Gold's demonstration of a glycoprotein antigen in human colon cancer in 1965 and Thomson's description four years later of a radioimmunoassay for carcinoembryonic antigen in serum stirred the imagination and interest of both lay and scientific communities. CEA and alpha-fetoprotein especially, as well as other tumor markers, have been extensively studied clinically. The simplicity of the original concept—that macromolecules identical to embryonic antigens are also produced by common human cancers—has been modified by practical clinical realities.

**CARCINOEMBRYONIC ANTIGEN**

**Detecting Colon Cancer**

Initial studies of CEA in patients with colon cancer reported 97 percent positivity. Such findings were confirmed by our 1970 series of patients with "overt" colon cancer, many of whom had metastases, and by other investigators. In another expanded study, however, patients with earlier disease were included, with a fall in positivity to 72 percent (Table 1.)

The positivity rate fell even further to 59 percent in patients seen preoperatively, but rose to 96 percent in those with evidence of metastases following surgery.

These findings have been widely confirmed. The combined Canadian National Cancer Institute/American Cancer Society Study reported 62 percent positivity in patients studied preoperatively using the Thomson-Gold assay.

Thus, CEA levels vary with the stage of disease. In three series of patients tested by three different assays, CEA positivity ranged from a low of 19 to 40 percent in patients with localized disease (Duke's Stage A) to as high as 100 percent in those with widespread metastases, commonly to the liver.

It is clear that the CEA assay is a better indicator of widespread disease particularly of metastases to the liver than it is of early colon cancer. A preoperatively negative assay (normal: <2.5 ng./ml) does not exclude the diagnosis of cancer, but it does make the diagnosis of metastases less likely.
Table 1. Positivity of CEA in Detecting Colon Cancer

| Series                          | Year | Method* | Percent Positivity |
|---------------------------------|------|---------|--------------------|
| Montreal General Hospital       | 1969 | T       | 97                 |
| Boston City Hospital Initial    | 1970 | T       | 91                 |
| Expanded Series                 | 1971 | T       | 72                 |
| Later Series                    | 1972 | T       | 59                 |
| Preoperative (all stages)       |      | T       | 96                 |
| Postoperative with known recurrence |     | T       |                    |
| New York – Nutley               | 1971 | H       | 86                 |
| Buffalo (Roswell Park)          | 1972 | H       | 83                 |
| London (Chester Beatty)         | 1972 | E       | 67                 |
| Joint NCI/ACS Study (preoperative cases) | 1972 | T       | 62                 |

* T – Thomson-Gold; H – Hansen; E – Egan-Todd

In patients with known colon cancer it suggests, but does not guarantee, a localized lesion and a favorable prognosis. Generally, the higher the level of CEA, the poorer is the prognosis. Markedly elevated preoperative CEA determinations are consistent with metastases.

It is also interesting to note that Livingston found a higher percentage of patients with detectable CEA in left colon cancers (splenic flexure, descending colon, and sigmoid) than in right colon cancers (cecum, ascending colon, and hepatic flexure) for all stages of disease.

Screening for Colon Cancer

Since a high proportion of patients with early colon cancer have normal values of circulating CEA, this test alone is not recommended for screening purposes. A clinical trial of serial CEA assays, however, is warranted, especially when combined with repeated stool tests for occult blood and when

“... the CEA assay is a better indicator of widespread disease ... than it is of early colon cancer.”

applied to groups at risk for colon cancer such as those with ulcerative colitis, a previous history of colonic cancer, or multiple polyposis.

Another, and perhaps the greatest limitation to the use of CEA as a screening test, is its nonspecificity for cancer of the colon or digestive tract. A high rate of positivity has been reported in patients with other...
Table 2. CEA Positivity in Cancer

| Cancer          | Incidence of Positive Assays |
|-----------------|-------------------------------|
|                 | Percentage  | No. of Cases |
| Colon & Rectum  | 73           | 316          |
| Pancreas        | 92           | 52           |
| Liver           | 67           | 18           |
| Breast          | 52           | 159          |
| Cervix          | 42           | 45           |
| Endometrium     | 27           | 11           |
| Ovary           | 35           | 20           |
| Testis          | 57           | 29           |
| Prostate        | 40           | 33           |
| Kidney          | 35           | 26           |
| Bladder         | 33           | 106          |
| Neuroblastoma   | 100          | 6            |
| Leukemia        | 22           | 27           |
| Lymphoma        | 25           | 14           |
| Bronchus        | 72           | 90           |

Compilation of reported observations made with Gold, Hansen or Todd assays from reports by Zamcheck, Lo Gerfo, Reynoso, and Laurence. Modified from Laurence and Neville.

