A.1 Introduction by Julian Jack

Rall, W. (1955a). A statistical theory of monosynaptic input-output relations. *J. Cell. Comp. Physiol.* 46:373–411.

Rall, W. (1955b). Experimental monosynaptic input-output relations in the mammalian spinal cord. *J. Cell. Comp. Physiol.* 46:413–437.

Rall, W., and Hunt, C. C. (1956). Analysis of reflex variability in terms of partially correlated excitability fluctuation in a population of motoneurons. *J. Gen. Physiol.* 39:397–422.

Not long after Wil Rall decided to shift from physics into biology, he was attracted to migrate from the United States to New Zealand because John Eccles, then the leading proponent of the electrical hypotheses of synaptic excitation and inhibition (Eccles 1945; Brooks and Eccles 1947) offered him a faculty position (in response to a tentative inquiry from Wil). When Rall arrived in 1949, relative calm prevailed in the literature with respect to the ideas about synaptic mechanisms. All the leading players in the field (Lorente de Nó, Eccles, and Lloyd) agreed that synaptic excitation was a dual-component phenomenon, with a brief, spatially restricted process that secured firing of the cell and a more prolonged, general process that could lower the effective threshold for the first process. These two processes were called "detonator action" and "residual facilitation" respectively (Brooks and Eccles [1948] used the terms α and β facilitation). A representation of their respective time courses is given in figure 1, taken from a chapter by Lloyd in the sixteenth edition of *A Textbook of Physiology*, edited by J. F. Fulton (1949). The actual mechanisms envisaged were various, but one possibility was that the "detonator action" might be a very brief localized process on the nerve cell body, akin to the "local response" that had been described in peripheral nerve (Hodgkin 1938; Katz 1947), whereas "residual facilitation" simply reflected the underlying depolarization ("catelectrotonus") that spread by passive electrical propagation throughout the nerve cell membrane surface.

Although the preceding account may read rather quaintly to younger neuroscientists, the issues that were being addressed are still very alive today. The "global" hypothesis of synaptic excitation, in which depolarizing effects from all over the cell surface are "collected" at the cell body initial segment where a decision is made about firing of the cell (Eccles 1957, 1964) has been the dominant account for the motoneurone in the past 30 years; the principal evidence in favor of this account came with the advent of intracellular recording from motoneurones (Woodbury and Patton 1952; Brock, Coombs, and Eccles 1952; Coombs, Eccles, and Fatt 1955a and 1955b; Fuortes, Frank, and Becker 1957). Nevertheless, there are plenty of suggestions from the experimental literature that regenerative responses and even action potentials may sometimes be generated as a result of more restricted activity, particularly in the dendrites (Kandel and Spencer 1961; Llinas et al. 1968; etc.). The purpose of this commentary is to present an abbreviated account of the development of thinking about

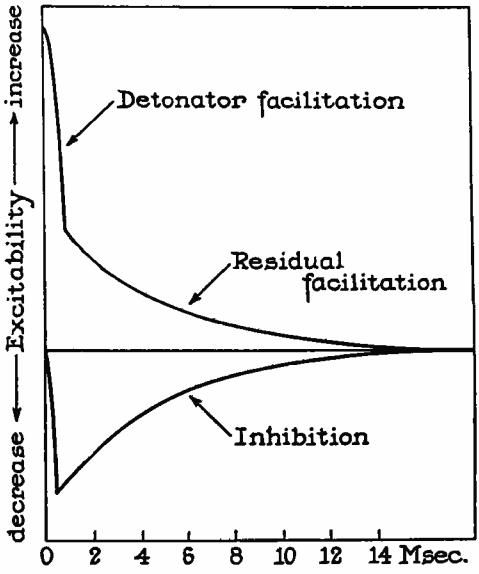

Figure 1
Schematic diagram of the presumed time course of excitability changes produced by the action of presynaptic excitatory or inhibitory volleys on spinal cord motoneurones. The illustration is based on the work of Lloyd and of Brooks and Eccles (from Lloyd 1949).

these issues in the period from 1938 to 1960 and to display the key role that Rall played in bringing quantitative clarity to some of the rather intuitive thinking that then prevailed.

