The Influence of Rheumatic Fever on Serum Concentrations of the Enzyme, Glutamic Oxalacetic Transaminase

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Variations in serum concentration of the enzyme, glutamic oxalacetic transaminase, in 64 patients with rheumatic fever were studied. Elevations were noted in 17 of 26 patients with carditis of definite or questionable activity and transiently in one rheumatic subject with viral myocarditis. Except for one patient with polyarthritis and equivocal evidence of acute cardiac involvement, serum concentrations were normal during noncardiac rheumatic manifestations and inactive carditis. There was no relationship to temperature, sedimentation rate, white blood count or C-reactive protein. Intermittent necrosis of myocardial fibers probably leads to these increased serum transaminase concentrations.

The enzyme, glutamic oxalacetic transaminase (GO-T), has been found in all human and animal sera that have been tested. This transaminase has been found in high concentration in heart muscle, skeletal muscle, brain, liver and kidney in decreasing order.1,2,3 The concentration in lung is very low. Marked increases in serum concentrations of GO-T have been demonstrated during the acute phases of myocardial destruction of many types, including acute myocardial infarction in man,4,5 experimental myocardial infarction in dogs, either following coronary ligation6 or the injection of plastic microspheres into the coronary circulation7 and following the intravenous injection of papain into rabbits.8,9 The rises in serum glutamic oxalacetic transaminase (SGO-T) appear to be roughly proportional to the amount of myocardial necrosis. Striking elevations of the serum level follow acute or chronic liver damage10,11 and lesser rises occur after acute renal or skeletal muscle damage12,3.

The serum level of glutamic oxalacetic transaminase has not been found to be elevated in a large group of patients with infectious, neoplastic, allergic and degenerative disease states unless evidence of acute damage to the liver, heart or skeletal muscle was present.

The observation that myocardial necrosis could be detected by measurement of the changes in the serum concentrations of glutamic oxalacetic transaminase led us to study alterations of enzyme concentration in different groups of rheumatic patients. Assay of the enzyme was performed by a simple rapid spectrophotometric method.6 The results with this method are comparable with those of the more laborious chromatographic assay.6

Previously the acute phase reactants such as C-reactive protein (CRP)13,14 erythrocyte sedimentation rate, serum complement14 and
white blood cell count have been used as indices of rheumatic activity. It has been recognized that these are nonspecific tests of inflammation and that they do not measure, per se, involvement of the myocardial fiber. In this study, an attempt is made to observe the behavior of the serum transaminase in patients with rheumatic fever, with particular reference to those showing manifestations of carditis.

**Material and Methods**

The patients included in this study were admitted to Irvington House in the acute, chronic or convalescent stages of rheumatic fever or were seen as routine admissions to the wards of the Second (Cornell) Medical Division of Bellevue Hospital, The New York Hospital or the Memorial Center for Cancer and Allied Diseases. Blood for the serum transaminase determinations was obtained three times weekly from the Irvington House patients for periods ranging from two weeks to six months. The sera were coded and analyzed for transaminase activity. Patients from the other services were bled less frequently. Sera were frozen and then analyzed within one week.

The test for C-reactive protein was performed by the capillary precipitation method as described by Anderson and McCarty, employing an antiserum prepared by injecting rabbits with purified, crystalline C-reactive protein of human origin. The erythrocyte sedimentation rate (ESR) was determined by the Wintrobe method and corrected for variations in hematocrit according to standard tables.

Liver function tests, performed in most patients exhibiting rises in serum levels of transaminase included sulfobromophthalein retention (BSP), serum alkaline phosphatase, cephalin flocculation and serum bilirubin determinations.

**Measurement of Enzyme (SGOT)**

The spectrophotometric method of assay was used (fig. 1), employing the Beckman (DU) spectrophotometer. In this method, the patient's serum is added to exceses of aspartic acid and α-ketoglutaric acid buffered by one-tenth molar phosphate (pH 7.4) in the presence of reduced co-enzyme I (DPNH) and an excess of malic dehydrogenase. The optical density of this solution decreases as reduced diphosphopyridine nucleotide (DPNH) is oxidized during the reaction. The rate of this reaction is limited only by the concentration of glutamic oxalacetic transaminase. One unit of transaminase is designated as a change in optical density of 0.001 per milliliter per minute at wavelength 340 μ. The normal range as determined in 150 healthy adults is 8 to 40 units per milliliter per minute (mean, 22.1; S.D., 7.1). The normal range in 75 healthy children was 10 to 40 units per milliliter per minute (mean, 25.1; S.D., 7.0). The standard deviation of any individual determination is approximately 5 per cent.

