The Neuron Doctrine: A Revision of Functional Concepts

GORDON M. SHEPHERD

Department of Physiology, Yale University School of Medicine, New Haven, Connecticut 06510 and The Institute of Neurological Sciences, University of Pennsylvania, Philadelphia, Pennsylvania

Received for publication September 12, 1972

INTRODUCTION

The functional tenets of the neuron doctrine were reviewed some time ago (1–3), but there has been little attempt to correct obvious deficiencies or formulate new concepts that take into account the great amount of anatomical and physiological work of recent years. Among these studies, the findings of synapses between dendrites of nerve cells are of particular interest (reviewed in 4). The reports are by now sufficiently numerous and well-documented to indicate that dendrodendritic synapses are a widespread and important phenomenon in the vertebrate nervous system, especially the mammalian brain. However, the patterns of connections and the functions they mediate have been difficult to comprehend within the context of the classical doctrine.

It is timely therefore to reappraise the neuron doctrine in the light of recent work. Discussion will be focussed on the mammalian olfactory bulb, where dendrodendritic synapses were first identified (5) and where the case for a revision of classical concepts can be set forth most clearly. Specific proposals will be made, that the neuron can no longer be regarded as the basic functional unit of the nervous system; rather, the nervous system is organized on the basis of functional units whose identity in many cases is independent of neuronal boundaries. It will be shown that these proposals are supported by increasing evidence from other work that goes beyond the confines of the classical doctrine.

1 This article summarizes views presented in a seminar course on “Principles of Neuronal Organization” (Fall, 1971) and in a lecture (May, 1972) while the author was visiting professor at The Institute of Neurological Sciences, University of Pennsylvania.
THE CLASSICAL DOCTRINE

The original formulation of the neuron doctrine (cf. 6) was primarily concerned with establishing that all nerve fibers arise from nerve cells and all fibers terminate in free endings. Communication between neurons is, therefore, through contacts (synapses) and not through a continuous reticular network. These two points established the neuron as the morphological unit of the nervous system. It is quite possible that future studies of intercellular connections (cf. 7) may modify our concept of the morphological independence of neurons, but the proposals to be developed here will be seen to be sufficiently general to take this into account. This also applies to the metabolic, trophic, and genetic independence of the neuron that have been assumed under the classical doctrine.

In establishing the nerve cell as a morphological unit, the early workers also identified the structural features of nerve cells and attempted to attach functional interpretations to them. Among the histologists, Cajal(6) was foremost in giving the neuron doctrine this orientation. His ideas were supported and extended by the concepts of the synapse and the integrative action of the nervous system introduced by Sherrington(8). Since their time, it has, therefore, been commonplace to set forth certain additional statements as a part of the neuron doctrine:

1. Each neuron has identifiable parts: a cell body (containing the nucleus) and two types of process: a single axon, and one or more dendrites.
2. Neurons have a functional polarization, from the dendrites and cell body (which are synaptic receptors) through the axon (which generates and conducts impulses) to the axon terminals (which are synaptic effectors).
3. The morphological neuronal unit is, therefore, also the basic functional unit of the nervous system. Chains of these units make up the reflex and central pathways of the brain.

These statements, in one form or other, may be found in virtually every textbook of biology, neuroanatomy, neurophysiology, psychology, and behavior; in accounts of neural modeling, and in popular expositions of the brain.

THE MOTONEURON MODEL

From classical times to the present day the motoneuron of the spinal cord has invariably been cited as the model that illustrates the functional aspects of the neuron doctrine. The modern version of the model may be summarized in relation to the diagram of Fig. 1. Axon terminals from a variety of sources make synapses onto the motoneuronal soma and dendrites. As is well known(9), impulses invading the terminals activate the synapses, producing either excitatory postsynaptic potentials (epsps) or inhibitory postsynaptic potentials (ipsps). Epsps depolarize the soma-dendritic membrane, and passive electrotonic spread of the depolarization to the axon hillock leads to impulse generation when threshold is reached. The impulse propagates into the axon and is conducted to the distant axon terminals, there to activate the effector synapses (onto the
Fig. 1. Schematic diagram of synaptic organization of spinal motoneuron. MO: motoneuron; IN: interneuron; RE: Renshaw interneuron. Large arrows indicate impulse traffic; small arrows indicate functional polarity of synapses, and direction of activity within motoneuron.

muscles). Ipsps, on the other hand, have a polarizing action which tends to hold the membrane potential below threshold, thereby inhibiting impulse generation by the epsps.

In this model the overall flow of activity is unidirectional, from presynaptic axon terminals through postsynaptic soma and dendrites to the axon hillock, thence through the axon to the axon terminals, in accordance with Cajal's concept of functional polarization (point 2 above). It is important to note that the only output from the motoneuron is through its axon. Exceptions to the model have been encountered in the motoneuron itself: interactions between axon terminals of primary afferents (9,10), interactions between dendrites (11,12), impulse spread from axon hillock into cell body and dendrites (13); remote inhibition (14); but these have never brought the model into serious question.

