ENZYME ESTIMATION AS AN AID TO DIAGNOSIS*

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The estimation of the levels of enzyme activity in the body fluids, as an aid to diagnosis, is by no means new. King and Armstrong introduced their method for serum alkaline phosphatase in 1934. This was adapted by Gutman and Gutman (1938) for serum acid phosphatase. Fairly reliable methods for the estimation of trypsin (using 'trypsin' in a broad sense) and amylase have been available for several years.

The discovery by La Due *et al* (1954) that there was an increase in the serum glutamic oxalacetic transaminase (SGOT) following myocardial infarction has proved to be a stimulus for the systematic investigation of the levels of various enzyme systems in health and in a variety of diseases. This paper enunciates general principles, reviews recent work in this field, and attempts to evaluate its practical importance in diagnosis.

GENERAL PRINCIPLES

In general, the enzymes which are to be discussed are intracellular, only small amounts being present in the blood of normal persons. This being so, if a cell dies, or if the integrity of its cytoplasmic membrane be lost, then the contained enzymes will escape freely into the circulation, resulting in a rise in the blood levels. This release appears to take place over a period of time which varies from enzyme to enzyme.

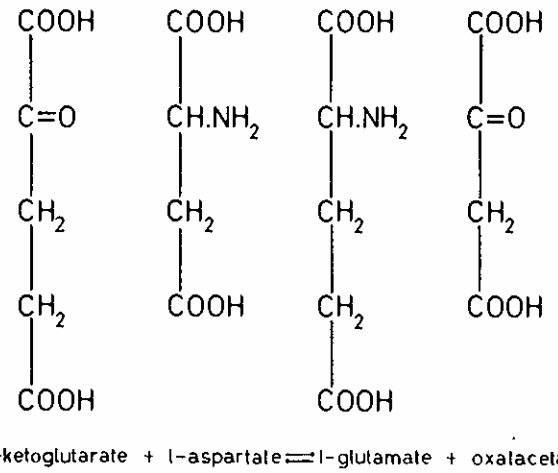

Fig. 1.

TRANSAMINASES

A transaminase is an enzyme which catalyses the transfer of an amino (NH_2) group from one amino-acid to a keto-acid, thus producing another amino-acid and another keto-acid. There are two transaminases of importance in diagnosis, glutamic oxalacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT). The action of the former is shown in Fig. I.

The transaminases are found in varying proportions in various tissues. The amounts of these enzymes which are normally present in serum are small compared to those locked up inside the cells. Hence, when a cell dies, and the integrity of its basement membrane is lost, the contained transaminases enter the circulation, causing a rise in specific transaminase activity. The transaminase is not all liberated at once, and may take some time to appear in the blood stream after necrosis commences. Not only is it of interest to know when transaminase appears in increased amounts, but it is also useful to know just how high the level becomes, in other words, the peak value, it being reasonable to assume that the more transaminase there is liberated, the more necrotic tissue there must be. Hence serial estimations should be done.

By the accepted methods now in use, the normal values per ml. serum are:

	Range	Mean
SGOT	4 to 40 units	16 units (S.D. ± 8 units)
SGPT	1 to 45 units	22 units (S.D. ± 12 units)

Although there is a fair range of normal, for an individual, it seems to be remarkably constant, not varying with diet, exercise, sleep, etc., or by venous occlusion (Agress, 1959).

Now for some practical applications.

INFARCT OR ANGINA?

It would be a reasonable assumption that if there is necrosis of heart muscle, such as must occur in an infarct, then the SGOT, in particular, will be raised. If the chest pain is due to coronary insufficiency without muscle necrosis, then the level of SGOT would remain normal. It is, of

*Based on a paper read to the Singapore Society of Pathology.

course, necessary to know how long will elapse between the onset of chest pain and the appearance of raised levels of SGOT in the blood if estimation is to be of assistance. This may vary considerably, depending not only on the severity of myocardial damage, but also, it would seem, on the individual. Two hours is the shortest recorded interval, four days the longest, but for the majority, 12 hours seems usual. For this reason, serial estimation for at least three days after an episode of severe chest pain would appear to be reasonable. Serial estimation has a further advantage, as by this means, a peak level may be determined, the height of the peak indicating the extent of the damage. This maximum figure usually occurs some 24 hours after the onset of the attack; by the sixth day, in the absence of further infarction, values should have returned to normal.

