DNA 3001T
30 October 1972

TYROSINE AMINOTRANSFERASE INDUCTION IN RAT LIVER AS A RESPONSE TO IRRADIATION AND/OR FLASH BURN INJURIES

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Washington, D.C. 20305

PREPARING AGENCY
Lovelace Foundation
for
Medical Education and Research
ALBUQUERQUE, NEW MEXICO

Contract No. DA-49-146-XZ-359

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This work was supported by the Defense Nuclear Agency
under NWER/subtask MA112-03.

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ABSTRACT

Tyrosine aminotransferase (TAT) activity was measured in rat liver to determine the extent to which thermal and/or irradiation injury resulted in induction of TAT synthesis and to determine the relationship between the severity of injury and the extent of TAT induction.

Flash burns elicited increased TAT activity in the liver, and the extent of induction was related to the severity of burn injury. Thermal injuries to the skin alone resulted in a detectable increase in TAT activity in about 30 percent of the animals, while deeper burns resulted in a uniform induction in all animals. The highest TAT activity occurred in the livers of animals just prior to death from thermal injuries.

Irradiation alone did not lead to a detectable increase in TAT activity but resulted in a "superinduction" effect in animals exposed to skin burns. The latter was considered to result from interference with repressor formation due to genetic damage, resulting in uncontrolled TAT synthesis.

Thus it appears that one of the events associated with the exaggerated catabolism of proteins following severe burns is the induction of enzyme synthesis in the liver. The manner by which excessive synthesis of enzymes such as TAT in the liver can contribute toward a poor prognosis is discussed.

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ACKNOWLEDGMENTS

This project was supported by the Defense Nuclear Agency, Department of Defense, under Contract No. DA-49-146-XZ-359. We wish to express our appreciation to Mr. Takeshi Minagawa and Mrs. Berlinda Martinez for assisting in the preparation of this manuscript and to Mr. John F. Viney for technical assistance.

The experimental work discussed in this manuscript was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care" prepared by the National Academy of Sciences-National Research Council.

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INTRODUCTION

One of the more severe injuries to an organism is a large, deep burn, and the gravest metabolic consequence of such thermal injuries is death. Yet, the precise mechanisms of death after thermal injury remain largely unknown. "The terms 'metabolic', 'cellular', 'enzymatic', 'metabolic paralysis', and 'energy deficit' have all been used to describe burn death, and all imply that some unknown, biochemical defect is responsible" (reference 7). Survival or recovery might be achieved more frequently if the severe reactions to burn or the exaggerated catabolic responses thereto were better understood and could be controlled.

Previous studies suggest that the metabolic responses to traumatic injuries can be divided into two phases, the early "ebb" or shocklike phase, followed in 24 to 48 hours by the "flow" phase (reference 13). The "ebb" phase appears to be characterized by an impairment of Krebs' cycle functioning and the "flow" phase by an increased nitrogen excretion.

Previous studies of animals exposed to flash burns and/or irradiation have indicated that the early "ebb" phase was likely to be characterized by a deficiency of citrate and other Krebs' cycle intermediates in vivo and that the impaired oxidative metabolism which is often noted after thermal injuries may be related to such deficiencies (reference 4). Also, sublethal irradiation exposure may interfere with recovery from the "ebb" phase following flash burns. This raised the question as to what is the nature of the radiosensitive processes which occur during recovery from the "ebb" phase?

Biochemical events that are likely to be involved in the secondary metabolic responses to thermal injuries are an increased synthesis of enzymes in the liver which catabolize amino acids for energy production, since protein catabolism is a prominent feature of the "flow" phase (reference 13). While it has long been apparent that muscle wasting and a marked increase in nitrogen excretion were some of the more striking metabolic responses in severely burned patients (reference 7), no studies have been reported of the extent to which exaggerated protein catabolism following thermal injury may be related to

induction of amino acid degradative enzymes in the liver. The biological significance of enzyme induction in the liver could be particularly important in thermal injuries, since the stimulus for enzyme induction may persist for prolonged periods following burns.

