Neurons seldom serve as relay stations; they typically transform their inputs in some manner to produce a new output function. A conventional processing path within a neuron includes a cascaded series of steps, each capable of contributing characteristic styles of computation: passive spread of PSPs to a spike trigger zone, spike initiation and repetitive firing, spike propagation, and ultimately synaptic output. We now know of many neurons where this one-way cascade must be supplemented with additional processes, such as intermittent conduction or dendritic spikes. There are also simpler cases, such as the passive-to-synaptic cascade of spikeless neurons. Styles of computation (e.g., arising from transient or sustained responsiveness, from high or low thresholds, and so forth) may be contributed by different stages of the cascade (e.g., from spike initiation regions, from conduction in axons, from synaptic input-output processes). Processing may thus differ among the various presynaptic regions of the same neuron.

Introduction

How do neurons transform their input to produce something new? This is accomplished partly by wiring (the hierarchical arrangement of receptive fields in the nervous system provide an example; see Hubel and Wiesel, 1977) and partly by the intrinsic properties of the neurons. Here we shall be concerned only with how transformations occur intraneuronally; in particular, we shall be concerned with the processing pathway through the neuron and how its cascaded stages each contribute characteristics that determine the various overall styles of neuronal computation.

An example of the processing pathway comes from the "conventional neuron" commonly described in textbooks, where there is a one-way cascade of processes by which the synaptic inputs (confined to the soma-dendritic region) communicate with the synaptic outputs on the axon terminals. After the transmitter produces a synaptic current, the current spreads passively to the spike trigger zone (e.g., the axon's initial segment) rather than producing a local spike. The low threshold trigger zone summates positive and negative currents from a multitude of excitatory and inhibitory synaptic inputs. A decision made at this single site determines whether or not a spike will be produced. Once a spike is initiated, it propagates more or less faithfully to the output synapses on the far end of the axon. A standard amount of transmitter is then released by the spike, although some historical effects such as facilitation, depression, or potentiation are allowed in this conventional view; indeed the synapse would be the major candidate for plasticity since the rest of the neuron seems rather rigid.

The processing path thus includes a number of discrete, cascaded stages: passive spread, spike initiation, spike propagation, and synaptic transfer. Yet this description of the birth and death of a single spike is misleading; for most neurons, processing varies over time in several stages of the cascade. Spike trains are initiated, they propagate through regions with varying safety factors, and the synaptic release varies for the spikes that do reach the terminals. Thus even in the conventional neuron the input-output characteristics of the various stages give rise to several styles of computation: a sustained input may give rise to either sustained or transient responses; output may decline or build up during a sustained input; near coincidence in time by several large inputs may be required to produce an output; output may grade smoothly with the net sum of many inputs; and so forth. The style of computation need not remain fixed; it can vary over time as a result of such extrinsic influences as synaptic inputs or hormones, besides any intrinsic time or use dependencies.

There is also a story within a story: there are neurons in which some synaptic outputs act semi-independently of other synaptic outputs—that is, there are multiple processing paths within one neuron. While the anatomical unity of the neuron is unquestioned (Peters, Palay, and Webster, 1976), whether the single neuron is always a single functional entity has been questioned for decades (Bullock, 1959; Shepherd, 1972; Graubard and Calvin, this volume) as the conventional neuron model has become increasingly inadequate. The existence of spikeless neurons and of synaptic outputs intermixed with syn-
aptic inputs (e.g., dendrodendritic and axoaxonic arrangements) are of particular concern. In Table 1 we contrast some of the major features of the conventional neuron with some of the analogous disturbing features. While one cannot replace the conventional neuron with a modern view of equal simplicity, we shall attempt to show that the processing path itself can serve as a substitute concept for the elementary computing entity. When there is only one processing path within a neuron, the neuron will function as a unit; if there are multiple paths, it may not.

Black boxes vs. the experimental situation

We can never measure the actual quantities of transmitter received by the neuron membrane and compare this input with the actual output of transmitter from the distant axon terminals. As in Figure 1, the neurophysiological study of neuronal properties often involves two neurons at a time, for example, an electrode in the soma of one neuron and another electrode in the soma of a downstream neuron. This transneuronal input-output function taps into the cascade at a similar place in each cell and thus represents one neuron’s worth of cascaded processes. We tend to translate this transneuronal input-output relation into a neuronal input-output function, considering it as if all of the cascaded processes were within a single neuron so that the usual black-box boundaries correspond to the cell membrane. It is for this reason that we speak here of input synapses and output synapses. The input synapse is the postsynaptic element of the synapse as seen in the electron microscope. The output synapse of the same neuron corresponds to a presynaptic terminal. We thus reference our terminology all within one neuron and avoid the entanglements (“postsynaptic to the presynaptic neuron”) involved with multiple-neuron terminology.