THE MITRAL CELL MODEL

The extent to which the motoneuron may serve as a model for other neurons may be assessed by considering the mitral cell of the olfactory bulb. The mitral cell resembles the motoneuron in many respects (see Fig. 2). It is a projection neuron, sending a long myelinated axon to distant regions; it has relatively large dendrites with smooth surfaces, and a well-developed system of axon collaterals. Like the motoneuron, it receives input from primary sensory afferents. In physiological studies the sequence of synaptic excitation by a volley in the
FUNCTIONAL CONCEPTS OF NEURON

Fig. 2. Schematic diagram of synaptic organization of mitral cell of olfactory bulb. MI: mitral cell; PG: periglomerular short-axon cell; GR: granule cell.

afferent fibers is similar to that outlined above for motoneurons(15,16). After impulse generation there is a long period during which the mitral cell is inhibited; this is similar to the inhibition mediated by the Renshaw pathway onto motoneurons (see below).

Beyond these similarities, the mitral cell has properties without parallel in the motoneuron. The schema emerging from a conjunction of physiological, biophysical and electron microscopical studies is as follows(15–23) (see Fig. 2). Input through the olfactory nerves produces synaptic excitation of mitral dendritic tufts in the olfactory glomeruli. The epsp has a dual function: one is to activate local dendritic synapses onto the dendrites of periglomerular (PG) cells; the other is to spread to the primary dendritic trunk, and through it to generate an impulse in the mitral cell axon hillock. This impulse in turn has a dual function: it propagates into the axon, and also spreads back into the secondary dendrites, activating excitatory synapses from them onto the dendritic spines of granule cells.

The new aspects of neuronal organization revealed by this work include: dendrites are presynaptic as well as postsynaptic structures; dendrites may have synaptic connections with other dendrites; activation of dendritic synapses may occur by local graded synaptic potentials (olfactory glomeruli) or by an impulse spreading from the axon hillock (mitral secondary dendrites). Note that the mitral cell has numerous synaptic outputs at all levels of its dendritic tree, in addition to the axonal outputs through its axon collaterals and distant axon
MODELS FOR INTERNEURONS

Comparison may also be made between the interneurons in spinal cord and olfactory bulb. In the spinal cord, recurrent inhibition is believed to be mediated by a pathway from motoneuron axon collaterals onto Renshaw cells, and thence from Renshaw cell axons onto motoneuronal dendrites (24) (see Fig. 1). Despite difficulty in demonstrating them histologically, Renshaw cells have become the prototype for inhibitory interneurons elsewhere in the central nervous system (e.g., cerebellar basket cells, thalamic short-axon cells, hippocampal short-axon cells, cortical stellate cells) (25).

From their external similarity, as viewed with Golgi stains, it might be expected that the short-axon (PG) cells of the olfactory bulb would resemble Renshaw cells. However, the schema emerging from them is much more complex (18,21–23) (see Fig. 2). Their dendrites receive synaptic excitation from the mitral dendritic tufts, as mentioned above. The epsp in the dendrites appears to have a dual role: local activation of inhibitory synapses from the PG dendrites back onto the mitral dendrites (through serial or reciprocal dendrodendritic synapses), and spread to the PG cell axon hillock to generate an impulse. The impulse propagates into the axon, and may also spread back into the dendrites, to further activate dendritic synapses onto neighboring dendrites. The similarity of these functional patterns to those outlined for the mitral cell is apparent.

The other type of interneuron in the olfactory bulb is the granule cell (GR, Fig. 2). This neuron lacks a morphologically identifiable axon, and hence has always stood out as an exception to the neuron doctrine (point 1). Its dendrites are covered with numerous spines, so that the motoneuron model offers few a priori insights into its functional organization. In fact, the granule dendritic spines and the mitral dendrites are interconnected by numerous reciprocal synapses (5,26–28). The mitral-to-granule synapses (activated by the impulse in the mitral cell) produce epsps in the granule spines as described above. These in turn activate the inhibitory synapses from the spines onto the mitral dendrites (19) (see Fig. 2). This dendrodendritic pathway is the only synaptic output from the granule cell. It appears to function through graded synaptic potentials, without need for generation of impulses. Note that the granule cell differs from the other two types of bulbar neuron, not in its having synaptic output at the sites of dendritic synaptic input (all three types have that), but rather in lacking the additional axonal output pathway.

CONCEPT OF A FUNCTIONAL UNIT

The inadequacy of the neuron doctrine in accounting for the new findings in the mitral cell and its interneurons is mainly due to the classical notion that
the morphological neuron is a single functional entity, and all types of neurons are functionally similar or equivalent. Bullock (2) previously pointed out the inadequacy of this view, particularly with regard to invertebrate neurons. That this notion should have prevailed for so long in the mammalian brain can be ascribed to the fact that the motoneuron has continued to be regarded in Sherringtonian terms as one final common path, a single integrative entity, for its many overlapping inputs.

The mitral cell and its interneurons, by contrast, appear as specialized neurons with multiple functions. In order to identify these functions we need to free the term "functional unit" from its association with the entire neuron. We can then propose that a functional unit may be defined in the most general sense as the morphological substrate for a specific function. We will identify several basic types of functional unit in the olfactory bulb, and compare them with examples drawn from other parts of the brain.