Agress (1959) collected 1255 clinically proven cases of myocardial infarction from the American literature. As well as clinical assessment of the patient, the relevant investigations, e.g. electrocardiograms, erythrocyte sedimentation rate, leucocyte counts, temperature and the like were undertaken. A raised SGOT was found in 96.6% of these cases. Some of the false negatives were due, he felt, to a failure to undertake serial estimations. Of the 1255 cases, 63 came to necropsy; all showed myocardial infarction. Sixty two had elevated SGOT levels prior to death. A reading of over 50 units was considered highly suggestive of myocardial necrosis, while values of 500 units were not uncommon.

Useful though this test is, it may fail to detect damage in the patient who has a relatively mild chest pain and does not seek medical advice for several days. In such instances estimation of serum lactic dehydrogenase (*vide infra.*) is useful as this may remain elevated for up to ten days after necrosis (White, 1956; Stewart and Warburton, 1961).

The sensitivity of an aid to diagnosis is always of interest. It would seem that as little as 1 gram of necrotic heart muscle, i.e., less than 0.5% of the total heart weight, will suffice to give a detectable elevation of serum enzyme concentration (Agress, 1959).

There is considerable experimental evidence to support the clinical which has just been presented. Loops were placed around the coronary arteries of 26 dogs by LaDue *et al* (1956). As this operation involved damage to skeletal muscle which contains large amounts of SGOT, the experimenters waited until the blood levels were normal before proceeding to gradually tighten these loops until ST and T wave changes occurred in the ECG, but not Q waves. Five of the dogs showed raised SGOT levels. At necropsy, these five, and these only, showed small subendocardial infarcts.

The consensus of opinion seems to be that in angina there will not be elevation of SGOT, and that values of 41 to 50 units suggest the presence of small infarcts. SGPT is not raised in myocardial necrosis. Lieberman *et al* (1957) who studied 51 patients, the victims of a variety of accidents, concluded that SGOT levels could not be relied upon to detect myocardial damage in such subjects.

OTHER HEART DISEASES

In a series of 41 cases of idiopathic pericarditis SGOT levels were normal in 36, and equivocal or slightly raised in the other five (Agress, 1959).

On the other hand, rheumatic pericarditis and myocarditis are frequently associated with high levels, especially when the disease is active (Nydick *et al*, 1955; Manso *et al*, 1956). It is worth remembering that aspirin and other salicylates may give high readings (Manso *et al*, 1956; Foulk and Fleisher, 1957).

Rapid cardiac arrhythmia is often associated with raised SGOT levels (Chinsky *et al*, 1957).

Pulmonary oedema, and chronic pulmonary venous congestion, do not give rise to raised SGOT levels (Chinsky *et al*, 1957; Lieberman *et al*, 1957). West *et al* (1961) have shown that in heart failure there is a slight, but appreciable, increase in SGOT and SGPT levels. In a series of 224 patients in heart failure, none of whom were considered to suffer from recent myocardial infarction, hypotension, cerebrovascular accident, alcoholism, liver disease, cancer, blood dyscrasia, pancreatitis, or disease of the skeletal muscles, there was a raised SGOT level in 12%, and a raised SGPT level in 11%. The SGOT was raised in both right and left heart failure, whereas the SGPT was elevated in right heart failure only. This finding suggests that the SGPT was of hepatic origin, possibly the result of centrilobular liver cell necrosis.

PULMONARY OR MYOCARDIAL INFARCT?

The SGOT level is probably not raised in pulmonary infarction, unless the infarct is of such a size that it would be seen on X-ray. Even then, the elevation tends to be small, not above 85 units, and the rise usually occurs on the fourth day after the chest pain (Ostrow *et al*, 1956).

CENTRAL NERVOUS SYSTEM DISEASE

The brain is high in SGOT, hence destructive disease might be expected to result in raised blood and C.S.F. levels. This appears to be true, although there is no correlation between the two (Agress, 1959). As SGOT due to disease outside the central nervous system do not pass the blood-brain barrier to the C.S.F. (Fleisher and Wakim, 1956), any rise in C.S.F. transaminase above the normal of 17 units/ml. can be taken to indicate central nervous system disease, but this is quite non-specific.

