ferences. It has been reported that an Indian Ocean gas-rich MORB glass shows xenon that is consistent with the ^{238}U fission spectrum (*5*). On the other hand, excess ^{129}Xe is commonly correlated with excess $^{131\text{-}136}Xe$. It has been argued that the correlation between excess ^{129}Xe and excess $^{131\text{-}136}Xe$ should be established by components that have similar time dependence, such as ^{129}I and ^{244}Pu, because diamonds also show such correlation (*4*). Because the amount of each excess xenon isotope in terrestrial materials is quite small, however, it is a hard task to separate each component, and analytical uncertainties in those samples were too large to distinguish each possibility.

In addition, on the basis of helium and neon isotope analogies, the occurrence of solar noble gases in Earth's interior is often inferred even for xenon isotopes. Because atmospheric xenon isotopes are definitely different from solar compositions, if solar Xe isotopes do occur in Earth's interior, a change in the hypothesis for the origin of the atmosphere and the evolutionary history of Earth would be required.

Kunz *et al.* (*1*) have succeeded in confirming the occurrence of fission-produced xenon components from ^{244}Pu in Earth's interior by using a special MORB sample, together with the information that the xenon in Earth's interior is of atmospheric composition, except for the occurrence of fission-produced Xe and ^{129}Xe created by radioactive decay. They have concluded that among the fission product components of Xe observed, about 30% is attributed to the component from ^{244}Pu and the remnant to ^{238}U (see figure). This is the first experimental evidence that the Xe derived from fission of ^{244}Pu surely exists in Earth's interior. Their analytical success depends on two main factors: technical improvements including the application of a counting system to measure quite small amounts of gases and the special properties of the sample used for analyses. The sample is called popping rock and has been known to contain anomalously large amounts of magmatic noble gases (*6*).

The results of Kunz *et al.* have provided a solution to the controversies over the occurrence of ^{244}Pu in Earth's interior and solved the paradox that only the signature of short-lived ^{129}I remains with no definite evidence for the occurrence of ^{244}Pu with a longer half-life in Earth's interior. Thus, the early rapid degassing model from at least the depleted mantle of Earth's interior is strengthened. Furthermore, the occurrence of atmospheric xenon apart from the addition of nucleogenic ^{129}Xe and fissiogenic $^{131\text{-}136}Xe$ implies the common origin of the terrestrial xenon for both the atmosphere and Earth's interior. This is an important constraint on the evolution of Earth, and some special process is required to produce terrestrial xenon compositions that are definitely different from those of extraterrestrial materials. This seems to favor the model of secondary degassing for the occurrence of the atmosphere, at least for the major part of xenon isotopes. On the other hand, relative excess xenon contributions from ^{129}I and ^{244}Pu estimated from the atmosphere and the MORB sample are different. Excess $^{129}Xe(^{129}I)/^{136}Xe(^{244}Pu) = 4.3$ for the atmosphere has been suggested (*7*), whereas that estimated from the MORB (*1*) is about 9.8. After the end of nucleosynthesis, the value of excess $^{129}Xe(^{129}I)/^{136}Xe(^{244}Pu)$ retained in the solid material should decrease with time because of the difference in the half-life of ^{129}I and ^{244}Pu. If the terrestrial atmosphere was formed by early degassing from Earth's interior where the MORB magma is formed, the value of excess $^{129}Xe(^{129}I)/^{136}Xe(^{244}Pu)$ for the atmosphere should not be less than that in Earth's interior. Yet the observed value is the opposite of what is expected from a simple degassing model of the atmosphere from Earth's interior. This may require some modification in both the degassing model for the evolution of the atmosphere and the evolution model of Earth. Because we have not yet established the heavy noble gas compositions (argon, krypton, and xenon) for the ocean island basalt source, the problem may also be related to their identifications. This knowledge about xenon in Earth's interior surely helps to clarify the model of Earth's formation and demonstrates the need for further information.

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BIOCHEMISTRY

The Era of Pathway Quantification

Daniel E. Koshland Jr.