**SYNAPTIC UNITS**

At the finest level of organization is the synaptic unit. The simplest such units are formed by a single axon terminal onto a single dendritic branch (Fig. 3 a) or spine (Fig. 3 a'). In the numerous instances in the olfactory bulb in which two types of dendritic terminal are interconnected by dendrodendritic synapses, a multisynaptic unit is formed (Fig. 3 b). In the diagrams of Fig. 3, summing points (\( \bullet \)) are noted for input–output relations. At each point there is summing

---

**Fig. 3.** Types of synaptic units. a. axodendritic branch unit. a', axodendritic spine unit. b. multisynaptic axodendritic and dendrodendritic unit (olfactory bulb). c. multisynaptic axodendritic glomerular unit (cerebellum). d. multisynaptic axodendritic and dendrodendritic glomerular unit (thalamus). Arrows indicate polarity of interneuronal (synaptic) and intraneuronal pathways. Convergence points for input–output relations are indicated by (\( \bullet \)). In (b–d), open profiles indicate principal neuron, shaded profiles indicate interneuron. Diagrams (b–d) summarize most common patterns reported for multisynaptic units; specific patterns vary and may include other types of synaptic terminals.
of input and divergence of output; in this sense each terminal functions as an input–output unit in analogy with the whole neuron of the classical doctrine. Note that the inputs to a summing point are both intraneuronal (by spread of electric current) and interneuronal (synaptic); similarly, the outputs are intraneuronal (for the axodendritic units a and a') and also interneuronal (for the dendrodendritic units in b). All possible variations on the synaptic patterns illustrated in Fig. 3 b are seen in the olfactory bulb; comparison should be made with the diagram of Fig. 2. These multisynaptic units in the olfactory bulb provide the morphological substrates for self- and lateral inhibition(5,19,21–23).

Synapses of the simple axodendritic type (Fig. 3 a, a') are, of course, widely found in the nervous system. In recent years, dendrodendritic synapses have been described in a number of regions besides the olfactory bulb. In the three sensory relay nuclei of the thalamus (medial geniculate body(29), lateral geniculate body(30,31), ventrobasal complex(32,33)), dendrodendritic synapses are localized within so-called synaptic glomeruli, which are tightly confined multisynaptic units surrounded by glial membranes(34). A common arrangement is for a large terminal of an afferent axon to have synapses onto two types of dendrite, one from the primary relay neuron of the nucleus, the other from an intrinsic short-axon cell (see Fig. 3 d). The two dendrites are also interconnected with synapses; both serial and reciprocal connections have been described. Note in Fig. 3 the similarity between the multisynaptic units in the thalamus (d) and the olfactory bulb (b). The single afferent terminal with synapses onto both dendrites (d) would appear to be a simpler and more rigid arrangement than in (b). It remains to be tested whether these multisynaptic units play a role in the feedforward and feedback inhibition that have been described in the thalamic nuclei(25). Ralston(35) has proposed a schema for activation of dendrodendritic synapses in the thalamus that bears a close resemblance to the previous suggestions in the olfactory bulb.

Synaptic glomeruli are also present in the cerebellum(34). The arrangement there is for the single large terminal of a mossy fiber to make synapses onto the dendrites of two types of neuron, granule cells and Golgi cells. If the granule cell is regarded as a type of relay neuron(6), and the Golgi cell is regarded as a type of intrinsic neuron with short axon, a schematic diagram can be constructed for comparison with the synaptic glomeruli in the thalamus (see Fig. 3 c). It can then be seen that the two types of multisynaptic unit differ chiefly in the lack of synapses between the dendrites within the cerebellar glomerulus. This would appear to provide for a still more simple type of transmission than in the case of the thalamus (Fig. 3 d) and olfactory bulb (Fig. 3 b).

In the retina, synapses between neuronal processes bear a close resemblance in their patterns of interconnection to the dendrodendritic synapses in the olfactory bulb(36,37). Dendrodendritic synapses have also been found in the superior colliculus(38,39) and, most recently, in the motor area of the cerebral cortex of primates(40). Although identification of dendritic processes is more difficult in these regions, it appears that the organization of multisynaptic units falls within the general pattern seen in the olfactory bulb. Physiological analyses
FUNCTIONAL CONCEPTS OF NEURON

are now needed so that comparisons can be made between the specific functions mediated by these dendrodendritic synaptic units in different parts of the brain.

DENDRITIC TOPOGRAPHICAL UNITS

Synaptic units feed into dendritic trees. Within these trees, subdivisions may be identified as functional units. In the mitral cell, synaptic potentials in the glomerular tuft spread through the branches and summate at the origin of the primary dendrite (cf. Fig. 2). The tuft, with its convergence point at the origin of the primary dendrite, thus forms a convergence unit analogous to the branching tree of the motoneuron. For the identification of such a convergence unit, the presence or absence of a cell body at the convergence point is irrelevant. Also irrelevant is the type of process at the convergence point; that it is an axon in the case of the motoneuron and a dendrite in the case of the mitral cell is important only insofar as it bears on the type of activity by which the summed result of local integration in the convergence unit is transferred to the next stage of processing.

