THE PLACE OF TRANSAMINASE IN THE DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION.

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An attempt has been made to assess the worth of serum glutamic oxaloacetic acid transaminase estimations in cases of acute myocardial infarction. The main points considered were accuracy of diagnosis, speed of diagnosis, relationship to ultimate prognosis, economy, and technical and administrative problems.

In general practice, speed of diagnosis is essential if decisions regarding whether to transfer the patient to hospital or not are to be reached at a stage early enough for anticoagulant therapy to be used with some hope of effect. I hope to show that serum glutamic oxaloacetic acid (SGOT) estimations can give quick, accurate diagnostic aid, offer guidance as to prognosis, and can be performed easily, cheaply and in some cases can obviate the need for domiciliary electrocardiography.

Transamination is a normal biological oxidative process involved in the utilization of ingested protein. The process is reversible and can be the means of synthesis of further amino-acids The process concerns the transfer of amino-nitrogen of an amino-acid to a ketonic acid. This transamination requires the presence of a specific amino-donor (e.g. glutamic or aspartic acid) or a specific amino-acceptor (e.g. *a*-ketoglutaric or oxaloacetic acid) depending upon the direction of the reaction.

1. Glutamic acid + oxaloacetic acid $\underset{\longrightarrow}{\overset{\longleftarrow}{\text{G.O.T.}}}$ *a*—ketoglutaric acid + aspartic acid.
2. Glutamic acid + pyruvic acid $\underset{\longrightarrow}{\overset{\longleftarrow}{\text{G.P.T.}}}$ *a*—ketoglutaric acid + alanine.

These transaminases; glutamic oxaloacetic (G.O.T.) and glutamic pyruvic (G.P.T.), are detectable in virtually all tissues of the human body (La Due, Wroblewski and Karmen, 1955) and are present in

particularly high concentration in cardiac and skeletal muscle, (Cohen and Hekius, 1941) and to a lesser extent in brain, liver, and renal tissue (La Due *et al.* 1954). Transaminases are thought to be associated with the secretory granules of cells (*Spectrum*, 1958) and are almost entirely intracellular in situation. Cell necrosis leads to liberation of the transaminases into the blood stream (Nydick *et al.* 1955), either as the cell breaks down or secondarily to increased permeability of the cell membranes. Agress *et al.* (1955) have shown that an infarct involving as little as 10 per cent of a dog's myocardium will result in a significant rise in serum transaminase level. This raised transaminase level is transient and later reverts to normal over a period of 4 to 7 days. Normal transaminase levels in humans are given as:

Serum G.O.T.	8–40 units/ml.
Serum G.P.T.	1–30 units/ml. (La Due, Wroblewski, 1955)

Before commencing the present study, a series of anticipated normal sera were tested and gave a range of readings as below:

Males (40 cases)	4-47 SGOT units/ml. (Average of 21 units/ml.)
Females (24 cases)	6-38 SGOT units/ml. (Average of 18 units/ml.)

The sera tested were taken from patients suffering from minor illnesses in which no muscle, brain, liver or renal tissue necrosis occurred.

Chinski *et al.* (1956) and Walters and Littlejohn (1958) have produced evidence that myocardial ischaemia causing angina can give rise to a transient elevation in the individual's " base-line " serum transaminase level but not to a level above that accepted as the upper limit of the normal range. Both before and during the present study sera have been collected from numerous patients during and just after attacks of angina and in all cases the serum G.O.T. levels obtained have been in accord with the above evidence.

Method

Throughout this study the local hospital laboratory used the method of estimation as outlined by Reitman and Frankel (1957). Briefly, the method is a means of estimating colorimetrically the amount of oxaloacetate or pyruvate formed in one hour, as a highly coloured " hydrazone ".