Lorente de Nó (1938, 1939) argued that his evidence was incompatible with the assumption that firing threshold for oculomotor neurones could be given simply by the total number of synaptic knobs activated because he noted that a large presynaptic volley could be ineffective but a smaller volley from the same source, when combined with synaptic input from another source, also subthreshold, could evoke discharge. Similar observations and conclusions were reported by Lloyd (1945) for spinal cord motoneurones; Lloyd made this point more quantitative by considering the relationship between size of the presynaptic input volley and the magnitude of the postsynaptic output (input-output curve). In his doctoral thesis, completed in 1953 and published in 1955 (Rall 1955a, 1955b), Rall considered these arguments and pointed out that all the observations were compatible either with a simple concept of threshold in terms of total number of knobs activated or as a zonal concept in terms of a certain number of knobs being activated at a discrete zone on the neurone. "With either threshold definition, it seems sufficient to assume that the first afferent source distributes knobs fairly evenly over a large motoneurone pool,

while the second afferent source distributes its knobs preferentially to a small group of motoneurones within the large pool" (Rall 1955a). The essence of Rall's point was that one could not necessarily think about the behavior of a population of neurones as if they were equivalent to a single "average" neurone. Rall went further and developed a theoretical treatment for the input-output relationship of a neurone population in which the distribution of synaptic knobs to the neurones of the pool was random in terms either of individual knobs or of knob clusters. The threshold criterion for firing of an individual neurone could be defined either in terms of total number of active knobs, irrespective of location, or as a local number of knobs active in a discrete area of the neurone. Finally, the distribution of the threshold value (on either criterion) across the pool of motoneurones was also assumed to be random and independent of active knob distribution.

With these models, Rall was able to predict the expected types of input-output curves for various values of the theoretical parameters, and in a companion experimental paper (Rall 1955b) he showed that the data for spinal cord motoneurones was equally compatible with models adopting either of the two competing threshold criteria. Thus, Rall did not claim to have disproved the zonal concept of neurone threshold, but he was able to conclude that the nature of the evidence so far offered was not adequate to establish it.

The concept of "detonator action" not only contained the idea of restricted spatial location but also of brevity: it was supposed to last about 0.5 msec (Lloyd 1949). As part of his thesis research, Rall also partly addressed this issue, by modeling the time course as well as the spatial summation properties of focal depolarizations on the membrane of a cell soma (modeled as a sphere). He was able to show that brief, focal depolarization tended to equalize around the soma on the time scale of a microsecond rather than a millisecond, so that the effect of one such input would have equalized and become uniform in its efffect over the time scale of the rising phase of a synaptic potential (Rall 1953, 1955a, p. 403). Thus, the mechanism of a brief, zonal "detonator action" could not be explained by the spatiotemporal summation characteristics of passive electrotonus, but this treatment did not exclude some form of "local response" mechanism, that is, the activation of the voltage-dependent sodium conductance in a restricted region, generating further inward, depolarizing current without necessarily securing the firing of an action potential by the cell. Indeed, this general possibility was left open by Eccles, on the basis of his intracellular studies (see Coombs, Eccles, and Fatt 1955b; Eccles 1957), although subsequently quietly forgotten.

There also still remained the experimental observations of Brooks and Eccles (1948) that there were two phases to the "facilitation" curve (see figure 2). It is interesting that Rall does not discuss this evidence explicitly in his 1955 papers, perhaps because he was skeptical about the experimental result. In the experimental paper, he does consider the problems of interpretation when two different motoneurone pools can both be contributing to the output measurement; this is certainly the situation that prevailed in the Brooks and Eccles experiment.

This was not the end of the story. Archie McIntyre had become the Professor of Physiology in Dunedin in 1952, when Eccles left to become the foundation Professor of Physiology at the Australian National University in Canberra. McIntyre had close links with Lloyd, having previously collaborated with him, and he doubtless reported to Lloyd the gist of Rall's criticisms. The obvious response for those still committed to a zonal theory of excitation was to study the behavior of individual motoneurones, rather than a population. McIntyre went on sabbatical leave to Lloyd's laboratory at the Rockefeller Institute (as Rockefeller University then was), where Carlton Hunt was also working. These three workers produced a series of five papers in volume 38 of the *Journal of General Physiology*, which occupied about 100 pages (Lloyd, Hunt, and McIntyre 1955; Lloyd and McIntyre 1955a, 1955b; Hunt 1955a, 1955b). With respect to the mechanism of firing of the motoneurone, the most detailed examination was contained in the final paper of the series (Hunt 1955b), in which it was concluded that the results "exclude the postsynaptic potential as the essential step in the normal production of discharge." By this Hunt meant that the effect he observed "could not result if transmitter potentiality resulted from a simple summation of independent knob actions. There must be an interaction between excitatory synaptic knobs." In another passage, Hunt also concluded that "transmitter potentiality must decay considerably within 0.2 to 0.3 insec." Thus, one major conclusion arising from this work was a reaffirmation of a zonal interaction of brief time course. Transmitter potentiality (the ability of synaptic input to secure firing of the cell) was concluded to have the same properties as had earlier been postulated for "detonator action."

