SYMPOSIUM ON CORONARY HEART DISEASE

Measurements of Enzymes in the Diagnosis of Acute Myocardial Infarction

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A significant recent advance in the diagnosis of heart disease has resulted from the development and widespread application of methods to quantitate levels of enzyme activities in the blood or serum of man. From the practical clinical standpoint, the major enzyme systems of present value in this regard are the transaminases (glutamic-oxalacetic and glutamic-pyruvic transaminase) and lactic dehydrogenase. An increase in the serum level of activity of these enzymes, in the appropriate clinical setting, has proved to be a valuable laboratory indicator of myocardial damage. It would not be practicable to discuss extensively the large and rapidly expanding pertinent literature; furthermore, detailed reviews of various aspects of this subject are available.

This communication, therefore, will attempt to summarize certain aspects of (1) the biochemical and experimental bases of the tests, (2) development of methodology, (3) clinicopathologic correlations with the laboratory results, and (4) a critique of their sensitivity, specificity, diagnostic and prognostic accuracy, advantages, and limitations.

Transaminases

Biochemical Background

The term “transaminase” (also called “aminopherase”) refers to a group of enzyme systems that catalyze the intermolecular transfer of an amino group (NH₂) from a donor α-amino acid to an acceptor α-keto acid—viz. R

\[ \text{R} \quad \text{NH}_2-\text{CH} \cdot \text{COOH} + \text{O} = \text{C} \cdot \text{COOH} \quad \text{(α-amino acid)} \]

(α-keto acid)

\[ \text{R} \quad \text{R'} \]

\[ \text{C} \cdot \text{COOH} + \text{NH}_2 \cdot \text{CH} \cdot \text{COOH} \]

Such a transamination had been demonstrated in model, nonenzymatic reactions. Braunstein and Kritzmann first demonstrated the presence of enzymes catalyzing such reactions in pigeon breast and rabbit muscle. Subsequent studies have revealed that transamination is probably the most important metabolic mechanism in both the formation and deamination of many amino acids in various tissues. There are two separable major transaminating enzymes in heart muscle:

A. The glutamic-oxalacetic transaminase (GOT), which catalyzes the reaction

1-Glutamic acid + oxalacetic acid \[ \rightarrow \alpha\text{-ketoglutaric acid} + 1\text{-aspartic acid} \]

and B. The glutamic-pyruvic transaminase (GPT), catalyzing the reaction

1-Glutamic acid + pyruvic acid \[ \leftrightarrow \alpha\text{-ketoglutaric acid} + 1\text{-alanine} \]

These two systems are widespread in higher plants, many microorganisms, and in the blood and tissues of animals (in man, in the following descending order of concentration: heart muscle, skeletal muscle, brain, liver, kidney, testis, lung, and spleen). Pyridoxal phosphate (vitamin B₆ derivative) is the fundamental coenzyme for this reaction. It is
postulated that the pyridoxal phosphate first reacts with the amino acid to form a keto-acid and pyridoxamine phosphate, which then donates the amino group to another keto-acid, thus effecting the ultimate transamination. In consonance with this view, B₆ deficiency results in lowered levels of transaminase activity.

Methods of Measurement

It is essential to note that, at the present stage of development, the available methods of enzymology measure rates of reactions, i.e., they reflect over-all levels of activity and not the actual concentration of a specific enzyme molecule. The manifold complexities of serum with its possible inhibitors, precursors, activators, complex formation, etc., necessitate this mental reservation and remind us of the completely empirical status of current methods. Furthermore, some confusion has resulted from the early multiplicity of methods with the resultant differences in "normal" and "abnormal" values, necessitating critical evaluation of the specific methods employed in the reporting laboratory.

GOT and GPT are the two major transaminases of clinical import. When their activities are measured in serum, the appropriate terms in current usage are SGOT and SGPT (serum glutamic-oxalacetic and serum glutamic-pyruvic transaminase, respectively). Various methods of measurement have been employed.

