccles and Sherrington, 1931). Occasionally, however, a flexor reflex response elicited by a small input will appear with latency nearly as short as that of the shortest latency response elicited by maximal input. This is exemplified by the two short latency responses at 18 per cent input (Fig. 3 B).

Another approach to the question of the relation between amount of discharge and reflex latency is to observe these quantities in a number of individual observations at fixed inputs, the two then varying only by reason of the excitability fluctuation of the spinal cord, which is temporally random, essentially normal, and partially correlated (Lloyd and McIntyre, 1955; Hunt, 1955 *a*; Rall and Hunt, 1956; Lloyd, 1957). If, in these circumstances one plots for each individual observation latency against discharge area there is for any given input up to some 25 to 30 per cent maximal, a degree of correlation discernible. There is in short a tendency for the larger responses to a fixed small input to appear with shorter latency than do the smaller responses. At greater input levels, however, latency variation is largely independent of output variation. This at first sight is a bit surprising for Rall and Hunt (1956) found the correlation coefficient of fluctuation in two parts of a motoneuron pool to be  $+0.73$  to  $+0.74$  which are large positive values. The probable explanation is not difficult to imagine. One must consider first that a monosynaptic reflex test samples the excitability states of the motoneurons in a nearly synchronous fashion. On the contrary a flexor reflex test of the motoneurons is dispersed over some 5 to 10 milliseconds during which time one cannot expect, by other than mere chance, that the excitability level of the motoneuron pool would remain constant. Latency variation is an expression of excitability status at the very beginning of the dispersed test presented to motoneurons on any given occasion. Variation in amount of discharge on the other hand is an expression of excitability status over the entire period of discharge. Thus, if excitability were rising at the time of internuncial barrage upon the motoneurons latency might be long implying low excitability and discharge in amount high implying greater excitability, with the converse a likely result if excitability were declining.<sup>1</sup> Presumably in a series of test flexor reflexes the motoneuron pool would be found in a variety of changing states, which would result in the observed low degree of correlation between the two measures of excitability under discussion.

*Concerning Fluctuation.*—All the experiments specifically devoted to the questions of excitability fluctuation in the spinal cord have involved sampling, by monosynaptic reflex test at intervals of 2 seconds or longer. They do not, therefore, give any information as to what one might call “short term” fluctuation which is of concern in the interpretation of the present experiments. There is seemingly no practical direct test of excitability that would tell what happens in a motor nucleus over a span of 5 or 10 milliseconds. One can resort to indirection, however, and rely upon correlation between ventral root elec-

<sup>1</sup> The argument as presented is simplified for the purpose of exegesis. Rising excitability and falling excitability during the course of a flexor reflex, by emphasizing different temporal segments of the response on different occasions, could, and in fact not infrequently do, result in reflex discharges of very different configuration but of insignificant difference in discharge area.

trotonus and motoneuron excitability. In recording ventral root electrotonus, of course, one is dealing with a segmental pool rather than specifically with a flexor nucleus. Nonetheless recordings of the spontaneous ventral root electrotonic potential changes (for which *cf.* Lloyd, 1952, Figs. 44 and 45) that occur in the unanesthetized decapitate preparation such as used for the present experiments show that rapid oscillations do take place in the motoneurons and that very significant change can occur within a matter of a few milliseconds.

#### DISCUSSION

Apparently all segments of the group II band of fibers in a cutaneous nerve feed into the internuncial system of the ipsilateral flexor reflex. Certainly not all the fibers in this band do so for extensor effects can be obtained by appropriate natural stimulation of certain parts of the skin area supplied by sural nerve (Hagbarth, 1952). But those that do, on the evidence presented, are fairly evenly distributed throughout the band. Other functions of the group II band that have been studied rigorously do not display such an even distribution. Thus the descending long spinal inhibition of flexor longus is in its afferent limb confined to the very lowest threshold fibers, and long spinal reflex facilitation of other hind limb muscles to the high threshold members (Lloyd and McIntyre, 1948). Also the production of the "N<sub>1</sub>" deflection of Bernhard and Widén (1953) is due to action of the lower threshold group II fibers, but the band, apparently, is not as highly restricted as is that for long spinal reflex inhibition of flexor longus. Such fractionations of the group II band would seem to indicate functional differences in receptor origin for the several effects noted. It is true that the group II band of cutaneous nerves, which is to say the alpha and beta fibers, contains fibers subserving, in terms of sensation, a variety of modalities (Gasser, 1943). The problem raised by the form of the flexor reflex input-output relation, then, is whether one of the modalities, associable with flexor reflex action, is rather evenly distributed throughout the group II band whilst others are not, or whether fibers concerned in the several modalities are associable in terms of flexor reflex production, but not in relation to other actions, reflex and sensory. Unfortunately there is no immediate prospect of solving the problem. One could wish that the situation were as clear-cut as it is with respect to flexor reflexes elicited by stimulation of group II afferent fibers of muscle origin which arise exclusively, insofar as one can tell, in a single receptor type, the secondary or flower-spray endings of muscle spindles (Hunt, 1954).

Although the upper limit in diameter of the "pain" fibers is uncertain (Gasser, 1943) they are certainly concentrated in the group III band (delta fibers) and in the C or unmyelinated fiber group. Thus, while it is unlikely that one would be in error supposing the group III reflex (Lloyd, 1943*b*) to be nocicep-



tive in character, it is equally unlikely that one would be correct in supposing the same of the group II flexor reflex. In this connection it is of interest that the group II fibers of cutaneous origin yield in the contralateral hind limb the flexor reflex noted by McCouch (1936) whereas it is the group III band in action that provokes the crossed extensor reflex that is linked classically with the ipsilateral withdrawal (i.e. flexor reflex) from a source of pain-producing stimulation (Perl, 1957). It is further of interest that the stretch threshold of the secondary spindle endings is so low (Hunt, 1954) that the group II flexor reflex of muscle origin cannot in the present state of knowledge reasonably be considered a nociceptive reaction. None of this, of course, proves that the group II reflex of cutaneous origin is not a nociceptive reaction.