Types of cancer: 90 percent or more in cancer of the pancreas (undoubtedly, partly due to the typically late diagnosis of this disease); 52 percent in breast cancer; 40 percent in prostatic cancer; 33 percent in bladder cancer; and 72 percent in cancer of the bronchus. (Table 2.)

CEA in Benign Disorders

With the exception of some heavy cigarette smokers, 97 percent of healthy normal individuals have normal levels of circulating CEA. Perhaps more than any other common benign clinical condition, liver disease may give elevated CEA levels, especially severe alcoholic cirrhosis\(^6,15,16\) or alcoholic pancreatitis.\(^7\) (Table 3.) In addition, some patients with benign obstructive jaundice may also show an increase in circulating CEA, which is usually reversed after release of the obstruction, provided persistent biliary inflammation or liver abscess does not supervene.\(^18\)

Most patients with inactive ulcerative
Table 3. CEA Positivity in Benign Disorders

| Disease                          | Incidence of Positive Assays |
|---------------------------------|------------------------------|
|                                 | Percentage | No. of Cases |
| Alcohol cirrhosis, severe       | 45         | 88           |
| Alcoholic pancreatitis          | 43         | 42           |
| Pulmonary tuberculosis          | 38         | 21           |
| Chronic bronchitis and emphysema| 25         | 63           |
| Inflammatory bowel disease      | 21         | 95           |
| Diverticulitis and peptic ulcer | 21         | 33           |
| Colorectal polyps               | 9          | 67           |
| Prostatic - hypertrophy         | 7          | 30           |
| Breast - fibroadenosis          | 7          | 70           |
| Gastric atrophy                 | 5          | 19           |

colitis have normal levels of CEA. Elevated levels tend to correlate with exacerbation of disease activity. The only one of our patients who had colorectal cancer had a persistently elevated level above 10 ng./ml.

Serial Pre- and Postoperative CEAs in Assessing Prognosis and Recurrence of Colon Cancer

Thomson and Gold reported five cases in which preoperatively elevated CEA determinations fell to normal levels after complete resection of colonic cancer. Many other investigators have confirmed this finding.

In our initial study, 26 patients had serial pre- and postoperative determinations within three weeks after resection. Fourteen patients with apparently localized tumors had normal CEA levels following presumably complete resections; 12 remained free of disease during the 18-month follow-up, but two developed recurrences.

In a prospective study of 102 patients with no evidence of metastases or recurrence immediately following potentially curative resections for colorectal cancer, 18 patients later developed elevated levels of circulating CEA. Six of these 18 patients had progressively rising CEAs, and all six subsequently had recurrences. Significantly, elevations in CEA were noted up to 20 months before clinical evidence of recurrence. Six others had transiently elevated levels, but did not develop cancer. None of the 84 patients with CEA levels of less than 2.5 ng./ml. had evidence of recurrence during an initial follow-up period. However, two patients with levels consistently under 2.5 ng./ml. were found to have small second primary colon cancers at sites distant from the primary lesion. All investigators agree that negative levels do not preclude primary, metastatic or recurrent disease.

Generally, the higher the level of CEA, the poorer is the prognosis.
A 76-year-old man with a Duke's C colonic adenocarcinoma had undetectable levels of CEA preoperatively, following an abdomino-perineal resection, and for 18 months postoperatively. Rising CEA levels were then noted, but no evidence of recurrence was seen on repeated complete examinations, including X-ray, colonoscopy and liver scan. Subsequently, a small lymph node in the neck was found positive. CEA levels continued to rise and he worsened despite chemotherapy and irradiation.

Holyoke, Mach, and Dykes reported confirmatory series of patients whose rising CEA levels preceded clinical evidence of cancer recurrence by two to 14 months. Holyoke has shown that the higher the preoperative CEA, the shorter the clinical disease-free interval before recurrence is apparent. On the other hand, Ravry felt that tumor recurrence is readily detectable by "other clinical means." It remains to be seen whether asymptomatic patients with rising CEAs can benefit from early "second-look" surgery, chemotherapy, radiation therapy, immunotherapy or their combination.

