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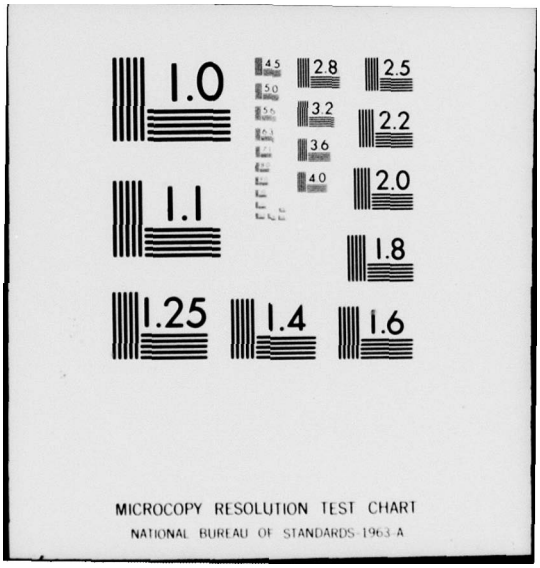
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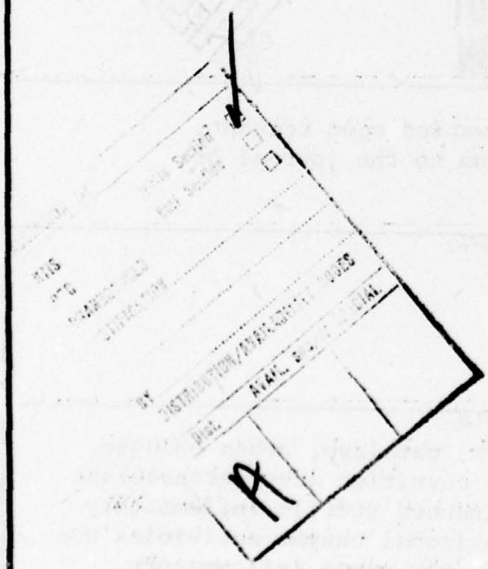
Hepatocytes isolated from turpentine-treated rats showed, respectively, decreased and increased capacity for lipid oxidation and fatty acid esterification. These results, which demonstrate the existence of an inverse relationship between hepatic peroxisomal content and lipid metabolism during inflammation, are analogous to the known relationship between liver peroxisomal proliferation and drugs which lower serum cholesterol and triglycerides.



Effects of Inflammation on Peroxisomal Enzyme Activity, Catalase Synthesis and Lipid Metabolism

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In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on the Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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RUNNING TITLE

INFLAMMATION AND HEPATIC PEROXISOMES

ABSTRACT

The activity of hepatic peroxisomal enzymes, catalase, urate oxidase, D-amino acid oxidase, hydroxy acid oxidase, and carnitine acetyltransferase were serially measured following a turpentine-induced sterile inflammatory lesion in rats. The ensuing depression in peroxisomal enzyme activities was shown to be temporally related to development of the acute inflammatory response indicating that depression of peroxisomal activity is a nonspecific host response to inflammation.

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Additional key words: Nafenopin, clofibrate, hypolipidemic drugs, acute-phase proteins, liver cells, infection.

INTRODUCTION

The name peroxisome designates a special type of intracellular respiratory particle characterized by the association of one or more H_2O_2 generating oxidases with large amounts of catalase (16). In a recent biochemical and morphometric study we reported that pneumococcal sepsis caused a marked reduction in the number of peroxisomes of rat liver cells and in the activity of two marker enzymes, catalase and urate oxidase (8).

A decrease in catalase activity has also been shown to accompany subcutaneous injury (34) and hepatectomy (23), and while the latter also induces a concomitant loss in activity of other peroxisomal enzymes, it is not known if hepatic depression of peroxisomal enzymes represents a generalized nonspecific response of the host to inflammatory stress. In the present study, a sterile inflammatory lesion was induced by subcutaneous injection of turpentine in normal rats as well as in rats treated with the peroxisomal proliferating drug, nafenopin. The activity of hepatic peroxisomal enzymes were then serially measured and the results temporally related with expression of known acute-phase reactants. The resulting pattern of change in the activity of peroxisomal enzymes was found to be consistent with development of the acute inflammatory response, suggesting that depression of peroxisomal activity is another nonspecific host response to inflammation.

