Biochemical Tests for Cancer

An interview with
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Editor: Largely because of your efforts during the last 25 years, the clinical laboratory has become an important and reliable adjunct in the diagnosis and management of disease. What are some of the most valuable biochemical advances in the management of patients with cancer?

Bodansky: A number of biochemical studies, especially certain enzyme determinations, are extremely valuable in confirming the clinical impression of cancer or in following the course of disease. (Table 1.) For instance, the determination of serum alkaline phosphatase activity aids in the diagnosis of patients with skeletal and hepatobiliary cancers; acid phosphatase has proved equally useful in patients with cancer of the prostate. In addition, 5’-nucleotidase, which is elevated in patients with hepatic disease but not in those with skeletal disease, is helpful in the differential diagnosis of liver and bone metastases.

On the other hand, the “ubiquitous” enzymes are not helpful in revealing the presence of cancer, but are extremely valuable in following the patient’s progress, once the diagnosis is established.

Editor: What are “ubiquitous” enzymes?

Bodansky: I applied the term “ubiquitous” to connote the wide tissue distribution of certain enzymes in the body. (Table 2.) Unlike alkaline or acid phosphatase, which are found in high concentrations in
Table 1. Biochemical Aspects Investigated in Frequently Occurring Types of Human Cancer

| Cancer site            | Mortality, 1973 estimated | Biochemical aspects                                      |
|------------------------|---------------------------|----------------------------------------------------------|
| Liver metastases       | 172,900                   | Alkaline Phosphatase; 5'-Nucleotidase                     |
| Bone metastases        | 95,200                    | Alkaline Phosphatase; Calcium excretion                   |
| Colon and rectum       | 47,400                    | CEA                                                      |
| Breast                 | 32,650                    | RNA homology; steriod sulfuration; estrogen binding; steriod excretion discriminant |
| Prostate               | 17,800                    | Acid Phosphatase                                         |
| Leukemia               | 15,300                    | Lysozyme                                                 |
| Bladder                | 9,200                     | Tryptophan metabolites                                   |

Note:
a) Frequencies are those given by Silverberg and Holleb (1973).
b) Estimated by author from data of Abrams et al. (1950).

Table 2. Incidence of Serum Elevations of Ubiquitous Enzymes in Cancer

| Group and Reference                                              | PHI | ALD | LD | GOT | ICD | MD | GR | GPT |
|----------------------------------------------------------------|-----|-----|----|-----|-----|----|----|-----|
| G.I. carcinoma (stomach, colon, pancreas), 119 patients         | 74  | 70  | 53 | 35  | 40  | 37 | 30 | 19  |
| Carcinoma of head, neck and esophagus, 88 patients              | 51  | 45  | 21 | 16  | 21  | 10 | 15 | 9   |
| Cancer of lung, 126 patients                                    | 72  | 62  | 53 | 15  | 24  | 25 | 28 | 7   |
| Cancer of breast, 57 patients                                   | 70  | 45  | 60 | –   | 40  | 40 | 36 | –   |
| Metastatic carcinoma of liver, 284 patients                     | 84  | 75  | 69 | 51  | 53  | 62 | 47 | 44  |
only a few tissues, the ubiquitous enzymes are present in all metabolizing tissues.

**Editor:** Isn’t their reliability somewhat controversial?

**Bodansky:** Yes, but primarily because differences in sensitivity are not always appreciated. Table 2 compares the activity of eight ubiquitous enzymes according to the incidence of serum elevations in several major types of cancer. Serum oxaloacetate transaminase (GOT), which is routinely used, shows a low incidence of elevations in every type of cancer; serum phosphohexose isomerase (PHI), which we developed about 20 years ago, has a high incidence of elevations. I remember one patient with metastatic breast cancer who showed slightly raised PHI levels, while clinically asymptomatic. Actually, the rise in PHI levels was a premonitor to the recurdescence of disease. (Fig. 1.) PHI is perhaps the most reliable of the enzyme tests for following patients with cancer.

**Editor:** The phosphatases and ubiquitous enzymes are helpful aids, but they are not cancer-specific. Is there any biochemical test which is specific for cancer?

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![Fig 1: Serum phosphohexose isomerase (PHI) levels in patients with metastatic mammary carcinoma of skeleton and liver](image)
Bodansky: Unfortunately, no. Perhaps, however, present investigation will confirm the possibility that determination of various isoenzyme activities may serve a specific role.