This method is apparently based on empirical comparison with the spectrophotometric method described by Karmen, Wroblewski and La Due (1955). During the course of the study the method was found to have several disadvantages. The cost of the reagents amounted to approximately £6 per 100ml. of reagents and standards, the coloured " hydrazone " formed was found to be liable to fade and, also, the term " unit " is obviously empirically based on repeated comparative analyses spectrophotometrically.

These disadvantages can be overcome if the method described by King (1958)

is used. A similar quantity of reagents, using King's method, costs about 5/-. However, to maintain uniformity throughout this series, the method of Reitman and Frankel was used until this work was finished.

Theoretical indications for transaminase estimations

Although most cases of myocardial infarction can be confidently diagnosed on clinical grounds alone, there is a smaller group in which the initial diagnosis remains in doubt. Such cases of doubt could receive anticoagulant therapy at a useful stage if the diagnosis was confirmed within the first 48 hrs. (assuming that no other contraindication to anticoagulation exists in any one case). Similarly, differentiation between prolonged anginal pain and actual infarction can be impossible, on occasions, on clinical grounds alone. An electrocardiograph in such cases may not be definitive initially, or the tracing may be confused as regards its significance, due to changes of left bundle branch block or previous infarction. A test to resolve such diagnostic doubts at an early stage could result in more precise therapy and more accurate prognostication.

It will be shown from the results of this study that, with awareness of certain limiting factors and used in conjunction with full clinical data, transaminase estimations can be of considerable help in diagnosis and possibly also in assessing prognosis.

Cases of myocardial infarction can be broadly divided into two main groups:

1. Cases of frank infarction.
2. Cases in which there is initial doubt as to the presence of infarction.

Let us consider each group in turn:

Cases of frank infarction.

Virtually all such cases are seen, in the first instance by the general practitioner. Clinical assessment leads to the first decision as to whether the patient should be immediately transferred to hospital or treated at home.

(*a*) Those transferred to hospital:

The decision to transfer the patient to hospital may be made on medical or social grounds and many would agree that hypotension of greater severity than 90/70, severe clinical " shock ", cardiac arrythmias and congestive heart failure are all strong indications for taking such a course. Probably the home doctor will have given an injection of morphia and possibly also of digitalis before transfer (Oliver, 1959). Arrival at hospital is followed by clinical appraisal and early electrocardiography. This last may be con-

firmatory of infarction or it may fail to reveal the typical changes, due to prior infarction, left bundle branch block or, it may simply fail to show changes for several days. Thus even if confirmatory later, the electrocardiograph in some cases will be of no immediate guide as to the presence and size of any infarcted myocardium. Here then is an occasion when transaminase estimations could prove to be of assistance. Transaminase levels rise during the period of 1 to 7 days after infarction so that evidence of such a rise could be confirmatory. Figures are given later showing this.

(*b*) Those treated at home:

This group falls naturally into two sub-divisions:

1. A larger group of so-called "good risk" cases (Honey and Truelove, 1957) i.e. patients in whom clinical evidence of infarction is definite but in whom there is every sign that the infarct is small or unassociated with wide-spread myocardial damage or complications secondary to infarction. Such cases can be treated and nursed at home, when the conditions are suitable (Russek and Zohmann, 1957). The home doctor has then two courses open to him; he can call on consultant help to advise on progress and ultimate prognosis or he can conduct the campaign himself. Whichever course he adopts, and even if electrocardiographic tracings are obtained, prognosis is fraught with difficulties when based on clinical and electrocardiographic evidence only. A home doctor however can take daily blood specimens for 5 to 7 days and, through the local laboratory services, obtain serum transaminase levels and so acquire more tangible evidence on which to base his advice as regards his patient's prospects and future mode of life.

2. A smaller group of patients who are so gravely ill as to be unable to withstand the journey to hospital. Here, too, transaminase estimations can add useful knowledge on which to base decisions regarding therapy, progress and prognosis.

Cases in which the diagnosis of infarction is in doubt.