We have, therefore, investigated the changes in activity of a model inducible enzyme, tyrosine aminotransferase (TAT) in the livers of rats exposed to flash burns and/or irradiation; TAT catalyses the transamination of an important amino acid, tyrosine, and is the first step in the catabolism of tyrosine to Krebs' cycle intermediates for energy or synthetic purposes. The activity of the enzyme is usually very low in rat liver but increases under conditions such as starvation or high protein intake, when increased catabolism of amino acids takes place. Experiments with cells cultivated in vitro suggest that the synthesis of TAT is regulated by a labile repressor which functions by reversibly inhibiting TAT messenger RNA translation into protein and by stimulating the degradation of TAT messenger RNA (references 6 and 14). Adrenal corticoids appear to be very active in blocking the action or synthesis of this repressor, although the system is also affected by other metabolites such as leucine or insulin (reference 8) and by the availability of the coenzyme, pyridoxal (reference 12). Inhibitors of RNA synthesis may either inhibit the induction of TAT in cell cultures or lead to an uncontrolled synthesis, depending on conditions (reference 9). Since genetic damage resulting in inhibition of RNA synthesis is thought to be one of the mechanisms by which irradiation affects mammalian systems (reference 1), an effect of irradiation on TAT induction and the control thereof would be expected.

METHODS

Female, 150 to 200 g Sprague-Dawley rats were obtained from Bio-Science Laboratories, Oakland, California, and maintained in a constant-temperature room at 25°C. and 70 percent relative humidity with water and Purina Rat Chow supplied ad libitum. When the animals reached a weight of 225 to 250 g, they were randomly divided into groups of 12 for exposure to thermal, irradiation, or both forms of injury. Irradiation exposure was carried out while animals were restrained in plastic baby nursing bottles mounted on Masonite panels, with 750 rad of ^{60}Co-gamma irradiation being delivered at a dose rate of 50 rad/minute. After irradiation or sham immobilization for a similar period, the dorsal and lateral surfaces were clipped. Then all animals were put into a state of deep anesthesia with 4 percent Halothane in oxygen, delivered from an anesthesia machine. The thermal and thermal plus irradiation groups were exposed to flash burns from a pulsed quartz-lamp source while anesthesized (reference 5). A thermal dose of 9.2 cal/cm^2 over a body area of 88 cm^2 of the lateral and dorsal surfaces corresponded to a full-thickness burn over approximately 30 percent of the body area. At this level of thermal injury, there was minimal penetration of radiant energy into muscle tissue. By omitting air jets which cool the quartz plates over the lamp sources, the output was increased to approximately 10 cal/cm^2, a thermal dose which penetrated through the skin and muscle of the rats but did not penetrate into the abdominal cavity.

All animals were sacrificed at 24 hours after exposure, as a maximum effect on TAT induction was noted at this time, and mortality was not as marked as at later times in the case of combined-injury animals (reference 5). Also effects of anorexia or starvation were minimal at these early times. At sacrifice, the animals were stunned and exsanguinated by jugular excision. The livers were removed, blotted dry, and weighed. A 20 percent homogenate was prepared in 0.15 M KCl and centrifuged for 30 minutes twice at 25,000 x g, 5°C. in an International B-20 refrigerated centrifuge. The final supernatant was used for assay of TAT activity.

The enzyme assays were performed as described by Granner and Tomkins (reference 3), except that serial dilutions were made of enzyme preparations to insure that the reaction rate was linear with the amount of liver supernatant present. Five to seven 1:5 serial dilutions were made in a solution containing 0.125 M phosphate buffer pH 7.6, 0.007 M L-tyrosine, and 0.0005 M pyridoxal-5'-phosphate. Following the addition of 0.5 ml of assay mixture, 0.1 ml of 0.5 M alpha-ketoglutarate, pH 7.0, was added and the reaction mixture incubated at 37° for 30 minutes. The reaction was terminated by the addition of 0.4 ml of 10 N KOH, and the solution was incubated another 30 minutes to convert the p-hydroxyphenylpyruvate to p-hydroxybenzaldehyde. The absorbance was measured at 331 nm in a Zeiss PMQ II spectrophotometer as described by Diamondstone (reference 2). Aliquots of p-hydroxyphenylpyruvate were run through the serial dilutions and incubation procedures for standardization.