While the decrease in peroxisomal enzyme activity following tissue injury has been correlated with a decrease in enzyme protein (24, 33) it is not known if the change represents decreased synthesis, increased degradation, or both. Hence, kinetic measurements of hepatic catalase degradation and synthesis were made using, for the former, allylisopropylacetamide to block catalase synthesis (41), and for the

latter, aminotriazole to inactivate specifically pre-existing catalase (41). Results indicate that the decrease in catalase activity during acute inflammation stems primarily from reduced synthesis of the enzyme.

Since a role for peroxisomes in lipid metabolism has been proposed (4, 15, 43), hepatocytes were isolated from control and turpentine-treated rats and their capacity for fatty acid oxidation and esterification evaluated. Results are discussed with respect to known alterations in lipid metabolism during infection and inflammation.

MATERIALS AND METHODS

ANIMALS AND SAMPLE PREPARATIONS

Male, Fisher-Dunning rats weighing 200-250 gm., housed in light-temperature-controlled quarters, were fed rat chow and water ad libitum. Rectal temperatures were monitored twice daily with a Yellow Springs Telethermometer. Rats were inoculated subcutaneously, at the nape of the neck, with turpentine at a dose of 2.5 ml./kg. body weight. Control rats, designated Day 0, were killed within 15 min. following the injection of turpentine. The remaining rats were killed, in groups of five, at selected 24-hour intervals. For collection of tissue samples, rats were anesthetized with Halothane (Ayerst Laboratories), the abdominal cavity was opened and 3 to 4 ml. of blood were collected from the inferior vena cava by venipuncture with a heparinized syringe. An aliquot of blood was taken for total and differential leukocyte counts, while the remaining blood was immediately cooled, centrifuged and the resulting plasma subsequently assayed for enzymatic activitites, trace metals and α_2-macrofetoprotein. The liver was excised, rinsed in 0.9 per cent NaCl, weighed and a portion homogenized in 3 volumes of 0.9 per cent

NaCl in a Brinkman polytron.

In a separate study, complete necropsy and microscopic examinations were performed on groups of three rats for up to 72 hours after turpentine inoculation.

CHEMICAL AND ENZYME ANALYSES

Hepatic catalase activity was assayed spectrophotometrically at 240 nm by measuring the rate of H_2O_2 decomposition (28). The first-order rate constant was calculated and converted to micromoles of H_2O_2 concentration of 37.5 μmole/3 ml. of reaction mixture. Urate oxidase was assayed in borate-HCl buffer, pH 9.0, by following the oxidation of uric acid at 292 nm (26); D-amino acid oxidase and hydroxy acid oxidase were measured in sodium pyrophosphate buffer, pH 8.6, using D-alanine and glycolate as substrates, respectively. The resulting α-ketoacids were then quantitated by a reaction with 2-4-dinitrophenyl hydrazine (26). Carnitine-dependent acetyltransferase activity was determined by following the thiol reagent, 5', 5'-dithio-bis (2-nitrobenzoate), coupled release of CoA-SH at 412 nm (29). Peroxisomal enzyme activities are reported in milliunits/nanomoles of substrate converted per milligram of protein per minute.

Plasma zinc and iron (36) concentrations were determined by atomic absorption spectrophotometry. Lysozyme levels were measured by the lysoplate method of Osserman and Lawlor (35) while β-glucuronidase activity was determined as described by Canonico and Bird (6). α_2-Macrofetoprotein was determined by the immunoprecipitation assay of Weimer and Benjamin (49).

Protein concentrations were assessed by an automated Lowry procedure using bovine serum albumin (BSA) as standard (27).

