SERUM LACTIC DEHYDROGENASE ESTIMATIONS IN MYOCARDIAL INFARCTION

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The clinical features presented by coronary occlusion with myocardial infarction are such that, together with electrocardiographic evidence, a correct diagnosis is usually possible (Price, 1950). Electrocardiographic changes, however, may sometimes be delayed, and in about 6 per cent of cases no change is detectable at all (Lancet, 1958). To assist in diagnosing these cases, enzyme tests have been introduced, the estimation receiving most publicity in recent years being the determination of serum glutamic oxalacetic-transaminase (S.G.O–T.). The rise in level of S.G.O–T. found following myocardial infarction, is generally accepted as being due to the liberation of the enzyme from necrosed myocardial cells into the blood stream and it seems also to be generally agreed that the level will rise in proportion to the amount of tissue involved (Chinsky et al., 1956; Bruce et al., 1958; Dewar et al., 1958; Keele et al., 1958). From a diagnostic point of view, the estimation suffers from the drawback that the rise in serum level attains a peak 24 hours after the onset and returns to normal in a further four days. It is obvious that small infarctions may be difficult to diagnose on this evidence, since the rise may be slight, and added to this is the necessity of obtaining a blood sample when enzyme activity is near to its peak. To obviate this difficulty serial estimations at frequent intervals have been suggested (Bruce et al., 1958).

Other enzymes besides G.O–T., however, are liberated from the damaged heart cells, the ones that have been most extensively studied being: serum lactic dehydrogenase, serum aldolase, serum hexose isomerase and serum oxidase (Rowell and Smith, 1959; White, 1956; King and Waind, 1960).

The popularity of S.G.O–T. estimations is no doubt partly due to this being the first enzyme test of this nature requiring only simple equipment which may be available in the smaller biochemical laboratories. The original method of estimation involved the use of an expensive ultraviolet-spectrophotometer (as did indeed the estimation of the other enzymes listed above) but special outfits provided by the Sigma Co. of U.S.A., and other similar firms have now made available simple and rapid methods for estimation of both S.G.O–T., and serum lactic dehydrogenase (S.L.D.).

SERUM LACTIC DEHYDROGENASE

Serum lactic dehydrogenase activity in myocardial infarction has been widely studied in the United States (White, 1956; Wacker et al., 1956; MacDonald et al., 1957; Wroblewski, 1957), and in England (King and Waind, 1960). All these authors have concluded that of all the enzymes liberated into the blood stream by necrosed heart cells following myocardial infarction, S.L.D. is raised, comparatively, to a higher level and remains raised for a much longer period than any other. It would therefore seem that this is the best enzyme estimation to undertake for diagnostic purposes.
particularly as the method of estimation is one of those that has been sufficiently simplified to allow of its being undertaken in all laboratories. It has, however, suffered two major criticisms that appear to have held back its application in this respect: first, S.L.D. is raised in several other conditions, and second, the conclusion that, because G.O.T. is present in higher concentrations in heart muscle than in other tissues, this is therefore the best enzyme test to adopt (Baron et al., 1960).

Having used S.G.O-T estimations as a diagnostic aid in myocardial infarction for many months with rather disappointing results, we decided to perform a comparative series of tests, using this and S.L.D. Before proceeding to discuss these tests and their findings, it is advisable to consider the enzyme lactic dehydrogenase in a little more detail, since a knowledge of its role and position in the catabolic pathways is most useful when assessing raised S.L.D. levels that may be due to conditions other than myocardial infarction.

Lactic dehydrogenase is an enzyme that catalyses the conversion of pyruvate to lactate (and vice versa), as shown diagrammatically in Fig. 1. The action is reversible, and besides the enzyme lactic dehydrogenase, the presence of a hydrogen carrier is required. This is provided in the form of di-phosphopyridine nucleotide (D.P.N. or co.—enzyme I), (Bell et al., 1959; Fruton and Simmonds, 1953). When assessing the significance of raised S.L.D. values a knowledge of its position in the breakdown of glucose is most useful. Normally, glucose breaks down as far as pyruvate by a long series of changes catalysed by enzyme actions, with which we are not concerned in this investigation. After the pyruvate stage is reached further breakdown of the pyruvate follows one of two pathways, depending upon the amount of oxygen available. This may be simply illustrated by Fig. 2. Normally the oxidative pathway (A) is followed, with oxygen readily available and then further breakdown of the glucose residue occurs via the Kreb’s cycle with the liberation of considerable energy. When oxygen is not so readily available (as occurs during athletic endeavour) the pathway followed is that shown on the anaerobic side (B) and lactic dehydrogenase is instrumental in converting pyruvic acid into lactic acid, which collects in the blood. As will be remembered from early physiological studies, this represents an “oxygen debt” which is repaid later, when sufficient oxygen is available. The reverse action occurs and lactic acid is converted back to pyruvic acid. It now seems fairly well established that while normal cells follow the aerobic pathway (A) malignant cells follow very largely the anaerobic pathway (B), and it is therefore not surprising to find that raised S.L.D. levels are a fairly common finding in the various types of malignancy. Wroblewski (1957) has shown that raised lactic dehydrogenase activity occurs in fluids that bathe malignant cells. Considerations of this nature must be borne in mind when assessing the significance of the raised levels.