**Diagnosis and Classification of Subjects**

All of the patients included in this study met the criteria of Jones for the diagnosis of rheumatic fever at some time during the course of their disease. Certain criteria were established in order to group the patients according to the probability of active cardiac involvement (table 1).

A child or adolescent was considered to show definitely active carditis if one or more of the following conditions was present: (1) congestive heart failure, (2) progressively enlarging heart, (3) pericarditis, as evidenced by a pericardial friction rub or a rapid enlargement of the cardiac silhouette on x-ray study compatible in size and form with that seen with pericardial effusions, (4) endocarditis, suggested by the appearance of a significant new murmur or definite increase in intensity of a pre-existing murmur and (5) the appearance of markedly abnormal T-waves on the electrocardiogram (prolongation of the P-R interval alone was not considered conclusive evidence of active carditis). Only one patient showed an abnormal electrocardiogram with no other evidence of myocarditis. This occurred during the course of virus pneumonia (table 1).

In the adult patients, in contrast to children, congestive heart failure, progressive cardiac enlargement or electrocardiographic abnormalities were not considered in themselves to be conclusive evidence of active carditis, unless gross or extensive microscopic evidence of activity was present in the heart at autopsy.

Group I includes only patients with rheumatic fever with active carditis. The presence of congestive heart failure formed the basis for a further division of this group, since the carditis responsible for the congestive failure in these patients was likely to be most severe.

**Figure 1.** The transamination reaction is shown. The reduction in the optical density of the solution as DPNH* is oxidized to DPN* is measured spectrophotometrically.
Group II includes patients with rheumatic fever and previously known rheumatic heart disease. The evidence for active cardiac involvement was considered to be equivocal in the absence of the appearance of new cardiac manifestations during the observed attack, despite laboratory evidence of continuing inflammation.

Group III contains two categories of patients with rheumatic fever, but with no known cardiac involvement; (1) polyarthritis, (2) chorea or erythema marginatum.

Group IV is composed of patients with inactive rheumatic fever but with known carditis in the past. This group is further divided into children convalescing from a recent attack of active carditis and adults who have recovered from rheumatic fever years previously and at present show inactive rheumatic heart disease.

The period of convalescence is dated from the day suppressive antirheumatic therapy was withdrawn if no laboratory or clinical evidence of an exacerbation of rheumatic activity supervened during the following two months. Group V contains patients with inactive rheumatic fever who developed virus pneumonia.

Group VI is composed of 16 patients with active rheumatoid arthritis (no evidence of cardiac involvement) and osteoarthritis.

The behavior of the transaminase in the untreated rheumatic could not be studied adequately because so many of the patients showed severe cardiac involvement and it was believed necessary to administer steroids or salicylates in an attempt to suppress inflammation.

**Results**

The 80 patients studied are listed in table 1. The incidence of abnormal serum levels of the enzyme can be seen in this table. Of nine patients who showed signs of active carditis with congestive heart failure (group Ia), the serum transaminase was abnormal at some time in eight. Of eight patients with active carditis who did not develop congestive heart failure (table 1, group Ib) only three showed any abnormality of the enzyme (SGO-T). Elevated serum levels of transaminase were seen in 6 of 9 patients with rheumatic fever and known cardiac disease but without definite clinical evidence of activity of the carditis (group II). The high incidence of abnormal results in this group may be due to the fact that five adults with suspected chronically smoldering carditis on the basis of persistent laboratory evidence of inflammation without frank clinical activity are included. One of these adults had congestive heart failure.