1. Chromatography: Under standardized conditions, aspartate or alanine is incubated with α-ketoglutarate and the enzyme source, and the resultant glutamate is measured by quantitative paper chromatography.

2. Fluorometry: Direct measurement by fluorometry is not possible. Instead, advantage is taken of the ingenious enzymologic technic of "coupling" wherein the product of one enzymatic reaction serves as a reactant in a more easily measured second reaction. Measurement of the rate of the second reaction serves to quantitate indirectly the rate of the first reaction. Thus, the glutamic-oxalacetic transamination reaction is coupled to a second reaction in which the oxalacetate serves to oxidize reduced diphosphopyridine nucleotide (DPNH) to DPN in the presence of an excess of malic dehydrogenase. The DPN is measured by fluorescence of its condensation complex with methyl-ethyl ketone. The rate of DPN formation thus serves to quantitate the rate of the first reaction.

\[
\begin{align*}
\text{Reaction 1—Aspartate} & \quad \text{+ α-ketoglutarate} \\
& \quad \text{transaminase} \\
& \quad \text{oxalacetate} & \quad \text{+ glutamate}
\end{align*}
\]

\[
\begin{align*}
\text{Reaction 2—Oxalacetate} & \quad \text{+ DPN} \\
& \quad \text{malic dehydrogenase} \\
& \quad \text{malate} & \quad \text{+ DPNH}
\end{align*}
\]

Similarly, for SGPT, the pyruvate formed in the first step oxidizes DPNH to DPN in the presence of lactic dehydrogenase and the rate of DPN formation serves as a measure of the rate of the initial reaction.

3. Colorimetry: For SGOT activity, the oxalacetate is converted to pyruvate; for SGPT, pyruvate is formed directly. The intensity of the color reaction of pyruvate with dinitrophenylhydrazine then serves as a measure of the over-all reaction.

4. Spectrophotometry: Here again, the coupling reaction is used and the rate of formation of DPN (reflecting the transamination reaction) is measured by the rate of decrease in light absorption at 340 nm, the absorption maximum for reduced DPNH.

Representative normal values for the different methods are presented in table 1.

Although such measurements have proved to be of distinct value in general clinical studies, certain theoretical objections have been raised. The technic of "coupling" the desired reaction with a second, dependent reaction introduces certain complexities of indirect measurement. Furthermore, nonlinear kinetics have been demonstrated in the coupled SGOT system. It has been reported that available preparations of malic dehydrogenase, the enzyme introduced to "make" the second reaction go, may themselves be contaminated with variable amounts of GOT. Finally, direct comparison of two or more different
methods has revealed poor correlations in certain instances. Once again, we are reminded of the completely empirical status of present-day methods and of the need for critical clinical evaluation of the seemingly precise laboratory answer. The method most widely used is based on the original, simpler spectrophotometric method of Karmen, Wroblewski, and La Due and the generally accepted normal range has been 8 to 40 units. However, Rowell and Smith found, in 50 normal adults, SGOT activity of 19 ± 4.5 units and thus believe that values greater than 28 units are abnormal. Similarly, for SGPT, an upper limit of normal of 21 units was based on findings in normal subjects of values of 12 ± 4.2 units. Their suggestion that previously reported "false negatives" may have been due to an erroneously high "normal" range underscores the need for further study and critical evaluation of this fundamental aspect of the problem.

Enzyme activity is strikingly constant in health, remaining essentially unaltered by ingestion of food, exercise, or storage at room temperature for 24 hours or at 0 to 5 C. for 2 weeks.

**Clinicopathologic Correlations**

Under normal conditions the abundant transaminases are confined, almost exclusively, within tissue cells and only very small amounts are found in the circulation. It is this relatively small "baseline" serum level which first suggested and has permitted ready detection of increased serum values resulting from destruction of tissue and the assumed release of enzyme from the large tissue stores. For example, dog heart tissue contains 300,000 units GOT per Gm. wet weight. It is not yet clear whether the increased serum levels, sometimes very large, are due wholly to the release of intracellular enzyme from necrosis of the myocardium, since it has been suggested that the increased amounts in serum are sometimes greater than the estimated stores of the entire myocardium. Alternative explanations then postulated, although not yet demonstrated, are a decrease in the body's degradative or excretory mechanisms or stimulation, by an unknown mechanism, of increased production or release of enzyme by other non-necrotic tissues.

