Cancer Tests Look for a Passing Grade

Manufacturers of several new tests for cancer antigens seek FDA approval to market them for therapeutic monitoring

Tumor cells must be different from other cells, the reasoning goes, because their growth is unchecked by normal cellular regulators. If they are different, they should produce unusual proteins, lipids, or other macromolecules that are not present in healthy individuals. Granted this, it should be possible to identify these indicators of tumor metabolism —generally called tumor antigens—and use them to identify previously undetected cancers, as an adjunct in diagnosis of suspected cancers, and to monitor the therapy of an established tumor.

Many such tumor antigens have, in fact, been discovered and tests for them are beginning to make their way toward the marketplace and the clinical laboratory. The newest of these, announced in January by Eugene A. Davidson of the Pennsylvania State University College of Medicine and Sally D. Bolmer, now at the Massachusetts Institute of Technology, shows preliminary promise both of being more specific and of having a greater range of sensitivity than other tests.

Davidson and Bolmer discovered a sialoglycoprotein—a protein linked to both sugar residues and a sugarlike compound called sialic acid—that is not identical with any known proteins and that is found in very high association with malignancies. They developed a radioimmunoassay (RIA) to detect it and used the assay on blood samples from more than 300 cancer patients and a slightly smaller number of healthy individuals. They found that the test correctly indicated the presence of cancer nearly 96 percent of the time and that the number of false positives (detection of the antigen in apparently healthy individuals) was very low, only 2 percent. The new assay, moreover, appears to have the potential to detect a broad spectrum of cancers, including sarcomas, carcinomas, melanomas, and Hodgkin's disease.

Davidson and Bolmer have licensed the assay to the Warner-Lambert Company of Morris Plains, New Jersey, through the mediation of the Research Corporation, a highly regarded nonprofit group that represents many universities and scientists in patenting and licensing products of academic research. Willard Marcy of Research Corporation praised the new assay at a recent press conference, saying, "It is seldom that we see an invention with the potential for public benefit this one has." Warner-Lambert plans to simplify the test somewhat and then, if permission can be obtained from the Food and Drug Administration (FDA), to begin extensive human trials late this year or early in 1982. Davidson, meanwhile, is attempting to characterize the sialoglycoprotein, to identify cell culture systems that produce it so that an animal model can be developed, and to obtain a test with greater sensitivity by using monoclonal antibodies.

The rapid licensing of the assay to Warner-Lambert despite the very limited amount of testing that has been conducted reflects the intense competition that is emerging in the cancer test field. Some analysts predict that the world market for cancer test kits will total $2 billion by 1990. Several such tests are already commercially available, and others are being considered by FDA. All are, or will be, marketed strictly for monitoring the progress of cancer therapy, since FDA has not yet been convinced that any test is sufficiently accurate to be used for detecting undiscerned tumors.

The best-known tumor marker, and the only one which has so far obtained FDA approval for marketing, is carcinoembryonic antigen (CEA). This antigen was first isolated from colon tumors in 1965 by Phil Gold and Samuel O. Freedman of the McGill University School of Medicine (*Science*, 5 August 1977, p. 543). High concentrations of CEA in the blood were initially thought to be associated exclusively with tumors of the colon and rectum, but subsequent studies have shown that they are also found in patients with certain other malignant tumors, with benign tumors, and with inflammatory bowel disease. Above normal concentrations are also found in blood samples from smokers.

Nonetheless, a consensus development conference at the National Institutes of Health last October concluded that CEA is useful for determining the stage of colon and rectal tumors, and possibly for monitoring therapy of breast and lung tumors. One RIA for CEA has been marketed in this country for about 7 years by Hoffmann-La Roche Inc. of Nutley, New Jersey. Two new tests for CEA, one an RIA and one enzymatic, manufactured by Abbott Laboratories of North Chicago, received FDA approval in October.

Another well-known marker is α-fetoprotein (AFP), a glycoprotein first discovered in 1963 by G. I. Abelov of the N. F. Gameleya Institute for Epidemiology and Microbiology in Moscow. Like CEA and many other putative tumor markers, AFP is produced by fetal tissues as well as by tumors, particularly tumors of the liver and testes. Pregnant women whose fetuses have certain severe birth defects, such as open neural tubes, spina bifida, and the like, have particularly high concentrations of AFP in their blood, and an RIA for AFP has been used in Europe and Japan to screen for such defects.

This usage is particularly controversial, however, since the test has a high incidence of false positives and a diagnosis of a potential severe birth defect generally leads to an abortion. Out of every 1000 women who take the test, says Joseph H. Irani of Nuclear Medical Systems, Inc., of Newport Beach, California, 50 will have elevated levels of AFP, but only two will have fetuses with severe birth defects. But if a positive test is accompanied by an ultrasound sonogram and amniocentesis, he argues, the incidence of false positives can be reduced to virtually zero. Hoffmann-LaRoche, Abbott, Amersham Ltd. of England, and Pharmacia Inc. of Piscataway, New Jersey, have each applied to FDA to market an AFP assay for detecting severe birth defects. That agency has already issued proposed regulations that would require the tests to be used only in a program that would include supplementary diagnostic techniques to rule out false positives. Physicians are already free to use the tests on an investigational basis for monitoring cancer therapy, says FDA.

A newer tumor marker is tissue polypeptide antigen (TPA), which was discovered by Bertil Björklund of the National Bacteriological Laboratory of

0036-8075/81/0227-0909$00.50/0

Some Other Tumor Assays

A recent listing by the American Cancer Society showed several other potentially specific tumor markers that are being investigated:

β-Glucuronidase: A normal enzyme occurring abnormally in leptomeningeal carcinomatosis.