## BIBLIOGRAPHY

- Alvord, E. C., Jr., and Fuortes, M. G. F., A comparison of flexor reflexes of cutaneous and muscular origin, *J. Physiol.*, 1954, **123**, 251.
- Bernhard, C. G., Distribution of internuncial activity in a multineuron reflex chain, *J. Neurophysiol.*, 1945, **8**, 393.
- Bernhard, C. G., and Widén, L., On the origin of the negative and positive spinal cord potentials evoked by stimulation of low threshold cutaneous fibers, *Acta Physiol. Scand.*, 1953, **29**, suppl 106, 42.
- Eccles, J. C., and Sherrington, C. S., Studies on the flexor reflex. 1. Latent period, *Proc. Roy. Soc. London, Series B*, 1931, **107**, 511.
- Forbes, A., The interpretation of spinal reflexes in terms of present knowledge of nerve conduction, *Physiol. Rev.*, 1922, **2**, 361.
- Gasser, H. S. Pain-producing impulses in peripheral nerves, in *Pain*, (H. G. Wolff, H. S. Gasser, and J. C. Hinsey, editors), Research Publication, Association for Research in Nervous and Mental Disease, Baltimore, The Williams and Wilkins Co., 1943, **23**, 44.
- Hagbarth, K. E., Excitatory and inhibitory skin areas for flexor and extensor motoneurons, *Acta Physiol. Scand.*, 1952, **26**, suppl. 94, 1.
- Hunt, C. C., Relation of function to diameter in afferent fibers of muscle nerves, *J. Gen. Physiol.*, 1954, **38**, 117.
- Hunt, C. C., Temporal fluctuation in excitability of spinal motoneurons and its influence on monosynaptic reflex response, *J. Gen. Physiol.*, 1955 *a*, **38**, 801.
- Hunt, C. C., Monosynaptic reflex response of spinal motoneurons to graded afferent stimulation, *J. Gen. Physiol.*, 1955 *b*, **38**, 813.
- Lloyd, D. P. C., Reflex action in relation to the pattern and peripheral source of afferent stimulation, *J. Neurophysiol.*, 1943 *a*, **6**, 111.
- Lloyd, D. P. C., Neuron patterns controlling transmission of ipsilateral hind-limb reflexes in cat, *J. Neurophysiol.*, 1943 *b*, **6**, 293.
- Lloyd, D. P. C., On the relation between discharge zone and subliminal fringe in a motoneuron pool supplied by a homogeneous presynaptic pathway, *Yale J. Biol. and Med.*, 1945, **18**, 117.
- Lloyd, D. P. C., Integrative pattern of excitation and inhibition in two-neuron reflex arcs, *J. Neurophysiol.*, 1946, **9**, 439.

- Lloyd, D. P. C., Electrical manifestations of action in neurons, *in* The Biology of Mental Health and Disease, New York, Paul B. Hoeber, Inc., 1952, 135.
- Lloyd, D. P. C., Monosynaptic reflex response of individual motoneurons as a function of frequency, *J. Gen. Physiol.*, 1957, **40**, 435.
- Lloyd, D. P. C., and McIntyre, A. K., Analysis of forelimb-hindlimb reflex activity in acutely decapitate cats, *J. Neurophysiol.*, 1948, **11**, 455.
- Lloyd, D. P. C., and McIntyre, A. K., Dorsal column conduction of Group I muscle afferent fibers and their relay through Clarke's column, *J. Neurophysiol.*, 1950, **13**, 39.
- Lloyd, D. P. C., and McIntyre, A. K., Monosynaptic reflex responses of individual motoneurons, *J. Gen. Physiol.*, 1955, **38**, 771.
- Lloyd, D. P. C., and Wilson, V. J., Reflex depression in rhythmically active monosynaptic reflex pathways, *J. Gen. Physiol.*, 1957, **40**, 409.
- Lorente de N6, R., Vestibulo-ocular reflex arc, *Arch. Neurol. and Psychiat.*, 1933, **30**, 245.
- Lorente de N6, R., Analysis of the activity of the chains of internuncial neurons, *J. Neurophysiol.*, 1938, **1**, 207.
- McCouch, G. P., Note upon crossed reflexes in the acutely spinal cat, *Am. J. Physiol.*, 1936, **115**, 78.
- Perl, E. R., Crossed reflexes of cutaneous origin, *Am. J. Physiol.*, 1957, **188**, 609.
- Rall, W., A statistical theory of monosynaptic input-output relations, *J. Cell. and Comp. Physiol.*, 1955 *a*, **46**, 373.
- Rall, W., Experimental monosynaptic input-output relations in the mammalian spinal cord, *J. Cell. and Comp. Physiol.*, 1955 *b*, **46**, 413.
- Rall, W., and Hunt, C. C., Analysis of reflex variability in terms of partially correlated excitability fluctuation in a population of neurons, *J. Gen. Physiol.*, 1956, **39**, 397.
- Ranson, S. W., and Hinsey, J. C., Reflexes in hind limbs of cats after transection of the spinal cord at various levels, *Am. J. Physiol.*, 1930, **94**, 471.
- Rosenblueth, A., Wiener, N., Pitts, W., and Garcia Ramos, J., A statistical analysis of synaptic conduction, *J. Cell. and Comp. Physiol.*, 1949, **34**, 173.