There appears to be a highly effective mechanism, at present obscure, for the rapid elimination or degradation of the enzymes. Fleisher and Wakim injected massive amounts of GOT intravenously into dogs, causing an increase in serum activity some 212 times the preinjection value. In 24 hours, 97 per cent of the enzyme activity had gone, and the control level was reached by the end of the third day. La Due, Wroblewski, and Karmen were the first to demonstrate that SGOT is increased above normal during the first few days after myocardial infarction in man— an observation that has been widely confirmed and extended. A significant rise has been detected within 6 to 12 hours of the estimated transmural infarction, generally reaching a peak some 2 to 15 times normal levels in 24

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**Table 1**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Method</th>
<th>Units</th>
<th>Normal values</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT</td>
<td>Paper chromatography</td>
<td>μM glutamate/ml./hr.</td>
<td>0.41—1.36</td>
<td>0.622 ± 0.191</td>
</tr>
<tr>
<td></td>
<td>Fluorometry</td>
<td>μM oxalacetate/ml./hr.</td>
<td>—</td>
<td>1 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>Colorimetry</td>
<td>Colorimetric unit*</td>
<td>4 —40</td>
<td>16 ± 8.0</td>
</tr>
<tr>
<td></td>
<td>Spectrophotometry</td>
<td>Unit/ml./min**</td>
<td>9 —40</td>
<td>20 ± 7</td>
</tr>
<tr>
<td>SGPT</td>
<td>Paper chromatography</td>
<td>μM glutamate/ml./hr.</td>
<td>0.21—1.01</td>
<td>0.525 ± 0.146</td>
</tr>
<tr>
<td></td>
<td>Fluorometry</td>
<td>μM pyruvate/ml./hr.</td>
<td>—</td>
<td>0.8 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Colorimetry</td>
<td>Colorimetric unit*</td>
<td>1 —45</td>
<td>22 ± 12</td>
</tr>
<tr>
<td></td>
<td>Spectrophotometry</td>
<td>Unit/ml./min**</td>
<td>—</td>
<td>16 ± 9</td>
</tr>
</tbody>
</table>

*One colorimetric unit = the activity of 1.0 ml. of serum resulting in formation of chromogenic material equal to 1 μg. of pyruvate under standard conditions.

**One spectrophotometric unit = decrease in optical density at 340 mμ of 0.001 under standard conditions.
to 48 hours and returning to normal range by the fourth to seventh day. In certain cases, however, an elevation was not detected until 36 hours after the onset of symptoms and return to normal occurred as soon as 48 hours.

These clinical findings have been strongly supported by experimental studies of myocardial damage by several workers using various technics, revealing excellent correlations of increased serum levels of enzyme activity with tissue damage. Significant elevations of SGOT, although short-lived, have been found with experimentally induced infarets of less than 1 Gm. of myocardium. There was a suggestive correlation between the size of the infarct and the height and duration of increased serum enzyme activity. Enzyme levels decreased rapidly in infarcted muscle as compared to normal muscle. In almost every instance, serum enzyme levels were not increased in the presence of significant myocardial ischemia without histologic necrosis. Similarly, experimental pulmonary infarction or pericarditis in dogs usually resulted in no increase in SGOT or SGPT.

In man, with the obvious limitations of precise definitions, a generally rough correlation of extent of damaged tissue and increase of enzyme activity has been suggested. Although a peak rise above 300 units has generally indicated a poor prognosis, frequent exceptions at both extremes (recovery in patients with extremely high levels, death in patients with only slight increases) render the actual level of little prognostic value in a given case.