In myocardial infarction, increases of S.L.D. activity are due to liberation of the enzyme from the damaged heart cells. For this reason, the increase is sudden, and attains a maximum peak at
about 24 hours, reverting to normal in a relatively short time, usually 10–20 days. In the case of malignancy the rise in S.L.D. activity is due rather to increased enzyme activity of the nature already described, so that it maintains a more constant level, and is not usually so greatly elevated as in myocardial infarction.

**METHODS AND RESULTS**

Bearing these facts in mind, we performed a series of comparative tests using S.G.O–T. and S.L.D. in cases of proven and suspected myocardial infarction. Both tests were performed with the reagents supplied by the Sigma Co. of the U.S.A., and although we were rather limited in the early stages by a short supply of S.L.D. reagents, we aimed to collect and examine by both tests blood samples taken at least every day in the early stages, and every two days in the later stages. Later we were able to modify this in many cases, to doing the estimations at 3-day intervals, when we found ourselves becoming more familiar with the expected pattern of results. From all the cases examined, we were able to select twenty in which the diagnosis of myocardial infarction was not in doubt, clinical findings being confirmed by electrocardiographic evidence and occasionally by post-mortem findings. It very soon became apparent that the findings of the various American workers would be confirmed, although for our series of investigations we were using Sigma reagents and not ultra-violet spectrophotometric methods.

A typical finding, taken from one of the twenty cases of proven myocardial infarction, is shown in Fig. 3. It will be seen that the S.L.D. returned to normal after 13½ days while the S.G.O–T.
Figs. 4 and 5 show the collective results of the tests made on the 20 cases, for the activity of both enzymes. In Fig. 5 the S.L.D. values are aggregated above the normal level for a period of up to 13 days from onset, with three exceptions. Two of these exceptions were in cases in which the rise appeared to be rather delayed, so that it was about 24 hours from the onset before a rise in S.L.D. activity was demonstrated. However, these two cases showed a very high level later, both of them rising to over 2000 units per ml. The other exception was a case that returned to normal after 9 days. The table showing S.G.O-T. findings (Fig. 4) is most interesting in view of the different figure suggested for the upper limit of normal. If one takes the suggested level of Sigma, of 40 units per ml., only 23 of the 100 tests are above this level. The suggested top normal value of 28 units per ml. certainly makes the test more sensitive, as another 18 results then appear above the normal level. It will be noted also that as the results become normal again the values from ten days after onset all lie within the upper limit of 28 Sigma Frankel units per ml.

A comparison between the two tables suggests that S.L.D. may be superior to S.G.O-T. as a test for myocardial infarction, mainly because it remains raised for so much longer after infarction. The latter has the disadvantage that small infarcts are responsible for only slight increases in the level and these are not easy to detect without serial estimations. The short period of elevation is also a disadvantage when one compares it with S.L.D., as samples taken at about 6 days after infarction invariably show a low or normal S.G.O-T., but still have an appreciably elevated S.L.D. level. There is much greater latitude with S.L.D. estimations, as for instance in the cases of patients whose admission to hospital is delayed for several days. Here serial S.G.O-T. determinations may all show a normal level, the lapse of time being such that the peak of activity has been passed, and the level has now returned to normal. With S.L.D. the chances of obtaining a reasonably raised value are good, and even if the level obtained is not sufficiently high to be fully diagnostic, further
samples can be taken at 2- or 3-day intervals to demonstrate a falling level, which is the finding one would expect in myocardial infarction.