The simplest black box has many inputs but only one output (Figure 2A). If the black box is separated into a cascaded series of boxes, it is recognizably the processing path of the conventional neuron (Figure 2B). When a neuron has two semi-independent outputs (Figure 2C), one attempts to take apart the black box to show the stages in the processing path for each output (Figure 2D). These graphical representations can be pursued with mathematical elaborations, but we shall treat the subject here at the phenomenological level suitable to the present level of knowledge in cellular neurophysiology.

In some cases, the passive-to-excitable-to-synaptic cascade of the conventional neuron is augmented with additional stages. We begin, however, with a simpler case than the conventional neuron: the spikeless neuron, having only passive and synaptic stages in its processing path. Later the passive assumption about the membrane will be made more realistic. Excitability will be treated in the context of both den-

<table>
<thead>
<tr>
<th>The Conventional Neuron</th>
<th>Additions or Substitutions</th>
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<tr>
<td>long axon</td>
<td>short axon, perhaps no axon</td>
</tr>
<tr>
<td>segregated input and output synapses</td>
<td>intermingled input and output synapses (e.g., dendrodendritic, axoaxonic)</td>
</tr>
<tr>
<td>spikes</td>
<td>spikeless neurons</td>
</tr>
<tr>
<td>all-or-none threshold decisions</td>
<td>graded firing rates, graded spikeless synaptic release</td>
</tr>
<tr>
<td>voltages as common currency</td>
<td>second messengers; metabolic modulation; indirect effects on pacemakers</td>
</tr>
<tr>
<td>a single decision-making site (e.g., initial-segment trigger zone)</td>
<td>multiple trigger zones; different decisions possible from different output synapses</td>
</tr>
<tr>
<td>faithful conduction of spikes</td>
<td>intermittent conduction: activation of normally silent branches?</td>
</tr>
<tr>
<td>standard amount of transmitter released by spike, or only minor historical effects</td>
<td>historical effects (e.g., facilitation, depression, potentiation), different at different output synapses from same cell.</td>
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Table 1

Conventional view of the neuron and aspects which, when seen in addition to (or substituted for) the corresponding aspects of the conventional neuron, raise questions about whether a single neuron can simultaneously produce different outputs.
1. SYNAPTIC TRANSFER
- facilitation
- threshold
- depression
- inversion
- sensitivity of graded release

2. CABLE GEOMETRIC PROPERTIES
- local PSP size
- attenuation

FIGURE 1 Cascade of intraneuronal processes in local spikeless computation. Since the reception and release of transmitter from a single neuron cannot be directly measured to obtain a true neuronal input-output relation, one works from the soma of one neuron to the soma of a downstream neuron and plots a transneuronal input-output curve (top). In spikeless cases, there may be only two stages to the cascade: passive spread and the synaptic transfer characteristics, sometimes supplemented by subexcitable phenomena such as rebounds.

FIGURE 2 (A) The simplest neuronal input-output relation involves only a single output, which is a function of time and the inputs. (B) Decomposing the black box into the intraneuronal cascade of the "conventional neuron." (C) A case in which a neuron produces two semi-independent outputs that are differing functions of time and the inputs. (D) An example in which C can be decomposed into a conventional neuron cascade plus an output synapse operating on both spike trains and the passive spread of input currents.
dritic-spike “booster stations” and the properties of axon trigger zones. Repetitive firing, and the conduction of the spike train through intermittently conducting regions of the axon, will be examined for their characteristics. Finally, synaptic input-output processes and their interaction with presynaptic inhibition and facilitation will be considered for their contributions to the last step of the cascade.

Processing in the spikeless neuron

The transneuronal input-output function for a spikeless neuron is primarily determined by (1) the weighting of the input PSPs, as seen at an output synapse (determined by cable-geometric factors) and (2) the synaptic input-output relation itself. Thus the various output synapses from such a neuron could differ from each other by nonuniformity in either aspect.

The weighting of input PSPs depends strongly on the neuron's geometry and the location of the output synapse within this geometry (see Graubard and Calvin, this volume). Two output synapses located on the distal portions of different dendrites will be especially likely to differ from one another (provided that randomness of synaptic input locations does not obscure the intrinsic capability to emphasize one set of inputs and attenuate another). Two proximal dendritic or somatic output synapses are unlikely to differ significantly in the input weighting perceived.