In order to determine the extent to which TAT induction might also be correlated with an increased rate of tyrosine oxidation, studies were also made of the rate of ^{14}C-tyrosine oxidation to $^{14}CO_2$ in vivo. The methods of $^{14}CO_2$ collection and counting after injection of rats with 5 μc of L-tyrosine-^{14}C-(U) have been described previously (references 4 and 5). The ^{14}C-tyrosine was obtained from New England Nuclear Corporation, Boston, Massachusetts (NEC-289; 396 mCi/mmol), neutralized before use with Tris base (Sigma Chemical Company, St. Louis, Missouri), and diluted to a final concentration of 10 μc/ml. A 0.5-ml sample of this solution was injected IP into rats at time zero as described previously (reference 5).

RESULTS

When TAT activity was measured in rat liver 24 hours after exposure to flash burns, the degree of TAT induction was related to the severity of thermal injury. Thermal injury to the skin alone (9.2 cal/cm^2) resulted in a detectable response in about 30 percent of the animals exposed, but the overall increase was not significant (figure 1). When the thermal dose was increased slightly (10 cal/cm^2), the radiant energy penetrated through the skin and into the skeletal muscle. In this case, figure 1, there was a uniformly high induction of TAT. The maximum induction noted in individual animals was similar in both cases.

A problem in studies involving experimental thermal injuries is that nonlethal injuries provoke a significant TAT response in only a few animals out of an experimental group, whereas the next higher level of injury results not only in a significant response but also a significant increase in mortality. In this instance, the 24-hour mortality observed in rats exposed to a 9.2-cal/cm^2 flash burn was less than 20 percent, and in those exposed to 10 cal/cm^2, burn was approximately 50 percent.

When the effects of gamma irradiation on TAT activity in the liver were measured, an exposure of 750 rads alone did not result in any detectable TAT induction in the first 24 hours after exposure (figure 2). However, when animals exposed to irradiation were simultaneously exposed to 9.2-cal/cm^2 flash burns, a marked increase TAT induction was noted (figure 2). This also appeared to be correlated with an increased mortality, since the mortality of animals exposed to irradiation and flash burns approached 100 percent in 7 to 14 days (reference 4).

Thus there appears to be an inverse correlation between the physiological state of the animal and the TAT activity in the liver at early times after thermal or combined injuries. Animals in the terminal stages of "necrobiosis" following critical burn injuries tended to approach the TAT activity found in livers from combined-injury animals but did not surpass it. Due to the high mortality of combined-injury animals, the changes in TAT activity as a function of time

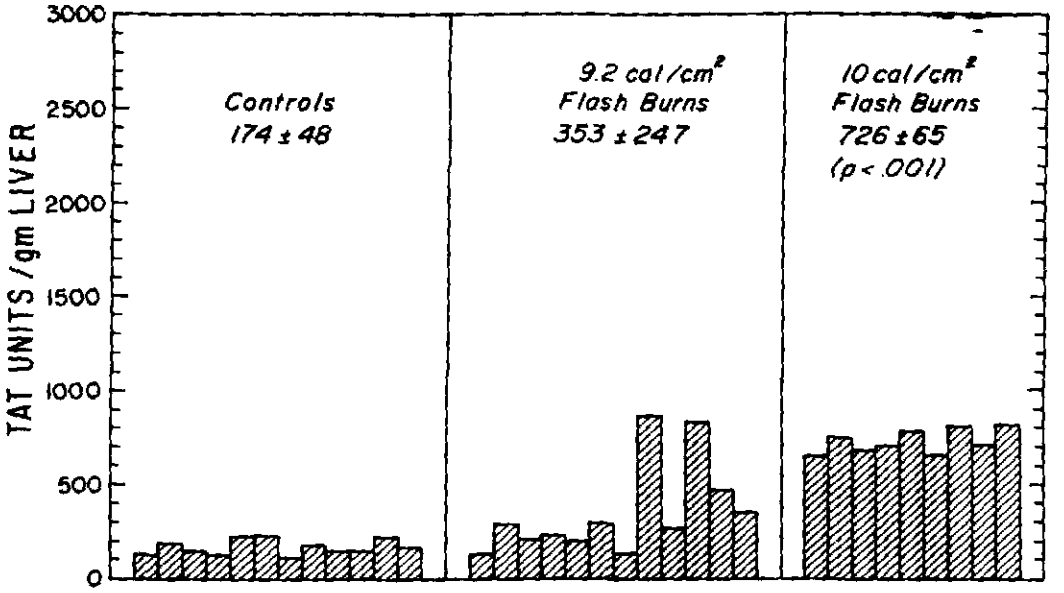

Figure 1.--TAT induction by flash burns. [Rats were exposed to flash burns while anesthesized with Halothane. Twenty-four hours later, they were sacrificed and the livers homogenized in ice-cold 0.15 M KCl and centrifuged 2x at 25,000 x g, 0°C. for 30 minutes. The supernatants were analyzed for TAT activity by the method of Diamondstone (reference 2) as modified by Granner and Tomkins (reference 3). One unit of TAT activity is defined as the production of 1 mμmole of p-hydroxyphenylpyruvate/hour in a total volume of 5 ml of assay mixture. Each bar represents an individual rat.]