DRUG TREATMENTS

Nafenopin treated rats were maintained on a diet of powdered rat chow containing 0.1 per cent (w/w) nafenopin for 1 week prior to use. 3-Amino-1, 2, 4,-triazole (AT) was given as an aqueous (50 mg./ml.) intraperitoneal injection at a dose of 2 ml./100 gm. body weight. Solutions of allylisopropylacetamide (AIA), 25 mg./ml. water, were administered twice daily at a dose of 1 ml./100 gm. body weight. Where applicable, turpentine was given subcutaneously 12 hours after the initial injection of AIA and coincident with AT.

PREPARATION OF SINGLE CELL SUSPENSION OF HEPATOCYTES

Hepatic parenchymal cells (HPC) were isolated from nembutal (50 mg./100 gm. body weight) anesthetized rats by in situ perfusion of a solution of 0.03 per cent collagenase (Type II, Worthington Biochemicals), 1.5 per cent fatty acid free BSA (Fraction V, Sigma) and 50 µg./ml. Gentamicin (Schering Corp.) in Ca^{++}-free Krebs-Henseleit bicarbonate (K-H) buffer pH 7.4. The perfusion and subsequent processing of the liver was according to the method of Berry (3). HPC viability (typically 85-90 per cent viable) was assessed by trypan blue exclusion and the concentration of cells was adjusted to 3.5×10^7 HPC/ml. in K-H buffer containing 50 µg./ml. Gentamicin.

LIPID METABOLISM

The metabolism of fatty acids, complexed at a molar ratio of 2:1 with BSA was monitored by measuring their incorporation into cellular lipids and oxidation to CO_2. Hepatocytes (3.5×10^6 in 1.5 ml. K-H buffer were incubated in polypropylene tubes with 2 µCi. of the [1-^{14}C] labeled fatty acids. The reaction mixtures were gassed for 15 seconds with a mixture of 95 per cent O_2 and 5 per cent CO_2, stoppered and incubated at 37° in a reciprocating water bath (160 osc./min.) for up to 60 minutes. Cellular

lipids were then extracted and quantitated by the method of Folch et al. (11). For fatty acid determinations reactions were terminated by injection of 0.5 ml. of 10 per cent trichloroacetic acid and after 30 minutes, radioactive CO_2 was measured on a Bactec R301 (Johnson Lab. Incorp., Cockeysville, Md.).

STATISTICS

Results obtained from days 1 to 5 turpentine-treated rats were compared to day 0 values and the statistical significance determined by Student's t test. The validity of this comparison was assured by initial studies which showed that saline-injected rats, pair-fed to turpentine-treated rats, did not differ from day 0 values in any of the measured prameters.

RESULTS

PATHOLOGY

Gross and microscopic observations revealed that the lesions significant to turpentine inoculation were the development of subcutaneous abscesses at the inoculation site, hepatic fatty changes and renal tubular changes. Subcutaneous turpentine inoculation sites progress from diffuse cellulitis characterized by liquifaction necrosis, edema, neutrophil and mononuclear cell infiltration 24 hours after inoculation to moderately well encapsulated abscesses by 72 hours. Compared with day 0 rats, minimal fatty changes were seen in periportal hepatocytes by 24 hours post-turpentine inoculation, increased by 48 hours and appeared to be reduced by 72 hours post-inoculation. In these studies the greatest fatty changes were only minimal to mild. Hyaline droplet changes were also observed in proximal convoluted tubules of all turpentine-inoculated rats.

RELATION OF THE INFLAMMATORY RESPONSE TO HEPATIC PEROXISOMAL ENZYME ACTIVITIES

Biochemical and physiological responses to turpentine-induced inflammatory subcutaneous lesions are shown in Table 1. Fever occurred on day 1, while leukopenia was recorded on days 1 to 3. Consistent with development of acute-phase response to inflammation are the depression of plasma iron on day 1 and plasma zinc on days 1 to 3, as well as the appearance of acute-phase serum protein as depicted by α_2-macrofeto-protein (MFP). Peak plasma MFP concentration, whose appearance in blood requires de novo transcription (46) and thus is indicative of de novo protein synthesis, occurred at 48 hours and was substantially reduced by 72 hours. Increasing concentrations of plasma lysozyme were consistent with development of an inflammatory lesion. Plasma β-glucuronidase, and enzyme proposed to be an indicator of hepatic cellular damage (7), showed only a small rise on day 1.

