Enzymes in Benign and Malignant Effusions

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ABSTRACT

A critical review of the work done in this area indicates that, of the available enzyme systems now used in clinical diagnosis, the LDH system is the only one of significant value in the examination of pleural and peritoneal effusions. In terms of differential diagnosis, estimation of pleural or peritoneal fluid LDH levels will enable the examiner to distinguish between poorly cellular vs. abundantly cellular effusions. In the abundantly cellular effusions, estimation of levels of LDH do not distinguish with any degree of accuracy between those effusions due to inflammatory processes vs. neoplastic processes. Results of studies of LDH isoenzymes are at variance and require more study.

Although the existence of substances with a demonstrable catalytic chemical effect has been known and studied for about 140 years, it was not until 50 years ago that the first enzyme was obtained in pure form. This chemical feat, performed in 1926, involved the isolation and crystallization of an enzyme, urease, from the jack bean, and won its discoverer, James B. Sumner, a Nobel Prize in 1947. It is interesting that until the advent of methods of analysis adapted to modern automation, the lowly jack bean, with its relatively simple contained enzyme, was the stock in trade of every laboratory performing a blood analysis for urea.

During the ensuing decades, various other types of enzymes, primarily digestive, were delineated, e.g., pepsin, rennin, trypsin, amylase. Some of these proved to be of value from the diagnostic point of view and resulted in the development of tests for amylase and lipase for pancreatic disease, pepsin for gastric achylia, and trypsin for pancreatic secretion. These were followed by the discovery of somewhat more exotic enzymes which proved to be of value in clinical medicine, e.g., alkaline phosphatase for liver and bone disease and acid phosphatase for carcinoma of the prostate.

Although enzyme chemistry has been the subject of intense activity in the research laboratory, the introduction of these substances in the diagnostic clinical laboratory awaited the development of methods applicable to the needs of clinical diagnosis. The introduction of these new methods in the mid 1950’s resulted in a tremendous increase in interest in enzymes as a means of diagnosis.

Since enzymes are essentially intracellular substances concerned with intracellular metabolism, it might be hypothesized...
that the appearance of these enzymes in body fluids represents the sum total of (1) normal intracellular activity (rate of synthesis and rate of metabolism) of the enzyme, (2) abnormal (increased or decreased) intracellular activity of the enzyme or (3) abnormal release of enzyme from its intracellular position as a result of damage to the cell or actual destruction of the cell. It must also follow that the appearance of enzymes in body fluids, such as pleural fluid and peritoneal fluid, must either be a reflection of the enzyme level in the intravascular and interstitial fluid compartments or must result from abnormal local activity of benign or malignant cells or actual destruction of benign or malignant cells closely associated with the body space. The understanding of these basic principles might explain some of the difficulties encountered in the interpretation of enzyme levels of exudates and transudates.

In addition to the extensive literature which has accumulated during the past 20 years dealing principally with enzyme analysis of blood, there has also appeared a number of studies on the use of enzyme analysis in the examination of various body fluids. The estimation of amylase and lipase in peritoneal and pleural exudates has proven of considerable value in the diagnosis of acute pancreatitis. The demonstration of increased levels of amylase in the urine is additionally a useful test in the diagnosis. Less well established is the diagnostic value of various enzymes in urine, vaginal exudates, gastric juice, cerebrospinal fluid and others.

Pleural and Peritoneal Fluids

Following the introduction of methods for enzyme analysis applicable to the clinical laboratory, the value of such enzymes as glutamic oxalacetic transaminase and glutamic pyruvic transaminase in clinical diagnosis was quickly established. However, it became equally clear that levels of these enzymes in effusion fluids were of much less value and of debatable utility in diagnosis.

Wroblewski and Wroblewski attempted to facilitate the detection of malignancy in patients with effusions of undetermined etiology by determining the relative activities of the enzymatic lactic dehydrogenase in the patient's serum and effusion fluid. Their studies indicated that, when an effusion was due to involvement of serosal surfaces by malignant tumor, the lactic dehydrogenase activity of the effusion fluid was higher than that of the simultaneously drawn serum.

