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Untangling Biological Reactions

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Elementary biological reactions are not in principle more complicated than the reactions encountered in simple systems. However, such reactions are usually catalyzed by enzymes which can be changed both reversibly and irreversibly from an active to an inactive state. Because of this, the typical biological reaction rate passes through a maximum with rising temperature. The maximum occurs when the Arrhenius reaction speedup associated with a rise in temperature is just balanced by the slowdown caused by heat inactivation of the enzyme associated with a temperature rise.

My active concern with biological reactions began with bacterial luminescence in 1942. Newton Harvey introduced me to Frank Johnson, with a brief summary of the peculiar effect of pressure on luminescence that Johnson, Brown, and Marsland had just observed (*1*). Below the temperature maximum hydrostatic pressure decreases the light intensity of luminescent bacteria in solution, and above this temperature maximum pressure increases the light intensity. Harvey emphasized the seeming paradox in these observations. Pressure should either increase the brightness of luminescence or decrease it, but not both. Equally remarkable is the magnitude of the pressure effect, which greatly exceeds the values for nonbiological reactions.

This extraordinary sensitivity of living things, in general, to external stimuli is astounding. The amplification of energy effects may be illustrated by an example. An ill-chosen remark to an unbalanced dictator might eventuate in a nuclear war that would make much of the planet uninhabitable. Untangling the entire chain of reactions, including the thought processes, that go into such a scaling-up in effects is still a distant goal, but at least some of the intermediate steps are becoming clearer.

A chain of reactions may be expressed in terms of a sequence of elementary reactions. Each elementary reaction, in turn, is governed by a specific rate constant—that is, the rate of reaction at unit concentration, k', of the form (*2*)

$$k' = \kappa \frac{kT}{h} \exp\left(-\frac{\Delta G\dagger}{RT}\right) \qquad (1)$$

Here $\Delta G\dagger$ is the work that must be done in forming the activated state from the reactants at unit concentration and kT/h is a frequency factor proportional to the absolute temperature and having the value 6.2×10^{13} at room temperature. For most reactions the transmission coefficient, κ, can be taken to be unity or, if different, it can be estimated. Thus the rate of reaction depends on the work $\Delta G\dagger$ required to form the activated state from the reactants, just as an ordinary equilibrium depends on ΔG, the work required to make products from reactants. We can now explain Harvey's question concerning the effect of pressure on luminescence. The activated state is more voluminous by 54 cubic centimeters per mole than the initial state, which corresponds to the compact native enzyme. Accordingly, it takes additional work to form the activated state from the initial state against an external pressure, and the reaction is therefore slowed by pressure and the luminescence is less bright. On the other hand, the inactive denatured state present at high temperatures is more voluminous by 20 cubic centimeters per mole than the activated state, so that above the temperature maximum, where many molecules are denatured, pressure helps form the activated state, making the system brighter. Such considerations explain all the qualitative effects, and detailed calculations succeed quantitatively (*3*).

Enzymes, in water solution at low temperatures, are folded with their hydrophilic groups extending out into the water and the hydrophobic groups folded inside against each other. For example, when a typical enzyme catalyzing luminescence in *Achromobacter fischerei* reversibly denatures, it increases in entropy by 266 entropy units, and the heat, ΔH, increases by 80 kilocalories. These values, together with a heat of activation, $\Delta H\dagger$, of 34 kilocalories, explain the maximum in the luminescence intensity occurring at 28°C (*4*).

If luminescent bacteria are placed in 3-percent ethyl alcohol, the light is almost extinguished. This is because alcohol induces the unfolding of the oxidative enzyme, catalyzing the oxidation of luciferin, by forming hydrophobic bonds between the ethyl group of the ethyl alcohol molecule and the hydrophobic groups of the enzyme which are exposed as it unfolds. This stabilization of the inactive form of the enzyme is reversed by pressure, with restoration of the luminescence, because of the smaller volume of the active enzyme. All molecules which make hydrophobic bonds, if present in water in sufficient concentration, inactivate luciferase and other enzymes. Tadpoles and salamanders are immobilized in a 3-percent alcohol solution but immediately start swimming when hydrostatic pressures of a few hundred atmospheres are applied, just as bacteria start luminescing under similar circumstances (*5*).