DISEASE OF SKELETAL MUSCLE

Elevations of SGOT were found in 54% of 87 patients with muscular dystrophy, these levels being sustained for many months (Pearson, 1957). This would suggest continuous necrosis of skeletal muscle cells. Similar observations were made in 52 cases of dermatomyositis, polymyositis and dystrophy by Siekert and Fleisher (1956). High levels were also found in Indian patients with pseudohypertrophic muscular dystrophy (Pannikar, 1961). As has been noted, muscle trauma results in the liberation of SGOT into the blood stream (Liberman *et al.* 1957); so may severe burns.

Jungner and Jungner (1960) found elevated SGOT and SGPT levels in acute poliomyelitis. Once the acute phase is over, poliomyelitis, like other neurogenic myopathies, does not, in itself, produce a pathological rise in serum transaminase (See also aldolase).

LIVER DISEASE

It is probably in hepatic disease that the transaminase estimations will prove to be of the greatest help in diagnosis. Molander *et al* (1955) fed rats with carbon tetrachloride, a well-known hepatotoxic agent. Blood was withdrawn from the heart by cardiac puncture and serum alkaline phosphatase, cholinesterase and SGOT levels examined. The SGOT rose earlier and in greater amounts than other enzymes, and this rise was proportional to the amount of carbon tetrachloride given and to the amount of liver damage sustained. Similar findings have been reported in human toxic hepatitis and in infectious hepatitis. SGOT is also elevated in obstructive jaundice, cirrhosis of the liver, infectious mononucleosis (Rennie and Wroblewski, 1957), and in carcinoma, both primary and secondary (Chinsky *et al,* 1957). This list, it may be felt, covers most of the known liver diseases; nevertheless there appears to be patterns of alteration which are more or less characteristic for each type of disorder. These are shown in Table 1.

TABLE I. THE TRANSAMINASES IN LIVER DISEASE.

(Table constructed from Data by Agress, 1959)

Acute toxic hepatitis	500-2,500 units, maximum 27,800 units SGPT usually higher than SGOT.
Viral hepatitis	
Cirrhosis	About 80 units. SGOT usually higher than SGPT.
Metastases	Up to 250 units.
Primary Carcinoma	90-160 units, determined by the rate of growth.

In toxic or viral hepatitis, SGOT levels are often raised one to four weeks before jaundice appears (Wroblewski and LaDue, 1956). This warning has proved particularly useful in mental hospitals where large numbers of patients may be on chlorpromazine therapy at any one time. Further, Wroblewski and LaDue (1956) felt that when SGOT levels returned to normal in patients recovering from hepatitis, then it was safe to allow them to walk, even though other liver function tests were still abnormal.

This finding is of such significance that in the U.S.A. transaminase estimations are carried out routinely on donors' blood in order to exclude the possibility of transfusion of blood from persons with hepatitis.

INTRAHEPATIC OR EXTRAHEPATIC JAUNDICE?

Estimation of the SGOT level may be of considerable assistance in differentiating between intrahepatic disease with jaundice and obstructive jaundice. If the cause lies within the liver, then the levels obtained are usually very high, above 300 units, and these levels are reached quickly. In extrahepatic jaundice, the rise takes place slowly, to level off somewhere below 300 units. Should obstruction be relieved then there is a rapid return to normal (Wroblewski *et al,* 1956). The importance of serial estimation, perhaps every eight hours, until a picture of the peak level and the rate of climb to that level can be ascertained, is evident.

Hargreaves *et al* (1961) estimated SGOT, SGPT, aldolase, cholinesterase, alkaline phosphatase, and the isocitric, lactic, and phosphogluconic dehydrogenases in a series of patients with liver disease, as well as undertaking the more conventional tests of liver function. They concluded that while certain of the enzymes, notably the transaminases, were more sensitive indices of liver damage than the conventional tests, particularly in a relapse, there was no justification for estimating all the enzymes, as this gave no further information. They were also unable to differentiate between various types of liver damage on studying patterns of enzyme level.

Sommerville *et al* (1960) studied transaminase levels in cirrhosis and found that although there was considerable overlap, in general, extrahepatic obstructive jaundice gave higher levels than in cirrhosis, and cirrhosis higher levels than metastatic malignant disease. Post-hepatic cirrhosis gave higher figures than the other forms of disorder.

TABLE II. SERUM TRANSAMINASE ACTIVITY IN THE DIFFERENTIAL DIAGNOSIS OF NEONATAL JAUNDICE.