Only 2 of the 54 patients in the other groups had abnormal serum glutamic oxalacetic transaminase levels at any time. These two patients showed suggestive evidence of cardiac involvement. One patient had virus pneumonia with T-wave inversions in the electrocardiogram, the other, acute rheumatic polyarthritis (case 5, J. B., see below). In all of the other patients, the transaminase concentration was consistently normal. The conditions studied included rheumatic fever manifested by polyarthritis, erythema marginatum or chorea minor without cardiac involvement, inactive rheumatic fever after previous carditis, virus pneumonia in rheumatic fever subjects and
active rheumatoid and osteoarthritis. Spinal fluid transaminase was normal in the three chorea patients studied and in four acute rheumatic fever patients without chorea. One of the latter patients showed normal (11 units) spinal fluid transaminase content when his serum concentration was elevated to 61 transaminase units.

Nine individuals were studied during and after reactions to intramuscularly administered benzathine penicillin. The reactions ranged in severity from local tenderness and induration of the muscles to a generalized urticaria with polyarthritis. The transaminase was normal on all occasions.

The behavior of the enzyme can best be illustrated by the following representative cases:

Case 1 (fig. 2) C. M., a 24-year-old Equadorian male, had a history of acute polyarthritis and fever five years prior to admission in March of 1949, which was treated at that time with aspirin for three months. No specific information is available concerning evidence of cardiac involvement at that time, but during the three years prior to his final hospitalization, he complained of progressively severe dyspnea, cough and intermittent scanty hemoptysis. Diffuse aching precordial pain had been present for six months. Three months prior to this admission, he developed anorexia, perspired freely, became more short of breath, lost 30 pounds of weight and required digitalis during this period.

Examination showed a dyspneic, perspiring patient with distended neck veins, a temperature of 102 F., blood pressure of 140/40, a heart rate of 120 per minute, and respirations of 24 per minute. A pleural friction rub was heard over the left chest and subclavicular areas were heard over the lower halves of both lungs. The heart was enlarged beyond the midaxillary line. The murmurs of mitral stenosis and insufficiency and aortic stenosis and insufficiency were heard. A pericardial friction rub was first heard on the thirty-ninth hospital day. The liver edge was felt 3 cm. below the costal margin.

The patient showed moderate improvement until June 10 when a shock-like episode associated with chest pain and hemoptysis occurred. This was interpreted as due to pulmonary embolization. Despite the administration of heparin and Dicumarol, pulmonary embolization recurred on three separate occasions. After June 12 he became progressively more dyspneic and expired on July 16.

During June, a five-day course of aspirin was discontinued because of salicylate toxicity and cortisone was administered for a short period in amounts inadequate to suppress any of the laboratory signs of inflammation. A low-grade fever persisted, the sedimentation rate ranged from 30 to 60 mm. in 1 hour, and the white blood cell count never fell below 11.2 thousand.

The electrocardiogram was interpreted as showing biventricular hypertrophy. On admission the bilirubin was 1.0 mg. per 100 cc. and the alkaline phosphatase 6.7 Bodansky units. On June 24, following three pulmonary emboli, the bilirubin was 5.1 mg. per 100 cc. and the alkaline phosphatase unchanged. The blood urea nitrogen was normal on all occasions.

The serum glutamic oxalacetic transaminase showed striking alterations. It was 140 units on admission at a time when there was moderate heart failure, signs of mild liver dysfunction and before pulmonary emboli had occurred. Pulmonary emboli occurred on June 12 and 16. A rise of serum transaminase to 2,000 units (the highest recorded in this series) occurred on June 18. The bilirubin subsequently rose and heart failure became more severe. Despite intractable heart failure, another pulmonary embolus and the appearance of a pericardial friction rub, the serum transaminase level gradually fell to normal before the patient died.

At autopsy, the heart weighed 735 Gm., an extensive fibrous pericarditis was seen, all chambers were dilated and their walls hypertrophied, and the mitral, aortic and tricuspid valves showed typical nonbacterial rheumatic involvement. Multiple small and moderate sized pulmonary infarcts were present. The liver and lungs were moderately congested.

Microscopic examination of the heart revealed extensive acute inflammation of the pericardium, myocardium and endocardium. Many Aschoff nodules and Antischckow myocytes were seen.
Deposition of fibrin, infiltration with polymorphonuclear leucocytes, lymphocytes and histiocytes, fibrinoid degeneration of collagen and extensive vascular granulation tissue were present. The myocardial fibers showed hypertrophy and there were multiple areas where they were vacuolated, necrotic and showed an increased amount of fat. There was congestion of the central veins of the liver with a small amount of necrosis in the surrounding cells.

