Biomedicine

Diane D. Edwards reports from New Orleans at the 79th annual meeting of the American Association for Cancer Research

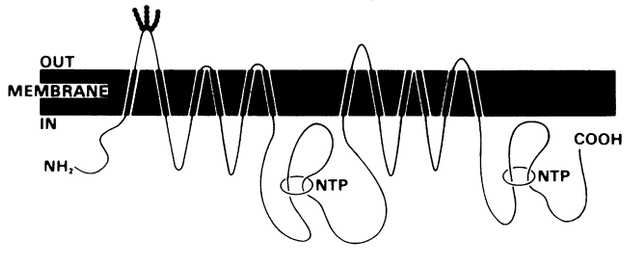
Looking for solid anticancer evidence

Cell suspensions living in the laboratory have given scientists much of what they know about cancer — how it grows and how it might be stopped. But basic differences exist between more diffuse malignancies, such as leukemia, and the so-called solid tumors, which are characterized by more tightly defined margins, discrete internal environments and an unfortunate propensity for becoming resistant to drugs. In the past, the search for anticancer drugs has been based on leukemia-like systems, says Thomas H. Corbett of Wayne State University in Detroit. Now he and others are creating *in vitro* systems they say will give better information on pathogenesis and treatment of the solid tumors like colorectal cancer.

One of those systems Corbett and his colleagues call a multiple-tumor-soft-agar-disk-diffusion assay. Cancer cells from solid tumors, when placed in soft agar, grow in tight colonies. By placing a drug-saturated paper disk on top of cancer cells in the agar, the scientists can look for colony-growth inhibition — a method similar to commonly used antibiotic screening tests. Roughly 85 percent of the drugs screened thus far have shown no activity against solid tumors, Corbett says, adding that fewer than 1 percent go on to animal testing. He says the ability to screen 5,000 to 6,000 new drugs a year, at a cost far cheaper than other methods, will speed drug development.

Whys and wherefores of drug resistance

To make a bad situation worse, cancer cells may be inherently resistant to one or more drugs, or become resistant after drug treatment begins. Proposed mechanisms for such drug resistance include gene amplification, where multiple copies of key genes are made by the cancer cell as protection, and the presence of a cellular protein called P-glycoprotein, or P-170 (SN: 1/3/87, p.12). Scientists recently reported progress in understanding these mechanisms, as well as in the use of other drugs that can reverse a tumor's ability to survive chemotherapy.



Gottesman/Science

After discovering P-170 in the mid-1970s, scientists noted that presence of the human *MDR*1 gene coding for the protein can confer multidrug resistance. Since that time, scientists at the National Cancer Institute (NCI) in Bethesda, Md., and elsewhere have cloned the gene and studied its protein product. P-170, which loops through the cell membrane (see drawing), apparently acts as a pump, pushing drugs out of a cell, says NCI's Michael M. Gottesman. He and his co-workers now have devised a theoretical model of how such a pump might work. In recent laboratory studies, they also found the pump is active in certain normal cells, possibly to remove plant toxins ingested in food. How the protein's presence in normal cells will impinge on research efforts to stop its activity in cancer cells is unclear, Gottesman says. "I don't think that problem is overwhelming, but we're not nearly ready for clinical trials [of new drugs that stop the P-170 pump]," he adds.

Scientists have looked at the well-known pump-blocking drug verapamil as a way to reverse drug resistance (SN: 4/13/85, p.237). At Long Beach (Calif.) Veterans Administration Medical Center, researchers report using verapamil and another pump blocker called lidocaine in combination with anticancer agents. Of five volunteers with drug-resistant, growing malignancies, three patients had partial remission, while tumors in the other patients stabilized. But because these agents lower blood pressure, researchers are seeking less toxic approaches. Among these are the recently developed drugs buthionine sulfoximine and aphidicolin, for which U.S. clinical trials are being designed, according to NCI's Robert F. Ozols. By inhibiting a specific enzyme, buthionine sulfoximine reduces the levels of a peptide called glutathione. Ozols says glutathione seems to be important in the development of multidrug resistance, because it is found in high levels in resistant cells. Aphidicolin, on the other hand, halts DNA repair, one mechanism used by resistant cells to recover from drug treatment.

While the presence of P-170 can cause a treatment dilemma, NCI's Bruce Chabner says scientists have developed laboratory screening tests that exploit the protein to identify agents against drug-resistant cells. And other researchers at NCI, the Mayo Clinic in Rochester, Minn., and Hospital Saint-Luc in Montreal recently isolated a DNA probe that identifies a glutathione-related enzyme, one they predict will be used as a marker to detect precancerous changes in cells. A report in the May 20 CELL says a change in just one of the 1,280 amino acids in P-170 can make a cell more drug resistant. That study, from the University of Illinois in Chicago and Cetus Corp. in Emeryville, Calif., supports the idea that gene therapy may someday make cancer cells more drug-sensitive and healthy cells more tolerant of toxic drugs.

Vitamin A therapy chews on oral cancer

Chewing tobacco or dipping snuff may be *de rigueur* in some circles, but oral cancer can devastate the lives of those with the habit. In recent years, scientists have looked at a possible role for vitamin A or its precursor beta carotene in reducing oral cancer risk, partly based on observations that oral cancer patients have low plasma levels of the vitamin. During preliminary studies in India among chewers of tobacco-containing betel quids, researchers at the British Columbia Cancer Research Center in Vancouver have found various oral doses of vitamin A and beta carotene not only cause remission of precancerous areas called oral leukoplakias, but also prevent new lesions from forming

Hans F. Stich and his co-workers report that weekly ingestion of 200,000 international units (IU) of vitamin A caused leukoplakia shrinkage in 12 of the 21 study participants given the vitamin alone. (The U.S. minimum daily requirement for the potentially toxic vitamin is 5,000 IU.) A smaller percentage of other betel chewers showed remission with a combination treatment of vitamin A and beta carotene, or beta carotene alone. Even more impressive is the observation that both compounds prevented the development of new leukoplakias during a year of treatment, the scientists say. Concerned that the doses used might prove toxic over long periods, the scientists are studying whether lower "maintenance" amounts can prevent new lesions after higher doses have shrunk established leukoplakias. Two other experiments are using beta-carotene-rich red palm oil as a possible preventive, in an attempt to avoid vitamin A toxicity.

Studying bovine papillomaviruses in mouse-cell cultures, the Vancouver group also discovered that a vitamin A relative called retinoic acid reduces viral DNA inside cells. The scientists say this suggests a possible mechanism for at least part of vitamin A's apparent anticancer potential, as human papillomaviruses have been found in precancerous and cancerous areas.