of these causes is the belief, in the minds of most people, that when it is considered totally, science is a relevant and important aspect of our society and individual lives.

Until radio astronomy is as important to the Paterson wards as it is to the administration, Noyes and others like him will do well to caution the government to save its money and go slowly. If New Jersey cannot afford to forego an additional TV channel, our nation cannot afford an accelerated science training program.

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## Memory, Enzyme Induction, and Porphyrins

C. E. Smith speculates shrewdly [*Science* **138**, 889 (1962)] on the question of whether memory may be associated with enzyme induction. He indicates at least three aspects of experimental evidence suggesting that the basis of a form of biological "memory" lies in an increase in enzyme concentrations associated with transmitter substances "as a long-lasting effect of stimulation."

From the viewpoint of enzyme induction it may be in order to consider the two different components in the enzyme—namely, the template protein and the prosthetic porphyrin. Chemically, these parts of the molecule are different in structure and action. While the bonding compound has not yet been identified, in the scheme suggested by Smith, the question arises whether the substance might be a porphyrin, either metal-containing or metal-free?

There seems to be another factor which deserves investigation. This is the increase in the concentration of porphyrins in the central nervous system with evolutionary development. This has been clearly shown by H. Klüver [*Science* **99**, 482 (1944); *J. Psychol.* **17**, 209 (1944); *Biochemistry of the Developing Nervous System* (Academic Press, New York, 1944), pp. 137–144]. Porphyrins have not been isolated from the peripheral nervous system. There appears to be an "ascending porphyrinization" in the postnatal development of the central nervous system in birds and mammals.

It has been found that porphyrins exist in both the metal-containing and the metal-free conditions. In the enzyme the porphyrin is associated with a metal; the metal-free derivatives are located

in the nerve system. How the sodium and the potassium ions pass through the nerve tissue, and whether the porphyrin residues are involved in allowing the ions to diffuse, is worthy of study. The holes which are known to exist in membranes and the open ring in porphyrins are of the same size.

Conductivity measurements have been made on closely allied chemical species of the porphyrins—namely, the phthalocyanines and the benzazporphyrins. At the meeting of the Organic Crystal Symposium in Ottawa on 10–12 October 1962, Harrison and Heilmeir demonstrated the Hall effect in metal-free phthalocyanines.

In view of the increasingly provocative relationships that are becoming evident between computers and brains, it would seem that any factor involving semiconduction might be an important aspect of "memory" phenomena. Memory may reside in the arrangement, stacking and interplay of the prosthetic moieties of the enzyme. Currently, we are engaged in the synthesis and the preparation of single crystals of porphyrins which may be examined from the viewpoint of conductivity.

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In his recent article "Is memory a matter of enzyme induction?" (*1*), Smith develops a theory which states essentially that memory may be a function of changes in the synaptic concentration of the neuroenzyme acetylcholinesterase. These variations in enzymatic activity are considered to be the result of alterations in the rate of neurostimulation which cause, momentarily, changes in the concentration of "free" substrate (transmitter substance). The amount of "free" substrate is considered to be the factor responsible for altered enzyme activity, since the transmitter substance induces the formation of the neuroenzyme. Therefore, the concentration of substrate present at any time regulates the rate of enzyme production.

In our laboratory we have come to these same conclusions independently, on the basis of results of several experiments in which changes in the level of acetylcholinesterase activity in the brain of the killifish *Fundulus heteroclitus* in response to thermal stress (*2*) were measured. It was found that a

homeostatic mechanism exists in the brain of this fish which regulates the activity of brain acetylcholinesterase and maintains it as a constant, after a period of acclimation, regardless of any modification in ambient temperature. We have considered this to be a case of alteration in the rate of enzyme induction due to temporal changes in the concentration of the neurohumor acetylcholine. Thermal stress changes the substrate-enzyme relationship by modifying enzymatic activity. It is clear from studies in which enzymatic activity has been depressed by treatment with irreversible cholinesterase inhibitors (*3*) and in which additional transmitter substance has been added to biological systems (*4*) that there is a dynamic balance between enzyme concentration and substrate liberation at all times. In normal neural function this balance is probably upset by the liberation of varying amounts of acetylcholine per unit of time, due to changes in the rate of neuronal firing. Thus, it is not necessary to postulate, as Smith does, "that each nerve impulse would release from the bound form more acetylcholine than an equivalent impulse released before induction" to account for changes in the rate of enzyme induction.