(Table constructed from Data by Kove, 1960a)

ENZYME LEVELS	CAUSE OF JAUNDICE
Normal values	Physiological
	Absorption of encapsulated haematoma
	Cretinism
	Extrahepatic infection
	Kernicterus due to Rh
	Haemolytic states unless very severe
Slow rise up to 800 units then level off (due to slow liver damage)	Complete biliary obstruction due to inspissated bile — rise in 1st week.
	Congenital obliteration of bile ducts — rise from 1½ months.
Raised from birth, sustained at 300-440 units (GP-T)	Cytomegalic disease with liver involvement.
Sharp rise well above 800 units of GO-T. Increase in GP-T less striking	Neonatal viral hepatitis.

JAUNDICE IN INFANCY

In a recent review, the application of these tests to the differential diagnosis of jaundice in infancy was evaluated (Kove, 1960a). Normal values for the newborn were found to be up to 120 units for SGOT and up to 90 units for SGPT. By the end of three months normal values were as for adults. A scheme drawn up from Kove's (1960a) paper is given in Table II.

URINARY TRANSAMINASE

Sepaha *et al* (1961) have examined urinary and serum glutamic oxalacetic transaminase denoting the former as UGOT. In normal subjects the UGOT was about 30% of the serum value, i.e. about 6 units per ml. In coronary thrombosis the urinary levels were greatly above normal, being again about 30% of those obtaining in the serum. However in infective hepatitis, although SGOT levels were high, UGOT fell to about 2.7 units per ml. Similar observations were made for UGOT in cirrhosis. It would thus seem that the ratio SGOT/UGOT may serve as a useful index for differentiating the high serum levels of myocardial infarction from those of liver cell destruction.

ALDOLASES

The glycolytic enzyme aldolase catalyses the reversible conversion of one molecule of fructose diphosphate to 2 triose phosphates. The normal serum values are: Average 0.39 units; mean 0.35 units; standard deviation 0.15 units (Thompson and Vignos, 1959).

The serum aldolase activity has its greatest value in the differential diagnosis between primary myopathy and secondary (neurogenic) muscular dystrophy (Thompson and Vignos, 1959; Evans and Baker, 1957; Soltan and Blanchaer, 1959).

In a series of Thompson and Vignos, (1959) the serum concentration of aldolase was elevated in all cases of primary myopathy. This included degenerative and inflammatory muscle disease, such as polymyositis, muscular dystrophy, and dystrophia myotonia. The highest levels were obtained in polymyositis and in juvenile muscular dystrophy. Patients with muscle weakness due to neurogenic atrophy or neuromuscular junction block had a normal serum aldolase activity.

Furthermore, serum aldolase levels in primary dystrophy have a prognostic value, by virtue of a positive correlation between the net loss of muscle mass and serum enzyme activity. The highest value is found in the earliest stages of

the disease, with a fairly regular decrease toward normal with increasing duration of clinical signs and symptoms (Soltan and Blanchaer, 1959). It appears that the increased serum aldolase activity is derived from diseased muscle (White and Hess, 1957).

Aldolase estimations also help in regulating steroid therapy in dermatomyositis, as a fall in aldolase blood level, reflecting changes in muscle, precedes a clinically demonstrable improvement in muscle strength.

Peterson (1959) comparing a group of patients with myocardial infarction and controls, concluded that a normal aldolase level excludes recent myocardial infarction with considerable certainty, while increased levels with an initial peak may serve as an adjunct to the clinical diagnosis, but should not be accepted as final evidence.

Papotti *et al* (1960) noted that aldolase was raised in 98% of patients with proven cancers. Levels tended to return to normal in those patients with a favourable post-operative prognosis.

Forster and Jenny (1959) studied 1-phosphofructaldolase, an enzyme which catalyses the conversion of fructose-1-phosphate to phosphodioxyacetone and glycerol aldehyde. Normal values were from 0.5 to 2 8 units. In liver disease values above 10 units were seen only in acute infective hepatitis.

CATALASE

This enzyme is important in relation to a rare, hereditary disease, acatalasaemia, the exact nature of which is not clear. This disease is sporadically distributed throughout Japan, and is as yet unreported elsewhere. Up to 1960, 36 cases of acatalasaemia in 17 sibships were known (Takahara *et al*, 1960). Analysis of the sibships indicates that the acatalasaemic phenotype is recessively inherited.