Once more it is the home doctor who must decide on the immediate course of action to be taken in a case of *possible* myocardial infarction.

It may be reasonable in some cases to treat on the assumption initially that infarction has in fact occurred. In such cases, serial transaminase estimations may well reveal a confirmatory transient rise in serum levels.

In other cases the doctor may feel reasonably confident that

infarction has not occurred but desire confirmation before allowing resumption of full activities by his patient. Here again, an absence of any rise in serial transaminase readings would help. Such estimations could be carried out by the local hospital laboratory either from daily samples of blood sent by the home doctor or direct from the patient on an outpatient basis. In either case, the diagnosis would be obtained more quickly and be more informative than that of a diagnosis reached retrospectively, following the wait usually involved in sending a patient by appointment to the local hospital physician as an outpatient " for investigation ". On the other hand, a domiciliary visit by the physician could be arranged but, if true clinical doubt exists as to the diagnosis, then even electrocardiography and a consultant's help may not resolve it.

Thus serial transaminase estimations could, in cases of diagnostic doubt, confirm or exclude the presence of myocardial infarction. Also, in cases in which electrocardiographic changes are found and these changes are of dubious age, transaminase estimations could reveal whether such changes were recent or old, a point very relevant to the problems of immediate management of the patient.

The above merely outlines how transminase levels could be of theoretical aid. Evidence is given later to show that such help is in fact obtained in practice but, as with most investigations, the results must be viewed only in conjunction with all other clinical data and the clinician must be aware of a few pitfalls which can cause variability in transaminase values.

Results

A total of 142 cases is available for study. Two major points have been borne in mind:

1. Due to the author's employment at the time of the study, the series includes hospital inpatients only.

2. The criterion for inclusion in the series was that one or more of the following three points must be fulfilled:

(*a*) ECG diagnostic of infarction.
(*b*) A typical history, clinical picture and subsequent progress of infarction.
(*c*) Autopsy proof of infarction.

Of the 142 cases, 114 were *recent* myocardial infarction, i.e. where infarction (episode of pain or collapse) occurred within the seven days prior to the establishment of the diagnosis as judged by the above three criteria. The interval has been taken as 7 days simply because both experimental and clinical experience show that SGOT

levels return to normal limits 4 to 7 days after the moment of infarction.

The remaining 28 cases will be discussed later as examples of old myocardial infarction, angina rather than recent infarction and from the point of view of transaminase estimations' value in the assessment of such cases and as an aid to differential diagnosis.

It is felt that although only hospital cases are included in the present study, this in no way prevents valid conclusions being reached as regards the worth of the estimations, particularly as to when transaminase estimations are likely to help and how best to interpret the results. Certainly there are no local standards as to which cases of myocardial infarction are referred to hospital by practitioners and the cases to be discussed enable all the types mentioned in the theoretical section to be examined from the point of view of transaminase estimations' indications and worth.

Cases of recent myocardial infarction. (114 cases)

Males 76. Females 38.
Average age of males—47 years.
Average age of females—66 years.

Of the total of 114 cases 96 (84 per cent) revealed transaminase levels of over 40 units/ml. at some stage of their illness.

In 84 cases (72 per cent) a diagnostic electrocardiograph was obtained at some stage. This apparent low percentage is due to local circumstances, electrocardiography not being possible every day.

More usual figures quoted for electrocardiographic accuracy of diagnosis are those of Plotz (1957) who gives an accuracy rate of over 95 per cent if more than 12 leads are used and 75 per cent if fewer than 12 leads are used. A 12-lead tracing was by no means always feasible during the time of the study and more commonly a 10-lead tracing was obtained. Thus even accepting Plotz's figures, 75 per cent accuracy is all that could be anticipated. The results are viewed with full awareness of the electrocardiographic limitations.

