ferent from the sharp evanescent fall in blood pressure produced by intravenous injection of activated Tremorine.

The fact that SKF-525A, an inhibitor of liver microsomal activity, blocks Tremorine but does not block activated Tremorine serves as a basis for determining the presence of the active form. It points, furthermore, to the liver microsomes as the site of the activation process.

Although the pharmacologic properties of activated Tremorine from different sources (urine of Tremorine-treated mice and rats, and incubates of Tremorine with preparations of liver from different species) are similar, it is clear that their chemical identity has not been established. Studies to determine the chemical nature of activated Tremorine are in progress.

*Summary.* Mouse liver slices converted Tremorine to an active form which differed from non-incubated Tremorine preparations (a) by its faster onset of action in untreated mice and cats, (b) by not being blocked by SKF-525A (diethylaminodiphenylpropylacetate), an inhibitor of liver microsomal activity, (c) by stimulating rabbit gut *in vitro* and (d) by producing an immediate slowing of the heart and fall in blood pressure on intravenous injection into anesthetized dogs. Material having the biological properties of activated Tremorine was also found in the urine of rats and mice given Tremorine and in solutions of Tremorine incubated with hamster liver slices and with hamster and rat liver homogenates.

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## Tissue and Serum Manganese Levels in Evaluation of Heart Muscle Damage. A Comparison with SGOT. (26738)

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The normal myocardium contains about 1800 μg of manganese per 100 g of dried tissue; this is roughly 2,000 times the manganese concentration present in the blood serum. Myocardial injury results in a sharp decrease in tissue manganese associated with a proportional rise in serum manganese content. Following myocardial infarction tissue manganese *decreases* to approximately 30% of its original value. Concomitantly, serum manganese *increases* approximately 2½ times. Thus, after infarction human serum contains more than 2.0 μg manganese per 100 ml, whereas prior to infarction, serum manganese content is about 1.0 μg manganese per 100 ml.

Because tissue manganese is lost very rapidly from the infarcted myocardium following cardiac injury, and a reciprocal rise in manganese concentration is observed in the serum, determination of serum manganese level should be of great value in detection of myocardial injury and, in equivocal cases, in confirmation of acute myocardial damage.

In a study at Los Angeles County Hospital, serial measures of serum manganese levels in 26 patients with unequivocal evidence of myocardial infarction were compared with serum samples from 25 patients of comparable age, sex and race admitted to the hospital with complaints other than myocardial injury. This report correlates clinical findings in our patients with serum manganese levels, as determined spectrographically from 80 blood samples taken from the patients with acute myocardial infarction, and

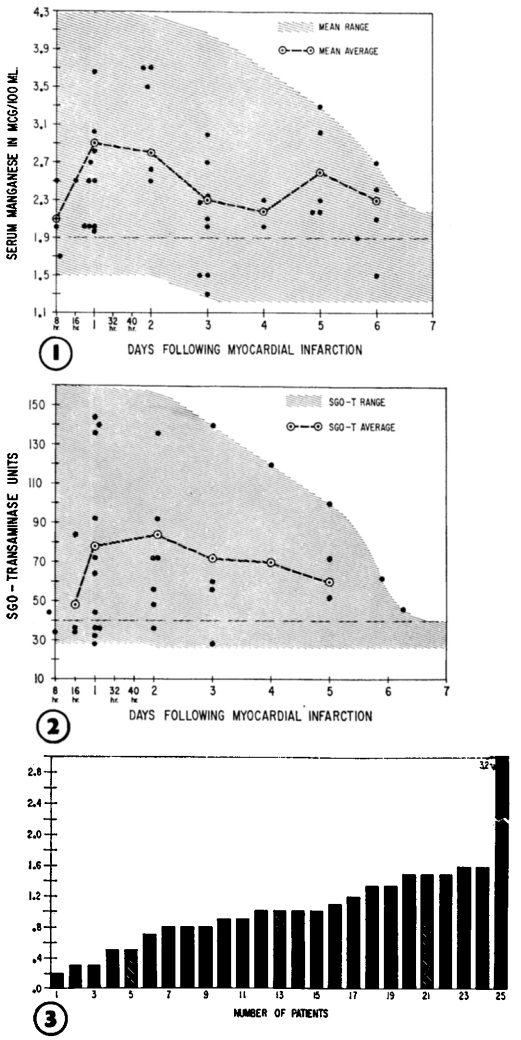


FIG. 1. Serum manganese level in myocardial infarction.