Monitoring Therapy
Studies have reported on the use of serial CEA determinations as an index of completeness of surgical excision in patients with cancers of the cervix, body of the uterus and ovary. The use of serial assays as a monitor of chemotherapy has been reported in patients with cancer of the colon, pancreas, stomach, and biliary tract, breast, cervix, body of uterus and ovary, lung and neuroblastoma.

Colon Cancer
Rising serial CEA levels in patients with known metastatic gastrointestinal cancer treated with chemotherapy correlated with disease progression. Persistently low (less than 2 to 3 ng./ml) and, especially, undetectable values were a favorable prognostic sign in patients with colon cancer. High or rising levels were unfavorable. Of 38 patients receiving chemotherapy for metastatic cancer of the colon, pancreas...
and stomach, almost all who had elevated CEAs did poorly. Elevation may remain stable despite progressive disease and may precede clinical evidence of deterioration. Persistently normal CEA levels were found in six patients with no evidence of disease progression. Decreased levels were noted only in the two patients with colon cancer who went into remission following chemotherapy. However, the relative ineffectiveness of chemotherapy for gastrointestinal cancer in this series makes it difficult to assess the potential use of CEA as a monitor of therapy. (Figs. 1, 2 and 3.)

Ravry confirmed these general observations and correctly pointed out the need to interpret CEA values cautiously and only in context with the overall clinical and laboratory picture. He also noted that a preterminal fall rather than a rise in CEA levels may sometimes occur, and that some colon cancers, which apparently do not produce CEA, may spread without a concomitant rise in blood levels.

Breast Cancer

Patients with metastatic breast cancer show a better response to chemotherapy than do those with gastrointestinal cancer. Accordingly, 13 patients with metastases undergoing chemotherapy and/or hormonal therapy were studied with serial CEA estimations for three to 18 months (mean of 14 months). Falling serial CEA values appeared to correlate with response to treatment and rising levels with non-response. However, Chu and Nemoto did not feel that serial CEA levels provided an adequate
monitor for breast cancer. Further studies are obviously needed.

Lung Cancer

According to Vincent and Chu, the CEA assay appears to be a valuable prognostic marker, capable of suggesting successful resection of lung cancer and of confirming clinical response to either radiotherapy or chemotherapy. They also noted that CEA levels anticipated clinical evidence of disease progression by several months.

These are all preliminary findings and longer follow-up is needed before firm conclusions can be drawn. Whether the changes in serial CEA levels which do occur will provide a reliable basis for altering the type or amount of chemotherapy or other treatment, has not yet been shown.

**ALPHA-FETOPROTEIN (AFP)**

The first report of alpha-fetoprotein in the serum of patients with primary liver carcinoma by Tatarinov has since been confirmed by many others. AFP was initially thought to be specific for primary liver carcinoma (with the exception of teratocarcinoma) but with the introduction of more sensitive immunoassays, up to 40 ng./ml. of AFP have been found in the sera of normal individuals. Small increases in serum AFP levels have also been noted in patients with benign liver disease such as hepatitis or cirrhosis, in patients with ataxia telangiectasia, and in pregnant women after the fifth month of pregnancy.

However, in approximately 70 percent of patients with primary liver carcinoma, the serum AFP may be markedly elevated (over 1000 ng./ml.). levels not reported in benign conditions. Increases in AFP have also been seen in some patients with gastric, pancreatic, and colonic carcinoma.
(Table 4.) McIntire showed that when AFP and CEA were measured simultaneously, 47 percent of patients with gastric carcinoma had increases in one or the other marker, whereas only 27 percent of the patients had elevations of AFP alone, and 22 percent had elevations of CEA alone.50

Serial determinations of serum AFP may prove as useful as serial studies of CEA since AFP may increase rapidly with the growth of the hepatoma.56 Observations have shown that serum AFP levels are dependent not only on the mass of the tumor, but also on its degree of differentiation.51 Like CEA, AFP may help to assess prognosis and recurrence,52 but its role as a monitor of chemotherapy is not yet adequately studied. For managing patients bearing hepatomas with low AFP production, other markers would be needed.