Comment. This was a fatal case of extensive, acute, rheumatic pancerditis. There were striking elevations of the serum glutamic oxalacetic transaminase. The peak elevations of the enzyme did not coincide with the maximum severity of congestive heart failure or liver dysfunction. The relationship of pulmonary infarction to the maximum rise is not clear. Transaminase was elevated initially before clinical signs of pulmonary infarction appeared. It is of interest that the level of transaminase fell to normal when the patient was critically ill, a few days before death, although extensive microscopic evidence of acute rheumatic fever was found at autopsy.

Liver cell injury undoubtedly contributed to the elevations of the serum glutamic oxalacetic transaminase but liver cell necrosis was not severe at autopsy. The elevated transaminase level is unusual on the basis of hepatic congestion alone. The variations in the transaminase concentration did not parallel the degree of congestive failure, having fallen to normal before death at a time when congestive failure was most severe.

Case 2 (fig. 3) F. F., an 11-year-old white boy, had his first attack of rheumatic fever three years prior to admission and a second attack occurred four months prior to admission. When he was admitted to Irvington House, his disease was characterized by fever, polyarthritis, elevation of the sedimentation rate and C-reactive protein, and a prolonged P-R interval and abnormal T waves in the electrocardiogram. While under observation at Irvington House, pancerditis developed and the patient was treated with cortisone for eight weeks. Following treatment no residual evidence of cardiac disease could be demonstrated.

However, his disease relapsed and he developed chest pain, dyspnea, temperature of 104 F., tachycardia and hepatomegaly. The heart became enlarged with distant sounds but no murmurs. The chest X-ray films showed a markedly enlarged cardiac silhouette compatible with a pericardial effusion. The cardiac pulsations were diminished. The cardiothoracic index was 14.1/24.1. The T waves were inverted in leads I, II, III, aV L, aVF and V 6.

Following the administration of 5.3 Gm. of aspirin daily, the temperature, sedimentation rate, C-reaction protein and heart size returned to normal in eight days. During the second hospital week a faint murmur of aortic insufficiency appeared. The P-R interval became prolonged and the T waves became “coved” and more deeply inverted. The liver function tests were normal. At this time the sedimentation rate, C-reaction protein and temperature were normal, but the serum transaminase rose to levels between 120 to 240 units for three weeks. Coincident with the administration of cortisone, the concentration of the enzyme rapidly fell to normal levels and remained so during convalescence. There was no relapse of clinical symptoms when cortisone was withdrawn. After four months, his cardiac status was unremarkable except that a faint aortic diastolic murmur was inconstantly heard. The electrocardiogram findings were within normal limits.

Comment. This patient had severe, active carditis treated with aspirin, then with cortisone. Initially the serum glutamic oxalacetic transaminase was normal in the presence of obvious clinical and laboratory evidence of acute inflammatory disease. Despite the rapid return to normal of all signs of acute inflammation, the serum transaminase rose to levels three to six times the upper limit of normal,
returning to normal limits coincident with the administration of cortisone.

Case 3 (fig. 4) L. DeT., a ten year-old white boy with severe, chronically active rheumatic carditis of more than two years duration. He had had repeated bouts of congestive heart failure, pericarditis with effusion, intermittent fever and persistently abnormal CRP and ESR. His heart was markedly enlarged. The murmurs of mitral stenosis, mitral insufficiency and aortic insufficiency were heard. During the period that determinations of SGO-T were made, he had two episodes of moderately severe congestive failure requiring the administration of mercurial diuretics and Digoxin. In spite of suppressive therapy with aspirin, then cortisone, the C-reactive protein was intermittently strongly positive. The sedimentation rate remained normal. The serum glutamic oxalacetic transaminase was elevated on several occasions during September when congestive heart failure was mild and the CRP was 2 to 4 mm. and was again elevated during October prior to an episode of severe congestive heart failure. The maximum rise of the transaminase to 76 units was seen in October when the CRP was 5 mm. The relationship of the elevated transaminase to a rise in CRP was not consistent, since during November the transaminase was normal although one C-reactive protein was 6 mm. Liver function studies were normal.

Comment. This patient had obviously active, severe, chronic rheumatic heart disease. While the patient was receiving cortisone, the SGO-T was intermittently abnormal with no consistent relationship to the severity of congestive heart failure or to the amount of CRP in the serum.