FIG. 2. Serum glutamic oxalacetic transaminase (SGOT) in myocardial infarction.

FIG. 3. Serum manganese level in conditions other than myocardial infarction. Barred columns indicate cases in which SGOT was elevated, giving false-positive results.

38 samples from the control patients.

In our patients the first sample of blood serum is received within 12 to 48 hours after onset of acute myocardial infarction. Samples also are obtained on the third and fifth day of the acute episode and, in a few instances, an additional sample is collected on the seventh day.

Blood samples are refrigerated until subjected to spectrographic analysis. Serum is separated from red blood cells before refrigeration to prevent gross hemolysis.

Within 8 to 12 hours following myocardial injury, manganese level rises; a maximum is reached within 24 to 48 hours. Serum manganese level remains elevated for 5 or 6 days, after which manganese level gradually falls to normal. Height and duration of serum manganese elevation are roughly proportional to amount of myocardial necrosis as estimated on the basis of ECG evidence. Although a close correlation exists between serum manganese level and SGOT value, serum manganese concentration is far less likely to give false positive values.

Fig. 1 depicts serum manganese values obtained in 26 patients with myocardial infarction. The shaded portion outlines the range of values. Solid dots represent actual values obtained; larger circles connected by broken lines indicate average values. In all instances but one, serum manganese level rose to above 2.0 $\mu$g/100 ml within 48 hours after onset of chest pain.

Secondary elevations in serum manganese level, noted in several instances following recurrent chest pain, apparently indicated extension of an existing infarction or development of a fresh infarction.

Determinations of SGOT values obtained simultaneously with our serum manganese values are depicted in Fig. 2. Note the similarity of ranges of values in the 2 measures; the averages, too, are rather similar in nature; however, myocardial injury is detected earlier in determinations of serum manganese, with the level rising indicatively within 8 hours of onset of pain, and remaining at elevated levels for longer periods than the serum GOT.

In 24 of the 25 patients in our control series, serum manganese levels were well below 1.9 $\mu$g/100 ml. Simultaneously determined SGOT levels in 3 of these patients were elevated and suggestive of myocardial injury; however, the low serum manganese levels in the 3 patients afford definite evidence that acute myocardial injury had not occurred.

Fig. 3 depicts the height of serum manganese in the 25 control patients in our series. The barred columns represent 3 pa-

TABLE I. Comparison of Tissue* and Serum Metal Concentrations† of Patients with and without Myocardial Infarction.

| | Tissue metal conc. in mg/100 g dried tissue | | Serum metal conc. in μg/100 ml | |
|---|---|---|---|---|
| | Acute M.I. (33 determinations) | Without M.I. (100 determinations) | Acute M.I. (38 determinations) | Without M.I. (80 determinations) |
| Metal | Mean value ± S.E. | Mean value ± S.E. | Mean value | Mean value |
| Aluminum | 1.770 ± .009 | 3.270 ± .237 | 4.30 | 3.70 |
| Calcium | 29.336 ± 6.451 | 44.800 ± 5.390 | 101,000.00 | 99,000.00 |
| Manganese | .072 ± .007 | .180 ± .011 | 2.42 | 1.01 |

* Tissues obtained at autopsy. † Mean values.

tients (Nos. 5, 13, and 21) with infectious hepatitis, hepatoma and cholecystitis, respectively, whose SGOT level was above 40 units and therefore consistent with myocardial injury. Low serum manganese levels in these patients definitely exclude the possibility of acute myocardial injury.

In the 25th patient in our control series, serum manganese concentration was 3.2 μg/100 ml on the first postoperative day, within the range usually indicative of myocardial infarction. This patient had undergone laparotomy, gastrostomy, and had had a liver biopsy the previous day. Apparently, following extensive major surgery, elevation in serum manganese concentration may mimic levels occurring after myocardial injury. Therefore, although a manganese level within normal limits definitely precludes the presence of acute myocardial injury, an elevated manganese level in the postoperative patient cannot be accepted as evidence of acute heart muscle injury.

In Table I, tissue aluminum, calcium, and manganese values obtained postmortem from "normal" patients (*i.e.*, without known cardiovascular disease) and patients with myocardial infarction are compared with serum concentrations of "normal" patients and patients with fresh myocardial infarcts. Note that concentration of all metals is lowered in tissues of the patient with myocardial infarction, and a reciprocal rise is observed in blood serum. However, the alterations in manganese are much more pronounced both in tissue and serum.