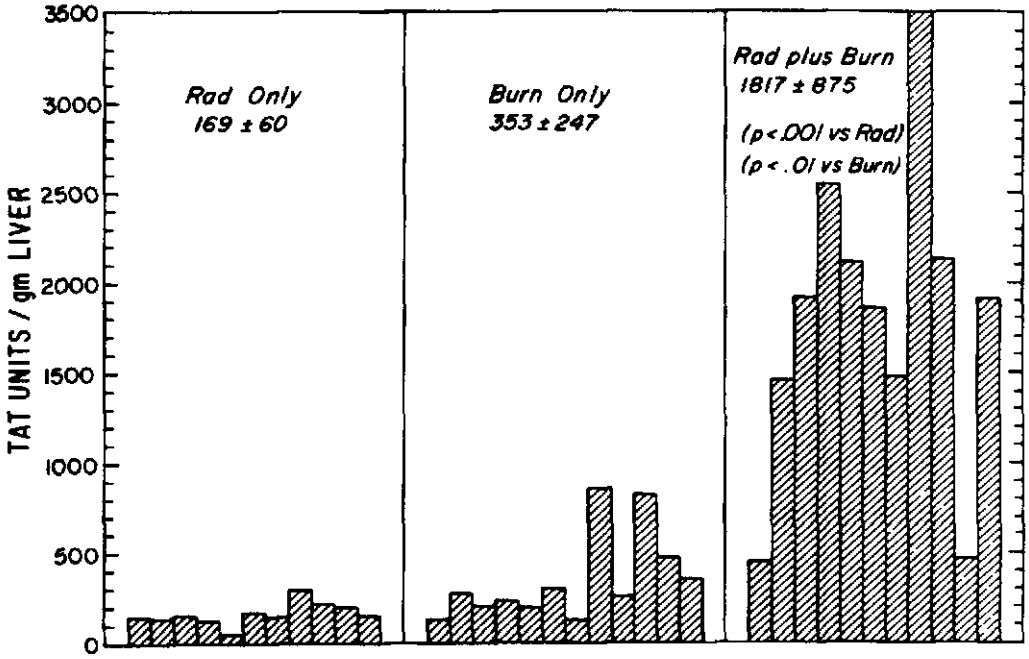

Figure 2.--TAT induction by flash burns and irradiation. [Conditions were as described in figure 1, except one group of animals was exposed to 750 rad of gamma irradiation and one group was exposed to both irradiation and 9.2-cal/cm^2 burn. The 9.2-cal/cm^2 burn group from figure 1 is repeated to facilitate comparison.]

until death could not be assessed because the few animals remaining alive after approximately 48 hours were not considered representative.

In view of the increased activity of TAT in animals exposed to irradiation and flash burns, we have investigated the rate of ^{14}C-tyrosine oxidation to $^{14}CO_2$ in vivo. Slight increases in the rate of ^{14}C-tyrosine oxidation were noted in animals exposed to irradiation or irradiation plus flash burns (figure 3); however, it was not the initial rate of tyrosine oxidation which was elevated but the rate of $^{14}CO_2$ production at later time periods--more than 1 hour after injection.

When the urinary excretion patterns following injection with ^{14}C-tyrosine were studied (figure 4), animals exposed to irradiation plus flash burns appeared to lack the peak of ^{14}C-citrate which was prevalent in control animals or animals exposed only to 9.2-cal/cm^2 flash burns. Animals exposed only to flash burns tended to exhibit increased excretion of acetate, alpha-ketoglutarate, and an unknown compound eluting after alpha-ketoglutarate. Urine samples from animals exposed only to irradiation (not shown) exhibited no significant chromatographic peaks at this time period after irradiation. This was probably due to early effects of irradiation in reducing metabolic pools of organic acids in vivo (reference 4).