Two additional integrative entities in the mitral cell are formed by the primary and the secondary dendrites converging on the axon hillock. The two types of dendrite are functionally distinct, in that the primary dendrite provides for transmission of the olfactory input, while the secondary dendrites provide for inhibitory feedback from the granule cells. The fact that these dendrites, like those in the glomerulus, are presynaptic as well as postsynaptic presents no problem in defining them as functional entities. The synaptic units are part of the larger topographical units, and provide for an additional component of local processing relative to the final integration at the convergence point. Since a synaptic unit may be part of several dendritic units, the latter are not, in general, loci within one dendritic tree; one has, rather, an ensemble of overlapping topographical units, as is well exemplified in the case of the olfactory glomerulus.

Topographical subdivisions within dendritic trees are common in the nervous system: only a few examples will be noted here (see Fig. 4). Although motoneurons are as a rule characterized by a great deal of overlap of afferent inputs onto their dendritic trees, in the sacral spinal cord, specific afferents to different parts of the dendritic tree have been described (Fig. 4 a). This was termed a “functional fractionation of dendritic field”(42,43). In the medial superior olivary nucleus (Fig. 4 b) the principal relay neuron has two main dendrites, one receiving auditory input originating in the ipsilateral ear, the other receiving input from the contralateral ear(44,45). In the cerebellum, Golgi cells send some dendrites to the molecular layer, where they receive input from

\footnote{In the primate olfactory bulb, myelin has been described around the initial part of the primary dendrite (41), extending as far as the cell body in the case of tufted cells (smaller versions of mitral cells). Such a finding has no place in the classical doctrine. It is readily assimilable to the view developed here, which does not require that a functional unit provide only for transmission from dendrites to axon; the requirement is that the unit provides for some specifiable processing, with ultimate transmission to the next stage or stages.}
Fig. 4. Examples of dendritic topographical units. a. motoneuron of sacral spinal cord of the cat (42, 43). b. principal neuron of medial superior olivary complex (44). c. hippocampal pyramidal cell (46). Synaptic inputs to restricted parts of these dendritic trees as follows: 1. lateral column; 2. dorsal root; 3. contralateral dorsal root; 4. ipsilateral ear; 5. contralateral ear; 6, 7, 8, short axon cells; 9. afferent fibers; 10. Schaffer collaterals; 11. association path; 12. mossy fibers; 13. basket fibers; 14. pyramidal cell axon collaterals.

The parallel fibers, and others to the granule layer, where they enter into the cerebellar glomeruli (cf. Fig. 3 c). The pyramidal neurons of cortical areas are well known for the separation of their dendritic trees into apical and basal types. Lamination of inputs to the apical dendrite of hippocampal cells indicates the presence of vertically overlapping functional units (46) (Fig. 4 c). Similar lamination has been described in prepyriform (47) and neocortical (48) pyramidal cells. These examples will suffice to indicate that a heterogeneity of topographical functional units has been found in mammalian neurons to match that in invertebrate neurons (cf. 2).

It should be clear that the examples cited above in which dendrites are postsynaptic to axonal inputs represent a restricted case of the general pattern in which dendrites may be presynaptic as well as postsynaptic (as in olfactory bulb, retina, thalamus, etc.). It may be noted that in this view the terms “conventional” and “unconventional” as applied to these types of synaptic orientations (49) lose any significance, and should not be retained.

MULTINEURONAL UNITS OF FUNCTION

Thus far we have identified functional units formed by synaptic terminals or parts of dendritic trees. The morphological limits of these units have been determined by functional considerations rather than by neuronal boundaries. The approach is a general one, and can be used to identify larger units of function. A well-known example is provided by the Renshaw circuit (See Fig. 1).
The elements of this circuit (motoneuron axon collateral, interneuron, motoneuron dendrite) may be said to form a functional unit, in that they satisfy the criterion of providing the morphological substrate for an identifiable function: recurrent inhibition of the motoneuron.

A functional unit of this type, forming a closed feedback loop, may be termed a loop unit. Reciprocal dendrodendritic synapses also provide a feedback loop for recurrent inhibition, and should, therefore, be considered as another, more spatially restricted, type of loop unit. In the olfactory bulb, both types provide for feedback control of the mitral cell at both the glomerular and the granule cell level. Because of the subdivisions within the mitral dendritic tree, the loop systems passing through the mitral cell at these two levels are spatially separated and functionally distinct.

The loop units formed by the mitral and granule cells are also part of other feedback circuits. One circuit runs through the anterior olfactory nucleus; another passes through the prepyriform cortex and thence through anterior olfactory nucleus back to the bulb (Fig. 5 a). Price and Powell(50) have developed the concept that the mitral cell is embedded within these progressively extending loops, and that these nested loops together may be regarded as a system in itself. They have pointed out the analogy to the feedback loops through which corticothalamic fibers connect each of the sensory areas of the neocortex to the related sensory relay nuclei (Fig. 5 b). As another type of loop system, the pathways connecting the cerebellum and the cerebral cortex may be mentioned.

