tively through the cell body and down the axon. If many different sites can thus control the neurons' output (the axon spike), Llinás *et al.* (*9*) envisage "Purkinje cells . . . as highly complex units able to attain a vast number of dynamic states which would lead to the generation of a large variety of functional patterns." Alternatively, of course, the dendritic spike might merely act more as a booster station, giving rise in the soma to something perhaps no larger than an excitatory postsynaptic potential, which would then sum together with the regular synaptic currents to determine the axon spike in the usual manner.

8) Can one "unequivocably identify" dendritic spikes by theoretical interpretation involving free parameters? Free parameter models are very useful for improving upon intuition and suggesting possibilities but are often very hazardous otherwise. Such parameters are freely adjusted for good fit by the theoretician, or they are measured from the very data that the theory attempts to predict. Their predictive usefulness is quite different from models where each parameter is independently measured and the model's prediction then compared with reality (*10*).

In summary, the present waveshape and conduction velocity interpretative techniques would seem sufficiently flexible that an unwarranted population explosion in dendritic spikes would probably take place if they were uncritically adopted. Suggestive evidence, such as the similarity to the Rall and Shepherd figures, does play an important role in the more intuitive processes by which scientific ideas are formulated, but it should not be confused with unequivocable demonstrations. Certainly, whatever the fate of dendritic spikes in Purkinje cells, Zucker's comparisons of cable theories to volume-conductor theory should prove quite helpful in the future to the neurophysiologist attempting to choose the appropriate approach to his data.

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Cable Theory and Gross Potential Analysis

There appears to be some confusion about the nature and applicability of the models used by Llinás *et al.* (*1*), Zucker (*2*), and Calvin and myself (*3*) for gross extracellular potential analysis. Calvin reviews Zucker's analysis in an accompanying note, with which I am in complete agreement. It seems that a few words of clarification are in order concerning the interpretation of gross cortical potentials.

In a population of parallel dendrites synchronously activated, extracellular currents are parallel and axial. This depends upon the packing density of the dendrites, and in neural tissue this density is high enough to assure such an axial distribution (*4*). When current flow in a resistive medium is parallel, the medium may be modeled by a resistor lying parallel to the current lines. Current flow in the interior of a dendrite may also be modeled by a resistor, because it too is axial (*5*). Hence interior and exterior media are accurately represented by two parallel resistors; the membrane of the dendrite, which couples the two media, may be represented by resistors and capacitors lying perpendicular to the dendritic axis, which connect the internal and external resistors to each other. This, then, is the cable model upon which we have drawn our conclusions regarding the interpretation of Llinás' data, and upon which Zucker has developed his critique.

A striking characteristic of the model is its symmetry about the dendritic membrane. If no values are attached to the axial resistors, it is impossible to tell the interior from the exterior of the model. This has important implications for the waveshape of the interior and exterior potentials. Because current lines are closed, any current injected into the exterior medium by a membrane "source" must be taken from the interior medium at the same point along the membrane; internally, the source appears to be a sink.

In general, from the symmetry of the model, any current source in the external medium must appear as a sink of equal strength at the same membrane locus in the internal medium, and it follows that current in the external and internal resistors must be of equal strength and of opposite sign at every point along the dendritic axis. Because potential is the integral of this current, it would appear that the internal and external potential must have the same waveshape (although different signs and amplitudes owing to different directions of current flow and different values of the axial resistances in the internal and external media).

This identity needs qualification, however. Every potential must be measured between two points. For internal and external potentials to have the same waveshape, one must use an internal reference at an "indifferent" point within the cell, that is, at a point where the membrane is at its resting potential (*6*). Similarly, for external measurements one must choose as a reference point a truly indifferent location, such as a point infinitely distant from the cell population. Under these conditions the internal and external potential indeed have the same waveshape. Because the membrane potential is the difference between the intra- and extracellular potentials, and because the difference between two potentials with the same waveshape also has that waveshape, the membrane potential has the same waveshape as the intra- and extracellular potentials. But the membrane potential is described by the cable equation, hence the cable equation describes the extracellular potential surrounding a population of synchronous parallel dendritic processes, provided that sources and sinks are introduced as driving terms to account for synaptic activity and other active membrane events.

These are the basic theoretical considerations on which our conclusions regarding Purkinje cell dendrites were based. They are founded upon the as-

sumptions (i) that the extracellular current distribution is parallel and axial; (ii) that the cable equation, with appropriate driving terms, represents the membrane potential of these dendrites; and (iii) that there exists a distant "indifferent" electrode, completely outside of local current pathways, with respect to which the local potentials are measured.