The synaptic input-output properties could differ between the various output synapses from a given neuron. The release threshold (see Figure 3 in Graubard and Calvin, this volume) might differ, or perhaps the extent to which the output synapse adapts to a sustained depolarization. (The term “threshold” is, of course, a descriptive convenience; Llinás discusses the actual S-shaped relation elsewhere in this volume.) There is no indication that all of the outputs from a given neuron behave uniformly in synaptic transfer properties.

Were all of the output synapses to be segregated onto one process (an “axon”) in a spikeless neuron, they would all receive the same relative weightings of the input PSPs. This is due to all of the passive spread being funneled through the bottleneck at the beginning of the axon. The only differences between such output sites would be greater attenuation and a lower frequency response for more distant terminals. Were all of these segregated output synapses to have uniform synaptic input-output properties, the spikeless neuron would then resemble the conventional neuron in that it could act as a “unit.” It is the segregation of output synapses onto a process different from the ones that receive input PSPs that is especially important for the “unitary” picture of neuronal computation, not spikes.

Adding complexity to the passive cable model

Two synapses active at the same time do not necessarily add their PSPs together linearly (e.g., $2 + 2 = 3$). The simplest case of interaction is shunting (e.g., $2 + 0 = 1$), where the second input produces a conductance increase but no voltage change because the reversal potential of that input is the same as the cell's resting potential. The conductance increase of this second synapse decreases the size of the first PSP by increasing the input conductance at the first synapse. This reduces the local size of the PSP as well as its size in the soma or at the spike trigger zone. Should an output synapse be located on the same process as the shunting input, its sensitivity to local and distant inputs would be reduced (see Calvin and Graubard, 1977).

Some synapses do not cause conductance increases but instead decrease membrane conductance (Weight, 1974; Carew and Kandel, 1976; but see Parnas, Rahaminoff, and Sarne, 1975); thus activity at an input synapse could increase the sensitivity of a neighboring output synapse to still other synaptic inputs. These sensitivity alterations are in addition to the effects of any synaptic current produced by the synaptic conductance changes when synaptic reversal potentials are not at the resting potential.

Second messengers such as cAMP, cGMP, and Ca$^{++}$ (see Greengard, 1978) introduce a whole new realm of nonelectrical modulation. Should the internal calcium ion concentration be modulated near an output synapse by input synapse activity, one could have a modulation of the synaptic release function. Such calcium modulation might be secondary to synaptic activity or might arise from calcium entry because of a membrane conductance with voltage sensitivity (e.g., calcium spikes).

This raises the problem of changes in passive membrane properties that affect the cable properties: membrane resistivity, for example, may change severalfold within a physiological range of variation of voltage about the resting potential, thus changing the local PSP size and its attenuation with distance.

Rebound phenomena are also seen in spikeless cells (Graubard, 1978). Upon the removal of a hyperpolarizing current, the membrane potential may over-
shoot the resting potential. If the rebound is large enough, it can cross the release threshold, just as rebounds in spiking neurons sometimes cross the spike threshold.

Excitability, the regenerative property whereby depolarization begets more depolarization, provides a nonlinear amplification of input PSPs. In some cells, spikes arise locally in the dendrites; such dendritic spikes (see, e.g., Kuno and Llinás 1970) often have poor safety factors and only spread passively into the central regions of the neuron. From the standpoint of central decision-making processes, they may serve as boosters for certain combinations of input synapses. They could cause a large increment in release from output synapses near their sites of origin.

In a short-axon neuron, axon terminal output synapses could operate upon a combination of passively spread PSPs and spikes (see Figure 4 in Graubard and Calvin, this volume). As the axon becomes longer, the passively spread PSPs would become quite small but the height of an actively propagating spike would stay the same. Graded synaptic transfer characteristics (where threshold and graded release are key factors in determining transneuronal input-output properties) would decline in importance as standard-sized spikes came to provide the sole drive upon the presynaptic terminal. Decision-making would thus shift from emphasizing synaptic characteristics (as in Figure 1) to emphasizing those of the spike trigger zone at the beginning of the axon (as in Figures 3 and 4). Synaptic input-output curves have characteristics such as an apparent release threshold, a graded release region with an associated sensitivity, adaptation, rebounds, and historical factors such as facilitation/depression. When the actual output synapses are merely repeating decisions made elsewhere, one must ask what are the relevant characteristics of the spike production processes.