A modern reader of these papers, not steeped in the literature of the period, would find them difficult to read and would likely dismiss them because the conclusions outlined here have not survived. This would be a mistake. These five papers, and the subsequent paper in which Rall was involved (Rall and Hunt 1956) remain important, not because they reached the aforementioned conclusions but because they were the first attempt to characterize a population of neurones in terms of the distribution of their functional responsiveness and also to give an account of the

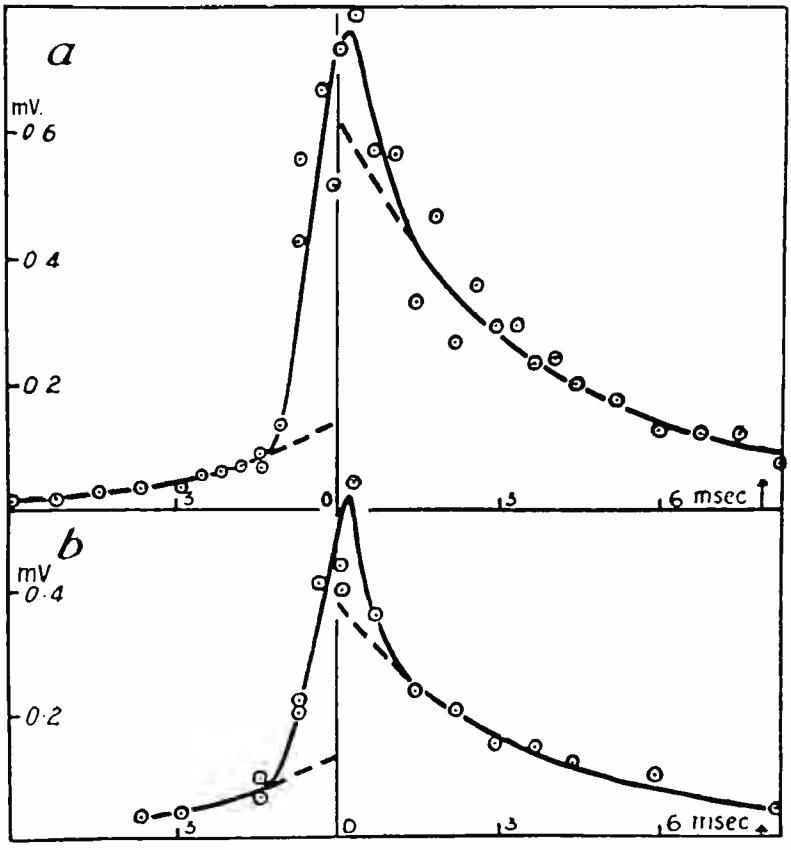

Figure 2
The time course of facilitation of monosynaptic reflex responses, recorded in the first sacral ventral root, to stimulation of the group I afferent fibres in both the medial and lateral gastrocnemius muscle nerves. When the medial gastrocnemius nerve was stimulated alone, a small reflex response was evoked, whose size is indicated by the height of the arrows to the right. Stimuli to the lateral gastrocnemius nerve alone did not evoke a reflex response. The ordinate plots the magnitude of the reflex firing when both nerves are stimulated; the abscissa gives the interval between the two stimuli, with zero being simultaneous stimulation and time intervals to the right showing how much the lateral gastrocnemius volley leads the medial gastrocnemius volley (and vice versa for intervals to the left). The upper curve (a) is for maximal group I stimuli to both nerves, and the lower curve (b) is for 30% below maximal stimuli (from Brooks and Eccles 1948).

fluctuations, about the average value, in this functional responsiveness. To my knowledge, this work has yet to be emulated for any other neuronal population, and it thus remains an exemplar for future neuroscientists who may wish to move away from models representing a single functional task by a single neurone or a population with identical properties, to the more realistic situation where a distribution of properties means the population of cells is realistically represented.

Before considering this aspect of these papers, it is best to consider why Hunt's conclusions are likely to be incorrect and, with the advantage of retrospection, to outline briefly how he came to misinterpret his data.