The identification of multineuronal functional entities has in fact been one of the traditional concerns of neuroanatomists and neurophysiologists. From this work we have a rich vocabulary of terms and concepts. The reflex arc and the motoneuron pool of Sherrington(8,51) are early examples. Cortical areas

![Diagram](https://example.com/diagram.png)

**Fig. 5.** Examples of multineuronal functional units (loop units for output feedback). a. olfactory system. MI: mitral cell; GR: granule cell; AON: anterior olfactory nucleus; PP: prepyriform cortex. b. corticothalamic system. PYR: pyramidal cell of cerebral cortex; TH: thalamus.
and pyramidal cell colonies(52) have been identified. The organization of cortical areas, both sensory and motor, into functional columns(53–55) has been a finding of much importance. These and the many other pathways, centers, and systems that have been described in the nervous system are all subsumed under a general concept of functional units of varying degrees of extent and complexity.

**NATURE OF STRUCTURE–FUNCTION RELATIONS**

We have seen that a major deficiency of the neuron doctrine was the concept of the morphological neuron as a stereotyped unit of function. Underlying this concept was the assumption of a rigid relation between structure and function. In the case of axons the relationship seems obvious; one would not question, for example, that myelinated axons everywhere in the nervous system provide for saltatory propagation of action potentials. But a simple relationship with this general applicability cannot be derived for dendrites. Some dendrites generate action potentials [e.g., cerebellar Purkinje cell(56)] while some provide only for passive potential spread [e.g., motoneurons(9)]. Some dendrites are only postsynaptic (e.g., motoneurons), while others, similar in their fine structure apart from synaptic regions, are both pre- and postsynaptic (e.g., mitral cells). Most dendrites are excited by depolarizing synaptic potentials, but some (e.g., in retina) are driven by hyperpolarizing potentials(57). The general principle may thus be formulated, that *similar structures may support different physiological properties*. The converse is also true, that *different structures may support similar properties*: the similar synaptic potentials recorded from many different types of neuron are a well-known expression of this fact. As a special instance, visual receptors, horizontal cells, and bipolar cells have distinctive morphologies, yet all give slow graded hyperpolarizing responses to light stimulation(57). These new principles place strong restrictions on making inferences about function from dendritic geometry, as viewed in Golgi-stained sections, or even from fine structural features as seen in the electron microscope.

These principles apply also to functional units. It has already been noted that both the Renshaw circuit and the dendrodendritic circuit provide for recurrent inhibition; the same general function is thus mediated by entirely different morphological substrates. The retinal bipolar cell and the mitral primary dendrite are distinctly different morphological entities, playing nonetheless similar functional roles in providing for transfer of sensory input from one synaptic level to the next(37). A striking example of the flexible relation between structure and function is provided by work on the abstraction of stimulus properties in the visual pathway. In some animals much complex processing is carried out in the retina, while in other animals these complex steps are deferred to the level of the cerebral cortex or the superior colliculus(58). This is clear proof that similar functional operations can be carried out by different morphological substrates.

This should not be taken to rule out the many instances in the nervous system in which similar structures provide valuable clues to function; the similar
patterns of connections in multisynaptic units in many parts of the brain, reviewed above, is strong evidence for units with similar functions. Nonetheless, it indicates that to the extent of our present knowledge, the relation between structure and function is both a flexible and a subtle one. An important research goal is to obtain more detailed evidence for the structural basis for specific physiological properties.

SUMMARY

It may be concluded that there is a need to formulate new principles at the level with which the neuron doctrine is concerned, that is, the relation between neuronal structure and nervous function. The concepts developed here, relating to the organization of the nervous system along functional lines, are a first step in that direction. They may be summarized as follows:

1. The nervous system is organized in terms of functional units. A functional unit is defined as the morphological substrate for a specific function.
2. Neurons (and functionally related cells) provide the morphological substrate for functional organization. Neurons have different combinations of morphological processes and physiological properties. For a given process of a given neuron, the synaptic position and physiological property depend on the integrative context within the functional units of which it is a part.
3. Functional units are formed at several levels of organization: synaptic terminals, dendritic trees, and multineuronal interconnections. The nervous system is built of overlapping assemblies and hierarchies of such units of increasing extent and complexity.

These proposals meet two criteria required of any basic doctrine: they have a wide applicability to all types of neuron, and they are relevant to present research interests. With regard to the first criterion, the above statements account not only for the modern findings; they are also sufficiently flexible to apply to the many cases that have traditionally stood out as exceptions to the classical neuron doctrine, such as the spinal ganglion cell, the axonless cell, and the monopolar cells of invertebrates. In the case of the spinal ganglion cell of mammals, for example, agreement could never be reached on whether the peripheral process is an axon or a myelinated dendrite. Such unsolvable terminological problems arose from the need to conserve the same relation between structure and function in dendrites and axons of all neurons (cf. 3). From a functional point of view that relation may be variable; the process may be defined by morphological criteria alone, and its function assessed independently in relation to its integrative context.