On the other hand, when effusion was due to transudation of fluid from congestive cardiac failure or portal hypertension, lactate dehydrogenase (LDH) values were lower than serum levels. Associated with the high LDH values of cancer effusions was hypercellularity of the fluid, while the low values of transudates indicated poor cellularity of the fluid. The mechanism of elevation of LDH activity of serous effusion containing or bathing malignant cells was presumed to be related to the contribution to the effusion of LDH by the proliferating malignant cells.

In a subsequent communication, it was indicated that purulent, chylous or hemolyzed effusions do not lend themselves to the study of LDH as a parameter of malignant cytological constituency since necrotic or destroyed leukocytes and erythrocytes contribute LDH to effusions without regard to presence or absence of malignant cells.

The studies of Erickson also indicated that LDH activity in effusion fluids could be used as a diagnostic test in the detection of malignancy. He found that effusions of nonmalignant origin, with the exception of those which were purulent or which involved massive tissue destruction, exhibited less LDH activity than did effusions of malignant origin.
The original wave of enthusiasm for this new diagnostic parameter in the care of the cancer patient was gradually replaced by a more critical and cautious approach. For example, Chandrasekhar et al subsequent showed that use of fluid LDH was of value in the differentiation between transudates and exudates but was of little value in differentiation of various types of exudative effusions.

In a study of use of LDH isoenzymes in pleural fluids, Light and Ball also found that concentration of total pleural fluid LDH was of no use in differentiating exudative pleural effusions of various etiologies, but could be of value in separating exudative from transudative effusions. In addition, they indicated that pleural fluid LDH isoenzyme patterns are sometimes useful in the separation of malignant from benign exudative pleural effusions. Their findings of a relatively high LDH2 and low LDH5 in some malignant pleural fluids with a high LDH4 and LDH5 in nonmalignant exudates was, however, in marked contrast to the findings of Richterich and his associates. Richterich and coworkers found that all benign effusions had an LDH isoenzyme pattern approximating that of serum whereas all malignant effusions were characterized by higher percentages of LDH4 and LDH5.

References


Abstracts

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The Evaluation of Serum Triiodothyronine Assay as a Thyroid Function Screening Procedure. Robert E. Ziff, Jr., M.D. (Riverside Methodist Hospital, Columbus, OH)

Sera from 500 patients was analyzed to determine if triiodothyronine by radioimmunoassay (T-3) can be utilized as an effective thyroid function screening test. Simultaneous determinations of T-3, total thyroxine (T-4), and resin T-3 uptake (RT-3U) were performed. Estimates of free thyroxine (FT4I), free triiodothyronine (FT3I) and a combined thyroid hormone index (CTI) were calculated. Thyroid stimulating hormone assays were selectively performed to confirm or rule out hypothyroidism.

The T-3 assay is as sensitive as the T-4 assay. The T-3 assay did not detect mild hyperthyroidism in five patients with thyroiditis. The T-4 was normal in four other hyperthyroid patients. Several hypothyroid patients had low normal T-3 and T-4 values. Because the T-3 is less affected by changes in thyroid binding proteins, it has a much greater specificity than T-4. The fewer false positives obtained using the T-3 assay instead of the T-4 assay as a screening test obviates the need for performing additional studies on many euthyroid individuals, particularly women who are pregnant or who are on oral contraceptives. This study suggests that the T-3 assay alone is as specific and as sensitive as FT4I.

The relative independence of serum T-3 from changes in thyroid binding protein levels makes it a more effective screening test for hyper- and hypothyroidism than the T-4 assay alone. In fact, its efficiency is comparable to that of the FT4I. (This project was supported in part by the Riverside Methodist Hospital Medical Research Foundation and the Corning Medical Diagnostics.)