If the "detonator action" concept of excitation was correct for the motoneurone, then the observed neurone threshold could not be equated with a fixed level of depolarization of the soma, when initiated by different excitatory afferent inputs, for the "critical assemblage" of synaptic knobs could be activated at different levels of net generalized depolarization of the motoneurone. Subsequent to the publication of these papers, both Fatt (1957) and Eccles, Eccles, and Lundberg (unpublished observations quoted in Eccles, Eccles, and Lundberg 1957) with intracellular recording observed that there was no significant difference in the levels of depolarization required to initiate discharge from different excitatory afferent sources. That is, the neurone threshold appeared to be simply a fixed membrane potential. Additional evidence against Hunt's view came from the observation that (with group Ia afferent monosynaptic excitation) the motoneurone spike invariably arose from one part of the motoneurone (Fuortes, Frank, and Becker 1957; Fatt 1957; Coombs, Curtis, and Eccles 1957).

Relatively little experimental attention was given to Hunt's conclusion that transmitter potentiality had a rapid temporal decay. If this conclusion were correct, it would be expected that monosynaptic reflex firing of individual motoneurones should have a narrow latency range. Coombs, Eccles, and Fatt (1955a) reported that the somatic impulse arose 0.3 to 1.2 msec after the onset of the EPSP, and later Coombs, Curtis, and Eccles (1957) recorded a similar latency spread. This range, of up to one millisecond, is wider than that predicted by a transmitter potentiality that "must decay considerably within 0.2 to 0.3 msec" (Hunt 1955b, p. 823).

Thus, the various experiments indicated that Hunt's interpretations of his experimental evidence needed to be reappraised. In retrospect there were two crucial assumptions made by Hunt that are unlikely to be correct. The first was that the group Ia excitatory input was recruited linearly through the group I afferent fiber range. Rall (1955b) had already questioned this point, and subsequent experimental studies strongly suggest that it is not correct (e.g., Jack 1978). Linked to this was a problem about

the measurement of input-output curves when interacting the afferent inputs from two sources. It is likely that the method used by Hunt was ineffective in separating the two pools of motoneurones that could potentially discharge; thus, his recorded input-output curve (which increased fairly linearly throughout the group I range) was a combination of a convex upward facilitation input-output curve for the conditioned motoneurone pool, and superimposed on this, a concave upward input-output curve for the effect of the conditioning volley on its motoneurone pool.

This same point is also likely to be the explanation for the time course of "facilitation" in figure 2 because the conditioning action of a volley can occur even when the conditioning volley follows the test volley into the nervous system, owing to the finite time taken to bring the motoneurones to near discharge. This effect is illustrated in figure 3 under conditions where the conditioning volley was so weak that it did not discharge its own motoneurones. By contrast, in the experiments of Brooks and Eccles illustrated in figure 2, both the "conditioning" and "testing" volleys fired

