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

suppose that sensors may respond to the products of producers, not only by activating their integrators, but in some cases by becoming altered in their receptivity to some other external stimulus, such as an inducer. This point is of such fundamental importance for embryological development that it needs to be emphasized.

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## Marihuana and Simulated Driving

The report by Crancer *et al.* (*1*) on the relative effects of alcohol and marihuana on a simulated driving task has limitations which seriously reduce the value of their work. They have designed their experiments carefully and have considered in detail the possible influence of subject bias on the results. They point out that all their subjects were favorably disposed toward marihuana, but that it would not have been easy for them to deliberately perform better during the marihuana trials. However, many marihuana users have a bias against alcohol, and Crancer *et al.* do not explain what safeguards were used to prevent this from influencing the results. Even if the subjects did not know the details of the scoring procedure, was it not possible for them to deliberately do badly on the simulated driving test in the alcohol trials? The finding of normal results in the trials before administration of the drug on alcohol days is of no help in this connection, since there would be no incentive for the subjects to do poorly before taking the alcohol. Since placebo controls are of little value in such a situation, it would have been desirable to include a second group of subjects who were experienced drinkers and probably biased in favor of alcohol.

My major criticism of the work of Crancer *et al.* is the arbitrary choice of a single dose of each substance for the comparison. The subjects, who were experienced marihuana users, smoked enough to achieve "a normal social marihuana 'high.'" In contrast, they consumed alcohol at a dosage of 112 ml of 95 percent ethanol (equivalent to 8 ounces of 86 proof liquor) for a 150-pound subject in a 30-minute period. This is far more than the amount required for a normal social alcohol "high" and would probably produce a peak blood ethanol concentration of about 0.15 percent (*2*). The objective was to achieve a concentration of 0.10 percent, but the authors do not indicate what values they actually observed. The finding that a heavy dose of alcohol caused more impairment than a mild dose of marihuana is neither surprising nor helpful in assessing the relative effects of the two drugs in the respective doses in which they are normally used.

If the authors had used three or more dosages of each drug with adequate numbers of subjects, the comparison of dose-response curves would have been a most satisfactory way of establishing the relative potencies of the two drugs; at the same time it would permit some inferences about the similarity or dissimilarity of their mechanisms of action. The studies by Goldberg (*3*) illustrate the sort of dose-response relations which are easily established for alcohol. Crancer *et al.* would have added greatly to our knowledge of *Cannabis* effects if they had obtained similar data with marihuana. They state that in four subjects the use of a tripled dose of marihuana did not result in any increase in error. They recognize that this was "a cursory investigation of dose response," and they do not indicate what measures were taken, if any, to ensure that the larger dose was effectively absorbed by their subjects. Therefore they would have been well advised not to draw from such limited observation the conclusion that "impairment in simulated driving performance is apparently not related to dose." Isbell *et al.* (*4*) have shown that changes in pulse rate as well as in subjective effects provided good dose-response curves for $\Delta^9$-tetrahydrocannabinol (THC) in man, and Dagirmanjian and Boyd (*5*) have observed dose-dependent impairment of polysynaptic reflexes by other THC derivatives. It is most likely, therefore, that the effects on complex performance tests in man will also prove to be dose-dependent when full studies are done.

A final note of caution must be sounded against making unwarranted extrapolations from this study. While performance on a simulated driving task may correlate well with actual driving performance, it does not follow automatically that lack of effect of a drug on the simulated task will correlate with lack of effect on the actual task. The simulation applies only to specific sensorimotor skills, and motivational factors may be quite dissimilar. Crancer *et al.* correctly drew no conclusion that use of marihuana will not impair driving or that it is safer than use of alcohol. It is to be hoped that their readers will also refrain from drawing unjustified conclusions.

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The fact that the test subjects did not improve in their performance (unlike the same subjects under control conditions) was not surprising. The average concentration of alcohol in the blood was 0.07 percent prior to their taking their third and last simulator test. Only 3 hours elapsed between the first and third simulator test. Average concentration of alcohol in the blood for our subjects before the first simulator test was 0.10 percent.

Comparison of normal usage of both alcohol and marihuana was not an objective of this study. As indicated in our report, we thought possibly that smoking marihuana may lead to impairment and that it would be of value to compare its effect to a recognized standard of impairment—the presumptive limit of 0.10 percent of alcohol in the blood.

Replicating the experiment with the same subjects would have provided us with information on the variability of the treatments within the subjects. This information is not necessary when our interests are primarily in comparing the effects of several treatments. This we did by obtaining a single score for each treatment for 36 subjects.

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