Breast-cyst fluid protein (BCFP): A tissue-associated antigen found to correlate with breast cancer.

Colon mucoprotein antigen (CMA): An apparently colon-specific substance.

Colon-specific antigen (CSAP): Another colon-specific protein.

Galactosyl transferase isoenzyme-II (GT-II): A normal antigen found in high correlation with cancers of the pancreas, stomach, and colon.

Pancreatic oncofetal antigen (POA): A fetal protein with a high correlation to pancreatic cancer.

Prostate-specific antigen (PSA): A new, highly prostate-specific marker.

Zinc glycinate marker (ZGM): A tissue-associated antigen found to correlate with tumors of the GI tract.—T.H.M.

Sweden. It is a small membrane protein (mass of about 25,000 daltons) that is secreted into the blood and urine by rapidly dividing cells, such as those of a fetus or tumor. Elevated concentrations of TPA are found in the blood or urine of roughly 75 percent of patients with several different types of cancer; the proportion rises as high as 90 percent in well-advanced tumors, such as disseminated breast cancer. Elevated concentrations are also found in perhaps 10 percent of healthy individuals and in a greater percentage of individuals with benign tumors or infectious diseases.

A few investigators, particularly Björklund and T. Ming Chu of the Roswell Park Memorial Institute, have found that sensitivity of cancer diagnosis can be substantially improved by using CEA and TPA together. They argue that the combination is now the most effective monitoring tool available for cancer therapy. Damon Corporation of Needham Heights, Massachusetts, has completed clinical trials with an RIA for TPA and is seeking FDA approval to market it.

Another new marker is the Tennessee antigen discovered by Tommye Jordan, who is now with JCL Clinical Research Corporation in Knoxville. The Tennessee antigen is a glycoprotein with a mass of about 100,000 daltons; it, too, is thought to be associated with cellular membranes. Jordan developed a test for the antigen, since licensed to Sherwood Medical Industries of St. Louis, based on its ability to inhibit hemagglutination. Clinical trials conducted by Sherwood indicate that the test detects 75 percent of lung cancers, 79 percent of stomach cancers, and 82 percent of both colorectal and pancreatic tumors. It has a false positive rate of about 8 percent; the majority of the false positives are among individuals with benign lung or gastrointestinal disease. Sherwood has also applied to FDA for marketing approval.

Perhaps the most intriguing of the potential cancer tests is based on the so-called B-protein isolated by Edsel T. Bucovaz and his associates at the University of Tennessee. They have found that a protein from yeast, known as coenzyme A synthesizing protein complex, binds specifically to B-protein; the concentration of B-protein in a patient's blood can be determined by labeling the yeast protein with a radioactive isotope.

Bucovaz has found that B-protein, which has a mass of about 120,000 daltons, is closely associated with the spleen in animals and probably also in humans. He speculates that it is produced by the spleen in response to the presence of a tumor and, perhaps, certain other conditions such as pregnancy. Support for this possibility is provided by the observation that, during the third trimester of pregnancy, B-protein is found in the mother's blood but not in that of the fetus. If this speculation is correct, B-protein could represent the long-sought universal tumor antigen, since it is produced by the same organ no matter where the tumor is.

Bucovaz has found that the B-protein assay successfully detects about 87 percent of all the common types of cancer, with a false positive rate of 8 percent. In patients whose blood contains B-protein when cancer therapy is initiated, he has found, the assay is virtually 100 percent accurate in predicting recurrences. The assay has already been licensed to both a Japanese and a German firm, who are already conducting clinical trials, and several American companies are conducting preliminary studies with a view toward licensing. In Japan, false positives have been reduced to 3 percent, albeit with a slight loss of sensitivity.

Several other assays are marketed without FDA approval under what is known as a "grandfather clause"; that is, the assays were already being sold when Congress, in 1976, gave FDA approval to regulate cancer test kits. Most of these involve specific enzymes and hormones whose concentrations are frequently elevated in patients with certain tumors. High concentrations of the enzyme prostatic acid phosphatase are frequently found in men with cancer of the prostate. High concentrations of the hormone human chorionic gonadotropin (HCG) are found in women who are pregnant or who have cancer of the uterus, and in some men with testicular tumors. High concentrations of the glycoprotein thyroglobulin or of calcitonin are often found in patients with certain types of thyroid tumors. High concentrations of various forms of the enzyme creatine kinase are found in patients who have had myocardial infarctions or those with tumors of the smooth muscles of the pelvic organs and the lung. And high concentrations of the enzyme lactate dehydrogenase are found in patients with leptomeningeal carcinomatosis. RIA's are commercially available for each of these materials.

Other assays can also be useful, adds Eugene Rice of FDA. "A number of diagnostic tests can be used under a given set of conditions" to help confirm a diagnosis of cancer, he says. There are also several other more specific assays that are still in the early stages of investigation (see box).

Some investigators are less sanguine about the prospects for specific cancer assays. The chief problem with such assays, says K. Robert McIntire of the National Cancer Institute, is insufficient specificity. Most such assays, he says, start off with claims for high specificity, but that is generally because an insufficient number of problem patients have been studied. As the number of patients that have been tested increases, the percentage of false positives also increases. This has been the case with CEA and AFP, and McIntire expects it to be the case with the other assays. He thus does not expect the assays to be used for diagnosis of undiscerned tumors in large screening programs at any time in the near future. But for managing acute disease processes, he adds, their future looks very bright.—THOMAS H. MAUGH