E and F, in doses of 4 mg or more, and their halogenated derivatives, in doses of 0.5 mg or more, regularly induced increases in the GFR of adrenalectomized dogs; this effect became apparent during the second hour after administration of the steroids and was sustained througout the remaining collection periods. The sodium loss that occurred following administration of E and F during renal clearance studies was invariably associated with an increase in GFR. Whereas the halogenated steroids administered in small doses (which did not increase GFR) regularly caused acute retention of sodium, these same steroids administered in larger doses (which did increase GFR) frequently induced sodium loss. This paradox can be resolved by the assumption that all these steroids increase tubular reabsorption of sodium. This enhancement of sodium reabsorption, however, may be insufficient to result in a net conservation of sodium if the filtered load of sodium that is presented to the tubules is simultaneously increased.

Effects on circulating eosinophils. In adrenalectomized dogs, the decrease in circulating eosinophils was determined 4 hr following the intravenous administration of graded doses of various steroids, as a simple index of their "glucocorticoid" activity. When compared on an equimolar basis, fluoro F Ac was 20 (11–36) and chloro F Ac was 8 (5–13) times as active as F Ac.

Effects in Addison's disease. Studies carried out in two patients with Addison's disease indicated that the fluoro- and chloro-derivatives of F were considerably more effective in the treatment of this disease than were equimolar quantities of either F itself or DOC. In the longer term clinical studies, the enhanced potency of the halogenated steroids appeared to be even greater than that which was anticipated on the basis of the acute assays in animals. The symptoms of Addisonian crisis (nausea, vomiting, asthenia, and so forth) were corrected within 4 hr of the oral administration of either 0.5 mg of fluoro F Ac or 1.5 mg of chloro F Ac. Repetition of these doses every 4 hr resulted in progressive improvement in feelings of well-being, depression of circulating eosinophils, marked retention of sodium, and transient increases in potassium excretion. Withdrawal of the steroids was followed by a reversal of these effects.

Substitution of bromine. Bromo F Ac in doses of 25 to 100 μg had no effect on the excretion of sodium or potassium in adrenalectomized dogs, while in doses of 100 to 400 μg it induced some increase in the excretion of potassium but no consistent retention of sodium.

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4. We wish to thank Joseph Fried of the Squibb Institute for Medical Research, Elmer Alpert of Merck and Co., and Robert Gaunt of Ciba Pharmaceutical Co. for generous supplies of the steroids employed in this study.

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Serum Glutamic Oxaloacetic Transaminase Activity in Human Acute Transmural Myocardial Infarction

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Glutamic oxaloacetic transaminase is widely distributed in animal tissues but is most concentrated in heart muscle (*1, 2*). This property led us to study its concentration in human serum following acute myocardial infarction.

The presence of this enzyme in human blood serum and whole blood hemolysates was previously demonstrated in our laboratory (*3*) using quantitative paper chromatographic analysis of the glutamate present after incubation of serum with aspartate and α-ketoglutarate. The chemical characteristics of the enzyme in serum were studied and found to be similar to those reported for animal tissues. The normal range of activity in human serums and hemolysates was established. The level was found to be elevated in certain disease states but notably so in two patients with acute transmural myocardial infarction.

These studies led to the development of a relatively rapid spectrophotometric assay of serum glutamic oxaloacetic transaminase activity and permitted the extension of our observations.

Transaminase activity is measured by adding serum to a substrate containing aspartate and α-ketoglutarate, which in the presence of malic dehydrogenare oxidizes DPNH to DPN. The resulting change in optical

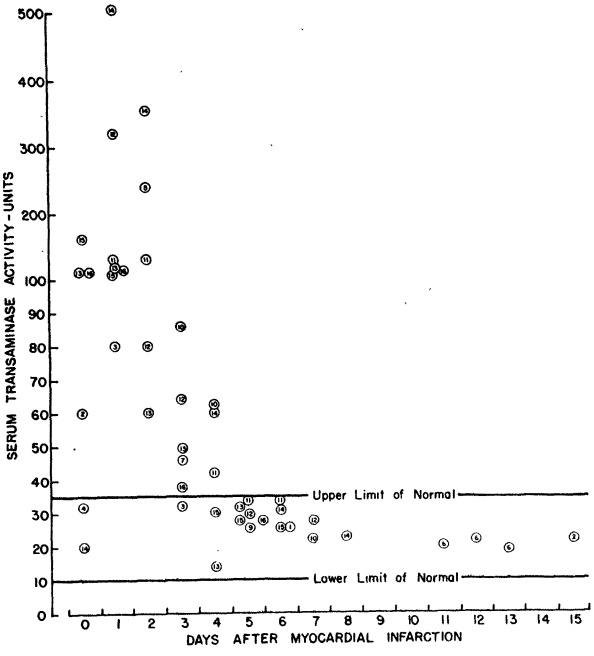

Fig. 1. Serum transaminase levels measured within a few hours to 15 days following acute myocardial infarction in 16 patients.