Clinically, about half the acatalasaemics (homozygotes) are afflicted with a peculiar type of oral gangrene in childhood (Takahara's disease). The heterozygotes (hypocatalasaemics) do not apparently have any clinical manifestations. Genetically, the hypocatalasaemic state is regarded as a carrier state for acatalasaemia.

The affected homozygotes have no serum catalase activity, whereas the activity for the heterozygotes is between that of the normal and the acatalasaemic state. The mean activity of a normal control group is 5.38 units (Kcat) while that of the heterozygotes is 2.17 units (Kcat), with no overlap in values between the two groups (Nishimura *et al*, 1959; Takahara *et al*, 1960).

Vella (1960) analysed the catalase activity of 10,226 blood samples mainly from Chinese subjects; no instance of acatalasaemia was found.

CHOLINESTERASE

The enzyme is manufactured by the liver and found in the plasma, pancreas, brain and certain other body fluids. Its actual physiological function is not clear (Wetstone *et al*, 1960). The normal cholinesterase activity is 130 to 310 units (de la Huerga *et al*, 1952).

The serum activity is known to be diminished in liver disease, but it would appear that cholinesterase determination is of little help in diagnosis, as its activity has been found to be lowered in so many other conditions, including carcinoma, certain mental diseases, severe malnutrition, severe infection, during normal pregnancy, in the newborn, and after administration of a great variety of drugs and chemical agents. The activity is raised in nephrosis, some cases of essential hypertension, etc. (Kekwick, 1960; Plum, 1960; Wetstone *et al*, 1960).

The indiscriminate use as pesticides of organic derivatives of phosphoric acid, notably 'parathion', has already had fatal repercussions in Singapore (Kanagaratnam *et al*, 1960). Such substances act by inhibiting cholinesterase, with consequential accumulation of acetylcholine. The estimation of cholinesterase, which is a relatively stable enzyme, has therefore considerable value in the detection of 'parathion' poisoning (Polson and Tattersall, 1961).

COERULOPLASMIN

Serum copper occurs in two forms: (a) A very small amount (0 to 17% of the total) is attached loosely to the albumin fraction and has no known enzymatic activity. This form reacts with the copper colorimetric agent sodium diethyldithiocarbamate — "direct reacting copper". (b) the remainder (83% to 100% of the total) is attached to the alpha$_2$ globulin and is active enzymatically on a number of substrates, but optimally on paraphenylenediamine, being a true oxidase. It does not react with sodium diethyldithiocarbamate — "indirect reacting copper" or coeruloplasmin (Gubler *et al*, 1953; Scheinberg *et al*, 1954; Vella, 1957). The physiological role of coeruloplasmin is still not clear. Changes in the serum copper levels reflect changes in the coeruloplasmin content.

Normal adult serum activity of coeruloplasmin (paraphenylenediamine oxidase) has been worked out by Vella (1957) for four ethnic groups as follows :—

European :	mean 0.320	range 0.235-0.505
Chinese :	mean 0.315	range 0.200-0.520
Indian :	mean 0.385	range 0.235-0.580
Malay :	mean 0.360	range 0.245-0.465

The serum copper is increased in acute and chronic infectious diseases, in pregnancy and other conditions, the increase being in the coeruloplasmin fraction (Gubler *et al,* 1953; Ch'en, 1957).

A low serum coeruloplasmin has more diagnostic value. Low values have been consistently obtained in Wilson's disease (hepato-lenticular degeneration), a familial disorder associated with abnormal copper metabolism. The basic defect is thought to be a failure of synthesis of coeruloplasmin at a normal rate — "primary hypocoeruloplasminaemia" (Bearn and Kunkel, 1952; Scheinberg and Gitlin, 1952; Earl *et al,* 1954; Ch'en, 1957). A decrease of serum coeruloplasmin therefore aids diagnosis, but normal findings do not rule out Wilson's disease.

The serum coeruloplasmin has also been found to be lowered in the nephrotic syndrome. There is increased urinary excretion of the enzyme, and the hypocupraemia is due, in part at least, to the urinary loss of coeruloplasmin — "secondary or renal hypocoeruloplasminaemia" (Cartwright *et al,* 1954; Ch'en, 1957).