Case 4 (fig. 5) C. L., a 12 year old Negro boy admitted to Irvington House on Oct. 28, 1954 from another hospital, had been given cortisone there for an attack of acute carditis, characterized by an enlarged heart, dyspnea, fever, murmurs of mitral stenosis and insufficiency, tachycardia, a prolonged P-R interval and the development of pericarditis and congestive heart failure while under treatment. One month previously he had received aspirin for an attack of acute polyarthritis. While evaluating his status at Irvington House in October, cortisone was discontinued and the patient soon developed severe congestive heart failure again. He required treatment with digoxin, mercurial diuretics and aspirin. The sedimentation rate was 25 mm. in 1 hour, C-reactive protein 4 mm., and the electrocardiogram showed a P-R interval of 0.22 second at a heart rate of 100 per minute. The murmur of aortic insufficiency then appeared. Despite this evidence of acute carditis, the serum glutamic oxalacetic transaminase was normal. Toxicity to aspirin and aminopyrine ensued and cortisone therapy was reinstituted. During cortisone therapy late in November, the transaminase in the serum rose to 54 units transiently. At that time mild congestive heart failure reappeared, perhaps partly the result of fluid retention from cortisone. The C-reactive protein and sedimentation rate were normal at the time the transaminase was elevated. After cortisone therapy was withdrawn, there was a temporary reappearance of C-reactive protein and an elevation of the erythrocyte sedimentation rate. Coincident
with this, there was a mild transient elevation of the serum transaminase to 50 units.

Comment. This patient had severe acute carditis which was not correlated with an elevation of the glutamic oxalactic transaminase of the serum when his symptoms were of maximum severity, his sedimentation rate elevated and his C-reactive protein strongly positive. The first transient rise in the transaminase of the serum that was observed occurred later in the course of the disease, while he was being treated with cortisone. At this time, the sedimentation rate and C-reactive protein were normal. The second rise occurred after cortisone withdrawal when C-reactive protein and sedimentation rate were again abnormal.

Case 5 (fig. 6) G. M., a 14-year-old white boy, gave a history of recurrent polyarthritis for five years. In May 1954, two weeks following cessation of prophylactic penicillin treatment, polyarthritis reappeared. The erythrocyte sedimentation rate and C-reactive protein were elevated. Apical diastolic and systolic murmurs were heard.

In August, therapy with aspirin was initiated at another hospital. The patient was transferred to Irvington House for further observation and the aspirin was discontinued. One day after admission, polyarthritis reappeared. The temperature was 102 F. The cardiac murmurs became more intense. During October, his polyarthritis persisted while he was receiving 30 mg. of hydrocortisone daily. This symptom disappeared in November when the hydrocortisone was increased to 50 mg. daily. The heart size enlarged progressively.

The sedimentation rate was persistently elevated to as high as 40 mm. in 1 hour and the C-reactive protein was intermittently positive to as much as 4 mm. The glutamic oxalactic transaminase of the serum was never elevated.

Comment. This patient had unequivocal evidence of acute carditis, although less severe than the preceding cases. There were never any manifestations of congestive heart failure. The serum transaminase was never elevated either during the course of cortisone therapy or after its withdrawal despite the laboratory evidences of acute inflammatory disease.

Case 6 (fig. 7) J. B. represents the one rheumatic fever patient who showed elevations in the serum glutamic oxalactic transaminase but did not have definite evidence of active carditis. He was a 10-year-old Negro boy with a history of migratory polyarthritis for two months. His arthritis had been suppressed by aspirin which was discontinued one month prior to his admission.

On the day of admission, October 8, he was noted to have a nasopharyngitis. The throat culture was positive for group A, β-hemolytic streptococci. He then complained of mild polyarthralgia. On October 11 he developed frank polyarthritis. There was no clinical evidence of involvement of the heart except for an apical systolic murmur of grade I to II intensity considered to be of questionable significance. No diastolic murmurs were heard. The erythrocyte sedimentation rate was 42 mm. in 1 hour and the C-reactive protein, 8 mm. There was prompt remission of the arthritis and return of the temperature and C-reactive protein to normal after the administration of aspirin in doses
of 4.3 Gm. daily. The sedimentation rate returned to normal more slowly.

