undergoing collapse therapy. The records from the proposed patients were examined centrally and the cases classified into three main groups and seven subgroups and allocated at random to the two methods of treatment to be compared. (3) Reports of progress were received at one month, two months, three months, and six months from the beginning of the trial.

The speed with which this trial achieved its objective is one of its most impressive features. In February, 1952, preliminary announcements were made in the American press indicating the effects of isoniazid on clinical tuberculosis. The Medical Research Council trial was initiated the same month and treatment begun on March 29, 1952. The preliminary report of the trial was published the same year (M.R.C., 1952), and it established that isoniazid alone was not superior to a combination of streptomycin and P.A.S. During this time 173 patients had been treated with 200 mg. of isoniazid daily, and 158 with 1 g. of streptomycin plus 20 g. of P.A.S. daily. Improvement in general condition was rather better on isoniazid alone, but radiological changes did better on the combination. Acquirement of bacterial resistance to isoniazid was a severe problem, and occurred in 11% of cases at the end of the first month, 52% at the end of the second month, and no less than 71% at the end of the third month. The trial was therefore modified to compare the results of 1 g. of streptomycin daily plus 200 mg. of isoniazid daily with those of streptomycin and P.A.S. It was concluded that the degree of radiographic improvement was essentially the same on streptomycin and isoniazid as on streptomycin and P.A.S., and better in either than on isoniazid alone. Improvement in general condition and conversion of positive to negative culture were more frequent with streptomycin and isoniazid than with streptomycin and P.A.S. Thus it seemed that a combination of streptomycin and isoniazid was in general the most effective treatment known for pulmonary tuberculosis.

In this account I have omitted many details of method and of the knowledge achieved, and I would refer those interested to the article by the late Dr. Marc Daniels (1951), to whose personal qualities so much of this success was due. But I do want to say that I cannot conceive how so much and so exact a knowledge of the relative efficacies of these drugs could have been got so quickly and with so little expenditure of human life and suffering in any other way. Imagine the fate of the tuberculous patients if these drugs had been prescribed without plan or purpose and their assessment left to "clinical judgment." When I reflect on this I am amazed, stupefied, and I confess rather horrified that some of my colleagues, of unquestioned integrity and of no mean intelligence, adopt the attitude they do to controlled therapeutic trials.

I would also like to add that the controlled clinical trial is to my mind the most important new method introduced into clinical science in recent years. It should not only tell us what drugs can do, but if only the practical details can be overcome it could tell us, for example, whether or not overindulgence in fat, or in a particular kind of fat, is a contributing factor in the pathogenesis of ischaemic heart disease. Patients must be treated, and it would seem only sensible that treatment should be designed so that the results shall add to knowledge and help us in the prevention and control of disease, so long as the trial is not against the best interests of the patients.

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SERUM GLUTAMIC OXALACETIC TRANSAMINASE IN ACUTE MYOCARDIAL INFARCTION

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The estimation of glutamic oxalacetic transaminase in serum (S.G.O.T.) as an aid in the diagnosis of acute myocardial infarction was first introduced into clinical practice by LaDue, Wróblewski, and Karmen in 1954. Since then a fairly extensive literature, most of it American, has developed. Particularly comprehensive papers are those of Chinsky *et al.* (1956), Ostrow *et al.* (1956), Kattus *et al.* (1957), and Ratner and Sacks (1957).

The enzyme is widely distributed in the tissues, and high concentrations are present in cardiac and skeletal muscle and in brain, liver, and kidney. It is liberated into the blood on the death of cells of these organs. It is also present in erythrocytes, so that when samples of blood are collected for its estimation, haemolysis must be avoided and the serum or plasma separated as soon as possible. The enzyme will retain its activity for two weeks if the serum is stored at 0–5° C. (LaDue and Wróblewski, 1955). Its concentration can be estimated by the spectrophotometric method of Karmen *et al.* (1955) or by the colorimetric method of Reitman and Frankel (1957).

The level of S.G.O.T. activity in normal controls varies from 5 to 40 units per ml. of serum, with a mean of approximately 21 units (Wróblewski and LaDue, 1955; Kattus *et al.*, 1956). In a normal person the level does not vary by more than 10 units from day to day and is independent of time of day, meals, or previous exercise (Chinsky *et al.*, 1956).