In addition to blood samples from patients with myocardial infarction and control series, serum samples from 3 patients with old myocardial infarcts, 4 patients with angina pectoris or coronary insufficiency, and 4 patients with pulmonary infarction were subjected to spectrographic analysis.

*Angina Pectoris, Coronary Insufficiency, or Slight Myocardial Damage.* Ordinarily, angina pectoris does not cause an elevation in serum manganese level. Nevertheless, in our series, 2 patients whose ECGs were not suggestive of acute myocardial infarction had elevations of serum manganese. The first of these patients had suffered a myocardial infarction 10 years previously. At hospitalization, she complained of severe chest pain of 5 days' duration. An SGOT value of 65 units was obtained at this time; her serum manganese value was 2.5 μg/100 ml. An SGOT determination on the second day of hospitalization, the sixth day of chest pain, was 113 units, which was accepted as definite evidence that a transmural myocardial infarction had occurred, and treatment for acute myocardial infarction was instituted despite lack of corroborative ECG evidence.

The second patient had for 12 years had angina pectoris relieved by nitroglycerin. She was admitted to the hospital because of crushing chest pain which radiated down the left arm and was not relieved by nitroglycerin. Although ECG confirmation of acute myocardial infarction was absent, the patient was treated for acute myocardial infarction. The SGOT value rose gradually until, on the fourth hospital day, it reached 60 units. A serum manganese determination also obtained on the fourth day showed 2.2 μg manganese per 100 ml. By the fifth day, serum manganese value had dropped to 1.5 μg/100 ml. Both erythrocyte sedimentation rate and white blood count were elevated.

*Old myocardial infarctions.* One patient

had suffered myocardial infarction 4 months previously. Although she complained of chest pain, her ECG showed no indication of acute infarction and her SGOT value was 58 units. Serum manganese determinations upon 3 separate occasions during her hospitalization all showed less than 1.5 μg of manganese per 100 ml of serum, suggesting absence of myocardial infarction.

*Pulmonary infarction.* Serum manganese levels of 3 of the 4 patients with pulmonary infarction were within normal limits. A serum manganese level compatible with myocardial infarction occurred in one patient, a 45-year-old man who complained of severe chest pain which radiated to the neck and left shoulder. This patient, who had suffered a transmural myocardial infarction 18 months previously, entered the hospital with pulmonary edema. An ECG taken at time of hospital entry was indicative of acute cor-pulmonale with severe right atrial and right ventricular hypertrophy. Serial determinations of SGOT and serum manganese are available for this patient: Blood specimens drawn on the first day showed an SGOT value of 4400 units and a serum manganese value of 3.5 μg/100 ml. On the second day of hospitalization, serum manganese level was 4.5 μg/100 ml. SGOT levels obtained on third and fourth day of hospitalization yielded values of 4400 and 2250 units, respectively. On the sixth day of hospitalization, SGOT concentration was 335 units. At autopsy the patient was found to have suffered massive pulmonary infarction.

We have found the serum aluminum value useful in differential diagnosis of pulmonary infarction and myocardial infarction. Following pulmonary infarction, the tissue aluminum value of the lung is lowered, and a 4-fold increase occurs in serum aluminum value. A comparably elevated serum aluminum value has not been noted in any condition other than pulmonary infarction. Additional information furnished by the serum aluminum value corroborates the diagnosis in pulmonary infarction and helps to differentiate between pulmonary and myocardial infarction. From our limited evidence it appears that a very high serum manganese value, above that ordinarily occurring in acute myocardial infarction, may indicate presence of massive pulmonary infarction, and serum aluminum value should be used as a check.

*Summary.* Whereas, in our series, serum manganese values in patients with congenital, infectious, degenerative, or neoplastic disease were below 1.9 μg/100 ml of serum, serum manganese was elevated above 2.0 μg following acute myocardial infarction in every instance. Massive pulmonary infarction, which also may be accompanied by high serum manganese levels, can be differentiated from myocardial infarction by additional information supplied by serum aluminum values, which are elevated following pulmonary injury but not following myocardial damage. In patients with myocardial infarction, height of the serum manganese level provides an index to extent and severity of cardiac damage as estimated on the basis of SGOT level and the ECG. Although a close correlation exists between SGOT and serum manganese values, our data indicate that serum manganese concentrations are less likely to yield false positive indications of myocardial damage.

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