It may be noted that a functional doctrine for nervous organization should include the many interactions that neurons have with nonneuronal cells, e.g., neuroglia, muscles, glands, and the various cells and tissues that are related to the movement of substances in peripheral axons (59) (i.e., functionally related cells as noted in point 2 above).

With regard to the second criterion, the concept of the single synapse as a
functional unit is explicit in the recent statement of Pappas and Waxman(60) that "... With the development of techniques for electron microscopy and for intracellular recording, it has become clear that the synapse must be viewed as a morphophysiological entity." The well-known studies by Katz and his co-workers(61) of the frog neuromuscular junction are practical evidence of this view. The complex molecular machinery of the single synapse is another level of organization, beyond the scope of the present review.

There have been several analyses of the dendritic spine as an input–output unit(62–64), along the lines discussed above in relation to Fig. 3. The concept of "dendritic integration"(56,62), for example, is relevant to the above discussion of functional units within dendritic trees. An important contribution of recent years has been the development by Rall(65–67) of mathematical techniques for extending the analysis of electrotonic spread of current in axons to the case of dendrites. These methods provide the necessary basis for analysis of integration in functional units at the level of synaptic terminals and dendritic trees.

At the level of multineuronal organization, Purpura(68) has stressed in recent years the need to identify the morphological substrates of functional operations, and the inadequacies of present concepts of the "model neuron" in the analysis of the cortex and thalamocortical systems. At this level, the Scheibels(69) have introduced the concept of hierarchies of interacting functional modules. In work on electrotonic interactions, Bennett(70) has concluded that the single neuron need not be a single unit.

All of these concepts and terminologies are consistent with the present view. They indicate the growing need to replace the classical doctrine with a more flexible set of proposals, such as has been set forth here, that will be valid and relevant to analyses at all levels of organization in the nervous system.

In the light of these considerations, the motoneuron appears, not as a model of a "conventional" type of nerve cell, but rather as a specialization of the neuronal substrate for a unique function: control of the muscles. Recent interest has attached increased importance to the central pathways controlling motoneurons, in addition to the peripheral arcs of classical neurophysiology(71). It may be anticipated that the development of new concepts will permit a clearer understanding of the many functional units of which the motoneuron is a part.

