structure of such molecules is high—more in the order of X rays than of nerve impulses. Finally, it is hard to imagine how vast amounts of informa-

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77. Sperry, R., Summation. In: The Anatomy of Memory (D. P. Kimble, Ed.). Science and Behavior Books, Palo Alto, 1965: 140-177.

And this, of course, does not alter the fact that knowledge of the chemical, membrane, or cellular changes involved in learning and memory may still leave as obscure as ever most of the more interesting informational features of the problem.

lem, as well as all the neurophysiological and psychological literature that is available, and have jumped directly into the molecules. Some passing effort is made to say how these molecular changes are implanted, and how they are read out; but these are the most puzzling and the most intriguing parts of the problem, and nothing that I have seen is even remotely satisfactory as an answer.

Pribram: I do not share your negative attitude. As of ten years ago or little longer, there was not one constructive statement that could be made about whether anything at all is going on in the brain as a function of some change in behavior. There was not a single experiment to cite. Then along came Galambos, Hernández-Peón, John, the Killams, Hydén, and others. It is very exciting to me to see almost any neural change that can be reliably correlated with a change in experience and in behavior, even if we cannot yet understand what that correlation signifies.

Sperry: But let us not confuse the physiological level (which I would regard as the more important level for explanation) with the underlying molecular substructure. I guess it is the reductionistic philosophy that can be read into headlines like "The Chemical Basis of Memory" that particularly bothers psychologists. In the case of the RNA changes associated with learning, as demonstrated thus far, I am personally inclined to wait until the Calvins and Jensens move in on these problems and look at them a little more closely.

Take one simple example along this line: the problem of timing in learning and memory is extremely important. In establishing conditioned reflexes, just the timing of the two stimuli being paired is critical: put them together simultaneously, in what might seem to be the best conditions for molecular association, and there is no conditioning; one stimulus must precede the other by half a second or so. It is important to relate these timing factors to the explanatory molecular or physiological level. Also, the synapse is commonly thought to be a key location for the molecular changes. I think we tend to overlook the possibilities for trace changes in the endogenous properties of neurons involved in their pulse pattern detection and firing properties. This could be, and perhaps is, a better place to look for the cellular or chemical changes that may be involved, rather than in the synapse and network alterations.

Galambos: It is a little strange to hear you emphasizing "pattern detection" and "firing properties" in connection with this problem you have worked on for so many years. This new molecular biological approach to the nervous system seems to be so much more relevant. I am thinking, of course, of your elegant regeneration and transplantation experiments. Long ago you considered (76) the various ways a given nerve cell could know how to go to the right place to get itself connected. If I remember correctly, you thought it an inescapable conclusion that some chemical relationship between the presynaptic and postsynaptic element was responsible for the

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connections finally accomplished.

Now, if all chemical events in a nerve cell ultimately stem from its DNA read-out through RNA of various sorts, then the chemical recognition, which your experiments and those of Weiss (00) and others have so magnificently demonstrated, is obviously also determined by the DNA-RNA reactions in the neuronal nucleus.

Sperry: Certainly, there is no question but that the morphological network patterning of the nervous system is based very largely on this differentiation of the nerve cell population which, of course, is based on DNA and RNA mechanisms. But also the physiological endogenous properties of different nerve cell types, insofar as they are inherently determined, are also dependent on this same system for cell lineage and differentiation. Both types of trace change that I discussed, the connectional synaptic changes as well as those affecting endogenous firing properties, would involve this system. It further follows that the two types of possible chemical answer I have mentioned, one where the type of chemical change is a universal common to all memories and the other in which all the information is coded within the molecule, are two extremes. Between these two, there are intermediate possibilities in terms of interaction between the different types of chemically specific nerve cells that might influence either the connections or the endogenous physiological timing properties. The chemoaffinity or neurospecificity effects envisaged here are, of course, highly diverse, but this kind of thinking is still a long way from anything that could be called the coding of mnemonic information into a memory molecule. The profound changes that the language of the chemists in the Neurosciences Research Program group has undergone in the past two years is revealing. Whereas initially everything was going to work out in macromolecules, the language is coming around now to where it is almost the same as that used by psychologists and the rest of us. The chemistry they are now looking for is the chemistry of the synaptic change and the "switching factor". It is quite a shift from the early idea that memory is coded in the DNA or RNA molecule.