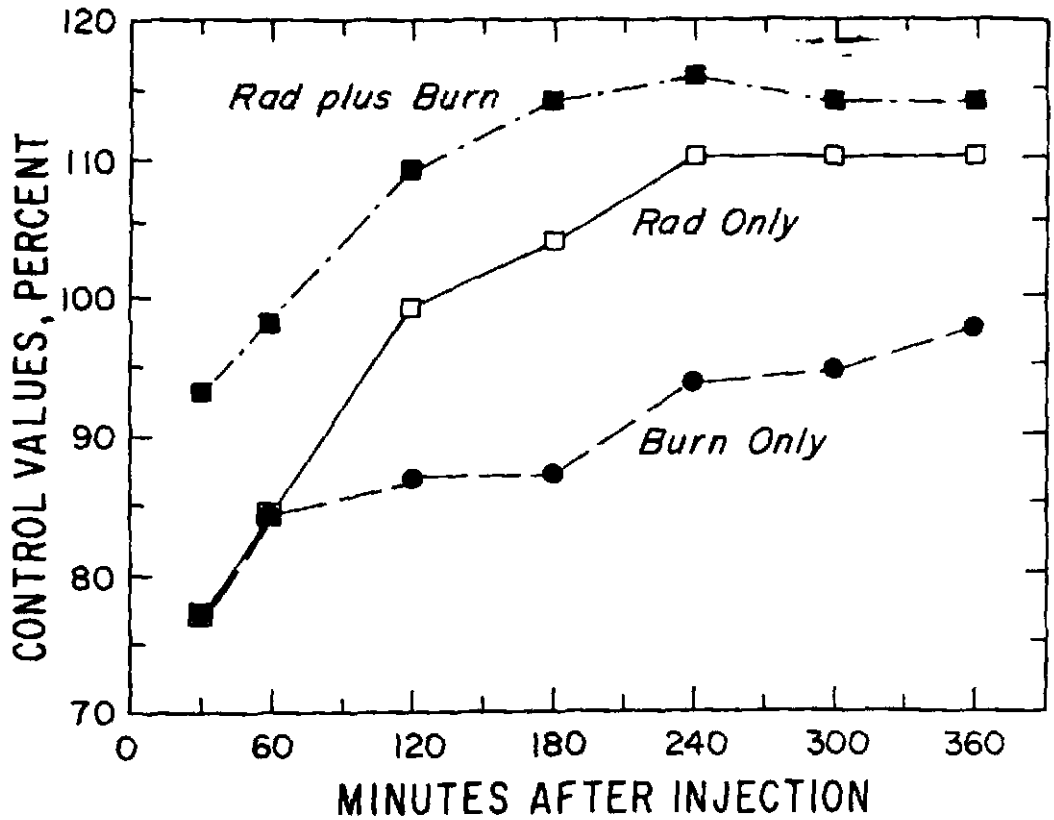

Figure 3.--Effects of single or combined injuries on ^{14}C-tyrosine oxidation in vivo. [Rats were exposed to 750 rad of gamma irradiation, 9.2 cal/cm^2 burn or both. They were injected with 5 μc of (u)-^{14}C-tyrosine 24 hours later and the $^{14}CO_2$ collected and counted. The rate of $^{14}CO_2$ production is given as percent of control values (n = 6).]

