of the idea of symbolic activity when there exist "simpler" explanations. But these explanations hold only if one restricts one's attention to special cases on an ad hoc basis. If the entire range of cases is considered, then it is clear that there will be no possibility of a unifying (simplifying) explanation of "spreads of effect" unless we begin to consider their functional meaning for perception; that is, their symbolic function.

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**References and Notes**

1. R. M. Steinman, *J. Opt. Soc. Amer.* **55**, 1158 (1965); recalculated 1970 (personal communication).
2. There was an inadvertant deletion in the original report which stated that the 25.8 minutes was the measurement from circumference to grating.
3. A. Gilinsky, *Psychonom. Sci.* **8**, 395 (1967).
4. Use of $\sigma$ permits calculation of the probability of extreme excursions. It is also of interest to examine average saccade amplitudes. R. W. Ditchburn and J. A. Foley-Fisher [*Opt. Acta* **14**, 113 (1967)] summarized data for 30 subjects in 14 studies; they found a 4.5-minute median and 6.5-minute mean. Suppose finally, then, that there are one or two subjects with extreme eye movements; since all subjects in my study showed the effect, eye movements could not explain it.
5. H. Barlow, personal communication.
6. It should be noted, in addition, that the control that both I and Sekuler and Armstrong suggested would not test this former contention. For such a test, one would need grating fields of short duration as masks.
7. M. Parlee, *Vis. Res.* **9**, 199 (1969).
8. M. Alpern, *J. Opt. Soc. Amer.* **43**, 648 (1953).
9. Studies other than Alpern's (*8*) in the Brown and Mueller chapter [J. L. Brown and C. G. Mueller, in *Vision and Visual Perception*, C. H. Graham *et al.*, Eds. (Wiley, New York, 1965), pp. 208–250] cited by Sekuler and Armstrong are not directly relevant.
10. In order of decreasing angular range of effect: Parlee (*7*), single target and mask, 90 degrees; R. Sekuler [*J. Exp. Psychol.* **70**, 401 (1965)], single target, grating mask, 60 degrees; F. W. Campbell and J. J. Kulikowski [*J. Physiol* **187**, 437 (1966)], grating target and mask, 20 degrees.
11. H. Werner, *Amer. J. Psychol.* **47**, 40 (1935); W. H. Buchsbaum and M. S. Mayzner, *Psychonom. Sci.* **15**, 111 (1969). Also see W. R. Uttal, *Percept. Psychophys.* **7**, 321 (1970); flanking rectangles do not mask a triangle, flanking triangles do.
12. Before this distance, if the target were translated until it overlapped the mask, the overlap would be less than 50 percent. Hence, either bars in the grating are mainly above the target, or they flank it but are much longer. When they flank it, they are also at a much greater separation.

16 October 1970

## Proteins in Excitable Membranes

The article by Nachmansohn (*1*) will probably do more to stimulate discussion than to provide definitive answers, as the closing sentence implies. Although it is pleasing to see reference to one's own work or to work in which one has shared (*2*), in this instance perhaps more is being imputed to the findings than is, as yet, warranted. It is true that the squid giant axon contains a high concentration of an enzyme which hydrolyzes and thereby detoxifies the powerful cholinesterase inhibitor, diisopropylphosphorofluoridate (DFP). The squid head ganglion is an even richer source of this enzyme, trivially called diisopropylphosphorofluoridase (*3*). However, the fact that (i) this enzyme is found predominantly in the axoplasm (*2*), (ii) the diisopropylphosphorofluoridase that appears to be associated with the axonal envelope may really have been due to residual axoplasm, and (iii) on ultracentrifugation the diisopropylphosphorofluoridase remains in the soluble fraction, raises the question of whether DFP applied to an intact squid axon at external concentrations which do not block conduction, for example, at less than $5 \times 10^{-3}M$, crosses the excitable membrane as DFP or as the hydrolysis product. Furthermore, DFP blocks conduction at about $5 \times 10^{-3}$ to $10^{-2}M$ in axons of squid, lobster, and spider crab and in the electroplax of the electric eel, although the approximate relative concentrations of diisopropylphosphorofluoridase in these four preparations are 100, 10, 1, and undetectable, respectively. Other organophosphates, even more potent cholinesterase inhibitors than DFP, are not detoxified, do penetrate into the squid axon in their inhibitory form, and block conduction *if at all* only at external (and now internal) concentrations of $10^{-3}M$ or higher (*4, 5*).