SGPT is frequently normal in the face of elevated SGOT in the less extensive infarctions, but may rise in the presence of large infarcts. Although it has been stated that SGPT is not elevated until SGOT values of 150 to 200 units are reached, Rowell and Smith found 14 episodes of elevation of SGPT with SGOT values below 150 units.

Critique
A large experience suggests that the determination of SGOT (and to a lesser extent SGPT) is an extremely valuable diagnostic tool. Elevated levels in a patient with the suggestive clinical picture of precordial pain and characteristic electrocardiographic changes are, of course, additional confirmatory evidence. Of perhaps greater value are rises in enzyme levels in a patient with a suggestive history whose electrocardiogram is atypical, or obscured by previous myocardial infarction, digitalis administration, bundle-branch block, or the Wolff-Parkinson-White syndrome. A secondary rise in a patient with recent myocardial infarction is an important indicator of extension of the necrotic process. In a recent review of the pertinent literature, Agress found that 96 per cent of 1,255 cases of clinically proved myocardial infarction revealed elevated SGOT levels—a very impressive correlation. He suggested that the occasional reported case of elevated SGOT without apparent infarction could be attributed to undetected small areas of infarction. Failure of serum enzyme activity to rise in most cases (usually all but the most severe) of pulmonary embolism or infarction, pericarditis, rheumatic carditis, cardiac arrhythmias, status anginosus, coronary insufficiency, or occlusion without infarction serves as a most useful adjunct in differential diagnosis of chest pain syndromes. The need for caution, however, is underscored by the scattered reports of occasional elevations in such instances, and by less complete correlation reported in other series. For example, White reported 12 instances of "false negatives" in 24 cases of myocardial infarction. A major consideration relates to the timing of the specimens for, as stated above, the elevation may occur early, reach a peak transiently within 24 to 48 hours, and return to normal levels by the second or third day, thus precluding confirmation in a patient seen first after this time period. In other instances, elevations may not occur until 36 hours after the onset of symptoms and may persist until the seventh day. Thus, serial determinations are necessary and various sampling schedules have been adopted, e.g., daily determination or one sample between 12 and 24 hours and a second one between 36 and 48 hours after the assumed clinical event.

The level of SGOT activity appears to be unaffected by the presence of several other
major disease processes, such as heart failure, various infectious diseases, metabolic and endocrine diseases, arthritis, anemias, renal shutdown, venous hypertension, or by the administration of digitalis or quinidine. Activity levels do not correlate with various other factors such as age, sex, race, alterations in leukocyte count, sedimentation rate, body temperature, or urinary volume.

Recent studies have correlated very high levels of SGOT (>500 units) in cardiac patients with central hepatic necrosis attributed to hypotension, reduced cardiac output, and reduced flow to acute right heart failure with or without demonstrable myocardial necrosis.

It is pertinent to note other disease processes that may lead to elevated values although the clinical picture usually suffices to exclude them from serious consideration. Thus, transaminase levels are increased in virtually every type of liver disease (infectious, nutritional, obstructive, toxic, and neoplastic). In addition to the usually distinctive clinical features, differential diagnosis is aided by judicious use and interpretation of other liver function tests and by the usually greater elevation of SGPT values (in conjunction with the SGOT) in cases of liver-cell injury. Other pathologic states that may be associated with increased enzyme levels are: (1) intracardiac surgery, (2) administration of salicylates, opiates, or coumarin-type anticoagulants, (3) various forms of primary muscular and neuro muscular diseases (muscular dystrophy, muscular pseudohypertrophy, acute dermatomyositis, paroxysmal myoglobinuria, surgical trauma, gangrene of the toes), (4) acute pancreatitis, (5) extensive central nervous system damage as in massive cerebrovascular thromboses or hemorrhage, (6) toxemia of pregnancy, (7) hemolytic crises, (8) crush injuries or burns, and (9) infarction of kidney, spleen, or intestine.