The theory that derives from these assumptions is simple, and leads to the startling conclusion that gross extracellular potentials obey the cable equation.

Rall and Shepherd (*4*), in a study of olfactory bulb potentials, base their analysis on assumptions very similar to assumptions (i) and (ii) above (*7*). However, they have developed an ingenious technique to avoid (iii), the requirement of a distant indifferent electrode. They reason that the reference electrode must lie somewhere on the return current path, hence they choose a point in the extracellular medium, that is, along the external resistor of the membrane model (*8*). Zucker has applied this analysis to the case of cerebellar potentials measured by Llinás *et al.* and, by moving his theoretical reference electrode up and down the external resistance, has found a point where the predicted potentials appear to match the data reasonably well. We wish to emphasize, however, that the basic tenets of his analysis, beyond the placement of the reference electrode, are precisely the same as ours. It is hoped that this simple interpretation will help to dispel some of the confusion that surrounds present theories of gross potential generation.

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6. This excludes from consideration events such as active spiking of a small spherical cell, in which no point in the cell is neutral. For synaptic potentials and local or traveling active events, however, this is not a restrictive constraint.
7. Because the olfactory bulb displays spherical instead of axial symmetry, Rall and Shepherd (*4*) assume that the extracellular current distribution is radial instead of parallel.
8. In the case of spherical symmetry, the extracellular current divides between linear and nonlinear resistances, hence the model Rall and Shepherd use requires a network of external resistances, rather than the single resistance described here. Nevertheless, the principles involved are exactly the same.

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The preceding comments by Calvin and Hellerstein were to have appeared simultaneously with R. S. Zucker, Science **165**, *409 (1969).*

Gene Regulation in Higher Cells

The hypothesis described by Britten and Davidson (*1*) is the first speculation about the molecular mechanisms that control the epigenesis of higher forms that begins to make sense to an embryologist who has been thinking along these lines for 30 years or more. These authors realize that we have to find a system which can control not single genes but batteries of genes. The notion that the gulf between the complexity of the control task and the apparent lack of specificity of such possible controlling agents as histones might be bridged by calling on the informational redundancy suggested by the reiterated DNA sequences is an attractive and rather obvious one—in fact I have suggested it myself, in a less fully worked out form (*2*).

Moreover, with only slight elaboration, the hypothesis could deal with the major problem of development, namely, determination, which is always emphasized by embryologists but commonly neglected by molecular biologists brought up on microbiology. We need a mechanism that accounts not only for gene activation or derepression in such instances as the puffing of particular salivary bands after treatment with ecdysone or a changed ionic medium; the synthesis of hemoglobin following erythropoietin; the development of a drosophila imaginal disc into adult structures after the action of pupation hormones; and so on. We also have to show what has happened previously to "determine" which particular bands will puff; why erythropoietin stimulates hemoglobin synthesis in determined blood cells but not in other cells; and why the cells of eye imaginal bud develop into adult eye cells and those of other discs into other structures, even many generations after this determination first occurred.

This implies that we need a "double action" control mechanism, with one action concerned with determination and the second with activation. This requirement could be met if the Britten-Davidson scheme is modified by inserting another controlling factor between the integrator genes and the receptor genes. The acceptance of an external stimulus by certain sensors would then alter the state of the corresponding integrator genes, and this would amount to a state of determination of the future developmental pathway open to the cell; but we have to suppose that the interaction between the integrators and the receptors does not take place until a second, "activating" external stimulus is received. The block could be an inhibition of transcription of the integrator DNA, or something to do with the rather mysterious interaction between the integrator RNA and the presumably double-stranded receptor DNA, which Britten and Davidson postulate.

Such a scheme requires a second set of sensors to accept the activating external stimulus. These probably need not be very elaborate, because most activating stimuli (for example, hormones) seem to act on many different types of determined cells (for example, all the different imaginal buds in an insect larva), and thus affect many different integrator-receptor links simultaneously.

The last element in the picture, which to the embryologist would seem to be essential, is an explanation of the phenomenon of competence—that is, the fact that the cell-character which becomes fixed at determination depends not so much on the nature of the inducing agent but rather on the state of reactivity of the cells (*3*). In Britten and Davidson's model, this means that the properties of the various sensors change, so that at one time certain of them will react to a certain external stimulus, while at another time certain of these sensors no longer react, whereas possibly other previously nonreactive sensors have now become reactive. Britten and Davidson hint at the explanation in their remark that "certain sensors respond to the products of producer genes," but they wrote this in connection with sequential patterns of gene activation [what I have called "cascade" control (*4*)]. What we need to explain changes of competence is to