Nachmansohn points out the difficulty of attempting to extrapolate from the concentrations of compounds in solution to their behavior in intact cells; one might even extend this to include their behavior in subcellular organelles. However, in the present instance there is some indication that the organophosphates have indeed reached one such "organelle" in a sense, namely, the postulated receptor (*6*). If this is so, it becomes increasingly difficult, but of course not impossible (*7*), to explain how a variety of cholinesterase inhibitors, some predominantly water-soluble, others more lipid-soluble, can reach the receptor but cannot reach the reputedly essential acetylcholinesterase, whereas acetylcholine is required to reach both.

It has been implied that the fact that "block of conduction is sometimes effected under conditions different from those expected from reactions in vitro" (*1*) is not an impediment to an essential role for acetylcholinesterase in conduction. Rather than a "sometimes" condition, it appears that almost all of the cholinesterase inhibitors which finally do block conduction do so between $10^{-3}$ and $10^{-2}M$, whether reversible or irreversible, penetrating or not penetrating, water-soluble or lipid-soluble, or detoxified or not. The effect of physostigmine (eserine) on the node of Ranvier of the frog sciatic nerve has been cited as an exception (*1*). It does not appear to be much of an exception; the pertinent words are these (*8*): "At . . . $10^{-3}M$ conduction was blocked within 25 sec. . . . At . . . $2 \times 10^{-4}M$, block . . . occurs, *if at all* only after 15–20 min. . . ." The italics are mine. Further, the legend under figure 3 of (*8*) implies that block may not always have occured even at $5 \times 10^{-4}M$. It should be noted that I refer only to block of action potential rather than partial reduction, prolongation, change of shape, and so on.

Finally, while it is true that "a successful dissociation of electrical and enzyme activity after exposure to organophosphates" (*1*) has not been accomplished, it seems premature to conclude that the failure to demonstrate such a dissociation of electrical and cholinesterase activities, especially for reasons of technical inadequacy, is proof that the two activities are directly associated. This is not to say that, in the second half of the 20th century, it will not be accepted a priori that bioelectric activity is controlled by macromolecules whose properties are expressed in terms of enzyme kinetics.

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**References and Notes**

1. D. Nachmansohn, *Science* **168**, 1059 (1970).
2. F. C. G. Hoskin, P. Rosenberg, M. Brzin, *Proc. Nat. Acad. Sci. U.S.* **55**, 1231 (1966).
3. F. C. G. Hoskin, *Biol. Bull.* **137**, 389 (1969).
4. ——— and P. Rosenberg, *Science* **156**, 966 (1967).
5. F. C. G. Hoskin, L. T. Kremzner, P. Rosenberg, *Biochem. Pharmacol.* **18**, 1727 (1969).
6. E. Bartels and D. Nachmansohn, *Arch. Biochem. Biophys.* **133**, 1 (1969); see also figure 2 of (*5*).
7. See, for example, evidence and speculation that regulatory sites on the acetylcholinesterase molecule may serve as receptor sites [J.-P. Changeux, T. R. Podleski, J.-C. Meunier, *J. Gen. Physiol.* **54**, No. 1, part 2 (supplement), 225 (1969)].
8. W.-D. Dettbarn, *Biochim. Biophys. Acta* **41**, 377 (1960).

3 August 1970

The data in Hoskin's comments are taken out of their proper context and present, therefore, a distorted picture. A series of recent observations has revealed that the procedures for a quantitative evaluation of the activity in vivo of the membrane-bound enzyme are inadequate due to many factors of the microenvironment not previously recognized. The difficulties are compounded after exposure to organophosphates. Therefore, the extent of enzyme inhibition in vivo affecting electrical activity in tissues after their exposure to organophosphates is at present unknown. However, in several instances the electrical activity of conducting fibers, irreversibly blocked by organophosphates, has been restored by PAM. Whatever the extent of the enzyme inhibition may have been, these observations support the assumption of its essential role since PAM specifically reactivates the enzyme. Similarly, physostigmine, as postulated by electrophysiologists, should first potentiate electrical activity, just as at synaptic junctions, and that is actually observed at the nodes of Ranvier in $10^{-6}$ to $10^{-5}M$. This is a more sensitive test for the role of the enzyme in conduction than the total block, which may be a complex process requiring high outside concentrations.