**Lactic Dehydrogenase**

**Biochemical Background and Methodology**

Lactic dehydrogenase (LDH) refers to a group of enzymes that catalyze the reversible oxidation-reduction reaction between lactate and pyruvate, involving *pari passu* the con-
version of the reduced and oxidized forms of the pyridine nucleotides (DPNH and DPN):

\[
\text{LDH} \quad \text{Lactate} + \text{DPN}^+ \leftrightarrow \text{Pyruvate} + \text{DPNH} + \text{H}^+ 
\]

This reaction is a critically important step in the carbohydrate metabolic cycle and, accordingly, the enzyme—a zinc-containing compound—is widespread, having been found in virtually every vertebrate and invertebrate species tested, in almost every mammalian tissue studied, and in many microorganisms. Recent exciting studies (see *Critique* below) have suggested a heterogeneity of the LDH enzyme moiety, not only in different species but also in different tissues within the same species, indeed within the same individual organism.

In the presence of the enzyme, lactate is oxidized to pyruvate ("forward reaction") while DPN is reduced to DPNH; conversely, the enzyme will also catalyze the "reverse reaction" in which pyruvate is reduced to lactate while the reduced DPNH is oxidized to DPN. Thus, measurement of enzyme activity can be carried out in either direction depending upon the initial substrates employed, proper conditions of pH, etc., and different clinics have adopted one or the other method. Snodgrass et al., in a detailed discussion of the respective merits, delineate their preference for the "forward" reaction (lactate → pyruvate) on the basis of greater precision and convenience. Recent methodologic advances have culminated in the development of a relatively simple, "bedside" method of sufficient accuracy employing a commercially available photometer and prep- prepared lyophilized reaction mixtures, requiring the addition only of the patient's serum. The basis of the quantitation is the direct spectrophotometric measurement of the rate of change of DPNH at its characteristic wave length of 340 nm (increase in "forward" reaction, decrease in "reverse" reaction). A unit of LDH activity is defined as an increase in optical density units of 0.001 per minute per ml. of serum. A representative normal range is from 25 to 100 units at...
23°C, averaging 59 units; thus a value greater than 100 units constitutes an abnormal elevation. As indicated above, however, different "normal ranges" have been established by various clinics using modifications of the basic technic. Thus, normal values have been published of 165 to 332 units per ml. of serum, 14 90 to 100 units per 0.01 ml., 11 200 to 680 units per ml., 3 or less than 270 micromols per 100 ml. 9 The serum may be obtained from fasting or nonfasting blood, and enzyme activity is essentially unchanged during storage at 4°C, for periods up to 10 days. Hemo-
lyzed serum is unsatisfactory because of the high LDH content of erythrocytes.

Clinicopathologic Correlations

The high content of LDH activity in cardiac muscle and relatively low serum values again suggested the possible usefulness of study of serum levels in cases of myocardial damage. In the course of their sequential studies of the serum concentration of copper, then zinc, in various diseases, Wacler et al. 15, 16 found a marked increase of serum LDH activity in patients with acute myocardial infarction. This observation has been amply confirmed and extended and is the basis for the widespread use of this laboratory aid in diagnosis of myocardial disease. In characteristic cases of myocardial infarction, proved at autopsy, serum LDH activity was significantly increased above normal at some interval from 12 hours to 10 days after infarction in an extremely high percentage of cases—up to 100 per cent in certain series. 5 In general, enzyme activity was increased within the first 12 to 24 hours, rose to a peak in 3 to 4 days, gradually returning to normal by the eighth to fourteenth day. Thus, the optimal period of detection is from 2 to 6 days after infarction and the pattern of an abrupt rise in the first 3 to 4 days, followed by a gradual decline may itself serve as a strong indication of myocardial infarction. Increased levels occurred even in the absence of definitive electrocardiographic changes or consistent alterations in leukocyte count, sedimentation rate, etc. Elevated values in atypical or clinically unsuspected cases were con-
firmed by autopsy findings. Conversely, autopsy failed to reveal infarction in several cases dying with the diagnosis of acute myocardial infarction but in whom repeated LDH determinations were within normal limits. Several other reports indicate a very high correlation of elevated values in patients with an ultimate diagnosis of myocardial infarction, although not subjected to autopsy confirmation. In a study of other types of myocardial disease, increased values were found in some cases of severe congestive failure (usually with "congestive cirrhosis" of the liver) bacterial pericarditis, and severe digitalis intoxication; normal values were found in patients given coumarin anticoagulants or with heart block, prolonged arrhythmias, ventricular aneurysms, or subacute bacterial endocarditis. Elevated LDH values have been found in acute viral hepatitis, muscular dystrophy, leukemia, and certain cases of metastatic carcinoma.