Agress *et al.* (1955) showed that graded experimental infarction in dogs was associated in all cases with increase in S.G.O.T. Infarction of as little as 10%, and possibly less, of the total myocardium produced a significant rise in S.G.O.T. and there was a linear correlation between the peak S.G.O.T. level and the amount of infarction at necropsy. Nydick *et al.* (1957) found that there was no rise in S.G.O.T. in experimental myocardial ischaemia in dogs unless myocardial necrosis had occurred. The rise in S.G.O.T. begins within three hours after infarction, attains a peak in 9 to 23 hours, and returns to normal in three to six days. Agress *et al.* (1956), in other experiments, made the useful observation that if pericarditis was produced by sand, talc, or bacterial infections the S.G.O.T. would rise only if the underlying heart muscle was involved in the injury.

Since the enzyme is widely distributed in the body it was realized early that elevation of S.G.O.T. would occur after necrosis of tissues other than heart muscle. In man a rise in S.G.O.T. has been found after necrotic

lesions of the liver (Wróblewski and LaDue, 1955, 1956; Madsen *et al.*, 1958); of brain (Lieberman *et al.*, 1957), where the peak concentration is attained rather later than in cases of myocardial damage; of skeletal muscle (Merrill *et al.*, 1956); and of the pancreas (Chinsky *et al.*, 1956; Shabetai *et al.*, 1957). A small rise in S.G.O.T. may occasionally occur after pulmonary embolism (Goldstein *et al.*, 1956; Nydick *et al.*, 1957). S.G.O.T. also rises in haemolytic crises (Ostrow *et al.*, 1956) and sometimes with salicylate therapy, but only if the dosage is heavy and prolonged (Manso *et al.*, 1956).

This paper is an account of the part that estimations of S.G.O.T. have to play in the diagnosis and management of acute myocardial infarction.

Material and Method

Observations were made upon 34 episodes of acute myocardial infarction occurring in 28 patients admitted to the Royal Victoria Infirmary, Newcastle upon Tyne. Of these, 18 gave a preceding history of angina of effort. Four patients died, and necropsies were obtained in three. In addition, three patients with status anginosus or acute coronary insufficiency were studied, as well as a few cases of acute cardiac failure with, or without, severe arrhythmias. The cases of myocardial infarction and acute coronary insufficiency were treated with anticoagulants (heparin and phenindione).

Specimens of blood were collected daily for 10 to 14 days, and in some instances for much longer, and examined by one of us (A. J. S.) for the level of S.G.O.T. by the colorimetric method of Reitman and Frankel (1957), using the standardized reagents produced by the Sigma Chemical Company. Estimations were also made of other enzymes, of which an account will be given separately. The erythrocyte sedimentation rate (E.S.R.) was estimated daily by the Westergren method. Twelve-lead electrocardiograms were taken on the day of admission and not less than twice weekly thereafter. In seven cases the electrocardiogram was taken daily.

Estimation of the level of S.G.O.T. in 25 healthy adults gave a range of 10 to 34 units with a mean of 19.0 units (standard deviation ± 6.0 units).

Time of Onset, Height, and Duration of Rise

In many instances the patient was not admitted to hospital early enough for the time of onset of the rise in S.G.O.T. to be gauged, but from observations from those who were, and those who had further infarction in hospital, the average time of appearance of an abnormal figure was one and a half days, and the average duration of the abnormal elevation was three and a half days from the onset of pain, with a range of one to six days. These figures agree well with those of other authors—for example, LaDue *et al.* (1954), Denney *et al.* (1956), Chinsky *et al.* (1956), and Ostrow *et al.* (1956), who found that the rise may begin as early as three hours after the onset and that the enzyme returns to normal in one to eight days, most often by the end of the third day.

The peak concentration reached in the uncomplicated cases in the present series varied from 24 to 620 units, with a mean of 194 units—that is, nine times the normal level. Two cases of myocardial infarction with congestive heart failure and centrilobular necrosis of the liver at necropsy had peak levels of 950 and 8,400 units.

Relationship to Body Temperature and E.S.R.

Compared with the fever and the rise in E.S.R., which so commonly follow myocardial infarction, the rise in serum transaminase appeared a full 24 hours sooner. It fell to normal again two days before the temperature and at least a week sooner than the E.S.R. Fig. 1 shows curves from a typical case.

It proved also a more dependable index of infarction, since in only three cases where the blood samples were taken early enough was the S.G.O.T. negative (8.8%). In one-third of the infarcts no rise in temperature took place at all, and even the E.S.R. remained normal in one-fifth. Presumably a larger infarct is needed to raise the E.S.R. than the S.G.O.T. and a still larger one to induce fever.

FIG. 1.—Curve showing the relationship between S.G.O.T., temperature, and E.S.R. in a typical case of acute myocardial infarction.

