COMMITTEE I
Unity of Science: Organization and
Change in Complex Systems

DRAFT - 11/15/85
For Conference Distribution Only

COMMENTS

by

Charles R. Park
Dept. of Molecular Physiology and Biophysics
Vanderbilt University
Nashville, Tennessee, USA

DISCUSSION PAPER

on

Claude A. Villee's

Organization and Change in Eukaryotic Cells

The Fourteenth International Conference on the Unity of the Sciences
Houston, Texas November 28-December 1, 1985

I congratulate Professor Villee for his masterly survey of an immense subject, "Organization and Change in Eukaryotic Cells."

We presently know the composition and structure of many of the molecules which make up these cells, and it seems likely that we shall be able to identify and synthesize virtually all molecules in biological systems within the next few decades. A much more formidable problem, however, is to learn how these molecules are programed to make a living cell, or, in the case of the human fertilized ovum, to differentiate into the variety of tissues that make up a whole man. We have presently only a small fraction of the knowledge necessary to describe the processes of growth and differentiation but this small fraction would nevertheless require many volumes to record. Multiply what we know many fold and then consider that the resultant huge volume of information is stored in one germ cell in a volume of space that requires a microscope to be seen. This is truly a mind-boggling achievement of organization.

This organization involves a compact coding of information in the DNA using only 4 rather small nucleotide molecules arranged in various sequences. The spatial packing of the DNA allows reading of the code in the proper sequence and transmission of the information to other molecules and cells. Professor Villee has outlined the main current concepts of structure and coding and has indicated some aspects of the

transmission of information. I would like now to add a few comments on the latter subject.

Manmade machines employ electrical, optical and mechanical signals for the passage of information, that is, for the control of function, but living organisms employ basically only chemical signals. For example, the information in the DNA of a cell is passed along to a specific RNA molecule. This substance in turn carries the information to other molecules associated with structures inside the cell called ribosomes to bring about synthesis of specific proteins. The latter are most commonly enzymes, and, in some cases, they catalyze formation of other molecules like the steroid hormones, as mentioned by Professor Villee. These steroids are part of a feedback regulation of the DNA complex which helps determine which genes will be expressed and which will be repressed.

This highly simplified outline of molecule to molecule transmission of information characterizes one of many thousands of similar processes going on simultaneously in the cell. We need to ask them why these messages don't get jumbled by inappropriate molecular interactions. The answer is that appropriate interactions involve only those molecules that fit each other like a lock and key. A message transmitting molecule is generally quite large and has a surface, therefore, which is unique as regards form, composition and electrical charge. It diffuses, that is, it collides with other molecules until it hits one that has a unique form, composition and charge which is complimentary

to itself. The two molecules therefore make a tight fit which results in a tight bond. Bond formation causes the shape of the second molecule to be altered and the new shape will make a tight fit for some other molecule within the cell. Another specific molecule interaction occurs and thus the signal is passed on. At first glance it would seem improbable that molecules could find each other frequently enough to make this transmission system work. Two factors are most helpful in this regard, the very high rates of collision of molecules in solution and the very short diffusional distances within a cell. Also the positioning of potentially reacting molecules close to each other or in the small compartments of the cell alluded to by Professor Villee facilitate appropriate interactions.

The development of a cell requires that the information in the DNA be expressed in an ordered sequence, just as letters and words must be correctly ordered in a sentence. There are indications that the order of gene expression is controlled in part by special molecules which inhibit or activate particular genes in the DNA complex. There is growing evidence that differentiation of primitive stem cells into specialized tissues may be controlled similarly by chemical mediators. For example, such mediators may turn on the particular genes which are needed to make a muscle cell, while other mediators suppress the genes which would lead to other cells types. For example, it is possible experimentally to cause two cell types, a and b, to fuse. A single cell is thus formed with two set of genes, each

set making different proteins. In a short time, however, the genes characterisitic of cell a will be repressed by chemical factors from cell b. These b factors were presumably those responsible for repression of the type a genes originally present in cell type b.

In fully developed man, we have long recognized transmission of information by hormones, about 50 different molecular species of which have been well characterized. Recent developments, however, suggest that many, many more such chemical messengers exist. For example, factors have been isolated which specifically stimulate growth of nerve tissue or vascular tissue, or cause the eyes of new born rats to open. There is a new body of research pointing to the existence of paracrine factors, that is, substances secreted by one cell that influence function of a neighboring cell. Somatostatin is one of the first discovered factors of this type.

The discovery of ever more hormones and other chemical mediators has been accompanied by recognition of a class of substances that are specific receptors for these mediators. These receptors, which often are proteins, are located on various structural components of the cell such as the plasma membrane or the DNA complex. These receptors pass on the information brought by the hormone by means of chemical mediation. A very well known example involves the hormone, adrenalin, which is the substance that makes your heart pound and your blood pressure rise in situations of acute stress. Adrenalin combines with its receptor

on the cell surface. The receptor then undergoes a complex series of molecule to molecule interactions eventuating in the activation of an enzyme which produces a substance, cyclic AMP, inside the cell. Cyclic AMP then activates another enzyme which in turn modifies the structure and function of a whole set of other enzymes. This cascade of steps involves upward of a 100 different specific molecule to molecule interactions. It takes less than a minute to accomplish and modifies very appreciably cell function, as we can recognize in ourselves.

The nervous system is the prime transmitter of information in man and here too the mechanisms involved are chemical. Signals pass from one cell to another within the nervous system through special junctions called synapses. Synaptic function depends on chemical mediators, some of which allow and others inhibit signal transmission. Best studied mediators include acetylcholine, nor-epinephrine, serotonin and gamma amino butyric acid, but the existence of dozens more appears certain. Even passage of a signal down a long peripheral nerve is not electrical, as often supposed, but depends basically on a rapidly progressing chemical alteration in the membrane of the nerve.

If we attempted to build machines that depended on chemical transmission of signals, information transfer would be extremely slow. Yet in many biological systems, it can be quite fast, that is in the range of a few thousands of a second. This speed is achieved as a consequence of the small size of cells and their internal structures. This allows chemical mediators to reach

their targets almost instantaneously by diffusion because the distances involved are so short. Where mediators like the hormone, insulin, have to travel long distances from one tissue to another, signal transmission is indeed relatively very slow.

In summary, information transmission which controls cell growth, cell differentiation and indeed all functions in the whole man is accomplished by sequences of highly specific molecule to molecule interactions.