**Figure 3** Cascade of intraneuronal processes in long-distance transmission utilizing spike trains. The net depolarizing current in the initial segment of the axon produces a spike train whose rate varies with depolarization, as shown in Figure 4. Intermittent conduction may occur between the spike trigger zone and the output synapses, modifying the characteristics contributed by the spike-initiation process. The synaptic process itself contributes fewer features than in the spikeless case (Figure 1) if it is merely driven by standard-sized spikes. The passive characteristics of the dendritic tree of the downstream neuron are similar to the spikeless case, but the temporal summation of spike-evoked postsynaptic potentials tends to produce an average depolarization proportional to the spike rate (and hence to the original depolarization that produced the spike train in the upstream neuron, provided there is no modification by intermittent conduction or facilitation/depression).
**Production of spike trains**

Spikes tend to originate from discrete sites called trigger zones; the initial segment of the axon is often the sole site from which spikes are initiated (although some cells utilize multiple trigger zones: see Iggo and Muir, 1969; Calabrese and Kennedy, 1974). It is the weighting of the PSPs at such a virtual output site that controls synaptic output at the far end of the axon. Central structures such as the soma and the initial segment often exhibit roughly equal weightings of input PSPs, with distal inputs being only 10–40% less effective than somatic inputs in their contribution to a steady depolarization level (unless extremely long, thin dendrites are involved; compare Figures 9–11 of Graubard and Calvin, this volume). Certainly the 35-fold range of relative weightings seen at some distal dendrodendritic synaptic sites is not characteristic of spike trigger zones (unless rapid transients in voltage are especially important, in which case somatic synapses are many times more effective: see Rinzel and Rall, 1974).

Besides weighting, one must consider the transfer characteristics of the spike production process. The conventional view of the neuron, which focuses on how a quiescent cell initiates a single spike, lends itself to the notion of a PSP standing on the shoulder of another PSP in order to reach the spike threshold. This “AND gate” view of neuronal computation may be valid for some neurons in which the spike-evoked PSP from a single upstream neuron is very large, (e.g., 50% of the distance from the resting potential to the spike threshold). Most synaptic inputs to most neurons (see Calvin, 1975, for a review) are probably smaller than this by one or two orders of magnitude. Their pitter-patter integrates to create a graded shift in the membrane potential. It is the area beneath a spike-evoked PSP that determines its contribution to the net shift, not its peak value (Calvin, 1975). Suprathreshold shifts often produce a sustained train of spikes at the trigger zone, just as if the neuron were a pacemaker that only required some depolarizing bias to begin producing a rhythmic train of spikes.

**Repetitive Firing Properties**

The relationship between depolarizing current and average rhythmic firing rate has been studied in many types of neurons, typically by injecting current steps through the intrasomatic recording microelectrode to mimic a steady asynchronous synaptic bombardment. Figure 4A shows a typical current-to-rate curve (usually called a “frequency-current” or “f-I” curve). It exhibits a threshold current for the production of a sustained spike train. At this minimum current, the firing rate jumps up to a nonzero minimum rhythmic firing rate (e.g., 20/second). With more current, the firing rate increases in a graded manner; the slope of this rela-
tionship is called the sensitivity. Such properties are often a function of cell size (as inferred from axon conduction speed): “fast” neurons can have a higher minimum current requirement than “slow” ones, as well as a higher minimum rhythmic firing rate and a higher sensitivity (Figure 4A, dashed line; see Kernell, 1966; Koike et al., 1970; Calvin and Sypert, 1976).

Another feature of current-to-rate conversions is sometimes an alteration in sensitivity (Calvin, 1978a), such as the sudden increase in sensitivity shown in Figure 4B. In cat spinal motoneurons, these are called primary and secondary ranges (Granit, Kernell, and Lamarre, 1966) and are due to a marked alteration in the properties of the pacemaker-like oscillator process at the transition point (Schwindt and Calvin, 1972; Heyer and Linas, 1977).

In some other cases, the rhythmic nature of the repetitive firing is interrupted by “extra” spikes occurring several msec after an “expected” rhythmic spike (Calvin, 1975, 1978a,b); the trigger zone is reexcited by depolarization from the antecedent spike. This two-for-the-price-of-one phenomenon can double the sensitivity of the current-to-rate curve, although compensatory processes may prevent the doubling in some cases (Calvin, 1978a). Sometimes this doubling of sensitivity occurs at the high end of the curve, as in Figure 4B; in other neurons, it occurs at the low end of the curve, with the extra spikes dropping out as current increases. The dropout can create a negative sensitivity region (Figure 4C; see Calvin and Hartline, 1977). Of course, the patterning of the spike train may carry a special significance beyond whatever changes it produces in the average firing rate; facilitation or potentiation at the output synapses may mean that extra spikes release much more transmitter.