There were in the series several cases where coincidental infections, such as pneumonia, were also responsible for a raised body temperature and E.S.R. as well as a few where the latter was depressed by congestive heart failure. Serum transaminase is unaffected by infections (Ostrow *et al.*, 1956), and, as shown below, rises only in a minority of cases of congestive heart failure. To sum up, the rise in S.G.O.T. is more prompt, more striking, more brief, more sensitive, and more specific than either the body temperature or the E.S.R.

Relationship to the Severity of the Infarct

The size of the infarct has been graded according to the number of leads in which Q wave and T wave changes were detected in the electrocardiogram. In Fig. 2 these have been plotted against the peak levels of S.G.O.T. in the blood of those patients in whom the form of the curve has demonstrated that the peak level had not been missed. It will be seen that there is a linear relationship, although this is a very rough one, not only because the electrocardiographic method of assessing the size of infarct is crude but also because when the S.G.O.T. curves are examined, and are related to the clinical history, a significant number of patients sustain their infarcts in stages over a period of several days. In them, a time-concentration curve would doubtless constitute a much better guide to severity than the single-peak reading, as has already been stressed by Kattus

et al. (1957). Fig. 3 is taken from a good example of such gradual infarction.

Since it has been shown experimentally that an infarct of less than 10% may not produce an elevation of serum transaminase (Agress *et al.*, 1955), it seems likely that in

FIG. 2.—Relation of peak S.G.O.T. level and E.C.G. grade of infarct in 20 patients with acute myocardial infarction.

human subjects, too, infarcts may be so small that they do not produce an elevation. This is borne out by experience in the present series, where, on three occasions, pain and electrocardiographic changes in the course of a patient's treatment in hospital suggested that there had been an extension of infarction but no rise of transaminase took place. There was one further and more clear-cut case where the electrocardiogram showed clearly a fresh infarct but the serum transaminase was not elevated. There was also one patient in whom the clinical features were extremely suggestive of fresh myocardial infarction but both electrocardiogram and transaminase remained normal.

FIG. 3.—Curve of S.G.O.T. showing myocardial infarction occurring in stages over several days.

In some instances, however, the probability is that the elevation of the transaminase above the normal does not attain the arbitrary 40 units which has been set as the upper limit of the normal range. Fig. 4 shows an example where the clinical features and the electrocardiogram strongly suggested a fresh infarct, and the acute rise in serum transaminase is in accord with this even though the maximal elevation is below 40 units.

Cases with Previous Infarction

In nine cases there was a history of previous myocardial infarction, and in five of these, as well as in two others—

that is to say, in 21% of the episodes of definite fresh myocardial infarction—the electrocardiogram was so distorted by the previous infarct that on the single initial tracing alone it was impossible to deduce with certainty that fresh infarction had occurred. In these patients the serum transaminase was abnormally high within 48 hours and proved most helpful. Subsequent electrocardiograms confirmed the diagnosis. There is no doubt that in cases of suspected acute myocardial infarction where there is either a history or electrocardiographic evidence of previous infarction the estimation of serum transaminase has its greatest value in establishing that there has been a fresh lesion. Such cases constitute about a quarter of the fresh infarcts seen.

The serum transaminase is also helpful when patients are already under treatment for an acute myocardial infarct and the occurrence of pain, collapse, or other signs suggests that there has been fresh extension of infarction. In such cases the electrocardiogram is often so distorted by the recent necrosis, and perhaps by pericarditis occurring with it, that it is most difficult and often impossible to decide whether

FIG. 4.—Curve of S.G.O.T. and E.S.R. in a patient with acute myocardial infarction, with the peak S.G.O.T. level below 40 units.

FIG. 5.—Curve of S.G.O.T. in a patient with further myocardial infarction during the course of treatment.

there has been fresh necrosis. It is in these cases that serial estimations of serum transaminase are most likely to be helpful, since they will show the baseline level to which that individual's transaminase falls, and any striking elevation above this closely following upon an attack of pain can be taken as evidence of new damage. Fig. 5 shows such a case.

Other Obscuring Factors in the Electrocardiogram

The diagnosis of myocardial infarction by electrocardiography is less often obscured by arrhythmias, such as the tachycardias and bundle-branch block, by digitalis effects, and by previous left ventricular strain than it is by previous infarction. In the present series there were only two cases in which such factors created serious difficulties compared with five in which previous infarction operated similarly. Nevertheless, the serum transaminase is helpful in this minority, for in both these cases it was normal and the conclusion reached was that there had been no infarction.