REFERENCES

1. Bishop, G. H., Natural history of the nerve impulse. Physiol. Rev. 36, 376–399 (1956).
2. Bullock, T. H., Neuron doctrine and electrophysiology. Science 129, 997–1002 (1959).
3. Bodian, D. The generalized vertebrate neuron. Science 137, 323–326 (1962).
4. Reese, T. S., and Shepherd, G. M., Dendrodendritic synapses in the central nervous system. In Structure and Function of Synapses (G. D. Pappas and D. P. Purpura, eds.), Raven, New York, pp. 121–136 (1972).
5. Rall, W., Shepherd, G. M., Reese, T. S., and Brightman, M. W., Dendrodendritic synaptic pathway for inhibition in the olfactory bulb. Exp. Neurol. 14, 44–56 (1966).
6. Cajal, S. R. Histologie du Système Nerveux de l'Homme et des Vertébrés. Maloine, Paris (1911).
7. Peters, A., Palay, S. L., and Webster, H. De F., *The Fine Structure of the Nervous System*. Harper and Row, New York (1970).
8. Sherrington, C. S., *The Integrative Action of the Nervous System*. Yale Univ. Press, New Haven (1906).
9. Eccles, J. C., *The Physiology of Synapses*. Springer, Berlin (1964).
10. Frank, K., and Fuortes, M. G. F., Presynaptic and postsynaptic inhibition of monosynaptic reflexes. *Fed. Proc.* 16, 39–40 (1957).
11. Grinnell, A. D., A study of the interaction between motoneurones in the frog spinal cord. *J. Physiol. (London)* 182, 612–648 (1966).
12. Nelson, P. G., Interaction between spinal motoneurons of the cat. *J. Neurophysiol.* 29, 275–287 (1966).
13. Nelson, P. G., and Frank, K., Orthodromically produced changes in motoneuronal extracellular fields. *J. Neurophysiol.* 27, 928–941 (1964).
14. Frank, K., Basic mechanisms of synaptic transmission in the central nervous system. *I. R. E. Trans. Med. Electron.* ME-6, pp. 85–88 (1959).
15. Yamamoto, C., Yamamoto, T., and Iwama, K., The inhibitory system in the olfactory bulb studied by intracellular recording. *J. Neurophysiol.* 26, 403–415 (1963).
16. Shepherd, G. M., Responses of mitral cells to olfactory nerve volleys in the rabbit. *J. Physiol. (London)* 168, 89–100 (1963).
17. Phillips, C. G., Powell, T. P. S., and Shepherd, G. M., Responses of mitral cells to stimulation of the lateral olfactory tract in the rabbit. *J. Physiol. (London)* 168, 64–88 (1963).
18. Shepherd, G. M., Neuronal systems controlling mitral cell excitability. *J. Physiol. (London)* 168, 101–117 (1965).
19. Rall, W., and Shepherd, G. M., Theoretical reconstruction of field potentials and dendrodendritic synaptic interactions in olfactory bulb. *J. Neurophysiol.* 31, 884–915 (1968).
20. Nicoll, R. A., Inhibitory mechanisms in the rabbit olfactory bulb: dendrodendritic mechanisms. *Brain Res.* 14, 157–172 (1969).
21. Pinching, A. J., and Powell, T. P. S., The neuropil of the glomeruli of the olfactory bulb. *J. Cell. Sci.* 9, 347–377 (1971).
22. Shepherd, G. M., Physiological evidence for dendrodendritic synaptic interactions in the rabbit's olfactory glomeruli. *Brain Res.* 32, 212–217 (1971).
23. White, E. L., Synaptic organization in the olfactory glomeruli of the mouse. *Brain Res.* 37, 69–80 (1972).
24. Eccles, J. C., Fatt, P., and Koketsu, K., Cholinergic and inhibitory synapses in a pathway from motor-axon collaterals to motoneurons. *J. Physiol. (London)* 216, 524–562 (1954).
25. Eccles, J. C., *The Inhibitory Pathways of the Central Nervous System*. Thomas, Springfield (1969).
26. Hirata, Y., Some observations on the fine structure of the synapses in the olfactory bulb of the mouse, with particular reference to the atypical configuration. *Arch. Histol. Jap.* 24, 293–302 (1964).
27. Andres, K. H., Der Feinbau des Bulbus Olfactorius der Ratte unter besonderer Berucksichtigung der synaptischen Verbindungen. *Z. Zellforsch.* 65, 530–561 (1965).
28. Price, J. L., and Powell, T. P. S., The synaptology of the granule cells of the olfactory bulb. *J. Cell Sci.* 7, 125–155 (1970).
29. Morest, D. K., Dendrodendritic synapses of cells that have axons: the fine structure of the Golgi type II cell in the medial geniculate body of the cat. *Z. Anat. Entwicklungs-gesch.* 133, 216–246 (1971).
30. Wong, M. T., Somato-dendritic and dendro-dendritic synapses in the squirrel monkey lateral geniculate nucleus. *Brain Res.* 20, 155–190 (1970).
31. Famiglietti, E. V., Dendro-dendritic synapses in the lateral geniculate nucleus of the cat. *Brain Res.* 20, 181–191 (1970).
32.Ralston, H. J. III, and Herman, M. M., The fine structure of neurons and synapses in the ventrobasal thalamus of the cat. *Brain Res.* 14, 77–98 (1969).
33. Harding, B. N., Dendro-dendritic synapses, including reciprocal synapses, in the ventrolateral nucleus of the monkey thalamus. *Brain Res.* 34, 181–185 (1971).
34. Szentagothai, J., Glomerular synapses, complex synaptic arrangements, and their operational significance. in The Neurosciences: Second Study Program (F. O. Schmitt, Ed.-in-chief), pp. 427–443. Rockefeller Univ. Press, New York (1970).
35. Ralston, H. J. III., Evidence for presynaptic dendrites and a proposal for their mechanism of action. Nature (London) 230, 585–587 (1971).
36. Dowling, J. E., and Boycott, B. B., Organization of the primate retina: electron microscopy. Proc. Roy. Soc. Ser. B. 166, 80–111 (1966).
37. Shepherd, G. M., The olfactory bulb as a simple cortical system: experimental analysis and functional implications. in The Neurosciences: Second Study Program (F. O. Schmitt, Ed.-in-chief), pp. 539–552. Rockefeller Univ. Press, New York (1970).
38. Lund, R. D., Synaptic patterns of the superficial layers of the superior colliculus of the rat. J. Comp. Neurol. 135, 179–208 (1969).
39. Sterling, P., Receptive fields and synaptic organization of the superficial gray layer of the cat superior colliculus. Vision Res. Suppl. 3, 309–328 (1971).
40. Sloper, J. J., Dendro-dendritic synapses in the primate motor cortex. Brain Res. 34, 186–192 (1971).
41. Pinching, A. J., Myelinated dendritic segments in the monkey olfactory bulb. Brain Res. 29, 133–138 (1971).
42. Sprague, J. M., The distribution of dorsal root fibres on motor cells in the lumbar-sacral spinal cord of the cat, and the site of excitatory and inhibitory terminals in monosynaptic pathways. Proc. Roy. Soc. Ser. B. 149, 534–556 (1958).
43. Frank, K., and Sprague, J. M., Direct contralateral inhibition in the lower sacral spinal cord. Exp. Neurol. 1, 28–43 (1959).
44. Stotler, W. A., An experimental study of the cells and connections of the superior olivary complex of the cat. J. Comp. Neurol. 98, 401–431 (1955).
45. Erulkar, S. D., Comparative aspects of spatial localization of sound. Physiol. Rev. 52, 257–360 (1972).
46. Lorente de No, R. Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammonic system. J. Psychol. Neurol. Lpz. 46, 113–177 (1954).
47. Heimer, L., Synaptic distribution of centripetal and centrifugal nerve fibres in the olfactory system of the rat. An experimental anatomical study. J. Anat. 103, 413–432 (1968).
48. Jones, E. G., and Powell, T. P. S., An electron microscopic study of the laminar pattern and mode of termination of afferent fibre pathways in the somatic sensory cortex of the cat. Phil. Trans. Roy Soc. Lond. Ser. B. 257, 45– (1970).
49. Bodian, D., Synaptic diversity and characterization by electron microscopy, in Structure and Function of Synapses (G. D. Pappas and D. P. Purpura, Eds.), pp. 45–66. Raven, New York (1972).
50. Price, J. L., and Powell, T. P. S., The afferent connections of the nucleus of the horizontal limb of the diagonal band. J. Anat. 107, 239–256 (1970).
51. Creed, R. S., Denny-Brown, D., Eccles, J. C., Liddell, E. G. T., and Sherrington, C. S., Reflex Activity of the Spinal Cord. Oxford Univ. Press, London (1932).
52. Phillips, C. G., The motor apparatus of the baboon’s hand. Proc. Roy. Soc. Ser. B. 173, 141–174 (1969).
53. Mountcastle, V. B., Modality and topographic properties of single neurons of cat’s somatic sensory cortex. J. Neurophysiol. 20, 408–434 (1957).
54. Hubel, D. H., and Wiesel, T., Receptive fields and functional architecture of monkey striate cortex. J. Physiol. (London) 195, 215–243 (1968).
55. Welt, C., Aschoff, J. C., Kameda, K., and Brooks, V. B. Intracortical organization of cat’s sensorimotor neurons, in The Neurophysiological Basis of Normal and Abnormal Motor Activities (D. P. Purpura and M. D. Yahr, Eds.), pp. 255–293. Raven, New York (1967).
56. Llinás, R., and Nicholson, C., Electrophysiological properties of dendrites and somata in alligator Purkinje cells. J. Neurophysiol. 34, 532–551 (1971).
57. Werblin, F. S., and Dowling, J. E., Organization of the retina of the mudpuppy, Necturus maculosus. II. Intracellular recording. J. Neurophysiol. 32, 339–355 (1969).
58. Michael, C. R. Retinal processing of visual images. Sci. Amer. 220, 104–114 (1969).
FUNCTIONAL CONCEPTS OF NEURON