Extra spikes and other phenomena altering the sensitivity are thought to be controlled by alterations in the retrograde invasion of the spike into the soma-dendritic region (Calvin, 1978a,b); for example, the retrograde invasion may actively involve the dendrites in some cases but only passively spread into the dendrites in other cases (see Heyer and Linas, 1977).

Intrinsic Properties Controlling Repetitive Firing There are some cells, usually called pacemakers, that have intrinsic biases upon the repetitive firing processes. Some pacemakers burst; there are time-varying intrinsic currents which provide rhythmic depolarizing waves and periodically drive the cell up its depolarization-to-rate curve. Cells may be observed to shift from rhythmic pacemaker activity to bursting pacemaker activity (see Chalazonitis and Boisson, 1978). In some cases, synaptic (Parnas and Strumwasser, 1974) and hormonal (Barker and Smith, 1977) influences provide long-lasting activation of pacemaker activity and shifts from “pacing” to bursting. Some neurons “latch up,” producing bursts that continue after a brief depolarization (Kandel and Spencer, 1961; Russell and Hartline, 1977); extra spikes can also be strongly influenced by recent history (Calvin and Hartline, 1977).

In addition, most neurons exhibit adaptation, that is, a decline in firing rate during a sustained depolarization. In some cases, this is due to electrogenic pumps providing a hyperpolarizing bias current (Nakajima and Takahashi, 1966); in other cases, the sensitivity of the depolarization-to-rate conversion declines (see, e.g., Schwindt and Calvin, 1972). In cells with extra spikes, the probability of extra spikes occurring may decline with time (Calvin and Sypert, 1976). When the minimum rhythmic firing rate is approached, the firing may shut off despite the sustained depolarizing drive. “Phasic” neurons are those with pronounced tendencies to shut down; this produces, of course, a distinct computational style.

As inputs fluctuate, one expects to see the spike rate vary along the current-to-rate curve, with time-locking to the input PSPs more noticeable when the input PSPs are individually large. As inputs fluctuate, the output patterning will change, reflecting not only the changing input but also any altered probabilities for producing extra spikes or bursts. As inputs fluctuate, adaptation will be reset.

Input-Output Characteristics of Repetitive Firing The overall characteristics of the spike production process may be briefly summarized as including a threshold, a region of graded response, adaptation, and rebounds from hyperpolarization. Thus the virtual output site has acquired the main features of spikeless synaptic processing, but it also has additional features (jumps to minimum output levels, distinct “ranges,” of differing sensitivities) not yet observed in synaptic input-output curves.

Intermittent conduction

Even if the repetitive firing process sends a long train of spikes down the axon, only a brief train may reach some terminals; this can be one result of intermittent conduction, described elsewhere in this volume by Parnas. In this sense, the process may be descriptively similar to the adaptation process, producing a tonic-to-phasic conversion from the standpoint of some...
Synaptic input-output properties: Basics and complications

The basic input-output features of a conventional neuron's synapse are essentially those of the transneuronal input-output curve in Figure 1. There is an apparent threshold presynaptic voltage which must be attained before there is any significant release. There is a suprathreshold region which is S-shaped, providing a roughly linear region, perhaps followed by a saturation region. Thus, for spike-evoked release, there is a standard-sized jump in release for a brief moment. For graded inputs, there can be graded output.

There are many phenomena associated with changes in synaptic input-output properties: facilitation, depression, and posttetanic potentiation are all historic effects known at many types of synapses. Parnas (1972) and Muller and Nicholls (1974) have noted that the extent of facilitation need not be identical at two different output synapses from the same cell and suggest that the differences lie in the presynaptic terminals.

The postsynaptic side of the synapse can also produce diversity in synaptic input-output properties. A single transmitter from a single presynaptic neuron can cause postsynaptic conductance changes that are brief or long-lasting, that increase or decrease, that affect different ions, and that selectively desensitize, all depending on the choice of postsynaptic receptor (see Kandel, 1976).