Quantitative analysis of the concentration effect of an alcohol, an ether, or acetone on luminescence reveals that three hydrophobic bonds are formed with these agents per enzyme molecule

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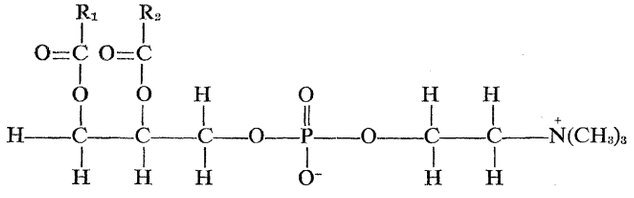
in the inactivation process. On the other hand, a single molecule of sulfanilamide or para-amino benzoic acid combines with a prosthetic group of luciferase, stopping enzymatic activity. Raising the temperature lessens the inhibition due to these agents while it enhances the inhibition due to alcohol and other hydrophobic bond formers. Because combination with a prosthetic group involves little volume change, pressure does not reverse this inhibition.

The concentration of alcohol or ether required to suppress luminescence or to immobilize tadpoles and salamanders is about ten times that in the blood of people adjudged to be under the influence of alcohol in a legal sense. Aside from this concentration difference, there is a striking parallel between the effectiveness of anesthetics in suppressing luminescence and in inducing anesthesia.

Membrane Permeability

Membranes enclosing cells vary in thickness and composition, but a reasonable interpretation of what is known suggests that they typically consist of a layer of lecithin two molecules thick lying between two layers of protein. The structure of lecithin is



The whole membrane is about 100 angstroms thick, and the inside is about 70 millivolts more negative in charge than the outside. The lecithin layer is about 50 angstroms thick. Nerve membranes are often surrounded by an additional thick myelin sheath. Typically, inside a nerve cell concentrations are about 0.4M in potassium, 0.05M in sodium, 0.04 to 0.15M in chlorine, 0.0004M in calcium, and 0.01M in magnesium. Outside the cell the corresponding concentrations are 0.02, 0.44, 0.56, 0.01, and 0.054 molal, respectively. These are the concentrations reported by Hodgkin (*6*) for freshly isolated crab axons. Presumably the long paraffin groups, R_1 and R_2, will be directed to the interior of the membrane as Davson and Danielli (*7*) supposed, and the choline phosphatidyl group will be resting in a receptor in the protein. The result is that the resting membrane has a very high electrical resistance of 1000 ohms per square centimeter, as compared with 20 and 30 ohms per centimeter for the fluid surrounding the axon and the fluid inside it, respectively. When a nerve impulse passes along the axon, the membrane becomes about 100 times more conducting.

Hodgkin and Huxley (*8*) have been conspicuously successful in accounting for the electrical behavior of nerves, using the simple equations

$$\frac{a}{2R\theta^2}\frac{d^2V}{dt^2} = C\frac{dV}{dt} + (V - V_K)\bar{g}_K n^4 + (V - V_{Na})\bar{g}_{Na} m^3 h + (V - V_L)\bar{g}_L \quad (2)$$

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \quad (3)$$

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \quad (4)$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \quad (5)$$

Here a is the radius of the axon and R is its resistance per centimeter; θ is the velocity of the traveling wave; V is the potential drop across the axon, and V_K and V_{Na} are the potentials which the corresponding concentration gradients would yield. The last term in Eq. 2 is due to currents other than those due to sodium and potassium; C is the capacity per square centimeter of membrane; t is the time; $\bar{g}_K$ and $\bar{g}_{Na}$ are the corresponding membrane permeabilities when the probabilities of m, n, and h are unity; m and n are described as the probabilities that certain facilitating "particles" are in the right place, and $(1 - h)$ is the probability that an event will block sodium. Probabilities n and m start near zero and follow a sigmoid curve toward unity with increasing time. Probability h starts near unity and follows a reverse sigmoid curve toward zero. The α's and β's are rate constants with complicated voltage dependencies. We can now consider an interpretation of the probabilities n, m, and h.