The hepatic peroxisomal enzymes, catalase, urate oxidase, D-amino acid oxidase and hydroxy acid oxidase manifested decreased activity following turpentine injecion (Table 2). Catalase showed the greatest depression in activity (a 60 per cent decrease by day 3), urate oxidase, D-amino acid oxidase and hydroxy acid oxidase showed reductions of 35, 33 and 46 per cent, respectively.

Fluxes in carnitine acetyltransferase activity were measured in Nafenopin-treated rats since this drug (which causes a marked proliferation of hepatic peroxisomes) also increases carnitine acetyl-transferase activity 100 fold and doubles the activity of catalase. While Nafenopin treatment did not qualitatively alter the physiologic and metabolic responses of rats to turpentine, carntine acetyltransferase

activity was decreased by 45 per cent within 48 hours of administration of turpentine (Table 3). This response was quantitatively and temporally similar to that observed for catalase.

KINETICS OF CATALASE SYNTHESIS AND DEGRADATION

The rate of catalase catabolism (K_d) was determined by using AIA to block catalase for the next 48 hours. In a semilogarithmic plot of the data (Fig. 1) straight lines are obtained from which the calculated half-life of catalase in control rats is 1.31 days (99 per cent confidence limits equal 1.22 to 1.42) while that in experimental rats was 0.95 days (99 per cent confidence limits equal 0.87 to 1.04 days). From these values the first order rate constant (K_d) for catalase destruction, calculated from the relationship $K_d = \ln 2/T_{1/2}$ are 0.0220 and 0.0304 for control and experimental rats respectively.

Although the rate of synthesis (K_s) of catalase in control animals can be calculated from the relationship $K_s = K_d D_N$, that of experimental rats cannot because the basal steady state activity (C_N) of catalase in turpentine-treated rats is unknown. Hence, the rate of synthesis was determined from the rate at which catalase activity returned following aminotriazole treatment (Fig. 2). The in vivo injection of AT rapidly caused a 95 per cent decrease in liver catalase activity resulting from the formation of an irreversible complex with the enzyme. Following a lag period of approximately 10 hours, during which excess AT was excreted, there was a return of catalase activity due to de novo synthesis of the enzyme. The rate of return of catalase activity can be approximated by comparison of the experimental data to a theoretical curve described by the relationship (41):

$$C_t = \frac{K_s}{K_d} \left(1 - \mathrm{EXP}^{-K_d t}\right) \qquad \text{eq. (1)}$$

The experimental data for control rats fit the theoretical curve on assuming a K_s of 17.5 units of catalase per hour (Fig. 2). In turpentine-treated rats, two distinct rates of catalase synthesis were evident. During the first 65 hours following the administration of turpentine, the rate of synthesis was equivalent to 7 units per hour, which when compared to control rats represented a 60 per cent reduction in the rate of synthesis. Subsequent to this initial period the rate appeared equivalent to that of the control group (Table 4).

The change in rate of catalase synthesis occurred at approximately the same time as the change in the concentration of the acute-phase serum protein MFP. This observation supports an earlier suggestion that the synthesis of acute-phase serum protein during infection and inflammation may occur at the expense of peroxisomal protein synthesis (8).

Fig. 3 shows the change in catalase activity, with respect to time, that would be expected from the calculated rates of destruction (curve B) or synthesis, (curve C), of the enzyme, either alone or together (curve D), following trupentine administration. It is calculated that the change in rate of synthesis can account for 76 per cent of the loss of catalase activity by 72 hours post-turpentine injection.