Presynaptic inhibition and facilitation Foremost among the possibilities for producing diversity at output synapses is presynaptic inhibition. Presynaptic inhibition (or facilitation) is the modulation in the size of a monosynaptic PSP subsequent to activation of a second pathway which itself produces no (or little) effect on the postsynaptic cell. Many mechanisms have been proposed to explain this phenomenon, and it is likely that there are, in fact, a number of ways to produce it.

Decreases in spike-evoked PSPs in a monosynaptic pathway can often be observed if one can activate other neurons that will somehow depolarize the presynaptic terminals of the monosynaptic pathway. This physiological phenomenon is often associated with the anatomical finding of axoaxonic synapses, and it is thought that such input synapses near output synapses somehow condition spike-evoked release.

Depolarizing conditioning can produce alterations in synaptic input-output curves which reduce the release from a standard-sized stimulus (Hagiwara and Tasaki, 1958; Bloedel et al., 1966). Hyperpolarizing conditioning of cells also reduces spike-evoked release, as has now been demonstrated in arthropods, molluscs, and annelids (Maynard and Walton, 1975; Shimahara and Tauc, 1975; Wallace and Nicholls, 1977).

Another possible mechanism for presynaptic inhibition is a reduction in spike size in the presynaptic terminal, thus varying the "standard-sized" stimulus to synaptic release. This line of evidence, from crustacea (Dudel, 1965; Kennedy, Calabrese, and Wine, 1974), suggests that axoaxonic synapses produce sufficient conductance changes in the terminal as to cause a reduction in safety factor. If the active propagation of the spike ceases upstream from the terminal at various distances (intermittent conduction), the passive spread of the spike into the terminal should vary in size and hence vary the stimulus to synaptic release.

Other variations upon the intermittent-conduction theme are consistent with the results of KunO (1974) in cat spinal cord, whose reductions in mean quanta content during presynaptic inhibition may be the result of the complete failure of spike-evoked release from some terminals contributing to a composite PSP. Recent investigations of "synaptic" facilitation and depression (e.g., Hatt and Smith, 1976) have uncovered a role of intermittent conduction well upstream from the axon terminals; while nonsynaptic factors such as extracellular potassium accumulation in critical regions of low safety factor are an identifiable mechanism (see Parnas, this volume), the influence of an axoaxonic synapse could likewise be well upstream of the actual output synapses at the axon terminals.

Presynaptic facilitation may be generated in the same manner as presynaptic inhibition, by activating a pathway that modulates spike-evoked transmitter release from the presynaptic neuron while itself causing little or no postsynaptic effect. In Aplysia—so far the only example (Castellucci and Kandel, 1976)—the mechanism is thought to involve a neuron synapsing on the presynaptic cell and causing an increase
in cyclic AMP (and thus of internal Ca\(^{++}\), which results in enhanced transmitter release). Unlike presynaptic inhibition, there is as yet no evidence that any particular synaptic geometry is involved in presynaptic facilitation or that the enhancement of release is selective in the output synapses it affects.

One need not view axoaxonic synaptic arrangements solely in the context of conditioning spike-evoked release, however. The small axon terminals are analogous to the distal dendritic tips in our prior discussion of dendritic geometry (Graubard and Calvin, this volume), and the input synapse may well produce a large local PSP, perhaps itself capable of stimulating release or modulating tonic release (Parnas, Rahamimoff, and Sarne, 1975).

**Retrograde Effects Upon Presynaptic Terminals?** Could the postsynaptic neuron exert an influence over its own inputs? A direct retrograde influence of postsynaptic dendrite upon presynaptic axon has been sought for decades. Recently Erulkar and Weight (1977) utilized the squid giant synapse and showed significant decreases in spike-evoked EPSPs after conditioning by a train of postsynaptic spikes. They found that increases in extracellular potassium could also produce such decreases in spike-evoked PSPs, suggesting that the release of potassium by the postsynaptic neuron “conditions” the spike-evoked release from the presynaptic terminal.

**Discussion**

The conventional neuron seemed rigid, lacking in major opportunities for plasticity except at the synapse itself. The present “complications” (summarized in Table II) point up the possibilities for flexible styles of computation elsewhere in the neuron. Now we have passive properties that might change (e.g., at the dendritic spine: Rall and Rinzel, 1971; Fifkova and Van Harreveld, 1977), excitable mechanisms influenced by more than just synaptic currents, and repetitive firing and intermittent conduction mechanisms with historic effects—all quite in addition to the promise of the synapse itself for plasticity.