A Lipid-to-Receptor Bond Theory of Nerve Action

Acetylcholine propagates (*8*) a nerve impulse across a synapse. When excited, a membrane swells, becomes more conducting and less opaque, and loosens its structure. Acetylcholine also makes the excised ileum of a frog contract. A sigmoid curve is obtained if the percentage of maximum contraction is plotted vertically against the logarithm of acetylcholine concentration (*9*). If, on the other hand, the voltage across a nerve membrane is dropped below a critical value and then held constant, and if now the time course of potassium conductance is plotted against time as the abscissa, this plot is likewise a sigmoid curve (*6*). This conductance-time curve can be approximately superposed on the curve for the percentage of contraction of frog ileum relative to the log concentration of acetylcholine if a suitable scale change is made in the abscissa of one of the curves. This suggests that, in the nerve membrane, $d \ln x = kdt$, where x acts on the nerve membrane as acetylcholine acts on the tension of frog ileum. Presumably, then, the protein of nerve membranes, when excited, acts like excited muscle and contracts.

The bond between the choline phosphatidyl of the lecithin and a receptor in the protein keeps the choline phosphatidyl from flopping over and penetrating into the lipid layer, an occurrence which would open up a channel more permeable to ions. At the same time, this receptor-to-lipid bond presumably keeps the protein stretched in an inactive state in which the membrane is comparatively impervious to water and ions. Any stimulus which will shift the equilibrium in favor of breaking the bonds between lecithin and the protein receptors will allow the protein molecules to fold up and act as active enzymes, and, at the same time, the free phosphatidyl choline will enter the membrane, making it permeable to ions. Stimuli which do this are (i) dropping the resting potential by about 0.02 volt, (ii) adding acetylcholine or some other chemical which stabilizes the non-bonded state by successfully competing for the receptor sites; and (iii) decreasing the calcium concentration outside the membrane, thus promoting receptor-lipid bond breakage. On the other hand, anesthetics such as ether and alcohol, with their proclivity for hydrophobic bonding, stabilize the resting state by making hydrophobic bonds with the stretched protein and by filling loose sites in the lipid, making it more difficult for wet conducting channels to

form. Narcotics, with their positive nitrogen, likewise stabilize the resting state.

This lipid-receptor bond theory can be formulated quantitatively. We indicate a lipid-receptor pair by P. The pair P may or may not add other substances onto itself, and this will be symbolically indicated in the way one ordinarily indicates compound formation. Thus, PN_n will indicate that n molecules of a narcotic N have combined in some way with the lipid-receptor pair. If the resulting compound breaks the lipid-to-receptor bond, thus increasing membrane permeability, we indicate this by using a star as a superscript. P_o is the total number of pairs. Thus we can write

$$(P_o) = (P) + (P^*) + \sum_i (PA_a)_i + \sum_j (P^*B_b)_j \tag{6}$$

The first summation is over all types of addends which stabilize the impermeable state of the membrane, and the last summation is over all molecules which stabilize the permeable state. We have the following equilibria

$$P \rightleftarrows P^*;\ K \exp\left(\frac{\gamma\delta V}{RT}\right) \tag{7}$$

$$P + aA = PA_a;\ K' \tag{8}$$

$$P + bB = P^*B_b;\ K'' \exp\left(\frac{\gamma\delta V}{RT}\right) \tag{9}$$

Thus

$$\frac{(P^*)}{(P)} = K, \text{ etc.} \tag{10}$$

Here the equilibrium constants are the values in the absence of an applied field. We suppose that an applied potential, δV, across the membrane stabilizes the starred state by the free energy, $\gamma\delta V$. Hence, using the equilibrium equations, we can rewrite Eq. 6 as

$$(P_o) = (P) + (P)K \exp\frac{\gamma\delta V}{RT} + \sum_i [(A)^a(P)K']_i + \sum_j [(B)^b(P)\ K''\ \exp\frac{\gamma\delta V}{RT}]_j \tag{11}$$