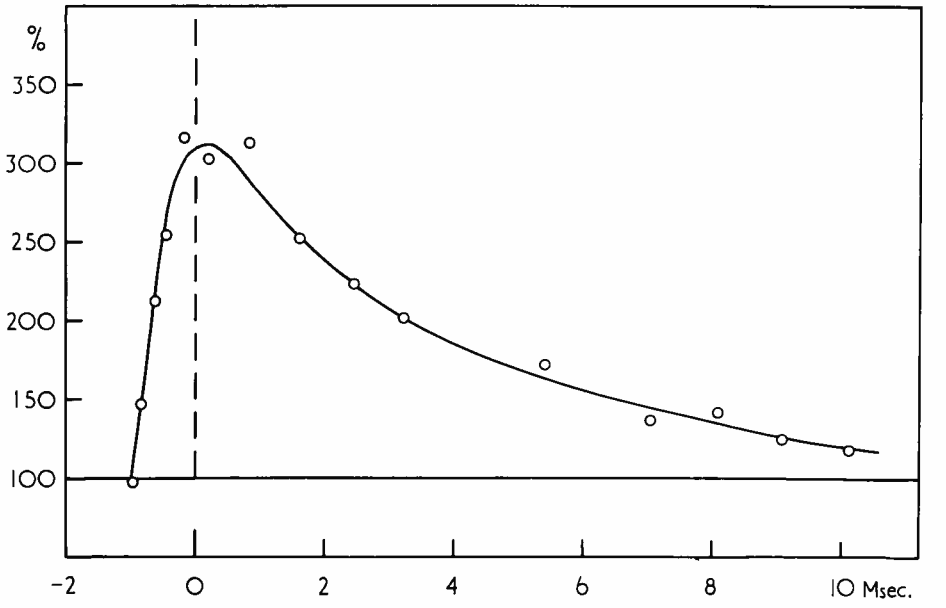

Figure 3
The effect of a weak lateral gastrocnemius-soleus afferent volley on a medial gastrocnemius test monosynaptic reflex, recorded in the first sacral ventral root. The convention for timing is that zero time represents simultaneity of the conditioning and testing volleys as they enter the spinal cord; intervals to the left of zero on the abscissa are for the testing volley leading the conditioning volley, and vice versa for intervals to the right. In this experiment care was taken to ensure that there was no discharge of the lateral gastrocnemius-soleus motoneurones, by using a very small group Ia lateral gastrocnemius-soleus conditioning volley, in contrast to the experiments shown in figure 2 (from Jack 1965).

their own motoneurones, and in the interval either side of "zero" time both volleys were acting to "condition" (i.e., facilitate) the other pool of neurones. Thus the α and β phases of facilitation ("detonator" and "residual" facilitation) do not represent two different types of facilitation; rather, facilitation has the same time course as the excitatory postsynaptic potential. β facilitation maps to the, decaying phase of the EPSP and α to the rising phase. The α phase in the left-hand half maps to the β phase in the right-hand half of the figure (and vice versa). What both Brooks and Eccles, and Lloyd, had done had been to make the attribution of both α and β phases on one side of the figure to a single conditioning volley, because they assumed that no effect could be produced before "zero" time. Once this error is realized, it is clear that "detonator action" or α facilitation could be correlated with the rising phase of the EPSP.

As already mentioned, one notable feature of the Rall and Hunt (1956) paper was to model a population of nerve cells as a distribution. The output of the pool that they analyzed was the distribution of the probabilities that individual motoneurones would fire. Lloyd and McIntyre (1955a) had already suggested that there was a uniform distribution in the average excitability of the motoneurones and a normal distribution of the fluctuation of the excitability level about the mean value. Rall and Hunt were able to define quantitatively "the extent to which excitability fluctuations of a motoneurone pool are correlated and the precise manner in which the response of the individual motoneurone is linked to the response of the population of which it is a member." They observed that for a particular motoneurone its probability of firing shows a systematic relationship to the magnitude of response of the motoneurone pool: a larger response from the pool being matched by a higher probability that the unit would fire. It is notable that Rudomin and his colleagues (Rudomin and Dutton 1969; Rudomin, Dutton, and Muñoz-Martinez 1969; Rudomin and Madrid 1972) are one of the few groups to extend and develop this pioneering population modeling by Rall and Hunt.

I would like to finish this discussion by briefly outlining how Rall and Hunt's paper inspired me to address in more detail the issue of "detonator" action of the motoneurone. Despite the observation that the motoneurone fired with a latency range of about one millisecond, it could be objected that this might have arisen as some artifact from intracellular recording; for example, that the microelectrode, as is now known, might induce a substantial electrical leak. Thus, in 1959, Lloyd and Wilson objected to the measurement of latencies of somatic spike potentials and suggested instead that the criterion should be reflex discharge of the axon.