There were 40 cases with initially normal or doubtful and non-diagnostic tracings (35 per cent of the 114 cases). Of these 40 cases, 39 (95 per cent) revealed diagnostically raised transaminase levels. Only one had both non-confirmatory transaminase levels and doubtful initial electrocardiography.

The time of the peak rise in the transaminase levels was assessed from those results in which there were two or more transaminase readings (88 cases; males 65, females 23). The moment of infarc-

tion was taken as the time of onset of pain or time of collapse, whichever occurred first. Both male and female patients revealed an identical time of peak rise at 2 days after infarction. This agrees well with the evidence given by Baron *et al.* (1958) which showed that transaminase levels were always raised at some stage in the interval 12 to 48 hrs. after infarction. It was impossible to carry out estimations of transaminase levels more frequently than once daily during this study so that the true peak levels may have been missed. Actually, the routine of a busy, understaffed, peripheral hospital prevented even daily estimations being taken in some cases. The figures obtained however do confirm that a rise in transaminase level of diagnostic worth does occur in the 48 hrs. following infarction.

Of those cases with raised serial serum transaminase levels (two or more SGOT levels) the peak value was related to the immediate outcome of the illness. "Immediate outcome" refers to the state of the patient at a stage at least 1 month after the moment of infarction.

TABLE I
RECOVERIES

	Total cases	*Peak* SGOT (*average value*)
Male	51	133 units/ml.
Female	19	106.5 units/ml.
Both sexes	70	126 units/ml.
	DEATHS	
Male	14	287 units/ml.
Female	9	128 units/ml.
Both sexes	23	225 units/ml.

(One male transferred to another hospital is not included in these figures)

TABLE II
THE OVERALL CHANGES OF SGOT READINGS

Males	Recoveries (53 cases)	128 units/ml.
	Deaths (22 cases)	287 units/ml.
Females	Recoveries (23 cases)	103 units/ml.
	Deaths (15 cases)	122 units/ml.
Both sexes	Recoveries (76 cases)	120 units/ml.
	Deaths (37 cases)	220 units/ml.

The figures in table I reveal average peak SGOT levels in both recoveries and deaths in females which are lower than the corresponding figures in males.

Recoveries: Males/females: 133/106.5 units/ml.
Deaths: Males/females: 287/128 units/ml.

If all 113 (excluding case mentioned under table I) cases are included in computing average figures, the overall averages are as in table II.

The following statistical conclusions can be drawn from the above tables.

1. Overall peak SGOT values in male deaths compared with male recoveries (287:128) *is just significant.* (Using $\sqrt{\frac{\delta}{n_r} + \frac{\delta}{n_d}}$ and accepting a factor of 2.)

2. Comparison of average SGOT peak values in cases with serial readings (two or more) in male deaths and male recoveries (287:133) *is significant.*

3. Overall average peak SGOT values in female deaths compared with female recoveries (122:103) *is not significant.*

4. Average SGOT peak values in cases with serial readings in female deaths compared with female recoveries (128:106.5) *is not significant.*

5. Overall average peak SGOT value in recoveries compared with that in deaths (120:220) *is almost significant.*

A total of 16 cases occurred in which the SGOT level was at no time diagnostically raised above normal. On detailed examination of the case records concerned 13 of the 16 cases reveal that the misleading SGOT levels can be explained by the fact that the estimations were carried out an inadequate number of times or at the wrong times if a rise in SGOT level was to be detected, or other serious pathology caused death before SGOT levels could have been expected to rise after infarction. In all therefore there were three cases in which false (and apparently inexplicable) SGOT values were obtained i.e. 2.5 per cent of the 114 cases.

Dewar *et al.* (1958) reported a rise in SGOT values due to liver congestion *per se.* It was therefore felt worthwhile to relate SGOT levels obtained in this study to the presence of congestive heart failure and to assess these readings in the light of the " immediate outcome " of the illness.

Cases with congestive heart failure

Average peak SGOT level in recoveries	110.4 units/ml.
Average peak SGOT level in deaths	168 units/ml.
Average peak SGOT level in both	137 units/ml.