Hence the fraction, f, of the pair states that are starred—that is, that support permeability—is given by the equation

$$f = \frac{\{K + \sum_j [(B)^b K'']_j\}\ \exp\frac{\gamma\delta V}{RT}}{\{K + \sum_j [(B)^b K'']_j\}\ \exp\frac{\gamma\delta V}{RT} + \{1 + \sum_i [(A)^a K']_i\}} \tag{12}$$

According to our lipid-to-receptor bond theory, f is the equilibrium value of n or m of the Hodgkin-Huxley theory if the appropriate equilibrium constants are used in the respective cases. In the same way $(1-f)$ is the equilibrium value of h for the appropriate values of the parameters. Since every equilibrium is a balance between a forward and a backward rate, it follows that any shift in the conditions which change the value of f will set in motion a complicated set of relaxations, each involving a forward and backward specific rate having measured Q_{10} values of about 3; that is, $\Delta H\dagger \simeq 18$ kilocalories. Many of these specific rates will be voltage-dependent. This is a sufficient basis for explaining the strange form of the voltage dependencies of the empirical "specific rates" used by Hodgkin and Huxley. The properties of f are interesting: f plotted as a function of δV is a sigmoid curve starting at zero, when $\gamma\delta V = -\infty$, and becoming one at $\gamma\delta V = +\infty$. It follows from Eq. 12 that the voltage clamp curve for the conductance of potassium plotted against voltage should have the observed sigmoid shape, and that the sodium curve should show the observed maximum. Since we have the identity

$$(B)^b K'' \exp\frac{\gamma\delta V}{RT} \equiv K'' \exp\frac{\gamma\delta V + b\,RT \ln (B)}{RT} \tag{13}$$

it follows that, when a single term is of overriding importance in the numerator of f, any property depending on f will have the same appearance when plotted against $\gamma\delta V$ or against $b\ RT$ ln (B). Here (B), for example, might be the concentration of acetylcholine.

The receptor-to-lipid bond theory explains why there is a partial summing of the effects of stimulants and of depressants and how stimulants and depressants partially counteract each other. It also explains why these algebraic summations are only partial, since each agent, as it acts on different nerves with differing types of receptor-to-lipid bonds, will have its own spectrum of effects which only partially overlap that of any other agent. Since our olfactory nerves, along with each of our other senses, should be reasonably well described in terms of some finite number, n, of different lipid-receptor bond types, it ought to be possible to represent each sense stimulus as a vector in the appropriate n-dimensional space; the totality of sensations at any moment would be a vector in the combined space of all the senses. From this point of view, the various senses are a somewhat arbitrary way of breaking up the total field of sensation, reflecting the way we group the senses conceptually.

The effect of Ca^{++} ion, which stabilizes the inactive state of the nerve, would be represented by one of the terms in the last summation in the denominator of f, as would an anesthetic or a narcotic. The effect of such terms is to raise the cathodic potential which must be applied to the outside of a nerve to make it conduct—that is, to raise the threshold for conduction. Because each nerve type has its own kind of receptor-to-lipid bond, depressants and stimulants will have their own characteristic spectrum of responses. Each agent will stimulate or depress each sensation, depending on whether it strengthens or weakens the particular lipid-to-receptor bonds for the nerve involved.

We suppose that during the time f is large—that is, while the membrane is permeable—certain enzymes in the protein membrane will be in their active state due to breaking of the restraining lipid-to-receptor bonds. Thus we expect muscles and nerve pathways to be strengthened by growth during excitation. This is in accord with the strengthening of muscles and of habits with repetition and the atrophy of muscles and the forgetting of routines with inaction. The craving for a drug because of the associated pleasant sensations is quite different from a dependence which is associated with violent withdrawal symptoms. In the latter case certain physiologic changes must occur with use of the drug, such as modification of the receptors by contact with the drug, or, in some cases, replacement of the choline in lecithin with some other molecule containing a tertiary nitrogen. Recovery in such cases requires time, and too rapid withdrawal of the drug may be fatal.