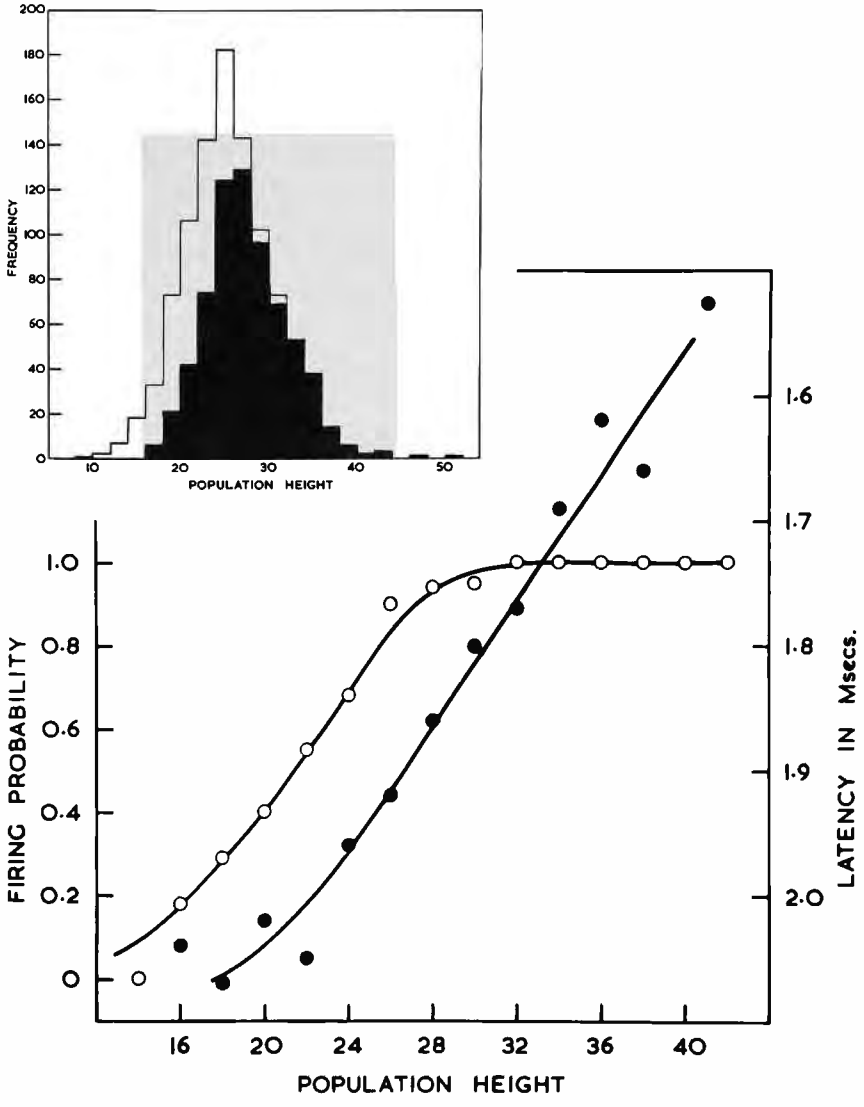

Figure 4
The abscissa plots the size (measured in arbitrary units and recorded in the first sacral ventral root) of a monosynaptic test reflex evoked by maximal group I afferent stimulation of the biceps-semitendinosus nerve. The mean amplitude was 27, with a range of reflex response sizes from 8 to 52 (see inset). In addition, the response of a single motoneurone was recorded from the seventh lumbar ventral root; this motoneurone had an average probability of firing of about 0.7. As illustrated in the inset, the single motoneurone was more likely to fire (blackened area of the histogram) when the response of the population of motoneurones was larger, indicating that the excitability of this single motoneurone was partially correlated with that of the population. In the main figure the estimated firing probability (open circles) and mean latency of firing (filled circles) for each class interval of population height is illustrated. The sigmoid shape of the firing probability curve is similar to those described by Rall and Hunt (1956). Data from Jack 1960.

As a check on the intracellular results, I recorded a single motoneurone discharge, as well as that of the population, in the ventral root. The latency range for the firing of the unit, with constant afferent stimulation, was 1.25 msec (Jack 1960), in complete accord with the intracellular data.

The data recorded included not only whether the unit fired (and, if so, at what latency) but also the size of the population response. In agreement with the results of Rall and Hunt, the probability of the unit firing was partially correlated with the size of the population response. The population response sizes were grouped, and, in addition to the firing probability associated with each size, the mean latency of unit firing was measured. As illustrated in figure 4, as the firing probability of the unit increases (with the larger population heights), the mean latency of firing decreases. Furthermore, although the firing probability curve plateaus when it reaches its maximal value, the mean unit latency continues to decrease. Associated with these changes in the mean of the unit latencies, there were characteristic changes in the distribution of the latencies about the mean, going from Gaussian for $p = 1.0$ to positively skewed for $0.5 < p < 1.0$ to Gaussian again for $p < 0.5$. It was possible, in a very informal model, to show that these latency distributions would arise if there were both correlated and uncorrelated variability between the unit and the population, with the excitatory time course being similar to that of the rising phase of an EPSP (Jack 1960). Thus, just as Rall's earlier (1955a, 1955b) papers had clarified the earlier discussion of the relationship between threshold and zonal aggregation of synapses, so did his later 1956 paper allow a further examination of this issue for the motoneurone. Doubtless the motoneurone will not prove to be typical of all cells (cf. pyramidal cells or Purkinje cells), but the vicissitudes of interpretation in the two decades from the late 1930s surely carry forward the lesson that quantitative clarity should be treasured.

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