Cases without congestive heart failure

Average peak SGOT in recoveries	127 units/ml.
Average peak SGOT in deaths	297 units/ml.
Average peak SGOT in both	166 units/ml.

In both recoveries and deaths, cases with congestive heart failure show a lower average SGOT level than do cases without congestive heart failure. In other words, in cases with congestive heart failure, the absolute value of the serum transaminase must be viewed in the light of the heart failure present and the significance of the level assessed with more than usual gravity. The implication is that in cases associated with congestive heart failure an infarct of relatively small size may, as would be expected, prove fatal though the infarct may be of a size such that the SGOT level shows no great rise. Also, congestive heart failure is associated with a state of hypervolaemia presumably leading to a dilution effect on serum transaminase levels as well as on the serum sodium levels. This dilution effect may account, in part at least, for the lower average SGOT levels found in cases of infarction associated with congestive heart failure.

There remains 28 cases in which evidence of recent myocardial infarction is lacking; 22 with evidence of old infarction; four suffering from anginal attacks but no actual infarction; and two with other diagnoses.

All the 22 cases of old infarction revealed SGOT levels in accord with a diagnosis of " no recent infarct ". The four cases of angina revealed SGOT levels in accord with the clinical and ECG pictures in every case. The final two cases were of speculative interest. One was a case of known systemic lupus erythematosus in whom an attack of chest pain raised the possibility of infarction. Serial ECG tracings were normal but the SGOT level was raised for over 10 days. Whether this was evidence of infarction missed on ECG or evidence merely of a disturbance in the behaviour of the collagen tissues is not known. The other case was one in which electrocardiography showed the presence of atrial fibrillation and digitalis effect before an episode of cerebral infarction. The SGOT level following this was raised but gross heart failure was present and also brain destruction so that the presence or absence or myocardial infarction could not be proved (permission for autopsy was not obtained).

Discussion

The results reveal an overall diagnostic accuracy of 84 per cent in cases of recent infarction, as gauged by SGOT readings. There were only three cases in which misleading readings were obtained and which could not be explained by faulty timing or the presence of other serious pathology. It seems valid to anticipate an accuracy of diagnosis in the region of 85–90 per cent if care is taken to

estimate the serum transaminase level during the two-day period following infarction.

The peak rise in SGOT level occurs 48 hrs after infarction so that this reading would be the one expected to give most useful information.

The overall accuracy of diagnosis as judged by electrocardiography was only 72 per cent under the prevailing circumstances. This estimate is inclusive of those tracings which were initially non-confirmatory but subsequently gave positive evidence of recent infarction. Thus the figure 72 per cent is optimistic as regards *early* finite diagnosis. It can therefore be said that SGOT estimations offer at least as accurate and possibly faster confirmation of the diagnosis as compared with electrocardiography. Even comparison between the poorest SGOT accuracy rate (84 per cent) and the best electrocardiographic accuracy rate (75–95 per cent) does not alter the fact that in 39 cases, SGOT estimations revealed the true diagnosis missed on initial electrocardiography.

The results suggest that the SGOT level on the second day of the illness may prove to be a guide to the severity of the infarct and the ultimate prognosis. However, the estimation must be carried out at the opportune time and the result taken in conjunction with all other clinical evidence.

The presence of congestive heart failure apparently results in levels of serum transaminase which would, in its absence, be assessed less gravely and obviously any individual SGOT level assessment must take into account the factor of heart failure. Similarly, multiple pathological processes, as might be expected, add to the significance to be attached to SGOT levels.

A possible accuracy rate of diagnosis of 85–90 per cent should be achieved using SGOT estimations at the optimum time.

Cost is no great problem since the modified method described by King allows 100 estimations for an outlay of about 5/- and also allows the calibration of results in a more scientific way. The test must be used discriminately and critically. The following outline for use and interpretation of the test is suggested.