Anatomists divide the neuron into morphologically characteristic regions; physiologists attempt to identify functional subdivisions and relate them to the anatomical ones. In the search for the elementary computing unit, how should one partition the neuron? Certainly not a priori along classical anatomical lines: outputs may occur from dendrites, while inputs may occur upon axon terminals. The usual physiological subdivisions of passive and excitable do not

<p>| Table II |</p>
<table>
<thead>
<tr>
<th>Variations in neurons that affect input-output properties</th>
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<tr>
<td>1. Neurons can be organized with dendritic and axonal regions or they may lack all or part of this arrangement.</td>
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<tr>
<td>2. Synaptic inputs may be on dendrites, the soma, the initial segment of the axon, axon spines, or axon terminals.</td>
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<td>3. A presynaptic neuron may distribute its output sites onto a single postsynaptic cell in a single restricted region, over several regions, or uniformly over the cell’s synaptic surface.</td>
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<td>4. Receptors for particular transmitters and conductance mechanisms may be uniformly distributed over the synaptic surface of the neuron or they may be regionally segregated.</td>
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<tr>
<td>5. Transmitter arriving at an input synapse may cause postsynaptic conductance changes that are brief or long-lasting, that increase or decrease, that affect different ions, or that selectively desensitize, all depending on the postsynaptic receptors.</td>
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<td>6. For conductance-increasing synaptic inputs, two simultaneous inputs will produce a PSP that may be equal to, but is often less than, the sum of the individual input PSPs.</td>
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<tr>
<td>7. For conductance-decreasing synaptic inputs, two simultaneous inputs will produce a PSP that may be equal to, but could be greater than, the sum of the individual PSPs.</td>
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<td>8. PSPs from single inputs may be very small, or their height may be an appreciable fraction of the excursion from the resting potential either to the spike threshold or to the threshold for graded transmitter release.</td>
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<td>9. Passive spread may weight inputs equally or may strongly emphasize local inputs.</td>
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<td>10. Passive spread could be affected by changes in membrane resistance with voltage (e.g., anomalous or delayed rectification).</td>
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<td>11. Depolarizing “rebound” following the removal of hyperpolarization may be large or small and may vary in different parts of the neuron.</td>
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<td>12. Action potentials can occur in dendrites, the cell soma, the axon and its terminals.</td>
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<td>13. Spikes may propagate actively without decrement or spread passively with decrement in any part of the neuron.</td>
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<td>14. Neurons may have a single low-threshold spike trigger zone, or there may be multiple trigger zones for initiating spikes.</td>
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<td>15. Spike threshold may be lower if a rapid voltage change is used to approach it.</td>
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<td>16. Slow approaches to spike threshold may never succeed in spike initiation, or they may always evoke a spike when a “ceiling” is reached beyond which accommodation no longer occurs.</td>
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17. Sustained depolarizations may evoke either a sustained or a transient train of spikes.
18. Adaptation may lower spike production rates, settling to a steady state in many seconds, within a few spikes, or instantly.
19. The minimum input current for producing a sustained spike train may be high or low (or zero for pacemakers), often depending on whether the cell is large or small.
20. The minimum rate at which a neuron will fire rhythmically can be low or high (usually depending on whether the spike afterhyperpolarization is long or short).
21. The curve relating depolarizing current strength to spike firing rate can bend over gradually, be linear, be piecewise linear, or exhibit hysteresis.
22. The sensitivity of the current-to-rate curve may be high or low (sometimes depending on whether the cell is large or small).
23. A sustained spike train evoked by a depolarizing current step may be rhythmic, irregular, rhythmic with occasional "extra spikes," or bursty.
24. Extra spikes following the expected spikes in a rhythmic discharge may increase the sensitivity of the current-to-rate curve, or compensation may occur by lengthening of the interval to the next expected spike.
25. Augmentation of current-to-rate sensitivity by extra spikes can occur at the high end of the curve or only at the low end (creating a "negative sensitivity region" at intermediate currents where extra spikes fail to occur).
26. Extra spikes may be augmented by fatigue or by lack of preceding activity.
27. Extra spikes may themselves reexcite the spike trigger zone to create another extra spike, or extra spikes may fail to create the conditions necessary for reexcitation.
28. Reexcitation may create extra spikes initiating from the axon trigger zone due to a delay, a change in conduction speed, or a prolongation of the retrograde invasion of the soma-dendritic region by the preceding spike.
29. Adaptation in spike rate during sustained depolarizations may be due to hyperpolarizing bias currents developing from a change in the sensitivity of the current-to-rate process or from a decreasing probability of extra spikes occurring.
30. Bursts of spikes may occur from reexcitation or from an underlying depolarizing drive upon the current-to-rate process.
31. Hormones or second messengers can modulate cell metabolism and ionic conductances and thus change the firing properties of the cell.
32. Spikes may propagate faithfully or may conduct only intermittently through some regions.
33. Spike conduction may begin to fail after only a few spikes, or only after many minutes, or never.
34. Synaptic outputs may be from distal or proximal dendrites, the soma, axon spines, axon swellings (en passage), or terminals and from almost any combination of regions.
35. Output synapses may be segregated from, or intermixed with, input synapses.
36. Synaptic release may be stimulated by spikes, graded PSPs, or a combination of both.
37. Hormones or second messengers may modulate synaptic release.
38. The synaptic input-output curve may be the same, or different, at the various output synapses from a given neuron.
39. The synaptic release threshold may be high or low.
40. Tonic release of transmitter from output synapses may be large or small, occasional or continuous.
41. Sensitivity (the slope of the synaptic input-output curve) may be high or low, positive or negative.
42. Synaptic release may increase or decline during long-lasting depolarizations.
43. Synaptic release during a sustained spike train may increase (facilitate), depress (antifacilitate), or remain the same with successive spikes.
44. Synaptic release may be potentiated, following a conditioning train of spikes, for a short time or for many days.
45. Facilitation may be the same or different, in magnitude and time course, at various output synapses from a given neuron.
46. Conditioning pathways may decrease (presynaptic inhibition) or increase (presynaptic facilitation) spike-evoked transmitter release from output synapses.
47. Presynaptic inhibition may be caused by conditioning depolarization or hyperpolarization of presynaptic terminals or by a conductance increase in the terminal region.
48. Tonic and spike-evoked release of transmitter may be modified by the ionic milieu, and thus perhaps by spike activity in the postsynaptic neuron.
style just as surely as if the spike-initiating process had done it. Trying to divide the neuron into computing units is even harder: if one cannot define the boundaries of the elementary computing unit, or tell how many are contained within a single neuron, should we simply revert to the syncytium and give up in our attempt to define the most elementary building blocks with which the computing machine of the brain is built?