Critique

Elevation of serum LDH activity is an extremely valuable indication of myocardial damage in appropriate cases. Although the question of sampling time must be considered in the failure to observe an increased LDH in suspected cases, repeated normal values are strong evidence against myocardial necrosis. It is pertinent to note that, although very high correlations have been observed in small series, the almost inevitable exceptions have been documented—normal values in patients with apparent myocardial infarction and elevated values in other disease states, without myocardial necrosis.

Such exceptions and the fact that, as with SGOT, elevated serum values are basically nonspecific, lend emphasis to recent basic investigations of the nature and mechanism of action of LDH. These studies have revealed findings of profound fundamental and potential clinical import, namely, the possibility that what is measured as over-all LDH activity of a given tissue or serum actually consists of several similar, yet actually different, molecular entities. Kaplan and his co-workers, 17 in a series of studies employing analogues of DPN and DPNH to measure catalytically
LDH activities of different tissues in several vertebrate and invertebrate species, in combination with electrophoretic and immunologic technics, have demonstrated striking differences in LDH of different species and, perhaps more pertinent to this discussion, differences of LDH in different tissues of the same individual organism, including man. Of potential import for the study of the evolution, classification, and differentiation of enzymes, such results suggest the possibility of defining more precisely the tissue of origin of the elevated serum levels. For example, by a comparison of reaction rates, using different analogues of DPN, liver LDH can be differentiated sharply from myocardial LDH as can also the enzyme derived from the lung. Studies are now under way to investigate the clinical application of these findings. Markert and Moller have also reported differences in LDH of different tissues by electrophoretic technics as have Mansour et al., employing kinetic and immunologic data. Vesell and Bearn, employing starch gel electrophoresis for the fractionation of plasma, found three different bands with LDH activity (called “isozymes”). Increased activity levels in one of the three bands—the α-1 band—was found in a small number of patients with myocardial infarction, whereas the elevated LDH level in leukemia was associated with increased activity in a different band. The unsettled state of this methodologic approach is reflected in a recent report by Wroblewski et al., describing a characteristic plasma electrophoretic pattern of five “isozymes” of LDH (LD1 to LD5) in normal subjects. In 15 patients with acute myocardial infarction, an elevation of one component, LD5, was observed for 8 to 15 days after infarction and considered more specific for myocardial damage than total LDH activity. They reported further that an elevated LD5 was observed in certain cases with small or subendocardial infarctions at times when total plasma LDH was within the normal range. Although the preliminary reports are encouraging, the technic of starch block electrophoresis, in its present state of theoretical and practical development, does not appear sufficiently practicable or convenient for routine clinical use. Some modification of the currently employed, simpler photometric catalytic method—such as the substitution of different DPH analogues as suggested by Kaplan—would appear more promising. In any event, the concept of molecular heterogeneity, the demonstration of “different” LDH’s contributing to the elevated serum levels, and the possibility of delineating the specific tissue source affords considerable promise of a major advance in the specificity and diagnostic accuracy of this (and possibly other) enzyme measurements in diseases of man.