Hospital cases of definite infarction.

A transaminase estimation on the second day of the illness would give some guidance as to size and prognosis of the infarct, though if would probably not lead to alteration in therapy.

"Poor Risk" hospital cases. A second-day test would aid in the assessment of prognosis.

Domiciliary cases of definite infarction.

"Poor Risk" at home. A second-day test would aid in assessing prognosis. Either a second-day or daily specimens could be sent to the local hospital laboratory by the general practitioner.

"Good Risk" cases at home. A second-day estimation may confirm diagnosis, aid in gauging severity and outlook. The family doctor will be visiting the patient in any case so that even daily specimen collection for a few days should be possible.

Other cases, in which initial diagnosis in doubt.

If infarction assumed: may be in hospital or treated at home. SGOT readings on the second day may confirm or exclude infarction and aid prognosis assessment. Daily estimations for 4–5 days are more accurate and informative.

If infarction confidently felt NOT to have occurred. Serial SGOT values over 5 days, if normal will exclude infarction. If the SGOT levels are found to be raised then the home doctor's diagnosis will have to be reviewed and attempts made to exclude other causes for these levels while assuming infarction had occurred until, or unless, some other adequate cause was detected.

Overall then, in cases of frank infarction, estimation of the serum transaminase on the second day is indicated and, in cases of doubtful infarction, daily estimations for the first 4–5 days of the illness may detect any transient diagnostic rise. If no rise occurred on the second day, an electrocardiograph may be indicated.

The advantages may be summarized:

1. High accuracy of diagnosis
2. Increased speed of diagnosis, especially in domiciliary work
3. Obviate the need for many ECG tracings
4. Avoid the need in some cases for domiciliary consultations
5. Allow a fuller clinical picture to be obtained of any one case
6. May prove of firm value as an aid to assessing prognosis, at an early stage
7. Aid in decisions regarding appropriate therapy.

The disadvantages are:

1. Administrative problems due to the resulting increased work sent to local laboratories
2. Inconvenience, in certain cases, to the home doctor
3. The estimations must be carried out at appropriate times and their results viewed critically if the test is to be useful to the clinician.

Overall there seems to be no question that wider use of SGOT estima-

tions is worth while as an aid to firm, early diagnosis and as a means of obtaining this knowledge more speedily and economically.

The author has found nothing in 3 years general practice to invalidate the conclusions of this study. SGOT estimations are cheaper, quicker and equally as accurate in diagnosis as ECGs.

Summary

Serum transaminase estimations were carried out in 114 cases of recent infarction and 28 cases of old infarction and angina. There would appear to be considerable value to be obtained from the use of this estimation as regards speed and accuracy of diagnosis. The cost of the test is reasonable and a scheme is outlined whereby the test could be used to obtain maximum information without putting too much strain on the local laboratory.

Two major points stand out:

1. Timing of transaminase estimations to cover the second day of the illness is vital in order to obtain a relevant peak-level of SGOT.
2. All SGOT levels must be viewed only in conjunction with all other clinical data before any significance is attached to any one SGOT reading.

The accuracy rate of diagnosis could be 85 to 90 per cent by using this test and there appear to be about 2.6 per cent of cases in which misleading results are obtained. 39 cases in the series revealed confirmatory SGOT levels although initial electrocardiography was not helpful. One case occurred in which both initial ECG and SGOT levels were non-confirmatory of infarction.

There is some evidence that the outcome of the illness at one month can be related to the peak SGOT level. The results are statistically significant in the case of male patients but not so in the case of female patients. Certainly a peak SGOT level of 287 units/ml. is of grave omen in male patients and a lower level is of similar gravity if heart failure complicates the illness.

Advantages and disadvantages of SGOT estimations have been considered and on balance there is felt to be strong evidence in favour of utilization of the test for speedy and accurate diagnosis.

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