Everyone who discusses anesthetics necessarily explains their effect in terms of an increase in the potential change necessary to excite a nerve impulse in the presence of the anesthetic. Overton (*10*) and Meyer (*11*) quite successfully correlated the effectiveness of anesthetics with the value for their distribution ratio between oil and water. High solubility of a hydrophobic substance in the lipid should stabilize the resting state. Pauling (*12*) pointed out that most oil-soluble substances tend to form clathrates with water and

will, accordingly, make the water at synapses less available for facilitating conduction, making it difficult for an impulse to cross the synapse. Besides these effects, the lipid-to-receptor bond theory requires that a fat-soluble molecule, because it preferentially forms hydrophobic bonds with the lipid groups of proteins of the membrane, will stabilize the membrane in the resting state. Quastel (*13*) was interested in this latter effect, but there was supposed to be a difficulty in understanding the effectiveness of such low concentrations of anesthetic.

It is difficult to find instruments having both high sensitivity and reliability. This combination is usually achieved by making individual events easily excited and only counting the events if a significant number of events occur simultaneously (that is, by coincidence counting). A 0.02-volt change in potential will stimulate a nerve, but this voltage times the charge on a monovalent ion is equal to 460 calories per mole, as compared with 620 calories for RT at blood temperature. Thus, before the voltage change is applied, the chance, P, of such a bond being broken spontaneously, if it can act independent of other bonds, is

$$P = \frac{\exp\left(-\frac{460}{620}\right)}{1 + \exp\left(-\frac{460}{620}\right)} = 0.32 \approx \tfrac{1}{3}$$

Accordingly, even if one knows the bond is broken, there is one chance in three that this breakage is not due to the stimulus. If, however, a nerve impulse is set off only if r of these bonds are broken, the chance that the event is not due to the stimulus drops to $(\frac{1}{3})^r$. Now if four bonds must break to open a potassium channel, the chance that the event is accidental drops to 1/81, and if many such channels must open before a nerve impulse will pass, our nerve-impulse mechanism has high reliability. If the bond, in breaking, has to do work against only a fraction of the 0.02 volt, then the 460 calories will decrease proportionately and P will come nearer to unity, and the nerve will become correspondingly more sensitive but still may be sufficiently reliable because many such events are required to initiate a nerve impulse. However, if P drops too far, the result may be hallucinations or seizures. When we see how little the stability of a bond must be shifted to be broken and yet how high the likelihood is that a nerve impulse is not accidental, it occasions no surprise to find that the senses may be stimulated or inhibited by a low concentration of compounds which are capable of making only very ordinary van der Waals bonds with the sense organs. Some chemists can recognize several hundred compounds by their odor. Structural differences that should cause changes of less than RT in the difference of the free energy of adsorption of molecules to the lipid receptor in its bonded and unbonded states can be readily distinguished by their odors. Differences between optical isomers are sometimes sensed, which is to be expected if adsorption is on the asymmetric protein molecules of the lipid-receptor bond. This sensitivity also explains why such delicately poised equilibria can be shifted into insensibility with low concentrations of anesthetic, and one sees, at the molecular level, the importance of space and time summation in establishing reliability.

Active Pumping of Ions

As is well known (*6*), when a sufficient excess concentration of potassium ion is built up inside a large axon and a similar excess of sodium ion is present outside, the axon can conduct many times even though the active pumping of ions has been suspended. However, eventually the concentration gradient must be built back if the axon is to continue functioning. We now consider briefly the principles governing the potential gradient across a membrane. Because the current at various points around a circuit must be the same, we can write

$$I = C\frac{dV}{dt} + \sum_i I_i - \sum_j I_j \tag{14}$$

Here I is the current in the outer circuit coming from a square centimeter of membrane. C is capacity per square centimeter of membrane. V is the potential difference across the membrane; I_i is the current across the membrane, due to the ith ion, flowing in a direction to increase the positive charge outside the cell; and I_j is the current due to the jth ion which decreases the positive charge outside the cell. If p, the permeability, is the number of moles of the ith ion which flow through a square centimeter of membrane when the activity, a_i, is unity then

