CANCER'S LINK WITH CELL MEMBRANE CHANGES

When cells become cancerous, they burn more glucose. Researchers believe they now know why. Their discovery may help find therapy alternatives.

by John H. Douglas

Bassham and Bissell adjust the tissue-culture apparatus they developed to maintain constant nutrient supply and waste removal for cultures of both normal and transformed (cancerlike) cells.

A team of biochemists at the University of California at Berkeley has discovered new evidence directly linking changes in cell membranes to the transformation of normal cells to cancer cells. Their discovery lends added support to the growing attitude among cancer researchers that determining cell-membrane changes may be a vital key to understanding the complex cancerous process and finding new approaches in the search for a cure.

Working in Nobel laureate Melvin Calvin's Laboratory of Chemical Biodynamics, Mina J. Bissell, James A. Bassham and their colleagues have applied the tracer isotope techniques developed by Calvin in his historic study of plant photosynthesis to a long-standing puzzle of cancerous cell growth in animal tissue cultures. Some 50 years ago, Otto Warburg found that when normal tissue-culture cells were "transformed" to behave like cancer cells, they immediately began to experience increased metabolism. Warburg concluded that some stage in the complex set of chemical reactions that convert the cell's food (glucose sugar) to useful energy (in the form of ATP) had begun to run amuck. But no faulty stage in the series of reactions (glycolysis and the Krebs cycle) was ever found.

Now, Bissell and Bassham have been able to follow radioactive tracers through the reaction chain carefully enough to determine that transformed cells have only normal reactions going on inside them. The fault, they say, lies in the transport of glucose across the surrounding cell membrane—a defect that some other investigators have also suspected for some time (SN: 7/8/72, p. 29).

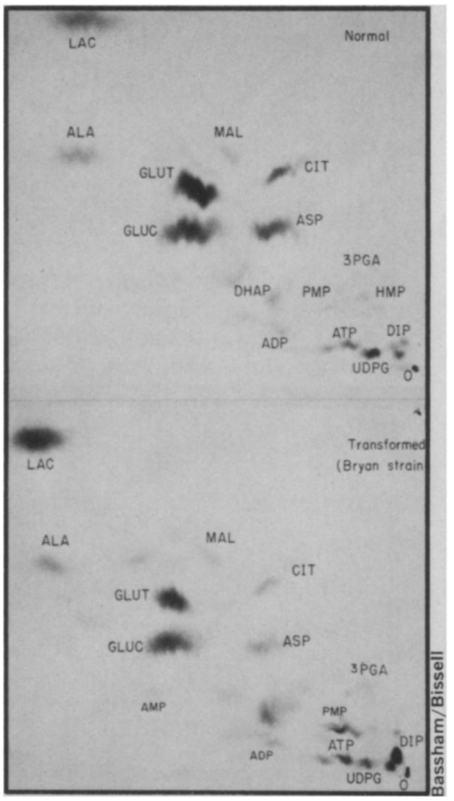
To determine this faulty transmission, the team developed an apparatus to precisely control the chemical surroundings of the tissue cultures. Other experimenters, they note, had erroneously concluded that transformed cells could not form glycogen, the compound that cells make to store energy by stringing together many glucose molecules. They say the error occurred because the liquid medium surrounding the transformed cells was not kept

constant; environmental changes prevented cells from making glycogen. Using their steady-state apparatus, they found to their astonishment that transformed cells could actually manufacture glycogen 10 times as fast as normal cells.

With a constant source of glucose assured by the steady-state apparatus, together with a constant flushing away of waste products such as lactic acid, transformed cells in tissue culture presumably behave more like the cancer cells in a living organism. Under these conditions, they were found to take in more glucose than normal cells, to manufacture and store more glycogen, to spew out more waste lactic acid, and then apparently to let most of the extra energy go to waste. For no matter how much glycolysis took place, the following Krebs cycle, which makes most of the ATP, plods on at the same pace in transformed cells as in normal cells.