The patient cooperated poorly and received his salicylates irregularly. This was reflected by fluctuating blood salicylate concentrations, falling to as low as 4 mg. per 100 cc. on one occasion. Polyarthralgia reappeared transiently (October 22) and lasted three days. Liver function tests were essentially normal although the cephalin flocculation was 2 plus on one occasion. At no time were the electrocardiogram or cardiac silhouette on x-ray films abnormal. The only suggestive clinical evidence of acute carditis was a slight alteration in the apical systolic murmur which assumed a somewhat harsher quality of grade II to III intensity for one week in December. The C-reactive protein was intermittently positive after the arthritis had disappeared.

Three marked peaks of serum transaminase elevation were observed, the first closely following the attack of polyarthritis, the second and third after the patient had long been completely asymptomatic except for a mild upper respiratory infection. The glumatic oxalacetic transaminase was normal on admission when the temperature, sedimentation rate and C-reactive protein were markedly abnormal. When the temperature, sedimentation rate and C-reactive protein had returned to normal, the serum level of the enzyme rose to 200 units. At the time of the second peak of the serum transaminase, the temperature, sedimentation rate and C-reactive protein were again normal.

During the period of this third elevation of the serum transaminase, the C-reactive protein rose to 5 mm. and the sedimentation rate to 28 mm. in 1 hour.

Cortisone was administered in a dose of 300 mg. on October 26 in an attempt to determine its effect on the serum concentration of the glutamic oxalacetic transaminase. However, the results of the experiment could not be interpreted because the control serum obtained immediately prior to therapy but analyzed the next day, showed that the concentration of the enzyme in the serum had already returned to normal.

Comment. This case of frank polyarthritis is of particular interest in that it is the only case in this series in which the transaminase of the serum was repeatedly abnormal despite the absence of previously known rheumatic heart disease or definite evidence of clinical cardiac involvement. There was, however, a transient change in the quality and intensity of the apical systolic murmur and there was laboratory evidence of persistent inflammation as manifested by the intermittently positive C-reactive protein. Polyarthritis, per se, did not seem to be related to the elevations of the serum glutamic oxalacetic transaminase, since the second and third peaks of enzyme concentration occurred when no polyarthritis was present.

One patient with known rheumatic heart disease showed an elevated transaminase level of 70 units on one occasion during the course of virus pneumonia. At this time, his electrocardiogram showed abnormal T-waves which reverted to normal with the subsidence of the pneumonia. We believe it is likely that this patient had the mild myocarditis occasionally seen during virus infections.17

Correlation with Microscopic Findings

Sections of the heart were available for microscopic study in 15 patients (table 2). This material consisted of biopsies of atrial appendages obtained at the time of mitral valulotomy in 12 patients and autopsy material in 3 patients. Only one of the patients (C. M., fig. 2, case 1) included in table 2 was also included in table 1. The remainder of the patients were excluded from table 1 because only one or two sera were obtained prior to surgery or death. This was considered to be

| Table 2.—Microscopic Findings: Incidence of Elevated Serum Glutamic Oxalacetic Transaminase (SGO-T) |
|--------------------------------------------------|---|---|
| A. Acute Inflammation                             | Total Number of Patients | Number of Patients Abnormal |
| (a) Aschoff Nodules                                | 7 | 3 |
| (b) Round Cell Infiltration                        | 4 | 2 |
| (c) Active Myocardial Cell Necrosis                | 1 | 1 |
| (d) Fibrinoid Degeneration of Collagen             | 4 | 3 |
| B. No Evidence of Inflammation                     | 5 | 1 |
| (a) Replacement of Myocardial Fibres              | 1 | 1 |

Microscopic evidence of myocardial hypertrophy was present in all cases; 27 sera were analyzed of which 12 were abnormal.

This table analyzes the correlation of the serum glutamic oxalacetic transaminase with the microscopic findings in autopsy and atrial biopsy material.
an inadequate sampling in view of some of the transient abnormalities noted in other patients in whom bleedings were performed three times weekly for many months.