$$\begin{aligned} I_i &= 96500\ |Z_i|\ a_i p_i \\ &= 96500\ |Z_i|\ a_{i0} p_i\ \exp\left(-\frac{\beta_i |Z_i|\ V\ 23060}{RT}\right) \end{aligned}$$

and

$$\begin{aligned} I_j &= 96500\ |Z_j|\ a_j p_j \\ &= 96500\ |Z_j|\ a_{j0} p_j\ \exp\left(\frac{(1-\beta_j)\ |Z_j|\ V\ 23060}{RT}\right) \end{aligned} \tag{15}$$

Here a_{i0} and a_{j0} are the activities when V is zero. The activities a_{i0} are enhanced at the point of no return (or the effective point of no return) by the corresponding exponentials as written in Eq. 15. The term β is the fraction of the potential drop which lies between the inside of the membrane and the point of no return. When the voltage on open circuit is not changing, we have

$$I = C\frac{dV}{dt} = 0$$

and

$$\sum_i I_i = \sum_j I_j \tag{16}$$

Equation 16 can be rewritten as

$$\begin{aligned} \sum_i |Z_i|\, a_{i0} p_i\ \exp\left[-\frac{(\beta_i |Z_i| - \beta Z)V\ 23060}{RT}\right] \exp\left[-\frac{\beta Z V\ 23060}{RT}\right] \\ = \sum_j |Z_j|\, a_{j0} p_j\ \exp\left\{\frac{[(1-\beta_j)Z_j - (1-\beta)Z]V\ 23060}{RT}\right\} \times \\ \exp\left\{\frac{(1-\beta)ZV\ 23060}{RT}\right\} \end{aligned} \tag{17}$$

hence

$$V = \frac{RT}{ZV\ 23060} \ln \frac{\sum_i |Z_i|\, a_{i0} p_i\ \exp\left\{-\frac{(\beta_i |Z_i| - \beta Z)V\ 23060}{RT}\right\}}{\sum_j |Z_j|\, a_{j0} p_j \exp\left\{\frac{[(1-\beta_j)Z_j - (1-\beta)Z]V\ 23060}{RT}\right\}} \tag{18}$$

βZ is chosen to minimize the importance of the exponential terms. When all the β's and Z's are equal and there is only one ion, i, carrying positive charge in one direction and the same ion, j, in the reverse direction, Eq. 18 becomes the Nernst equation:

$$V = \frac{RT}{ZV\ 23060} \ln \frac{a_{i0}}{a_{j0}} \tag{19}$$

When all the β's are equal and all Z's are equal, we have an equation obtained by Goldman (*14*) in another way:

$$V = \frac{RT}{ZV\ 23060} \ln \frac{\sum_i |Z_i|\ a_{io} p_i}{\sum_j |Z_j|\ a_{jo} p_j} \qquad (20)$$

Planck (*15*) derived a useful form of some of these equations. The more general equation (Eq. 18) is required when we have ions carrying current with different valences and different asymmetric barriers, as is sometimes the case. Active transport occurs whenever the ion current in one direction is not balanced by its reverse current. This happens in corrosion, for example, and it is always associated with a decrease in the free energy of the system. For example, if sodium forms a complex with some agent (or agents) which has much higher permeability than ordinary sodium ions, there will be active transport of this complexed species down its gradient, although the gradient of ordinary sodium is opposite. If the chelating material for sodium is formed at higher concentration inside the cell and if this material is modified outside the cell to chelate with potassium, making potassium highly permeable for the return journey, we have a shuttle system which will build up the potassium concentration inside the cell and the sodium concentration outside. The chelating material can be part of the membrane, provided it is able to make the journey with the ions through the impermeable part of the membrane. The energy for modifying the chelating material comes from adenosine triphosphate, but what this chelating material is, is much less clear. Since it has not been possible to isolate the chelating material, the conclusion is that it must be used very efficiently and with little loss. If acetylcholine and phosphoric acid chelated with sodium for the outward journey, and acetic acid and the choline ester of phosphoric acid chelated with potassium for the backward journey, we would have a neat fitting together of a number of the facts concerning active transport. Something like this must happen. Skou (*16*) has recently made some very interesting observations concerning active transport.