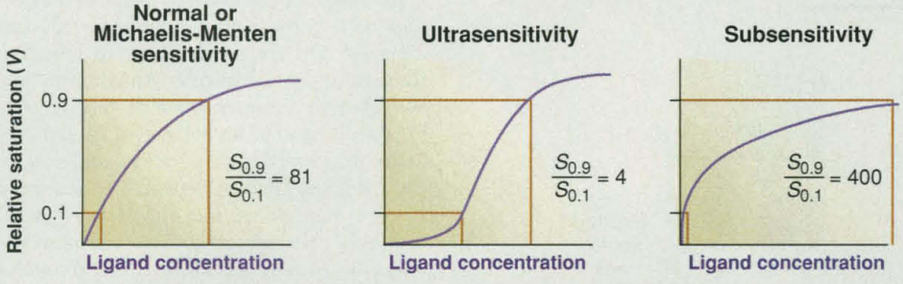
On page 895 of this issue, Ferrell and Machleder (*1*) highlight a new era in our understanding of cellular metabolism. Knowledge of metabolic processes in cells can be roughly divided into three eras: the Era of Pathway Identification (1890–1950), the Era of Pathway Regulation (1950–1980), and the Era of Pathway Quantification (1980–?). In the first era, the individual steps in the biochemical pathways were identified. In now classical studies, the substrates, products, and enzymes of pathways such as glycolysis, fatty acid metabolism, and nucleic acid metabolism were identified by Emden, Meyerhoff, Warburg, Kornberg, Cori, Brown, Goldstein, and many others (*2*). In the second era, the control of pathways through feedback, feedforward, cooperativity, allostery, phosphorylation, and covalent modification was delineated by Pardee, Krebs, Fischer, Stadtman, Jacob, Monod, this author, and many others (*3*). In the third era, now in its childhood, the quantification of pathways is being examined to calculate the rates at which metabolites and substrates are produced and degraded in cells and in organs.

Ferrell and Machleder (*1*) examine the turning on and off of the cell cycle in oocytes, showing that this control process is quantitatively "ultrasensitive" (*4*) and that the enzymes responsible are the mitogen-activated protein kinase (MAP kinase) cascade. In their report, they examine this process in intact oocytes (*1*); in a previous paper, Huang and Ferrell analyzed a cell-free system of the same MAP kinase cascade (*5*). Because individual enzymes of the cascade do not show cooperativity, it seems clear that some form of zero-order ultrasensitivity or multistep ultrasensitivity (*4*) is at work in this pathway, likely involving the kinetics of phosphorylation and dephosphorylation in the enzymes of the kinase cascade.

The author is in the Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720, USA. E-mail: dek@uclink4.berkeley.edu

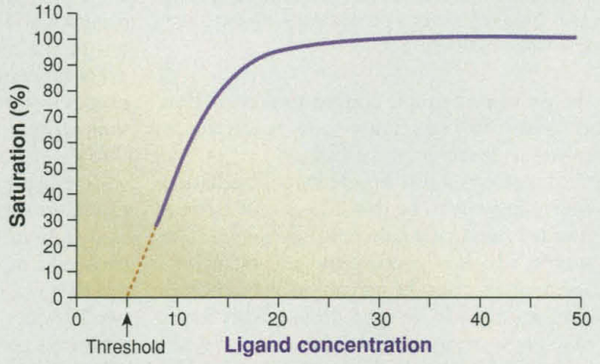
Ultrasensitivity has been defined (*4*) as the response of a system that is more sensitive to changes in the concentration of the ligand than is the normal hyperbolic response given by the Michaelis-Menten equation. A Michaelis-Menten or hyperbolic response requires an 81-fold change in ligand S (the ligand can be a substrate or an effector of an inhibitor) to generate a ninefold change in response [for example, $V_{0.9}/V_{0.1}$ = 9 when $S_{0.9}/S_{0.1}$ = 81, where V is velocity and S is substrate concentration (see figure above)]. The ratio, 81, will be true of any Michaelis-Menten curve (which is a hyperbola) regardless of the midpoint of the curve. An ultrasensitive response is defined as that in which the change from 10% to 90% can be achieved with less than an 81-fold change in ligand concentration, and a subsensitive response is one in which it can be achieved only with a greater than 81-fold change in ligand concentration. One can also use the Hill coefficient (n_H), as Ferrell and Machleder have done, to indicate Michaelis-Menten or hyperbolic sensitivity (n_H = 1.0), ultrasensitivity (n_H > 1), and subsensitivity (n_H < 1).