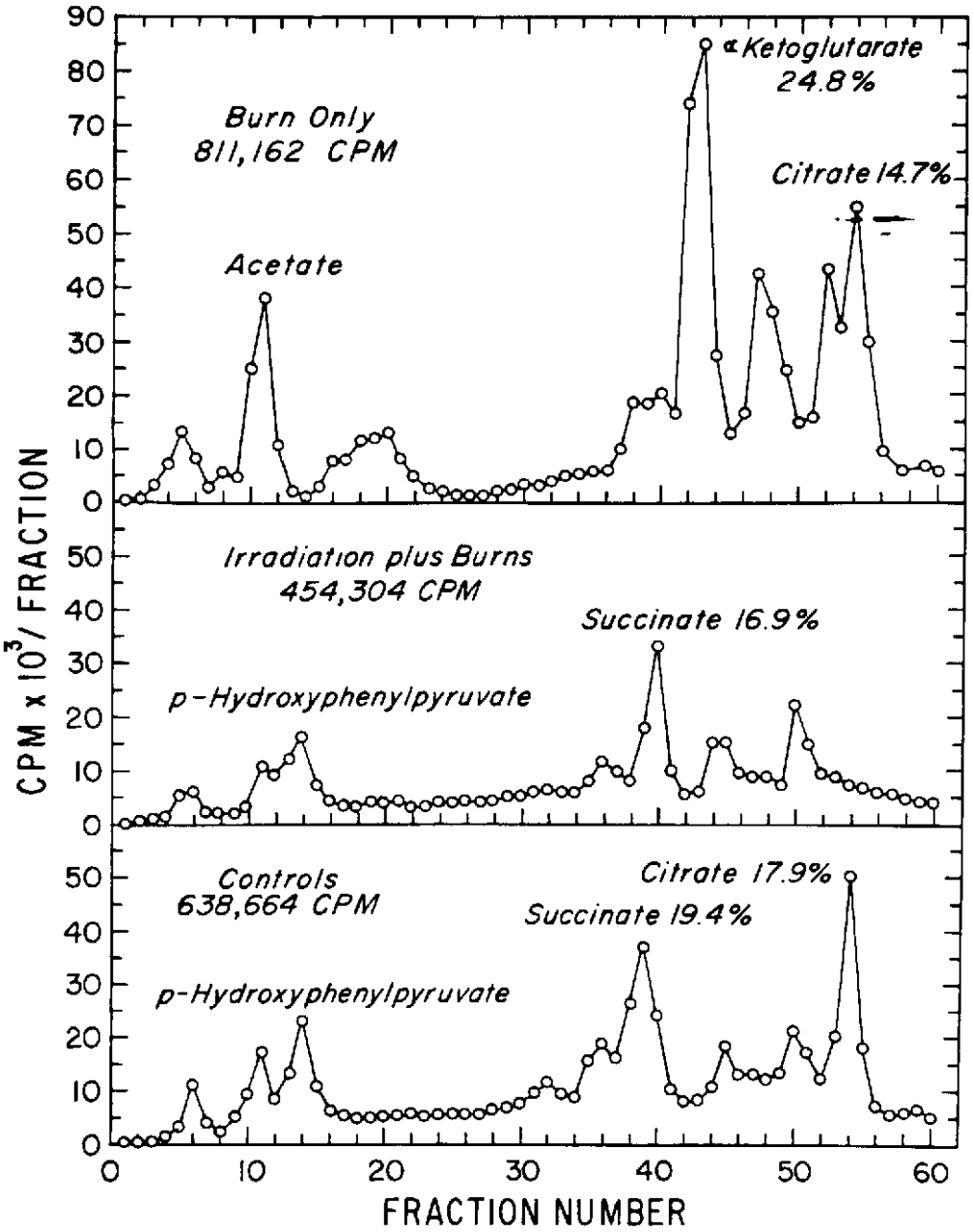

Figure 4. --Urinary excretion patterns after ^{14}C-tyrosine injection. [In the experiment described in figure 3, the animals were maintained in glass metabolic cages overnight and the urine collected under toluene. The samples were lyophilized and analyzed for radioactive organic acids by partition chromatography on silicic acid columns.]

DISCUSSION

The finding that TAT activity is significantly increased in the livers of rats exposed to irradiation and/or flash burns raises several questions: (1) Why is there an apparent relationship between the severity of thermal injury and the TAT activity in the liver? (2) Does increased TAT activity in the liver mean that the rate of tyrosine catabolism is increased proportionately? (3) Is the induction of TAT synthesis a beneficial or a deleterious response?

Present knowledge of the regulation of TAT activity in the liver predicts that the level of TAT activity is related to both the rate of synthesis and the turnover rate of the enzyme (references 6, 8, 9, 11, 12, and 14). While certain metabolic inhibitors (reference 6) and high concentrations of amino acids such as leucine (reference 8) tend to reduce the rate of TAT turnover in cell cultures, there is little information available about factors which influence the rate of TAT turnover in vivo. The rate of synthesis of TAT in vivo, on the other hand, appears to be greatly influenced by a number of agents including insulin, hydrocortisone, inhibitors of RNA synthesis, etc. Since adrenal corticosteroids are particularly active in stimulating the synthesis of TAT, they have been considered as the more important physiological inducers (reference 14).

