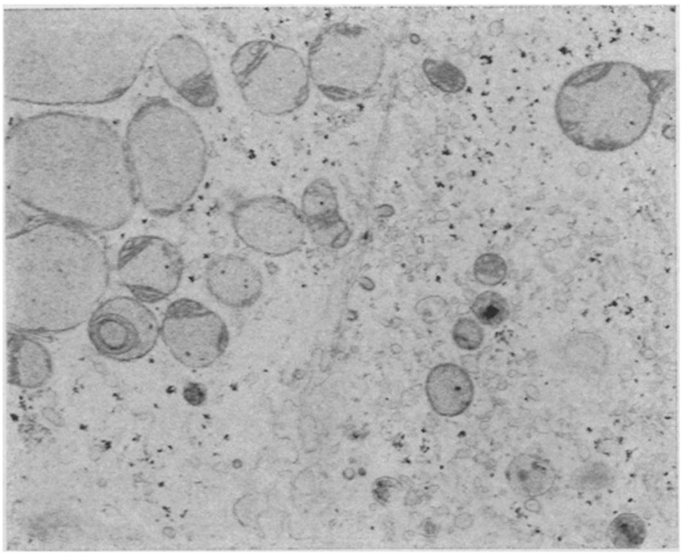


D. J. Svoboda

Membrane abnormalities (center) are seen in cancer cells.

Expanding on a classic view

Membranes play an active role in cellular structure and functioning; they may hold a key to the understanding of cancer

by Barbara J. Culliton

Scientists know a great deal about cancer. They know that tumor cells grow rapidly and without control. They know that these cells possess an unusual and deadly ability to spread throughout the body. They know that chemicals, radiation, mutant genes and viruses in animals can trigger the transformation of a normal cell into a malignant one.

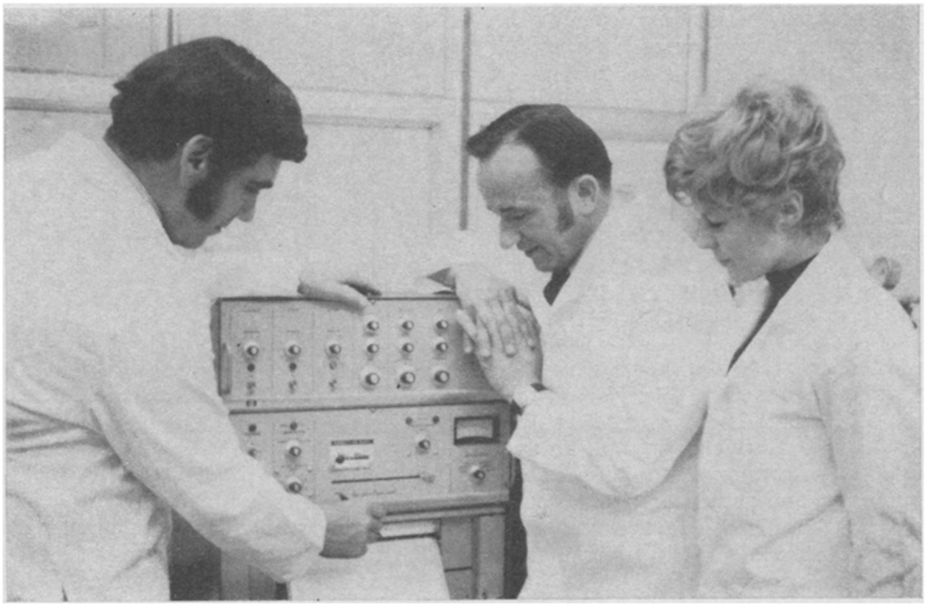
From laboratory experiments and from experience with human cancer patients, the body of specific information about the nature of these transformations is growing steadily. Every year investigators publish literally thousands of papers reporting new advances in understanding the details of cancer. They measure the levels of certain enzymes in cancerous tissue and compare them with normal tissue: they quantify comparative levels of RNA and DNA synthesis; they look at shape and size.

Yet the fundamental chemistry of malignancy remains elusive. The question is not one of cause as much as it is one of mechanism. Researchers have still to determine just what it is they are dealing with after a tumor has been initiated.