**DISCUSSION**

Raised S.L.D. levels have been reported in conditions other than myocardial infarction, and it seems well established that the findings of MacDonald et al. (1957), are typical. They found increased levels in the following conditions: myelogenous leukaemia, carcinomatosis, skeletal muscle trauma, acute hepatitis, diabetic ketosis, and rheumatoid arthritis. None of the cases that we examined in selecting the 20 patients with proven coronary occlusions were complicated by diseases of the above type. Perhaps the nearest cases we encountered to these were lymphosarcoma (S.L.D. = 620 units), and carcinoma of the bronchus (S.L.D. = 560 units). These patients were sent to the hospital suspected of myocardial infarction, and originally this diagnosis was entertained, but cardiographic findings were negative, and thus the enzyme tests were helpful. The first of these two patients showed an S.G.O–T. below 30 Sigma Frankel units per ml. each time the test was performed. The S.L.D. gave a steady result of 620 units per ml. on each of three successive occasions. The second patient showed S.G.O–T levels remaining below 30 units per ml., but gave a steady S.L.D. level of 560 units on each of three successive occasions.

Other patients examined before an accurate diagnosis had been made included cases of peptic ulcer, angina pectoris, and pulmonary embolism, none of which gave a sufficiently increased S.L.D. level or showed a decreasing level that would warrant them being considered as cases of myocardial infarction.

All the patients with proven myocardial infarction examined had S.L.D. levels that rose to
at least 600 units per ml., and we came to the conclusion that the test could be conveniently adopted for routine use as follows.

If cardiographic findings on admission to hospital are inconclusive, a sample of blood is taken and examined for S.L.D. activity. A result of over 600 units per ml. is almost conclusive evidence of myocardial infarction, but if any doubt exists the test can be repeated again after two days. At the same time, further cardiograms will be taken and if these are still negative or inconclusive the evidence of the tests can be examined. If the S.L.D. is falling, or rising, according to the position on the graph when the sampling is taking place, this is very strong evidence for a myocardial infarction having occurred. Occasionally, a third sample may be required if the two previous results are close together or identical. The usual findings in myocardial infarction appear to be an S.L.D. value of over 600 two to three days after the onset, and it is very rarely necessary to repeat the investigations outlined above. We have found the method to be most useful in cases which have been admitted to hospital three or four days after the onset, and when a single S.G.O-T. determination has shown a normal value.

A most interesting reason for the greater and longer period of elevation of S.L.D. following a myocardial infarct has been postulated by Wacker et al. (1956). They found that coincident with myocardial infarction, a decrease in serum zinc occurred. Lactic dehydrogenase is a metallo-enzyme, which incorporates zinc in its molecule, so that this might seem to be an anomalous finding, since an increase in S.L.D. from damaged cells should cause a corresponding increase in serum zinc. However, these workers were also able to demonstrate that zinc ions have a depressant effect on lactic dehydrogenase activity, so the correct explanation would appear to be that a decrease in serum zinc reduces the depressant effect of zinc ions on S.L.D. activity. Hence, of all the enzymes liberated from damaged heart cells following myocardial infarction, lactic dehydrogenase, since it has its activity further enhanced by the lowering in concentration of depressant zinc ions in the serum, becomes raised to a comparatively higher degree, and remains raised for a longer period than any of the other enzymes that do not have a similar enhancing factor. Why zinc ion concentration is depressed initially is still unknown.

**Summary**

A comparison of results obtained in 20 cases of myocardial infarction has been made, employing S.G.O-T. and S.L.D. estimations. The findings show that the results of American workers have been confirmed, and that S.L.D. estimation allows of greater latitude in sampling, due to its longer period of elevation. Its estimation by the method of the Sigma Co., using Sigma reagents, is satisfactory for the purpose. Although it is raised in other conditions, it is doubtful if this represents a drawback to its use by discriminating workers as a test for myocardial infarction, as these other conditions are mostly clinically distinct from myocardial infarction. In doubtful cases, where the S.L.D. is not greatly elevated, one or two serial tests will usually resolve the difficulty, as the levels tend to remain static in conditions other than myocardial infarction over the short period of time involved, instead of following the typical course of rise and fall (Fig. 3). The explanation of this would appear to be that in myocardial infarction the enzyme is liberated from damaged cells, causing the serum enzyme activity to reach a peak, usually about 3–4 days after infarction, and then slowly to return to normal. Other conditions have raised S.L.D. activity, due to reasons explained but the serum level remains steady over the period involved, and is not usually so greatly raised.

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