A model for the control of TAT synthesis has been presented in which synthesis is regulated by a labile repressor which acts by reversibly inhibiting messenger RNA translation and hastening degradation of TAT messenger RNA (reference 14). The utility of the model of Tomkins is that it can explain why inhibitors of RNA synthesis can either inhibit or augment TAT synthesis, depending on conditions. Once TAT messenger RNA is made, inhibition of RNA synthesis resulting in inhibition of repressor formation would be expected to stabilize TAT messenger RNA and increase the rate of TAT synthesis. This could explain the increased TAT activity in rats exposed to both flash burns and irradiation, since genetic damage from irradiation could result in inhibition of repressor formation, allowing an uncontrolled synthesis of TAT. Inhibition of RNA synthesis is considerably more sensitive to irradiation than protein synthesis from preexisting RNA because of the smaller molecular size of RNA

compared to DNA molecules and because the biological processes of translation of existing RNA's appear to be less radiosensitive than transcription and replication of DNA (reference 1). The findings that irradiation of rats with skin burns resulted in a higher TAT activity in the liver than even a deep burn are in agreement with the hypothesis that irradiation has damaged the mechanisms controlling the rate of TAT synthesis.

If increased TAT activity accumulates in liver cells, the question becomes one of whether this enzyme is active in vivo? Studies of TAT activity in vitro suggest that the main factors limiting the action of this enzyme are the availability of substrates--tyrosine, alpha-ketoglutarate and the cofactor, pyridoxal phosphate (references 3, 8, 9, 11, and 12). Since there was a slight stimulation of $^{14}CO_2$ production but no increased urinary excretion of ^{14}C-p-hydroxyphenylpyruvate in single or combined-injury animals injected with ^{14}C-tyrosine, it may be concluded that TAT is active in the liver of animals exposed to injuries and that the p-hydroxyphenylpyruvate formed is being oxidized completely to $^{14}CO_2$ through the Krebs' cycle.

The question remains, however, whether the increased activity of TAT in animals exposed to penetrating thermal injuries or combined injuries contributes significantly to the poor prognosis of these animals. As seen in figure 5, the response can be either beneficial or deleterious. The degradation of tyrosine provides a net source of C_4 acids needed for glucose production or to prime the Krebs' cycle for energy production. However, excessive, uncontrolled catabolism of tyrosine (and probably other amino acids) may impair energy production, since the "transaminase shunt" results in a net gain of only 2 ATP compared with 9 ATP by utilization of alpha-ketoglutarate through the Krebs' cycle to oxalacetate (reference 14). The principal difference in the two pathways is due to the 4 ATP consumed in urea synthesis and the lesser number of reducing equivalents produced in the "transaminase shunt." A heavy drain on the mitochondrial supply of alpha-ketoglutarate and other Krebs' cycle intermediates by activation of the "transaminase shunt" is a possible explanation for the markedly reduced level of ^{14}C-citrate excretion in animals exposed to single or combined injuries (reference 4). The rate of citrate synthesis in isolated rat liver mitochondria appears to depend mainly on the availability of substrates, acetyl-CoA