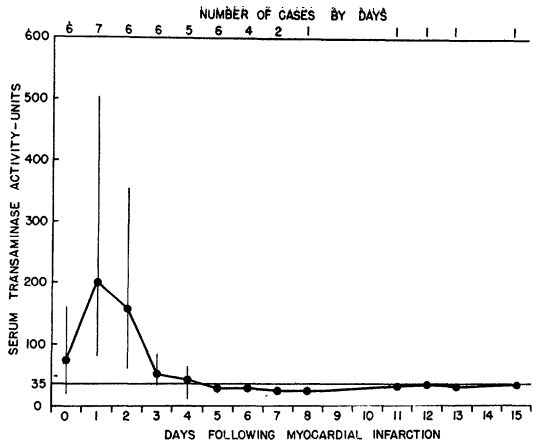

Fig. 2. Average level of serum transaminase on various days following acute myocardial infarction. The extremes of the vertical lines represent the highest and lowest values from which the averages were calculated.

density of the solution is measured in a Beckman spectrophotometer (*3*). The unit of activity was defined as the amount present in 1.0 ml of serum that causes an optical density decrease of 0.001 at wavelength 340 mμ in 1 min under the conditions described. In 50 normal individuals, the normal range was between 10 and 40 units, which agreed in range of magnitude with the values reported by us previously using paper chromatographic assay.

Serum glutamic oxaloacetic transaminase was measured in 50 normal individuals, 22 patients with cardiovascular disease uncomplicated by acute infarction, 14 patients with various infections, 17 patients with neoplastic diseases, and 16 patients with acute transmural myocardial infarction. Venous blood was obtained for serum transaminase determination without regard for the fasting state; the serum was separated from the clotted blood within from 2 to 12 hr after collection. It has been found that the activity is essentially unchanged if the separated serum is stored in a refrigerator from 1 to 10 days after collection. When possible, daily tests were made during a 5- to 15-day period.

The normal values of serum glutamic oxaloacetic transaminase activity ranged from 10 to 40 units. Figure 1 summarizes the serum transaminase activity on various days after infarction in 16 patients with acute transmural myocardial infarction. Figure 2 presents the average values in the same patients and indicates the range of activity on the first 4 days following the infarction. Figure 3 shows the serum transaminase activity along with the sedimentation rate during a 9-day period in a 60-yr-old patient who incurred an acute transmural posterior wall myocardial infarct. It is noted that 3 hr following the onset of pain, the transaminase activity was within normal limits but rose to 500 units within 12 hr, falling off gradually to normal by the sixth day. This series has now been extended to 30 patients, all of whom exhibited transaminase levels of from 100 to 6000 units on at least one of the five days following the onset of myocardial infarction.

In 22 patients with heart disease uncomplicated by acute myocardial infarction including arteriosclerotic heart disease associated with angina or coronary insufficiency and acute and chronic congestive heart failure of varying etiology, the serum transaminase activity ranged between 12 to 45 units. In two instances the level was above upper limits of normal (40 units); one patient had acute pulmonary edema and expired within 24 hr, and in another with neurogenic shock the serum transaminase was 45 units but fell to 19 within 24 hr.

All patients with acute febrile and chronic infectious diseases had serum transaminase activities within the normal range. There was little observable change in the enzyme level from the acute to the convalescent state of the illness and little variation in daily samples tested. Normal values were also encountered in uremia, pulmonary infarction, neoplastic disease per se, and other chronic processes. High levels were encountered in jaundiced patients with active liver disease.

It has been estimated that 1.5 percent of the dry weight of pig heart muscle is the protein enzyme, glutamic oxaloacetic transaminase (*4*). We have calculated that if 1 g of dried pig heart homogenate of the value reported by Cammarata (*5*) was diluted to 6 lit, there would be 400 units of activity per milliliter.

Our observations show that the serum transaminase activity rises with regularity within 12 to 24 hr in acute human myocardial infarction and returns to the normal range within 3 to 6 days thereafter. The mechanisms by which the level of the enzyme activity is altered are under study. The limited number of cases presented does not permit final evalution of these ob-

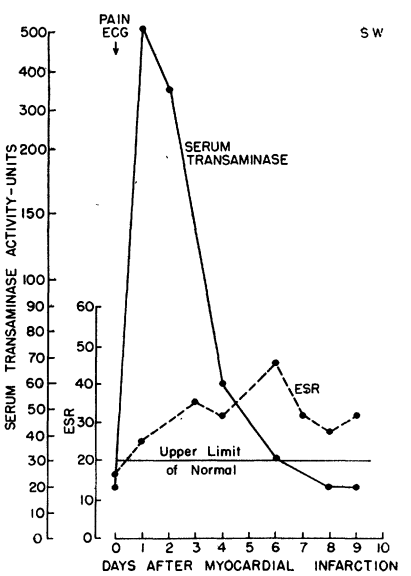

Fig. 3. Transaminase levels obtained during a 10-day period following acute myocardial infarction in patient S. W. The dotted line represents the erythrocyte sedimentation rates done on the same blood samples.

servations in regard to their diagnostic and/or prognostic significance.