We have expanded this theory to consider the role of a feedback mechanism for neuroenzyme induction in terms of neuro-integration, and also to consider the method by which the individual neurons can reliably retain their independent and integrated functions (memory) over long periods of time in the apparent absence of repetitive input.

If the enzyme-induction hypothesis is correct, we may postulate a dual role for synaptic cholinesterase. First, this enzyme must, within a very short time, hydrolyze all of the transmitter substance liberated, to prepare the nerve for further transmission. Second, since the presence of acetylcholine at the presynaptic membrane depolarizes the nerve and prevents further impulse transmission, the synaptic concentration of this enzyme apparently must also function to regulate the time interval before a second action potential can be transmitted. Cells containing more enzyme will hydrolyze acetylcholine at a higher rate, with resultant shortening of the "no-impulse" period, and will therefore be capable of transmitting impulses at a higher frequency. Cells having a lower concentration of enzyme will have a longer "no-impulse" period, and therefore the maximum

rate of impulse transmission will be lower.

Since much information is passed through the nervous system in terms of impulse frequency alone (*5*), and since it appears possible for neurons to modify their frequency response, "learning," on the biochemical level, may be considered to be the result of altered synaptic enzyme concentrations, mediated by changes in the rate of enzyme induction. Thus, repeated stimulation of a nerve with, initially, low-frequency transmission capability should result in attenuation of the nerve for the passage of coded information of high as well as low frequency,

Finally, we have postulated that long-term stability of synaptic enzyme concentrations and "memory" may be a function of rhythmic excitory waves that are found in the brain and also in individual nerve cells (*6*). It is possible that a single periodic pulse through a nerve or a neuronal relay system may be sufficient to maintain synaptic enzyme concentrations that allow for passage of impulses at a preset frequency.

The hypothesis outlined certainly cannot in itself account for the complex nature of neuro-integration, but, in connection with other information about coding, may clarify the picture of brain function. The question of whether there are similar compensatory mechanisms in other neurohumoral systems remains to be answered.

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Baslow's data do suggest both enzyme induction and a feedback system, but I feel that he and I are not talking about the same thing when we refer to learning. He states that it is not necessary to postulate an increase in the amount of transmitter liberated by any one impulse in order to account for induction. My point is quite the opposite: After induction has occurred —the induction of enzymes essential to *synthesis* of a transmitter—the consequence would be the liberation of

more transmitter per impulse. Briggs and Kitto [*Psychol. Revs.* **69**, 537 (1962)] reached essentially similar conclusions in a paper I wish I had written. Although they published the hypothesis at the time I did, they have clear priority because their manuscript was accepted some 7 months before mine was. Their work, like Baslow's, deserves the attention of readers interested in this problem.


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## Smoking, Arteriosclerosis, and Age

The excellence of the report "Cigarette smoking and arteriosclerosis" [*Science* **138**, 975 (1962)] is lessened by the fact that the statistics were not adjusted for age. In large epidemiological studies the average age of nonsmokers is usually 4 or more years higher than that of smokers. In this particular study the age difference of the two groups might have been greater or it might have been insignificant. It is not possible to correctly interpret the author's conclusion without this information because of the association of arteriosclerosis with age.


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In the report "Cigarette smoking and arteriosclerosis," Sigmund L. Wilens and Cassius M. Plair state, "There is no proof that sclerosis of coronary arteries develops more rapidly in cigarette smokers than in nonsmokers." However, they fail to present the distribution, in tabular or statistical form, of their subjects' ages, and their most sophisticated evidence (Table 3) seems to contradict their statement. They do say that the cigar and pipe smokers (for whom they have no criterion for determining intensity of smoking) tend to be older than the other groups, and that the light and moderate smokers of cigarettes are "a somewhat younger group on the whole, than . . . the other groups." No comparison of the age of the nonsmokers and the heavy smokers is presented, though such a comparison is essential if we are to interpret the findings objectively. The authors are analyzing for evidence of degenerative diseases (or the effects of aging), such as myocardial infarcts, vascular scars of kidneys, cerebral infarcts, and