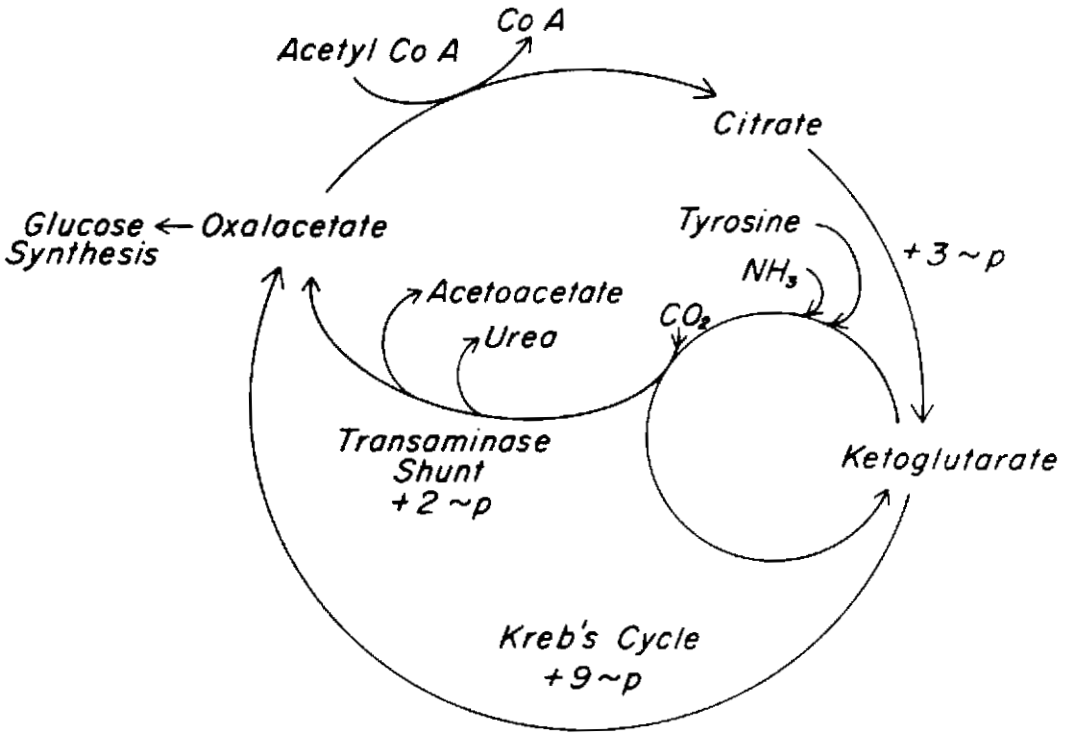

Figure 5.--Tyrosine metabolism in liver.

and oxalacetate, of which oxalacetate is more often limiting (reference 10). This interpretation suggests that the high levels of TAT noted in severe injuries may interfere with the recovery processes.

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Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1 ORIGINATING ACTIVITY *(Corporate author)*
Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico 87108

2a. REPORT SECURITY CLASSIFICATION
UNCLASSIFIED

2b. GROUP

3 REPORT TITLE
Tyrosine Aminotransferase Induction In Rat Liver as a Response to Irradiation and/or Flash Burn Injuries

4 DESCRIPTIVE NOTES *(Type of report and inclusive dates)*
Topical Report

5 AUTHOR(S) *(First name, middle initial, last name)*
Thomas R. Henderson and Robert K. Jones

6 REPORT DATE	7a. TOTAL NO. OF PAGES	7b NO. OF REFS
October 1972	32	15

8a. CONTRACT OR GRANT NO	9a. ORIGINATOR'S REPORT NUMBER(S)
DA-49-146-XZ-359	DNA 3001T
b. PROJECT NO NWER: QAXM	
c. Task and Subtask: A112	9b. OTHER REPORT NO(S) *(Any other numbers that may be assigned this report)*
d. Work Unit: 03	

10 DISTRIBUTION STATEMENT
Approved for Public Release; distribution unlimited.

11 SUPPLEMENTARY NOTES	12 SPONSORING MILITARY ACTIVITY
	Director Defense Nuclear Agency Washington, D.C. 20305

13 ABSTRACT

Tyrosine aminotransferase (TAT) activity was measured in rat liver to determine the extent to which thermal and/or irradiation injury resulted in induction of TAT synthesis and to determine the relationship between the severity of injury and the extent of TAT induction.

Flash burns elicited increased TAT activity in the liver, and the extent of induction was related to the severity of burn injury. Thermal injuries to the skin alone resulted in a detectable increase in TAT activity in about 30 percent of the animals, while deeper burns resulted in a uniform induction in all animals. The highest TAT activity occurred in the livers of animals just prior to death from thermal injuries.

Irradiation alone did not lead to a detectable increase in TAT activity but resulted in a "superinduction" effect in animals exposed to skin burns. The latter was considered to result from interference with repressor formation due to genetic damage, resulting in uncontrolled TAT synthesis.

Thus it appears that one of the events associated with the exaggerated catabolism of proteins following severe burns is the induction of enzyme synthesis in the liver. The manner by which excessive synthesis of enzymes such as TAT in the liver can contribute towards a poor prognosis is discussed.

DD FORM 1 NOV 65 1473

UNCLASSIFIED

Security Classification

14 KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Tyrosine aminotransferase						
Enzyme induction						
Burns						
Irradiation						
Combined injury						