"What we need," says Dr. Donald F. H. Wallach of the Massachusetts General Hospital in Boston, "is a unifying theory of carcinogenesis, one that speaks to the essential biochemistry of tumors and one into which the vast array of known data fits."

The key to such a unifying view of cancer, suggests Dr. Wallach, lies in the study of membranes. Each of the known and suspected causes of malignancy involves a chemical event that can alter the structure or composition of membranes, and these alterations, he says, may be the common underlying feature of cancer.

In the classic view cellular membranes were little more than physical barriers with a gate-keeping function. They allow certain molecules to enter a cell or an intracellular organelle such as a mitochondrion, and forbid the entrance of others.



Barber

Tinberg, Barber and Foritano see some promising and directed beginnings.

Recent studies in molecular biology, however, reveal that membranes play a far more active role in determining the structure and function of cells. Membranes are built of proteins and lipids woven into interacting lattices. Thus an alteration of any portion of that lattice will alter the activity of the membrane.

With regard to cancer cells, variations in the plasma membrane or outer surface are probably of primary importance. This is because the ability of cells to recognize one another and maintain normal tissue patterns depends on the structural and immunological specificity of the cell surface. From this it follows that the immune system's failure to reject tumors in cancer patients may be because antigens on the tumor surface are too weak to elicit an immune response.

Mass. General Hospital

Wallach: We need a unifying theory.

And again, scientists now reason that

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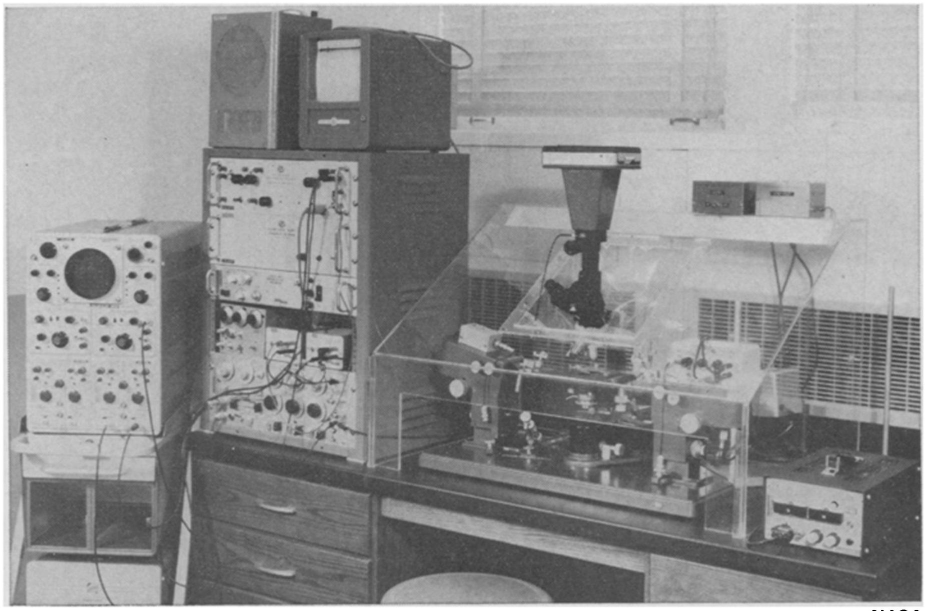

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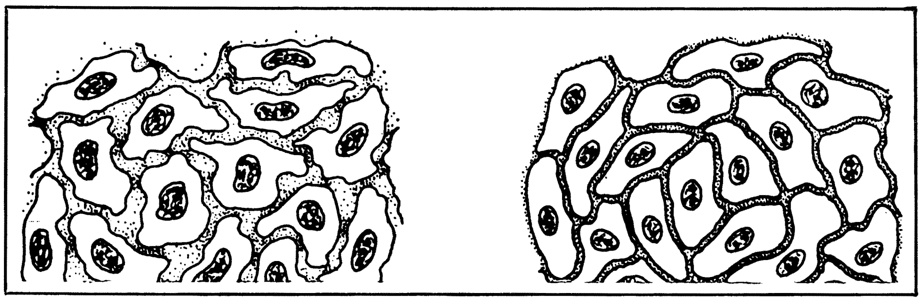
Membrane voltage experiment: Altered voltage can be related to malignancy.