59. Weiss, P. A., Neuronal dynamics and neuroplasmic ('axonal') flow. Symp. Int. Soc. Cell Biol. 8, 5–34 (1969).
60. Pappas, G. D., and Waxman, S. G., Synaptic fine structure: morphological correlates of chemical and electrotonic transmission, in Structure and Function of Synapses (G. D. Pappas and D. P. Purpura, Eds.), pp 1–44. Raven, New York (1972).
61. Katz, B., Nerve, Muscle, and Synapse. McGraw-Hill, New York (1966).
62. Diamond, J., Gray, E. G., and Yasargil, G. M., The function of the dendritic spine: an hypothesis, in Excitatory Synaptic Mechanisms (P. Andersen and J. K. S. Jansen, Eds.), pp. 213–222. Scand. Univ. Books, Oslo (1970).
63. Llinás, R., and Hillman, D. E., Physiological and morphological organization of the cerebellar circuits in various vertebrates, in Neurobiology of Cerebellar Evolution and Development (R. Llinás, Ed.), pp. 43–75. Amer. Med. Ass., Chicago (1969).
64. Rall, W., Dendritic spine function and spine attenuation calculations. Abstr., Soc. Neurosci., p. 64 (1971).
65. Rall, W., Theoretical significance of dendritic trees for neuronal input-output relations, in Neural Theory and Modelling (R. F. Reiss, Ed.), pp. 73–97. Stanford Univ. Press, Stanford (1964).
66. Rall, W., Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input. J. Neurophysiol. 30, 1138–1168 (1967).
67. Rall, W., Cable properties of dendrites and effects of synaptic location, in Excitatory Synaptic Mechanisms (P. Andersen and J. K. S. Jansen, Eds.), pp. 175–188. Universitetsforlaget, Oslo (1970).
68. Purpura, D. P., Operations and processes in thalamic and synthetically related neural subsystems, in The Neurosciences: Second Study Program (F. O. Schmitt, Ed.-in-chief), pp. 458–470. Rockefeller Univ. Press, New York (1970).
69. Scheibel, M. E., and Scheibel, A. B., Elementary processes in selected thalamic and cortical subsystems—the structural substrates. in The Neurosciences: Second Study Program (F. O. Schmitt, Ed.-in-chief), pp. 443–457. Rockefeller Univ. Press, New York (1970).
70. Bennett, M. V. L., Comparison of electrically and chemically mediated synaptic transmission, in Structure and Function of Synapses (G. D. Pappas and D. P. Purpura, Eds.), pp. 221–256. Raven, New York (1972).
71. Evarts, E. V. (Ed.). Central Control of Movement. NRP Res. Progr. Bull. vol. 9, no. 1 (1971).