The serum coeruloplasmin activity in the newborn is normally only a third to a fifth of the activity of adult blood. Adult levels are reached by the 2nd week of extrauterine life (Scheinberg *et al,* 1954; Vella, 1957).

Studies have been made by many workers on the serum coeruloplasmin activity in schizophrenics. Conflicting results, however, have been obtained. A high blood copper level was discovered in schizophrenics, by Bischoff (1952), and Leach *et al* (1956). Others, however, have detected no significant difference between schizophrenics and mentally sound individuals (Horwitt *et al,* 1957; Scheinberg *et al,* 1957; Aprison and Drew, 1958; Frohman *et al,* 1958). It is apparent, therefore, that the serum coeruloplasmin activity has not proved to be of value in psychiatric diagnosis.

A low serum coeruloplasmin has been observed in cases of sprue and of kwashiorkor, most probably due to malabsorption of protein, and an inability to synthesise the protein portion of coeruloplasmin. The possibility, however, of a dietary deficiency of copper in these cases exists (Butterworth, *et al,* 1958; Lahey *et al,* 1958).

GLUCOSE-6-PHOSPHATE DEHYDROGENASE

Lack of this enzyme in the red cells is known to be common in Singapore children (Smith and Vella, 1960; Weatherall, 1960), this being responsible for many of the cases of kernicterus seen in the State, as such enzyme-deficient erythrocytes are easily haemolysed. Favism is associated with the same defect (Beutler, 1959).

Giles and Ikene (1960) reported the presence of G6PD deficiency trait in Nigeria, and suggested that many of the haemoglobinuria cases among adult Nigerians, which were cursorily dismissed as blackwater fever, were probably drug induced haemolytic anaemias in patients who were carriers of this trait.

Myocardial infarction also causes a rise in serum G6PD activity for 3 to 10 days after the onset of the disease (Kerppola *et al,* 1959, 1960). The decline of serum G6PD after coronary occlusion occurs rather more slowly than that of SGOT, so that combined determination of these 2 enzymes enhances diagnostic accuracy in myocardial infarction.

In a series of 12 thyrotoxic patients investigated by Pearson and Druyen (1961), 11 had raised levels of this enzyme, 232 $\pm$ 39 units (normal 137 $\pm$ 18.9 units). Levels in two of these persons returned to normal in the course of treatment.

GLUTATHIONE REDUCTASE

West *et al* (1961) have studied the behaviour of glutathione reductase. For adults, the normal range is 11-75 units, for those under 18 years, 28-92 units. This enzyme, in the presence of a co-enzyme, triphosphopyridine nucleotide, reduces glutathione to the oxidised state. It is present in highest concentration in the liver and kidney.

GR levels are raised in so many forms of disease that it is scarcely worthwhile estimating. Nevertheless, West *et al* (1961) state that if the level is raised above 200 units, investigations to exclude leukaemia or carcinoma should be carried out.

ISOCITRIC DEHYDROGENASE

The determination of serum ICD does not seem to be of great value, as it is increased in many conditions, including acute and chronic liver damage, metastases in the liver, myelogenous leu-

kaemia, adrenal cortical hyperfunction (and after administration of adrenal cortical hormones), in patients with pulmonary tuberculosis receiving isoniazide (Sterkel *et al,* 1958; Kerppola *et al,* 1959; Bodansky *et al,* 1960), in kwashiorkor and protein malnutrition (Baron, 1960), in severe pre-eclamptic toxaemia, accidental haemorrhage and in women with previous still-births (Dawkins and Wigglesworth 1961). Okumura and Spellberg (1960) believe that the transaminases are much more useful in the differential diagnosis of liver disease than ICD.

The normal serum value of this enzyme is 2.0 to 4.1 units per ml. (Kerppola *et al.* 1959).

LACTIC DEHYDROGENASE

Lactic dehydrogenase, which has already been mentioned in connection with the diagnosis of myocardial infarction, is present in appreciable quantity in cardiac muscle, although found in other tissues in greater amounts (Wroblewski and LaDue, 1955). It is concerned primarily with the reduction of pyruvic acid to lactic acid. Rapp and Bell (1961) give normal limits as 150-350 units/ml.

Myocardial infarction, both clinical and experimental, is associated with a characteristic rise in serum LDH activity. It (together with malic dehydrogenase) appears to be a more sensitive indicator of myonecrosis than is SGOT (Rodney *et al,* 1959). In suspected myocardial infarctions which give bordering values for SGOT, determination of serum LDH activity may permit enzyme detection of muscle damage which is otherwise unobtainable.