NASA

Weak membranes of malignant cells (left) could explain growth of cancer.

what they call a loss of contact inhibition among tumor cells is directly related to alterations in the structure of the cells' plasma membranes. Normal cells stop synthesizing DNA and hence cease dividing when they come into physical contact with each other. Malignant cells show no such constraint.

While changes in the lipoprotein lattice of plasma membranes appear to be central to cancer, alterations in internal membranes can play an indirect role. For example, fatty acids are an essential component of the lipid portion on membranes and these fatty acids are synthesized in a complex sequence of chemical events with the aid of mitochondrial membranes. Disruptions in mitochondrial membranes affecting fatty acid manufacture would, therefore, affect the production of lipids, initiating a chain reaction that could ultimately end in cancer. By the same token, any factor altering the formation of membrane proteins would also serve to disrupt the normal lipoprotein lattice.

Experiments with a mutant of a microorganism, *Neurospora*, show, for example, that the mutant DNA miscoded a single amino acid in the sequence of structural protein in the membrane. As a result of this seemingly minor alteration, the entire membrane was defective.

Interest in approaching cancer from the perspective of membranes is growing, although it is not a dominant field of cancer research at present. In fact, much of what is currently known about the design and activity of various types of membranes has come from molecular studies ostensibly quite unrelated to cancer, or even to each other.

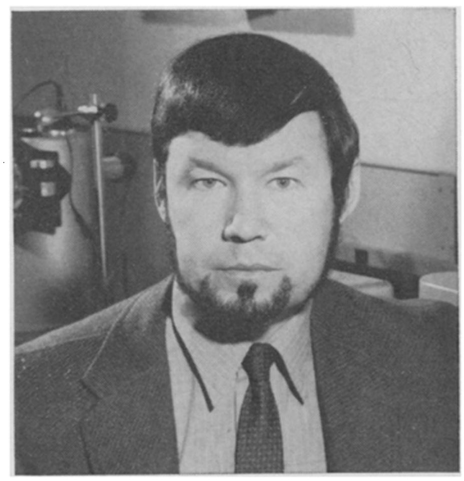
There are, however, some promising and directed beginnings. At the University of California at Los Angeles, Dr. Albert A. Barber and his colleagues are examining the lipid component of membranes and its relationship to the whole. "The chemical nature of interactions within a membrane are not understood," Dr. Barber explains, "although their specific associations are considered to play a major role in membrane function. As yet, we're in the stage of making observations. We need a unifying theory of cancer, but we also need a unifying theory of membrane function and do not have it yet."

With graduate students Lynn Foritano and Harold Tinberg, Dr. Barber is investigating changes in membrane lipids and the enzymes associated with them. Chemically induced hepatomas, or liver tumors, he points out, are almost always accompanied by a decrease in the amount of cellular membranes. In fact, he says, "In hepatomas, the membrane systems virtually disappear. We are following lipid alterations in these cells as markers of the change occurring in membrane function."

Observations of membrane lipid changes in aged animals provide the team with another model system for evaluating and hopefully elucidating the mechanism of alteration. From studies of rat liver cells, Miss Foritano finds that the lipid content of membranes of 24-month-old animals is 54 percent less than that of younger ones, and that the level of a lipid-dependent enzyme, glucose-6-phosphatase, is reduced by 81 percent.

Taking vitamin E deficiency as another model system, Tinberg reports, the vitamin appears to function as a stabilizer of membrane structure and that its deficiency could render membrane lipids susceptible to destruction.

Other evidence linking membrane alterations to the transformation of normal cells into malignant ones was reported recently at an American Cancer Society seminar by Clarence Cone (SN: 3/28, p. 312), where Dr. Barber also spoke. Cone, from the National Aeronautics and Space Administration's Langley Research Center in Hampton, Va., reports studies in mammalian cells showing that alterations in the electrical voltage across membrane surfaces can be correlated with malignancy. Nondividing cells, he finds, have high negative voltages, while dividing cells, including rapidly proliferating tumors, have markedly lower negative voltages. □



NASA

Cone: Low voltages in dividing cells.