Sera obtained after surgery were not included. It has been noted that the serum level of transaminase invariably rises after chest surgery in animals1 or patients,20 presumably as a result of trauma to the pectoralis and intercostal muscles. Hence, any abnormality in the glutamic oxalacetic transaminase of the serum during the first two weeks following chest surgery is influenced by the skeletal muscle damage from surgical trauma. Patients were listed in table 2 according to microscopic findings of the pathologist before the transaminase values were known.

Despite the small number of analyses and the probability that atrial appendage biopsies will be seen to have Aschoff nodules in only approximately 75 per cent of patients subsequently shown to have Aschoff nodules elsewhere in the heart,19 table 2 shows a high incidence of elevated transaminase determinations in those patients with microscopic evidence of acute inflammation. Criteria for microscopic evidence of an acute inflammatory process in the heart included the presence of any of the following: (1) Aschoff nodules, (2) infiltration with round cells or polymorphonuclear leukocytes, (3) fibrinoid degeneration of collagen and (4) active myocardial fiber necrosis. Myocardial cell hypertrophy was present in all 15 patients and was not considered evidence of active disease.

Five of the 10 patients with microscopic evidence of acute inflammation showed an abnormality of serum transaminase within 1 to 5 days before the pathologic specimen was obtained. Only 1 of the 5 patients without microscopic evidence of inflammation showed an abnormal serum level of transaminase. This patient had extensive fibrosis of the myocardium, although no acute fiber degeneration could be demonstrated.

**DISCUSSION**

It appears most likely from analysis of these clinical and pathologic data that abnormalities of serum glutamic oxalacetic transaminase in rheumatic fever reflect myocardial damage. The high incidence of positive tests, in the patients with definitely or questionably active carditis, contrasts with the frequency of negative tests in the groups of patients with inactive rheumatic fever, active rheumatic fever without evidence of carditis, active joint involvement in rheumatoid arthritis and many other inflammatory diseases in which heart, liver and skeletal muscle are uninvolved. No marked rise in transaminase has been observed following pulmonary infarction.20

Liver function when tested was normal in all the patients in the series except one (C. M.). Although skeletal muscle damage as seen in dermatomyositis will cause an elevation in serum glutamic oxalacetic transaminase20, this diagnosis was not suspected in any of the patients included in this study. The influence of mercuhydrin, digitalis and aspirin administration upon the serum level of glutamic oxalacetic transaminase was studied in a group of nonrheumatic adults. No effect of these drugs was noted.

Previous observations have shown that a rise in the transaminase level may occur following experimental production of necrosis of as little as 1 Gm. of myocardial tissue.3 It was further demonstrated that a necrotic area of myocardium may contain less than 10 per cent of the concentration of transaminase in normal myocardium from the same animal.

Although the number of determinations performed in the patients included in table 2 is small, it can be seen that 50 per cent of patients with microscopic evidence of acute myocardial inflammation due to rheumatic fever showed abnormalities of serum glutamic oxalacetic transaminase. The one patient without evidence of active inflammation, but with a high serum transaminase level, showed patchy fibrous replacement of myocardial fibers in the amputated auricular appendage.

In view of the belief of some21 that the Aschoff nodule arises from the myocardial cell itself, it is of some interest that there was no evidence in this limited series of a higher incidence of abnormal serum levels of glutamic oxalacetic transaminase in the patients with Aschoff nodules than in those with other evidences of an inflammatory process, such as
round cell infiltration or fibrinoid degeneration of collagen.

The relationship of fluctuations in the serum transaminase to variations in the clinical course of the patients is not clear. Although the appearance of congestive heart failure in children with acute rheumatic carditis is considered to be a sign of severe myocardial involvement, the serum level of the enzyme was not consistently elevated during these episodes in our group of patients. One of the nine patients in this category (table 1, group I, a) showed no elevation of the serum transaminase at any time during his hospital course.

In addition, the serum glutamic oxalacetic transaminase did not correlate consistently with alterations in the acute phase reactants. This suggests that the degree of functional impairment and inflammation of the myocardium in the rheumatic process may not be the same as the degree of injury or necrosis of myocardial fibers as measured by serum levels of transaminase. It suggests that during the course of the acute interstitial inflammatory process in the myocardium, myocardial fiber damage may supervene. Intermittent elevations of transaminase in the serum may reflect periods when damage to the myocardial fiber is occurring. The effect of the acute inflammatory process may be partly toxic causing functional impairment of the myocardium without concomitant liberation of transaminase.