Other Enzymes

In addition to studies of transaminase and lactic dehydrogenase, changes in other enzyme activities have been investigated in cases of myocardial infarction. To date none has proved as consistently accurate, sensitive, or helpful. Several may be considered briefly:

1. Malic dehydrogenase (MDH)—another widely occurring metallo-enzyme, catalyzing the important reaction of the citric acid cycle:

    \[
    \text{MDH} \quad \text{Malate} + \text{DPN} \quad \leftrightarrow \quad \text{oxalacetate} + \text{DPNH}
    \]

    Measurement of this enzyme activity is technically less ideal than that of LDH, requiring a 20-minute waiting period. Serum levels are comparably increased in both experimental and clinical myocardial infarction. In general the time course parallels that of transaminase, reaching a peak within 24 hours, dropping sharply thereafter. It is similarly nonspecific, being elevated in liver disease, muscular damage, hemolyzed serum samples, etc. There is no direct correlation with LDH levels in given cases and there appear to be no outstanding advantages of MDH measurement.

2. Aldolase. This enzyme catalyzes the reaction:

    \[
    \text{Fructose 1-6 diphosphate} \quad \leftrightarrow \quad \text{d-glyceraldehyde-3-phosphate} + \text{dihydroxyacetone-phosphate}
    \]

    In one study, serum levels were increased in 11 of 17 patients with myocardial infarction. The level rose promptly, and returned to nor-
normal rapidly in a pattern similar to that for SGOT. In another study, a increased levels were found in 13 of 14 cases, with an unexplained secondary rise about 5 days after the first peak, unassociated with clinical evidence of extension of infarction or rise of SGOT.

3. Phosphohexose isomerase—a glycolytic enzyme, occurring in plants and tissues and serum of animals and man, it catalyzes the reaction:

\[
\text{Glucose-6-phosphate} \xrightarrow{\text{fructose-6-phosphate}}
\]

Again elevated values followed the pattern of transaminase values with a prompt rise, followed by a rapid return toward normal. a, b Elevated values were found in liver disease, muscle damage, certain tumors, hemolyzed samples, etc.

4. Oxidase. Ceruloplasmin, the blue, copper-containing serum protein, exhibits oxidase activity with a number of substrates, most actively with p-phenylene-diamine. A high degree of correlation has been found among the total plasma copper level, the concentration of ceruloplasmin, and serum oxidase activity in normal subjects as well as in myocardial infarction, pregnancy, and chronic infections (increased levels) and in Wilson’s disease and some nephrotic patients (decreased levels). Measurement of serum oxidase activity is by far the simplest test and is considered to reflect the others with sufficient accuracy for clinical purposes. Vallee first demonstrated in 1952 a significant increase in serum copper levels in each of 12 cases of myocardial infarction, which rose in the first 5 days, reached a plateau in 5 to 11 days, and progressively returned to normal within 19 to 30 days. Rowell and Smith found a similar pattern of increase in serum oxidase levels in 10 of 13 cases of myocardial infarction. Although the pattern of change permitted diagnosis at later time intervals, they noted that oxidase activity usually failed to show the secondary rise exhibited by the other enzymes in episodes of extension of the infarction.

Several recent studies have attempted to correlate multiple enzyme activities on the same samples. For example, in one series of 24 patients with recent myocardial infarc-
mains essential. Despite this limitation, demonstration of elevated serum levels of certain enzymes (the two most useful at this time being SGOT and LDH) serves, in the proper clinical setting, as a highly valuable indicator of myocardial necrosis; failure to observe this on serial testing is an important negative finding. The SGOT activity rises promptly after myocardial infarction, permitting early confirmation. LDH, simpler to measure, affords the advantage of a more persisting abnormality (up to 10 to 14 days after infarction). In most comparative studies, LDH measurements appear to afford a greater over-all positive correlation with the ultimate diagnosis. The rapid development of this area of knowledge has already increased the diagnostic armamentarium of the clinician. Recent promise of methods to increase the specificity of the results augurs well for the future.

References
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MILTON W. HAMOLSKY and NATHAN O. KAPLAN

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