Editor: *How are isoenzymes different from other enzymes?*

Bodansky: Isoenzymes are molecular variants of a "parent" enzyme. For instance, lactic dehydrogenase has four isoenzymes, each with slightly different molecular and immunological properties. It has been shown that the isoenzymic composition of certain enzymes is altered in cancerous tissues.

Editor: *Is this changing composition reflected in the blood?*

Bodansky: Obviously, change in the character of the isoenzyme must be reflected in the blood for this procedure to have practical application. Until recently, isoenzymes which were found to change in cancerous tissue, such as those of lactic dehydrogenase, were not altered significantly enough to be detected in the blood. Fishman and his associates in this country have found that a placental-like isoenzyme of alkaline phosphatase appears in the serum in a small percentage of patients with cancer. More recently, Japanese investigators have produced evidence of an isoenzyme associated with a specific cancer that can be detected in the blood—aldolase. They have shown that the isoenzymic composition of aldolase changes in the presence of primary liver cancer and that this change is, fortunately, reflected in the serum. Although relatively unknown in American literature, this type of isoenzymic change holds great promise as a cancer-specific biochemical procedure for this type of neoplasm.

Editor: *Do you feel the carcinoembryonic antigen (CEA) test for colon-rectum cancer also shows promise for the future?*

Bodansky: No. The concept behind the CEA test was excellent—that human neoplasms have tumor-specific antigens which could engender antibodies in the rabbit or goat and that the antiserum thus produced could, through a suitable radioimmunoassay, detect the presence, in the entire circulation, of only a few micrograms of a specific tumor substance. However, in my opinion, the test has not fulfilled its initial promise of cancer specificity in spite of truly prodigious efforts to document it.

Editor: *Dr. Bodansky, please explain.*

Bodansky: The first report by Thomson, Krupey, Freedman and Gold in 1969 showed that CEA was positive—the serum concentrations of CEA were greater than 2.5 ng./ml.—in 97 percent of 36 patients with colon-rectum cancer, in nine percent of 32 patients with cancer of other digestive organs and in zero percent of patients with non-cancerous digestive tract diseases or cancers of nonenteric organs.
Fig. 2. Results of various investigators with the CEA test in colon-rectal cancer. T: Thompson, D M P., Krupey, J.; Freedman, S.O., and Gold, P. The radioimmunoassay of circulating carcinoembryonic antigen of the human digestive system. Proc Natl Acad Sci U.S. 64: 161-167, 1969. Ger: LoGerfo, P.; Krupey, J., and Hansen, H.J. Demonstration of an antigen common to several varieties of neoplasia. New Eng J. Med. 285: 138-141, 1971. Z: Dhar, P., Moore, T., Zamcheck, N., and Kupchick, H. Z. Carcinoembryonic antigen (CEA) in colonic cancer. Use in preoperative and postoperative diagnosis and prognosis. J. A. M. A. 221: 31-35, 1972. C: A collaborative study of a test for carcinoembryonic antigen (CEA) in the sera of patients with carcinoma of the colon and rectum. Can. Med. Assn J. 107: 25-27, 1972.
Figure 2 shows the results of subsequent investigations including a large collaborative study by five university centers in Canada and the United States. Note that the incidence of positive CEA tests in patients with colon-rectum cancer has continued to decrease while the incidence of positive tests in patients with cancer of other digestive organs rose from nine percent in the original report to that of patients with colon-rectum cancer in the final collaborative study. In addition, the incidence of positive tests in patients with nonenteric cancer or with non-neoplastic digestive disease rose from zero percent to approximately 40-60 percent.

Nevertheless, the investigators who developed this very thoughtful concept were on the right track: they kept within a specific theoretical framework and they turned their attention toward understanding a common cancer. It is impressive how relatively little biochemical study has been devoted to the most common cancers, while rare and esoteric tumors have been subjects of the most elegant and detailed investigations.

Editor: Is there any biochemical study underway on another common cancer?

Bodansky: Results from a prospective study, set up in 1961 on the Isle of Guernsey by Bulbrook and his associates, to determine whether routine measurement of urinary androgens and corticosteroid metabolites in 5,000 women might reveal abnormal steroid excretions and herald the appearance of breast cancer are just coming in. By the end of 1970, 27 women had developed breast cancer; 20 of these patients had past histories of low urinary excretions of etiocholanolone. If results continue at the same rate, determination of urinary steroid excretions could eventually become a valuable preventive measure. Hopefully, other future investigations will also deal with the biochemical aspects of common cancers—those responsible for 95 percent of all cancer deaths.

Editor: Thank you, Dr. Bodansky.

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