Some of the observations during cortisone and aspirin therapy support this concept, since in a number of patients striking abnormalities of serum glutamic oxalacetic transaminase were noted at a time when the nonspecific indices of inflammation had been suppressed. This again indicates that elevations of transaminase in the serum and the nonspecific acute phase reactants are measurements of different aspects of the rheumatic process.

The influence of therapy with cortisone and salicylates upon alterations in the serum transaminase is unclear. Because of the severity of the illness in the patients studied, it was not feasible to compare the behavior of serum transaminase in treated and untreated groups. It is apparent, however, that despite the administration of antirheumatic therapy with relatively large doses of cortisone, elevations in serum transaminase occurred. This was true even when the laboratory signs of systemic inflammation were suppressed. This observation may indicate that the powerful anti-inflammatory effects of cortisone do not completely prevent myocardial injury and is consistent with the lack of curative effect of these compounds upon chronic rheumatic myocarditis.

The question of whether steroid or salicylate therapy may influence the serum level of glutamic oxalacetic transaminase is of considerable theoretic and practical importance. At present, the index of "adequate" antirheumatic therapy is considered to be suppression of laboratory evidence of inflammation as well as a satisfactory clinical response. However, the ultimate goal in treating rheumatic fever is protection of the patient against permanent cardiac injury. If the concentration of transaminase in the serum is an index of myocardial fiber injury, as suggested above, it is possible that an attempt should be made to increase or continue antirheumatic therapy until the serum transaminase returns to normal levels.

The normal transaminase concentrations in the spinal fluid in the three patients with chorea who were studied are not surprising in view of the absence of changes in the cerebrospinal fluid in chorea usually associated with inflammatory disease. The most common microscopic finding in the brain is perivascular infiltration with round cells. No necrosis of brain tissue is seen, hence a release of transaminase would not be expected.

In a total of six rheumatic fever patients, simultaneous measurements of transaminase in the spinal fluid and blood were performed. The ratio of serum concentration to spinal fluid concentration ranged from 2:1 to 5:1, indicating that a barrier to free diffusion of transaminase is present at the subarachnoid membrane.

**Summary**

Serum glutamic oxalacetic transaminase (SGO-T) was studied in 64 patients in various
stages of rheumatic fever and in 15 patients, either at autopsy or in whom atrial biopsy was performed during mitral commissurotomy.

Elevations in the level of this serum enzyme occurred with greatest frequency in patients with clinical or histologic evidence of active rheumatic carditis. Normal values were found in rheumatic patients without clinical evidence of active cardiac involvement. The serum level was within normal limits in all patients after the acute rheumatic process subsided.

Although frequently high, the levels of serum glutamic oxalacetic transaminase were not consistently elevated in patients with active carditis and did not follow the clinical course of the disease closely.

The effect of aspirin or cortisone upon the concentration of transaminase in the serum could not be evaluated clearly in the absence of a control group. Some patients with severe, protracted carditis continued to have an elevated serum level of glutamic oxalacetic transaminase despite the prolonged administration of relatively large doses of cortisone.

The probable relationship of increased transaminase activity to myocardial damage in rheumatic carditis is discussed.

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SUMMARIO IN INTERLINGUA

Esseva studiata in 64 patientes con febre rheumatic le variationes in le concentration seral del enzyma transaminase oxalacetic glutamic. Elevationes esseva notate in 17 ex 28 patientes con carditis de definite o dubitose activitate e transientemente in un patiente rheumatic con myocarditis viral. Con le exception de un patiente qui habeva polyarthritis e signos equivoci de un acute involvimento car-

diac, le concentrationes seral esseva normal durante rheumatic manifestationes noncardiac e in carditis inactive. Il non habeva ulle relation con temperatura, rapiditate de sedimentation, conto leucocytic, o proteina C-reactive. Il es probabile quen un intermittente necrosis de fibras myocardial causa iste aumentate concentrationes seral de transaminase.

REFERENCES


The Influence of Rheumatic Fever on Serum Concentrations of the Enzyme, Glutamic Oxalacetic Transaminase
IRWIN NYDICK, JAMES TANG, GENE H. STOLLERMAN, FELIX WRÓBLEWSKI and JOHN S. LADUE

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