Acute Coronary Insufficiency

Other authors (Rudolph *et al.*, 1955; Nydick *et al.*, 1957) have found in experimental narrowing of coronary arteries in animals that unless necrosis is produced in the myocardium a rise of serum transaminase will not be observed, and it has been found in human beings, too, that if the clinical and electrocardiographic picture is solely one of ischaemia without necrosis then the transaminase remains unaltered (Kattus *et al.*, 1956). In the present series there were three such cases of acute coronary insufficiency or status anginosus, all treated with anticoagulants. The usual difficulty in such cases is to distinguish on the electrocardiogram between such ischaemia and limited infarction, often subendocardial. Repetition of the tracings, trying the effects of nitroglycerin upon them, and observing the E.S.R. and body temperature may all help, but sometimes the difficulty remains unresolved. One would expect the serum transaminase to assist in a similarly circumscribed way, for if necrosis is small enough and gradual enough in onset, it would seem likely that no diagnostic curve or level might be observed. Experience of the three cases in this series has borne this out, and has suggested that the enzyme estimation is complementary to, but not necessarily more reliable than, the electrocardiogram in showing whether or not necrosis has taken place.

False Negatives

The S.G.O.T. was elevated in all except three of the cases of definite infarction here described where the blood samples had been taken early enough—that is, false negatives were 8.8%. Denney *et al.* (1956) found false negatives

FIG. 6.—Curve showing transient elevation of S.G.O.T. in acute myocardial infarction.

in only 4.75% of definite infarcts, while Kattus *et al.* (1957) had none amongst 111 patients with proved myocardial infarcts, probably because of the frequency with which they took blood samples for analysis. In a review of 264 patients, Ratner and Sacks (1957) had 8% false negatives among 64 patients with definite myocardial infarction, and this will probably prove to be a representative figure in clinical practice, for the S.G.O.T. rise may be very transient, as is shown in Fig. 6, and very frequent sampling is hardly practicable as a routine.

False Positives

Since the enzyme is so widely distributed it is obvious that significant rises in the blood level may be produced by a variety of mechanisms. If care is taken to separate the

serum or plasma of the blood sample from the red cells then false elevation due to liberation of the enzyme from haemolysed erythrocytes should not occur. Its liberation into the blood stream from other tissues is a much more important cause of false-positive results. Destruction of red cells in the tissues is one important cause, and particularly so where there has been some tissue destruction as well as haemorrhage; haemorrhagic pancreatitis is a conspicuous example of this. Where the enzyme content of the tissue is low, as in the brain and in the lung, infarction brings only slight rises. When it is high, as in the liver, the elevation consequent upon tissue damage may be enormous. This does not often cause trouble in diagnosis, although one patient, not included in this series, was admitted under the care of one of us (H. A. D.) with the diagnosis of suspected myocardial infarction, and investigation showed that the rise in his transaminase (109 units) was due to subacute alcoholic hepatitis, his heart being clinically and electrocardiographically normal.

It is apparent that serum transaminase is helpful in the differential diagnosis of myocardial infarction only if one is fully aware of the capacity of other tissues to liberate it. Much more important in cardiology is the possibility of the enzyme being liberated in substantial amounts from a liver congested and necrotic from heart failure. The literature about this is scanty. Conrad (1957) mentions DuToit's (1956) report of an elevation in S.G.O.T. in 16 out of 23 patients in uncomplicated cardiac failure. When it does occur the blood level attained may be very high, as in one case in the present series where a young woman of 29 years with acute cor pulmonale due to emphysema and pulmonary infection was found to have a transaminase level of 710 units; nothing in the history or the electrocardiogram suggested that there had been myocardial infarction. Two of DuToit's cases had S.G.O.T. levels of more than 2,000 units, and one of these had advanced central necrosis of the liver at necropsy. It has been said that in cases of liver disease the serum glutamic pyruvic transaminase (S.G.P.T.) is elevated to a greater extent than the S.G.O.T., in contrast to the findings in myocardial necrosis. In the present series this was occasionally true, but exceptions were too numerous for the double estimation to be worth while as a routine test.

Prognosis

It has been said (Chinsky *et al.*, 1956) that a peak level of S.G.O.T. greater than 200 units carries a poor prognosis. However, the peak level may not be observed, either because the patient dies before the maximum is reached or because the patient is admitted on the downstroke of the transaminase curve. In this series two patients died with S.G.O.T. levels of 57 and 70 units, and in both of these the peak was probably missed. There were eight patients with a peak S.G.O.T. level above 200 units and only two died. Both of these, with S.G.O.T. levels of 950 and 8,400 units, had only moderate-sized recent infarcts at necropsy, but there was marked centrilobular necrosis of the liver.