EFFECT OF INFLAMMATION ON LIPID METABOLISM

Since it has been postulated that peroxisomes may have a role in lipid metabolism, freshly isolated hapatocytes were tested for their capacity to metabolize fatty acids. Shown in Table 5, hepatocytes from turpentine-treated rats oxidized the added fatty acids, oleate, palmitate, and octanoate to $^{14}CO_2$ at a significantly lower rate than control hepatocytes. On the other hand, incorporation of ^{14}C into esterified cellular lipids was significantly increased when compared to control cells.

DISCUSSION

Depression of liver catalase activity has been a consistent finding in hosts with bacterial infections or sterile inflammatory lesions (1, 8, 34). A decrease in liver catalase activity in tumor-bearing rats, subsequently shown to result from bacterial contamination of the tumor (19, 20), was found to be related to a reduction in the absolute concentration of the enzyme protein (33). The results obtained in the present study demonstrate that while catalase catabolism is slightly increased, the depression in activity during the acute phase of the inflammatory reaction results primarily from a 60 per cent reduction in the rate of synthesis of the enzyme.

The depressions of urate oxidase, hydroxy acid oxidase, D-amino acid oxidase and carnitine acetyltransferase activity which were temporally similar to the change in catalase activity suggests that the synthesis of these enzymes may be similarly reduced. A decrease in synthesis of peroxisomal enzymes may thus result in reduction of the actual number of liver peroxisomes such as has been reported to occur during pneumococcal sepsis (8).

Nishimura *et al.* (34) suggested that the depression in hepatic catalase occurring after subcutaneous injury may be mediated by release of an intermediate substance at the site of injury, which when transported to the liver, effects the synthesis of the enzyme. Such an intermediary substance has been shown to be released from phagocytic cells following their ingestion of microorganisms or necrotic tissue (2). The leukocytic mediator can elicit the nonspecific acute-phase reactions associated with infection and inflammation by stimulating hepatic RNA synthesis, amino acid flux and synthesis of acute-phase globulins (48). In addition,

leukocyte-derived factors had been shown to cause an array of physiological alterations in a traumatized host which include fever (42), increased plasma copper (37), ceruloplasmin (37), glucagon and insulin (12).

Since the alterations in peroxisomal enzyme activities during the turpentine-induced inflammatory response appear temporally related with expression of the known acute-phase reactants, we propose that the depression of peroxisomal activity is another nonspecific host response to infection and inflammation. That this effect is a nonspecific response to tissue injury and not a toxic effect of turpentine is supported by the similarity of the peroxisomal response following subcutaneous injections of talcum powder (34, unpublished observations), bacterial infections (8), and partial hepatectomy (23). Whether the peroxisomal response is a direct effect of a leukocytic mediator remains to be determined.

Similarly obscure is the survival value of such an adaptation. The reduced levels of peroxisomal enzyme activity may represent biochemical lesions which contribute to cellular dysfunction. Alternatively, the observed enzymatic changes may represent a normal response to inflammation which is of some yet undetermined benefit to the host. The possibility also exists that peroxisomes may contribute little to cellular homeostasis and their synthesis may become expendable or subordinate to synthesis and release by hepatocytes of acute-phase serum proteins.

The difficulty in differentiating between these possibilities results from our incomplete understanding of the precise role of peroxisomes in cellular metabolism. Their predominance in cells associated with lipid metabolism and the inverse relationship between hepatic peroxisomal content and drugs which lower serum cholesterol and triglycerides have suggested a specific involvement for peroxisomes in lipid metabolism (4, 15, 43).

Lazarow and de Duve (25) have recently demostrated the presence in purified peroxisomes of a cyanide-insensitive fatty acetyl-CoA oxidizing system using oxygen and NAD as electron acceptors. The activity of this system increased approximately 10 times in rats treated with an antihyperlipidemic drug (clofibrate) which is known to cause peroxisomal proliferation. The observed reduction in the rate of fatty acid oxidation by hepatocytes isolated from turpentine-treated rats, as well as septic infected rats (unpublished observations), may be the result of a decrease in activity of the peroxisomal fatty acetyl-CoA oxidizing system. This possibility is intriguing in light of the observation that mitochondria isolated from infected rats oxidize fatty acids in vitro equally well as control mitochondria (32).