Blanchaer *et al* (1958) showed that serum LDH was increased above normal in acute and chronic myelocytic leukaemia, and in acute lymphocytic, but not in chronic lymphocytic leukaemia. It also reflected changes in the course of the disease, falling during remission and rising during relapses.

It has recently been noted that in gastric cancer, LDH levels in the gastric juice are significantly higher than in pernicious anaemia or in benign gastric ulcer (Schenker, 1959). Raised levels have been noted in extensive carcinomatosis, in megaloblastic anaemia, in sickle cell anaemia (Rapp and Bell, 1961), muscle trauma, acute hepatitis, diabetic ketosis, and rheumatoid arthritis (McDonald *et al,* 1957).

Erickson (1961) has shown that effusion fluids due to causes other than cancer, notably those of heart failure and cirrhosis provided these were not purulent,, exhibit significantly lower LDH levels (p 0.01) than those effusions associated with malignancy.

LECITHINASE A

Zieve and Vogel (1961) have studied Lecithinase A in serum and other body fluids. This enzyme, secreted by the pancreas, splits a fatty acid off the phospholipid lecithin, forming lysolecithin, the fatty acid group being replaced by a hydroxyl group. The estimation of the enzyme in serum is technically easy, but requires a period of incubation of 18 hours. Normal values are 0-20 units/ml. Tenfold rises are common in acute pancreatitis, and in a series of patients with this disease none had normal values. The long incubation period necessary would appear to reduce the usefulness of this test as an adjuvant to diagnosis.

LEUCINE AMINO-PEPTIDASE

The source of this enzyme is unknown; histochemically, there is a high concentration in the bile passages; less in the liver cells. Its serum activity is usually estimated by the hydrolysis of l-leucine beta-naphthylamine. Normal values are up to 200 units for males, and up to 184 units for females.

Great hopes were held out for its enzyme in the diagnosis of carcinoma of the pancreas, but subsequent work has shown that values may be raised in other conditions, while normal levels have been obtained in cases of pancreatic carcinoma (Floch and Grossier, 1960; Harkness *et al,* 1960; Hoffman *et al,* 1960).

However, it has been shown that elevated levels are almost invariably associated with diseases of the liver, biliary tract or pancreas, and are seldom found apart from these conditions, excepting the third trimester of pregnancy (Arst *et al,* 1959, Banks *et al,* 1960). In the individual case, the test will not distinguish the various conditions in these organs, but, nevertheless, determination of serum LAP may be of value in the differential diagnosis of hepato-biliary-pancreatic diseases from other intra-abdominal conditions. The highest levels, however, were found in patients in the last trimester of pregnancy and particularly at the time of delivery (up to 500 units).

Golisch (1960) examined the urine of a selection of patients for LAP activity. 42% of those with a cancer had raised levels, while in other diseases no such increase was found.

ORNITHINE CARBAMYL TRANSFERASE

This enzyme has been extensively investigated by Reichard (1961). An upper limit of normal has been set at 0.050 uM $C^{14}O_2$ per 0.5 ml. serum. The enzyme, usually abbreviated to SOCT, is to be found in maximum concentration in the liver and the wall of the small intestine, and if disease of the small gut can be excluded, raised levels point to liver cell damage.

Infectious hepatitis, cirrhosis, obstructive jaundice, biliary attacks, congestive cardiac failure, rapid arrhythmia, shock, and delirium tremens have all been associated with raised SOCT levels. Reichard (1961) found that in a series of 181 patients with liver disease, nearly all patients with infective hepatitis, most patients with cirrhosis, most patients with obstructive jaundice, most patients with biliary attacks, and two-thirds of those with primary liver cancers, had raised SOCT levels.

PHOSPHOHEXOSE ISOMERASE

This enzyme mediates the reversible conversion of glucose-6-phosphate to fructose-6-phosphate. The normal serum levels are: mean 17.6 units, standard deviation ± 4.3 (Blanchaer *et al*, 1958).

A significant correlation was found to exist between the PHI and alkaline phosphatase activities in the sera of patients with liver disease or secondaries of the skeleton (Bodansky, 1953). Individuals with liver disease or skeletal metastases also tended to have high serum PHI activity.