Ninety percent of patients with testicular tumors are positive for AFP or human chorionic gonadotrophin or both. These markers are especially valuable in following the efficacy of chemotherapy for these tumors. Thirty percent of patients undergoing intensive chemotherapy have an apparently complete clinical remission, but persistently elevated AFP levels although much reduced from pretreatment values.45

**OTHER TUMOR MARKERS**

**Alpha2-H Fetoprotein (Alpha2-HFP)**

A protein immunologically identical to ferritin, this marker was identified in the liver and serum of the human fetus.53 It was initially detected in the serum of approximately 50 percent of patients with various malignant diseases, 60 percent of patients with primary liver carcinoma, and 20 to 30 percent of patients with benign diseases, such as gastric ulcer, inflammatory bowel disease, hepatitis and cirrhosis. More recent studies have shown that ferritin is detectable in the serum of 60 percent or more of patients with any type of liver inflammation.54
In children's hepatoma, alpha\textsubscript{2}-HFP appears more specific (81 percent positivity),\textsuperscript{55,56} despite 10 percent false positive results.

Subsequent studies have demonstrated the existence of at least six or seven molecular forms of ferritins, some of which were found only in hepatoma and in fetal liver.\textsuperscript{57} Elevated serum ferritin has been found in 68 percent of patients with Stage III and IV Hodgkin's disease, and 32 percent of patients with Stage I and II. In these patients, it may be a useful serum marker, in the absence of active liver disease.\textsuperscript{58}

**Beta-S Fetoprotein (Beta-SFP)**

This third protein is found in fetal liver and in the serum of 48 percent of patients with primary liver carcinoma, 12.2 percent of the patients with other cancers, as well as in some cases of benign liver disease.\textsuperscript{59} The synthesis of Beta-SFP may correlate with a well-differentiated type of primary liver carcinoma.\textsuperscript{60}

**Gamma-Fetoprotein (Gamma-FP)**

Gamma-FP has been detected in the serum of 10 percent of the patients with cancer.\textsuperscript{61} Clinical data are still very limited.

**Fetal Sulfoglycoprotein Antigen (FSA)**

In his initial clinical study, Hakkinen reported that 75 out of 78 patients with gastric carcinoma had a positive FSA test in gastric juice, as did 15 percent of those with benign ulcers.\textsuperscript{62} Complete removal of the cancer, however, was not necessarily followed by elimination of FSA from the gastric juice. Its role in clinical practice is not established.

**Carcinoplacental Alkaline Phosphatase (Regan and non-Regan Isoenzymes)**

A great deal of work has been done by Fishman and his colleagues on isoenzymes of alkaline phosphatase in the sera of patients with various solid cancers.\textsuperscript{63,64} This marker is nonspecific and its highest frequency of occurrence is in ovarian (45 percent), testicular (40 percent) and pancreatic (30 percent) cancers.\textsuperscript{65} It remains under active investigation.

**Oncofetal Antigen for Human Pancreatic Cancer**

In a preliminary study, Banwo and his colleagues reported the presence of a new tumor-associated fetal antigen in the sera of 29 of 30 patients with carcinoma of the pancreas; in seven other patients, the test correctly predicted the diagnosis of carcinoma of the pancreas.\textsuperscript{66} If these findings are confirmed, this tumor-associated fetal antigen may prove most useful.

**DISCUSSION**

The demonstration that CEA and alpha-fetoprotein are useful in managing patients with cancer has restirred interest in other potential tumor markers including enzymes such as alkaline and acid phosphatase, phosphohexose isomerase, gamma-glutamyl transpeptidase, 5-nucleotidase and aldolase, and ectopic hormones such as adrenocorticotropic hormone, human chorionic gonadotrophic hormone and gastrin, and parathormone among many others. Their selective use, possibly in combination with CEA, alpha-fetoprotein and other markers or tests of cell-mediated immunity\textsuperscript{67} may prove advantageous. Bodansky\textsuperscript{68} pointed out that a major contribution of the work on CEA is that it emphasized the clinically common solid cancers (digestive tract, lung, breast, prostate, etc.), an emphasis badly needed.

The need for more specific (i.e., "useful") markers for all types of cancers is urgent, and many laboratories are now seeking to identify, isolate and purify them. In the coming years, considerable advances can be expected.
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