One known mechanism of ultrasensitivity is the cooperativity observed in hemoglobin (*6*); others are zero-order ultrasensitivity, as observed in kinase reactions running near saturation (*7*), and multistep ultrasensitivity, in which there are multiple regulators of the same enzyme (*8*). Ferrell and Machleder show that the change in Hill coefficient in the oocyte cell cycle response is very high (n_H = 5.0, compared to 2.8 for hemoglobin) to illustrate the powerful ultrasensitivity of this system. They also illustrate an important principle in this quantitation: Individual oocytes show an even greater ultrasensitivity than the ensemble as a whole, and they declare that this is caused by the individual systems having different midpoints to their saturation curves—that is, the average of highly sensitive systems with different $S_{0.5}$ values will give a much less sensitive overall response to a stimulus than would the individual systems themselves. They also postulate a feed-forward phenomenon to explain the added ultrasensitivity in the intact oocytes beyond that in the cell-free system.



Enzyme responses to changes in ligand concentration. Relative differences in ligand concentration(s) that give 10% saturation ($S_{0.1}$) versus 90% saturation ($S_{0.9}$) of the response to a stimulus.

Ferrell and Machleder use some terms that will become increasingly important in the new Era of Quantification. Terms such as "switchlike" or "all-or-none" give the flavor of switch phenomena in mechanical systems—a good analogy and one that implies a very high ultrasensitivity. Switches in nonbiological systems refer to such phenomena as light switches that go from darkness to light in an instant or a melting point that goes from one state to another with a small change in temperature. In both of these cases, either in the mechanical device or the melting solution, millions of molecules are involved, and therefore the sigmoid character of the response is obscured. As shown in the figure directly above, with smaller numbers of molecules (for example, four subunits in hemoglobin), the change is gradual but is markedly more sensitive than a hyperbolic curve to changes in the environment. Thus, a lack of knowledge of the mathematics would lead one to suggest that a drug acts only when it exceeds a threshold. In fact, low concentrations of a drug will have an effect, but it will be undetectable against the large background of a biological system (see figure below).



Explanation of threshold effects. A typical drug response curve produced with decreasing concentrations of a drug until the analytical method is no longer accurate (dashed line). The extrapolation (seen frequently) implies a threshold. A truly accurate assay would give a sigmoid curve as shown for ultrasensitivity in the figure above.

Some steps have already been made in the new Era of Quantification. Calcium spiking has been quantitated and allows the cell to set a sharp threshold to stimuli (*9*). The pathway of chemotaxis in *Escherichia coli* has been calculated in relation to the actual concentrations of the components of that response (*10*). The switch between the Krebs cycle and the glyoxalate shunt has been correlated quantitatively with the rates through each of the individual steps in the Krebs cycle and glyoxalate bypass (*8*). The use of energy in maintaining a phosphorylation system has also been quantitated (*11*). These are just a few illustrative examples of the quantitative conclusions that are possible when quantitation and the mathematics of quantitation become part of the arsenal of investigators of metabolic interactions. Investigators will be increasingly concerned with responses initiated by small fluctuations in the environment or cellular media, small changes in hormone supplies, and increases or decreases in enzyme levels, for example, as cells differentiate and dedifferentiate. We have gone from the era of "who" to that of "how" and are now entering the era of "how much". Ferrell and Machleder's report is a prime example of excellent data and thinking applied to a very important problem.

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