Blanchaer *et al* (1958) in studying a series of leukaemic patients and controls, showed that the serum PHI activity is of assistance in the differential diagnosis between myelocytic and lymphocytic leukaemia, the enzyme activity being abnormally elevated in myelocytic leukaemia (both acute and chronic), but not in lymphocytic leukaemia. Furthermore, the serum enzyme activity reflects changes in the course of the disease, being diminished during remission and increased during relapses. The PHI activity found in patients with myeloid leukaemia probably originates from disintegrating granulocytes (Israels *et al*, 1958).

DISCUSSION

There can be little doubt that the value of several of these enzymatic aids to diagnosis, notably the transaminases, is now firmly established. While it is probable that more enzymes remain to be discovered and investigated, it can be anticipated that the vast majority of these, like many under current assessments, will prove to have little place in diagnosis. Most will fail to meet the criteria required by the clinical pathologist, in that they will prove to be very widely and fairly evenly distributed in a large variety of organs, and lack disease specificity. Yet others, apparently useful, may demand an elaborate technique for estimation, or may require too long a period in contact with substrate to permit of rapid determination, and hence lose the interest of the clinician. Nevertheless, it is fair to say that, despite a lack of specificity, if intelligently used, that is, to assist in the confirmation of a diagnosis made clinically, then many tests will be of considerable help. To ask for a battery of non-specific tests, and to expect to conjure forth a diagnosis from the results, betokens ignorance.

As with drugs, it is better to know a few enzymes well, than many badly. From the preceding we feel that it is evident that for acute chest pain, SGOT is the test of choice, keeping in mind the usefulness of LDH for the patient who had a chest pain several days before seeking medical care.

For the jaundiced, the estimation of both transaminases would seem reasonable, and if obstruction is suspected the estimation of LAP could be considered. In Singapore, G6PD is a must.

Lecithinase A may be of use in suspected acute pancreatitis, if the surgeon can wait.

The value of serial estimation cannot be overemphasised, as Kove (1960b) has repeatedly stressed. While other enzymes such as aldolase, PHI, caeruloplasmin and catalase are of great diagnostic value, it is felt that they will be required but rarely.

If the results of these tests are to be interpreted properly then it is imperative that there be no trace of haemolysis in the blood submitted, as red cells often contain much more of a particular enzyme than the serum. Once separated, the serum can be kept in temperate climes, at room temperature for up to a week, and frozen for up to 14 days, without apparent loss of enzyme activity.

Techniques for estimation have not always been as rigid as they might, and recently several reviews, notably that of Henry *et al* (1960), have appeared on this subject. The commonest pitfall seems to be lack of temperature control, e.g. in the original Karmen procedure for SGO-T, a difference of one degree centigrade entails a difference of 7% in the final reading. For several techniques the final readings should be done on narrow band spectrophotometers, and it is possible that this may account for differences in published figures of normal values.

The normal values for the enzymes in common diagnostic use do not seem to show any racial variation when American, Chinese, European and Indian populations are compared (Bharucha *et al*, 1961, Sun and Yang, 1959; Vanikar *et al*, 1959). However, the racial distribution of deficiencies in enzyme systems is of great interest, and if more examples are discovered, may prove to be of considerable importance to the geneticist as well as to the clinician.

SUMMARY

The general principles underlying the use of enzymes as diagnostic aids are enunciated.

The role of the transaminases in the differential diagnosis of myocardial infarction and liver disorders is discussed at some length.

The information to be derived from the estimation of aldolase, catalase, cholinesterase, coeruloplasmin, glucose-6-phosphate dehydrogenase, glutathione reductase, isocitric dehydrogenase, lactic acid dehydrogenase, lecithinase A, leucine amino-peptidase, ornithine carbamyl transferase, and phosphohexose isomerase, is examined.

The importance of serial estimations of enzyme levels is stressed.

The need for unhaemolysed blood, and for rigid control of technique, is reiterated.

It is concluded that although many of the enzymes mentioned above are of diagnostic importance in certain, usually uncommon, diseases, the transaminases seem to be of the greatest value.

ACKNOWLEDGEMENTS

We wish to thank Professor K. Shanmugaratnam for kind help and encouragement, Dr. P. C. Leong for much useful advice, and Miss June Tham and Mr. P. A. Samuel who typed the script.

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