Neither the difficulty in establishing a quantitative relationship between the in vivo activity of the enzyme and the electrical activity, nor the failure to dissociate the two activities are considered as "a proof that the two activities are directly associated." But they cannot be used as an argument against the theory. The theory proposed for the role of acetylcholine in excitable membranes is based not on a single fact but on a vast number of data established over three decades. Not one of the facts mentioned by Hoskin contradicts the theory. As in all theories of biological mechanisms, there remain many unsolved problems. The questions raised are discussed in great detail in a forthcoming handbook article (*1*).

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**Reference**

1. D. Nachmansohn, in *Handbook of Sensory Physiology*, W. R. Loewenstein, Ed. (Springer-Verlag, New York, 1970), vol. 1, pp. 18–102.

26 October 1970

## Work Demands or Food Deprivation?

Carder and Berkowitz concluded that rats will work for food in the presence of free food, provided that the work demands are not too high. Although this conclusion may be valid, I don't think it necessarily follows from the evidence presented because, in their experimental procedures, Carder and Berkowitz failed to consider the possibility that food deprivation ("hunger" if you will) was confounded with work demands.

Essentially, their experimental procedure was as follows. Several rats were individually trained to bar-press for food under a reinforcement schedule in which every second response produced a pellet of food (FR2). After two training sessions, free food was made available in the experimental chamber for two test sessions. Generally speaking, the rats continued to respond on the FR2 schedule to obtain food rather than to partake of the free food. In the following two sessions, with the free food removed, the rats were trained under a schedule in which every tenth response produced food (FR-10). Finally, two test sessions were conducted in which free food was again made available. This time, however, without exception the rats preferred to eat the free food rather than earn their food on the FR10 schedule.

During these training and testing sessions, which were 1 hour and 15 minutes and 1 hour long, respectively, the rats had to obtain their entire daily ration of food, because no food was provided outside of the experimental chamber. Under such conditions, it seems quite likely that the rats were not able to obtain as many food pellets during the FR10 training as they did during the FR2 training, simply because the training sessions were so short (1 hour and 15 minutes) and the extended-ratio, bar-pressing experience was so limited (2 days). Thus, the FR10 trained rats would have been much "hungrier" during the test sessions when free food was introduced, and for this reason would have been more eager to eat the free food.

If this reasoning is correct (and no evidence was presented to the contrary), then perhaps work demands may be less important than food deprivation in determining whether a rat will work for food in the presence of free food. And as one thinks about this possibility one begins to wonder whether any animal, rat or man, would work very diligently in a food factory if on the verge of starvation.

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**Reference**

1. B. Carder and K. Berkowitz, *Science* **167**, 1273 (1970).

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MacDonald raises an important question when he suggests that deprivation may influence the rat's preference for earned, in comparison with free, food. As yet we have not completed a systematic investigation of this influence.

The data, however, do not support his contention that our rats were hungrier during testing with FR10 than with FR2. The session of 1 hour and 15 minutes gave the subjects ample time to earn their daily ration even under an FR10 schedule. Thus on FR2 training sessions prior to free food tests the six rats earned an average of 290 pellets, while on FR10 training sessions the rats earned an average of 282 pellets. Three of the rats earned more on FR2 training sessions while the other three earned more on FR10. This difference cannot account for the fact that all six rats showed a reduced preference for earned food under FR10.

It might be argued, however, that the rats were, for some reason, hungrier during FR10 testing than during FR2 testing, in spite of the fact that they had received equivalent amounts of food before each type of test. If this had been the case, we would expect the rats to eat more pellets, whether free or earned, during FR10 testing. Actually the six rats ate an average of 304 pellets on FR2 tests and 307 pellets on FR10 tests. Again the data fail to suggest a significant difference in hunger under the two conditions.

In the spirit of MacDonald's comment, we would point out that a job can be undesirable even if it pays a living wage.

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