References and Notes

1. D. E. Brown, F. H. Johnson, D. A. Marsland, *J. Cellular Comp. Physiol.* **20**, 151 (1942).
2. H. Eyring, *J. Chem. Phys.* **3**, 107 (1935); S. Glasstone, K. J. Laidler, H. Eyring, *The Theory of Rate Processes* (McGraw-Hill, New York, 1941).
3. F. H. Johnson, H. Eyring, R. W. Williams, *J. Cellular Comp. Physiol.* **20**, 247 (1942).
4. F. H. Johnson, H. Eyring, M. J. Polissar, *The Kinetic Basis of Molecular Biology* (Wiley, New York, 1954), p. 226.
5. F. H. Johnson and E. A. Flagler, *J. Cellular Comp. Physiol.* **37**, 15 (1951).
6. A. L. Hodgkin, *The Conduction of the Nervous Impulse* (Thomas, Springfield, Ill., 1964).
7. H. Davson and J. F. Danielli, *The Permeability of Natural Membranes* (Cambridge Univ. Press, New York, 1943).
8. D. Nachmansohn, *Chemical and Molecular Basis of Nerve Activity* (Academic Press, New York, 1959).
9. K. Takagi, K. Watanabe, Y. Ishi, in *Second International Pharmocological Meeting*, H. Rasková, Ed. (Pergamon, New York, 1963), vol. 7.
10. E. Overton and G. Fisher, Jena 1901, unpublished.
11. H. H. Meyer, *Arch. Exp. Pathol. Pharmakol.* **42**, 109 (1899).
12. L. Pauling, *Science* **134**, 15 (1961).
13. J. H. Quastel, *Current Researches Anesthesia Analgesia* **31**, 151 (1952).
14. D. E. Goldman, *J. Gen. Physiol.* **27**, 37 (1943).
15. M. Planck, *Wied Ann.* **39**, 161 (1890); *ibid.* **40**, 561 (1890).
16. J. C. Skou, in *Progress in Biophysics and Molecular Biology*, J. A. V. Butler and H. E. Huxley, Eds. (Macmillan, New York, 1964), vol. 14, p. 131.

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The Art of Talking about Science

Lawrence Bragg

I propose to analyze "Talking about Science." How is it best done? Why is it that a subject presented by A is a thrilling account which leaves a deep impression, whereas the very same material presented by B is dull and boring and produces no impression whatever? How should we present our branch of science to fellow scientists who work in quite another field? How can we present science to those who have little or no scientific background, as is often the case with men of high ability who are important in affairs of state? How can we make the nonscientist understand why its study means so much to us, a passion they sometimes find very difficult to understand? The gap between C. P. Snow's two cultures is not so much due to a lack of understanding as to a lack of desire to understand. There are philistines as regards science as well as regards the arts.

These problems have been brought vividly home to me in a number of ways. I was for many years president of the Physics Solvay Conference. It must be one of the most exclusive of international science gatherings, because only some 20 participants are invited to discuss the subject chosen for the meetings which are held every 3 years. I have listened for 12 years to all the Friday evening discourses at the Royal Institution, where a broad review of some branch of science is given, and the speakers are both well known in their fields and artists in framing their talks. I talk to many thousands of school pupils every year, and find the nature of their response to be a fascinating study. Recently we have been framing courses for men and women who are new entrants to the Civil Service, and who have had no scientific training. I cannot help but be interested in the basic principles which apply to all talks of this kind.

What is the basic character of a "talk"? I think it can be expressed by saying that its primary object is to create a state of mind, or point of view, not to convey information. I can perhaps illustrate what I mean by dwelling on the vast difference between the spoken and written account. Under the heading "talk," I am not including a course of lectures where students take notes and the lectures follow each other

The author retired this year from the directorship of the Royal Institution, London.

This article is adapted from an address delivered 28 December 1966 at the AAAS meeting in Washington, D.C.