Difficult though it may be to delimit the boundaries of the computing unit, one can usefully trace the processing path through the cascade of intraneuronal processes linking the input synapses with the output synapses. We have seen both local and long-distance versions of this processing path, and it is apparent that an obvious candidate, upon which to base an elementary computing unit, is the processing path leading to an individual output synapse. Must one therefore treat a neuron with 100 separate output synapses as containing 100 elementary computing units? Not necessarily.

It is clear that we shall be able to view many CNS neurons as "units" much of the time. For example, cat spinal motoneurons are not reported to possess dendrodendritic synapses, and their various axon terminals are not known to differ functionally from one another in a manner that might segregate messages. Some neurons are perhaps "dual," such as the class of retinal horizontal cells studied by Nelson et al. (1975). These have two regions of extensive arborization, each with input and output synapses; one region synapses with rods, the other with cones. The two regions are connected by a long, thin axon that should severely attenuate PSPs. The cells seem to be spikeless. All of this suggests a neuron with two independent regions, almost as if it were two neurons (at least). In other cases, such as a superior colliculus horizontal cell (see Figure 11 in Graubard and Calvin, this volume), each output synapse along a long, thin dendrite might favor local inputs, with input effectiveness falling off with distance. Thus a dozen output synapses from one neuron might accomplish the job that otherwise would require a dozen neurons with more restricted dendritic trees.

Just as anatomists have long classified neurons by the shapes of their dendritic trees, so cellular neurophysiologists may come to recognize classes of neuronal computation styles. In the absence of the kind of analysis that has been partially done for a few cell types, can one use spiking/nonspiking as a major clue? This seems unlikely. Both spiking and nonspiking neurons can, under some conditions, function as elementary computing units; both types can also have diverse outputs, with regional influences superimposed upon central influences. Spike trigger zones do tend to provide strong central influences which, in the absence of additional processing between the trigger zone and the output synapses, will force all output synapses to act briefly as a unit. Combinations of Table I features such as "spikeless" and "intermixed input and output synapses" do make one suspect multiple computational units in such neurons. Until functional types of neurons are more clearly established by examining how they combine features such as those in Table 11, the modern view of neuronal computation will be complicated by the necessity of examining each output synapse from a single neuron for the possibility that it is sometimes, in some sense, an elementary computing unit.

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