Many factors are involved in the prognosis of acute myocardial infarction, of which the size of the infarct, reflected in the peak level of S.G.O.T., is only one, and this peak level may in any case be further raised if there is acute heart failure with hepatic centrilobular necrosis, and perhaps also if there is acute haemorrhagic pericarditis complicating the picture.

S.G.O.T. in other Cardiac Conditions

Also of interest in cardiology are the affections of the heart other than acute myocardial infarction in which a raised S.G.O.T. may be found. The role of pericarditis has already been mentioned. The arrhythmias *per se* do not raise the enzyme level, but may do so in occasional instances, including one case of the present series and one case out of 14 in the series of Chinsky *et al.* (1956), where the extremely rapid heart rate precipitated acute heart failure with presumed centrilobular necrosis of the liver. The same is true of acute pulmonary oedema (Chinsky *et al.*, 1956).

Ostrow *et al.* (1956) quote one case of Fiedler's myocarditis in which the S.G.O.T. was elevated as one would expect, and Chesler (1958) reports elevated levels in diphtheritic myocarditis. Nydick *et al.* (1955a, 1955b) give an interesting account of its elevation in acute rheumatic carditis. The latter at any rate cannot often be confused with myocardial infarction, and no such difficulty arose in the present series.

Summary

Serial daily estimations of serum glutamic oxalacetic transaminase (S.G.O.T.) for at least 10 days have been made in 34 acute episodes of myocardial infarction occurring in 28 patients. The results have been compared with changes in erythrocyte sedimentation rate (E.S.R.), temperature, and electrocardiogram.

Estimations of S.G.O.T. are most useful (a) when the electrocardiogram is obscured by previous myocardial infarction, arrhythmias, bundle-branch block, left ventricular strain, and digitalis; (b) when extension of myocardial infarction is suspected; and (c) to distinguish between acute coronary insufficiency and myocardial infarction.

There was no rise in S.G.O.T. in 8.8% of the cases of fresh myocardial infarction.

The maximum elevation of S.G.O.T. roughly corresponds with the electrocardiographic estimation of the size of the infarct only if other causes of a raised transaminase can be excluded. The most important of these in myocardial infarction is centrilobular necrosis of the liver secondary to cardiac failure.

In small infarctions serial estimations of S.G.O.T. may show a characteristic curve even though the peak does not exceed 40 units.

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SERUM TRANSAMINASE: ITS CLINICAL USE IN DIAGNOSIS AND PROGNOSIS

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Human serum contains several enzymes concerned with the reaction of transamination. The one most commonly determined is serum glutamic oxalacetic transaminase (SGO-T), which catalyses the reversible reaction:

Similarly serum glutamic pyruvic transaminase (SGP-T) catalyses the reaction:

Cohen and Hekhuis (1941) showed that transaminase was in highest concentration in cardiac and skeletal muscle. LaDue *et al.* (1954) also found it to be present in the brain, liver, and kidney in lower concentrations.

The serum transaminase level (SGO-T) has been found to be elevated following myocardial damage, hepato-cellular necrosis, pancreatitis, trauma to skeletal muscle, myositis (including dermatomyositis), active rheumatic carditis, and any process associated with active damage to skeletal or cardiac muscle (LaDue and Wróblewski, 1955; Wróblewski and LaDue, 1956; Ratner and Sacks, 1957).

The curve of serial serum transaminase estimations would appear to be characteristic in cases of myocardial infarction, and it has been suggested that a characteristic curve occurring within the normal range of values may be found in some cases of angina (Chinsky *et al.*, 1956) or associated with a very small infarct (Ratner and Sacks, 1957). These authors also found that the serum transaminase level remains normal in patients with cerebrovascular damage, acute or chronic infections, acute phlebitis, uraemia, neoplastic, allergic, or metabolic diseases, unless associated with damage to skeletal or heart muscle. Further, there appears to be no apparent correlation with age, sex, colour, weight, leucocyte count, blood sedimentation rate, the presence or absence of fever, heart failure or shock, or the use of anticoagulant drugs or cortisone.

The above evidence suggests that serial transaminase readings are a possible aid to diagnosis in cases of doubtful myocardial infarction and might prove to be related to the actual size of infarct and, because of this, a possible guide to prognosis. We felt, therefore, that a small series of cases investigating these points was justified.

Technique Employed.—The technique we used was that devised by Frankel and Reitman (1957). In this method the amount of keto-acid formed in one hour is determined colorimetrically by the formation of