Calvin: I am inclined to think that Dr. Sperry may be right in his statement that the memory trace is a pattern rather than a molecule, and I differ from him only in the amount of interest I attach to the chemical basis of that pattern. Assuming for the moment that the trace is a pattern, whether of synaptic interactions or various other microstructural features, the chemical basis upon which this pattern has been produced is of great interest to me. I have the feeling that, as an intermediate step, we need to find some simple cellular system which shows a definitive response, either behaviorally or electrically, such as the relationships the physiologists are now finding associated with learning. If we could find some way to translate that kind of electrical activity into molecular changes which, in turn, might effect structural changes, and so on, the whole sequence of events would be a great step forward.

Sperry: To bolster further your argument against my own, I think that it is very possible that the chemical approach to the organic basis of memory in general will arrive at the answer first, because we know so much about the cell, and because the alternative possibilities are more limited than are the physiological network approaches. Perhaps we will arrive at the nature of the memory trace more quickly by working up through cytochemistry than by working down through the tremendously complicated organizational system. Whether the answer will be recognized when seen by the molecular approach is another question.

[illegible]r. We have the problem of getting the information from the neuron language, which is a series of pulses, into the molecular language, which is a structure of atoms. Furthermore, the energy levels required to change the

(from discussion in Dr. Gaito's section)

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Sperry: I think the interesting material that has been presented tends ~~largely~~ to be concerned only indirectly with the fundamental ~~basis~~ of learning and memory. My inclination ~~at the moment~~ is to try to orient our thinking back toward the learning-memory problem in its more ~~basic~~ form before we move into its more ~~complex~~ aspects.

problems, as discussant, general, try to

Regarding the general problem of the chemical or molecular basis of memory, my attitude at the moment is that the problem is not very relevant. This is only a provocative way of suggesting that the chemistry of memory is not of primary interest for the memory problem as we know it at the behavioral level. I like the comment on this subject made by Oliver Lowry, a neurochemist at the University of Washington, who pointed out at a meeting at the Salk Institute that the molecular approach to memory is rather like taking a television set and a computer, grinding them up and doing a chemical analysis to try to determine the source of all the pretty pictures and all the computations.

In my own case I have described the search for there chemical basis of memory as the search for a secret code of an unknown code for mental imagery that in itself is a will o' the wisp (77). The reasoning here is that, in trying to get at the chemistry of last year's memories, we must first translate these subjective images into brain dynamics. This is the first code; to solve it we are required to solve the mind-brain problem. Once this is achieved the dynamic brain states must be translated into a memory trace code, i.e., the frozen, static trace systems. Even the simplest principles of both these coding processes are completely beyond us at present. So far as the underlying chemistry goes, it is a situation with possibilities for unlimited confusion. The restraints on chemical imagination and chemical model building are simply nil, except for those imposed by cytochemistry and cytophysiology in general.

The main point I am trying to make is that the most interesting unknown aspects of memory lie in these coding problems, particularly the first, and that these are meta-molecular problems. Until these meta-molecular phenomena are worked out, the underlying chemistry is of little help in understanding the most interesting aspects of memory.

We can recognize two possible alternative types of answers to the chemical basis of memory: one is that there is a memory molecule and that mnemonic information is indeed coded at the molecular level; in this case the discovery of the chemical code for memory would, of course, be tremendously interesting and important. The other possibility is one in which the chemistry is a kind of universal change, with the coding of information at the network level, in the patterning of the distribution in the brain networks, in synaptic changes, membrane changes, and the like. In this case it would be nice to know what these cell changes are. To go a step further and analyze the chemistry of the membrane or endogenous changes involved is not particularly intriguing compared to other unknowns in memory. It is nothing like knowing where and how the information is coded. For decades, people who have thought about the problem have been inclined to think the information was coded mainly at the network level. It is only within recent years, of course, that the molecular theories have become popular.