Conclusions. (i) Glutamic oxaloacetic transaminase activity has been measured in human serums by a spectrophotometric method. (ii) The variations in enzyme activity in some disease states have been discussed. (iii) The serum transaminase activity in 16 patients with acute transmural myocardial infarction rose to levels 2 to 20 times normal within 24 hr and returned to normal range within 3 to 6 days thereafter without exception.

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Biuret Toxicity of Urea Foliage Sprays on Citrus

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Urea was first used as a foliage spray to supply nitrogen on apples in 1943 (*1*). Since that time it has been used as a foliage spray on other crops (*2–4*). When attempts were made to use such sprays on citrus, leaf injury resulted (*5*). This injury was a yellowing of, or loss of chlorophyll from, the distal part of the leaves and has been called "yellow-tip." It was found that the amount of yellow-tip varied with the location and with the age of the leaf. The yellow-tip is a permanent injury; the leaves do not regreen. However, subsequent new leaves do not have yellow-tip unless additional urea sprays are applied. The extent of the yellowing may vary from none to more than half of the leaf.

Since crystalline urea "sets-up" and becomes hard, most of the urea for foliage spray application now on the market has been conditioned in various ways to avoid the hardening. To determine whether yellow-tip is caused by urea or by some impurity in the urea, several spray experiments have been made (*6*). Since yellow-tip had also been observed on trees in the field to which soil applications of conditioned urea had been applied, soil experiments were also made.

One experiment was performed in a grove of mature navel orange trees in August 1953. In this experiment, sprays of 10 lb of crystalline urea per 100 gal of spray were compared with sprays of the same concentration of conditioned urea. Approximately 6 wk after spray applications, yellow-tip was prevalent on the trees sprayed with the conditioned urea but not on the trees sprayed with crystalline urea. This suggested that yellow-tip was the result of something in the conditioned urea and was not caused by urea alone.

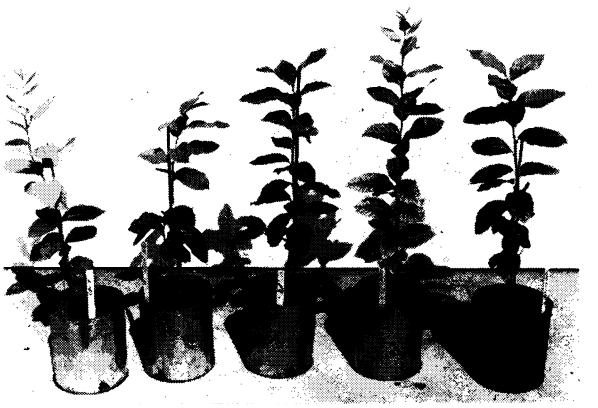

Fig. 1. Foliage sprays of combinations of biuret and urea on young budded lemon trees. Left to right: Check no spray, 0.2-percent biuret, 2-percent crystal urea, 0.2-percent biuret plus 2-percent crystal urea, and pelletized urea. Note yellow-tip (mottling) except on check and 2-percent crystalline urea plants.

Most of the conditioned urea on the market is in the form of pellets. In the making of such pellets, the urea is warmed. It has long been known that on warming, urea is converted to biuret (*7*). Biuret toxicity following foliar application of urea has been reported on pineapples (*8*). Thus biuret was the first suspect as the cause of yellow-tip. Several sources of pelletized urea were examined for biuret by the use of alkaline copper sulfate and were found to contain from 0.5 to 2.5 percent of the dry weight of a biuret-reacting material.

Following the field results, several greenhouse experiments were made to compare pelletized urea, crystalline urea, biuret, and combinations of crystalline urea and biuret. For these experiments, young budded lemon and Valencia orange trees (*9*) were used. Figure 1 shows the results of one spray experiment on

Fig. 2. Soil applications of biuret and urea to young budded lemon trees. Left to right: Check no treatment, 50 ml of 0.2-percent biuret, 50 ml of 2-percent crystal urea, 50 ml of 0.2-percent biuret plus 2-percent crystal urea. Note yellow-tip (mottling) except in check and crystalline urea treatment.