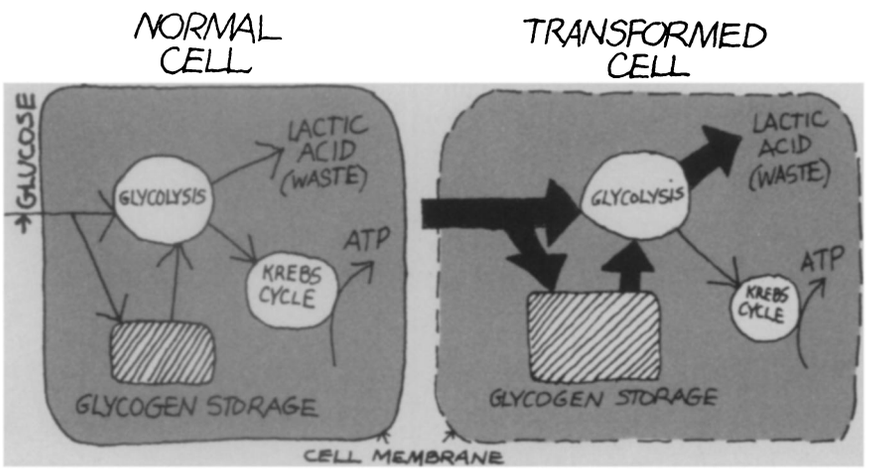
The researchers were thus led to two important conclusions: Normal and transformed cells metabolize and store glucose by exactly the same internal mechanism, but the membranes of transformed cells are "leakier," admitting more glucose and thus stepping up the rate of some of the internal reactions.

For several years, other evidence, often less direct, has implicated changes in cell membranes in cancerous transformation of cells. In tissue culture,



Paper chromatograph of radioactive tracer isotopes in both normal and transformed cells. The excess of lactic acid (LAC) and other compounds in transformed cells (lower) indicates an increase of glycolysis in such cells.

cancerous cells do not stop growing, as normal cells do, once they have spread over the bottom of a culture dish. Such growth inhibition, which clearly seems to depend on contact of a cell's outer surface with an external object, has long been thought to result from membrane changes (SN: 6/17/72, p. 393). Certain plant proteins, called lectins, cause transformed cells to clump together, apparently because



Cells in tissue culture that have undergone cancerous transformation are "leakier," admitting more glucose into the cell where it is stored as glycogen or metabolized through glycolysis and the Krebs cycle. Only glycolysis seems to increase, however, since the formation of energy-rich ATP by the Krebs cycle proceeds at a normal rate in both cells. Unidentified changes in cell membranes seem responsible.

of some reaction with their surface membranes that differs from reactions with the membranes of normal cells. When broken down for chemical analysis, the membranes of transformed cells are found to have slightly different composition than those of normal cells. But none of the observed differences can yet account for the greater flow of glucose.

Bissell and Bassham believe their discovery will give researchers a new tool in their quest for a chemical inhibitor of cancerous growth. Already the team reports some success in killing transformed cells in culture using glucose transport inhibitors. But the question remains whether such inhibitors can be made to work selectively on cancerous cells in living organisms. As another researcher recently pointed out, the transport of glucose across cell membranes in both normal and transformed cells may depend on the same, as yet undiscovered, mechanism. In that case, knocking out this mechanism in cancerous cells would almost surely kill the surrounding healthy cells in an animal.

Clearly, more research is necessary. If cell membranes do indeed play a vital role in the cancerous process, then many new questions arise: What genetic change within the cell brought about the change in membrane surface, and what, in turn, caused the genetic change? Since viruses must first come into contact with a cell membrane before they can cause the cell to transform, what is the interaction of the virus with this surface structure and how may that interaction be involved in transformation? Finally, in live animals, cancer cells seem less "sticky" (causing their spread) and less able to be recognized as dangerous by the body's immune system; could these too be properties related to membrane changes?

Cancer seems so intimately involved with subtle variations in the most basic processes of life that finding a cure will almost certainly be linked to more basic discoveries about the nature of these fundamental processes. For their part, Bissell and Bassham are turning to consideration of how the elements of cell membranes are synthesized. Meanwhile, other researchers are finding new links between membrane changes and the actions of viruses, genes and antibodies. □