obtained in patients with tumors of internal organs, which are generally harder to detect by other means. The largest number of false positives occurred with blood from burn patients and women in the third trimester of pregnancy. Bucovaz has filed a patent application for the assay and is now trying to arrange a much larger test of its efficacy.

Another general blood marker has been discovered by Robert G. Parsons and his associates at Scripps. They find that a protein that binds to DNA is present in much higher concentrations in the blood of patients with leukemias, lymphomas, and melanomas than in healthy individuals. The protein is apparently a degradation product of a component of the immune system known as complement 3 and is thus named C3DP. They have shown so far that the concentration of C3DP correlates with the severity of the malignancy in the majority of these cancer patients and that it is a useful marker for monitoring therapy.

Carbohydrates bound to proteins in the blood may also serve as markers for cancer, according to a group headed by Joseph F. Weiss of the Armed Force Radiobiology Research Institute and Paul B. Chretien of NCI. They have found that the concentrations of sialic acid, hexoses, hexosamine, and fucose are all higher in cancer patients than in healthy individuals. The increased concentrations correlate with the severity of the disease. These compounds appear to be bound to glycoproteins found in the α-globulin fraction of blood serum. The group is now studying use of these glycoproteins to monitor therapy of a variety of malignancies. They have also found an inverse correlation between serum levels of certain glycoproteins and immune status. These results agree with previous findings by other investigators that high concentrations of some glycoproteins may suppress immune activity.

Hormones in the blood may also be nonspecific markers. Many investigators have, for example, found the pregnancy hormone human chorionic gonadotropin (HCG) in association with various malignancies and it is frequently one of the markers used in multiple assays. Studies by Griff Ross of NCI and by others have shown that HCG is particularly useful for monitoring therapy of choriocarcinoma. K. Robert McIntire of NCI has also shown that it is useful for monitoring testicular tumors. Armand Tashjian of Harvard Medical School and others have shown that high concentrations of calcitonin are associated with several types of tumors and can be used to monitor therapy of medullary carcinomas of the thyroid. And Rosalyn S. Yalow of Mt. Sinai Hospital in New York City has found high concentrations of a precursor of adrenocorticotropic hormone (ACTH) in many patients with lung cancer.

Compared to the search for markers in the blood, the search for markers in urine has been much more limited. This seems rather surprising because, according to Daniel Rudman of the Emory University School of Medicine, most patients with disseminated cancer excrete as much as a gram of protein in the urine each day. The healthy individual excretes little or no protein, but some patients with kidney diseases excrete normal blood proteins with masses higher than 70,000 daltons. Cancer patients, Rudman says, excrete unusual proteins that have masses ranging from 10,000 to 60,000 daltons.

Rudman and his colleagues have so far isolated and purified five of these proteins and developed assays for them. They have found that one or more of the proteins appear in the urines of as many as 70 percent of patients with disseminated cancers and in a smaller percentage of patients with localized disease. They have also found that the amount of protein in the urine is a good indicator of the efficacy of chemotherapy for tumors of the head, neck, and lung.

Another class of materials found in urine is polyamines, such as spermidine, putrescine, and spermine, which are thought to be by-products of the increased concentrations of RNA that accompany cellular growth and proliferation. Diane H. Russell and her associates at the University of Arizona first reported high concentrations of polyamines in the urines of as many as 70 percent of cancer patients in 1971, and their work has been confirmed and extended by many investigators. It now appears that changes in the concentrations of polyamines in urine and other biological fluids are useful for monitoring chemotherapy in more than half of patients with Burkitt's lymphoma, melanomas, cancers of the blood, and tumors of the colon, rectum, and brain.

Most of the discoveries of the biological markers now under consideration have been serendipitous; the specificity of the markers is still undetermined because no one knows for sure what substances should be in the blood. This situation may change soon. Norman G. Anderson and his associates at Argonne National Laboratory have developed an automated, high-resolution electrophoresis system for separating the large number of proteins and glycoproteins in biological fluids. By looking at samples from large numbers of healthy individuals, Anderson plans to produce a catalog of all the proteins that are normally present. He has already cataloged most of the proteins in blood serum and is now studying erythrocyte proteins.

When Anderson is finished with the cataloging, he will make a survey of fetal tissues and tumors to determine what proteins are present. He thinks that it should be possible to find a whole spectrum of specific biochemical markers.

Use of Multiple Markers

Until such highly specific markers are developed, however, many investigators think the best results in screening can be obtained with a battery of assays. Paul Franchimont and his colleagues at the University of Liège in Belgium, for instance, use a battery that tests for five substances in the blood—CEA, AFP, HCG, a subunit of HCG, and kappa-casein, a phosphoprotein of human milk. In tests on more than 1450 individuals, they found that the battery detected 72 percent of the cancers and had a false positive rate of about 15 percent. Most of the false positives occurred in patients with hepatitis or cirrhosis of the liver, conditions in which tissue regeneration produces some of the fetal proteins.

Franchimont argues that the sensitivity of the test can be increased to 85 to 95 percent by inclusion of two other assays—one for another oncofetal protein and one for fragments from a virus. He plans to test the efficacy of the enlarged screen by monitoring some 500,000 workers in the Liège area. Many of these are workers from metallurgic and radioactive isotope industries who might be expected to have a higher than normal incidence of tumors.

A few other groups of investigators are also using batteries of assays, some analyzing for as many as 18 different markers, but few are as optimistic as Franchimont about the prospects for screening. Most would probably agree with McIntire, however, that use of multiple markers when a tumor is first suspected provides the best opportunity to find one or more markers for monitoring the course of therapy and detecting recurrences of the disease. Most would also agree that the use of multiple assays will continue to increase in the future and that the incorporation of newer assays will increase their efficacy. It may not yet be possible to recognize the presence of a tumor and identify its site by means of a simple blood test, but it now seems much more likely that such a day will eventually arrive.—THOMAS H. MAUGH II

Erratum: The cost of semiconductor grade silicon was incorrectly stated as $65 per ton (29 July, p. 446). The correct figure is $65 per kilogram.