Consistent with a role for peroxisomes in lipid metabolism are observations which suggest the existence of an inverse relationship between peroxisomal activity and the capacity of the liver to synthesize cholesterol and esterify fatty acids. As outlined in Table 6, rats treated with antihyperlipidemic drugs show an increase in peroxisomes, catalase, carnitine acetyltransferase and fatty acid oxidation, and a decreased capacity to synthesize cholesterol and triglycerides. In contrast, conditions such as infection and inflammation which are accompanied by a reduction of hepatic peroxisomes are associated with a pattern of lipid metabolism which is inversely related to that induced by antihyperlipidemic drugs. The possibility therefore exists that peroxisomal proliferation and fatty acid oxidation, on the one hand, and cholesterol and triglyceride synthesis, on the other, may be linked genetic functions whose level of activity and expression are inversely modulated by mediators of inflammation and antihyperlipidemic drugs.

Although the significance of these relationships as well as the real extent to which peroxisomal activity contributes to altered patterns of hepatic lipid metabolism during infection and inflammation remains to be determined, this study has served to identify a decrease in hepatic peroxisomal activity as another nonspecific acute response of a host to infection and inflammation. Furthermore, the inflammation-induced modificaiton of peroxisomal activity offers a new experimental approach to evaluate further the contribution of these organelles to cellular metabolism.

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TABLE 1. PHYSIOLOGIC AND METABOLIC RESPONSES IN RATS FOLLOWING TURPENTINE INJECTION

Parameter	Mean Values + S.E. by days post-turpentine injection[a]				
	0	1	2	3	5
Body temperature °C.	37.2 ± 0.1	38.9 ± 0.3[b]	37.5 ± 0.1	37.0 ± 0.1	37.8 ± 0.2
WBC (x 10^{-3}/mm.^{3})	6.22 ± 0.48	4.00 ± 0.29[c]	4.35 ± 0.49[d]	3.94 ± 0.29[c]	6.66 ± 0.75
PMN (%)	16.8 ± 2.6	14.0 ± 2.8	4.3 ± 2.0[c]	17.2 ± 5.0	29.2 ± 5.5[d]
Plasma Fe (µg./dl.)	315 ± 17	151 ± 13[b]	328 ± 9	315 ± 14	376 ± 18[d]
Plasma Zn (µg./dl.)	125 ± 6	86 ± 4[b]	86 ± 4[b]	74 ± 7[b]	113 ± 17
Plasma α_2-MFP (mg./ml.)	1.1 ± 0.3	35.8 ± 7.8[b]	62.6 ± 14.3[b]	26.2 ± 6.3[b]	14.0 ± 4.6[b]
Plasma lysozyme (µg./ml.)	2.5 ± 0.3	3.3 ± 0.1	4.1 ± 0.2[c]	3.7 ± 0.2	4.3 ± 0.2[b]
Plasma β-Glucuronidase (U/dl.)	57.5 ± 6.4	86.8 ± 10.8[d]	60.1 ± 4.2	37.7 ± 3.5	53.3 ± 5.7

[a] N = 10 for day 0, 5 for days 1-5.

[b] $p < 0.001$

[c] $p < 0.01$

[d] $p < 0.05$

TABLE 2. HEPATIC PEROXISOMAL ENZYME ACTIVITIES FOLLOWING TURPENTINE INJECTION

Enzyme	Milliunits ± S.E. by days post-turpentine injection[a]				
	0	1	2	3	5
Catlase	795 ± 28	607 ± 51[c]	400 ± 46[b]	319 ± 9[b]	668 ± 2[c]
Urate oxidase	4.41 ± 0.29	4.12 ± 0.39	3.36 ± 0.57	2.89 ± 0.36[d]	5.03 ± 0.22
D-amino acid oxidase	7.61 ± 0.76	6.41 ± 0.28	4.56 ± 0.34[d]	5.07 ± 0.21[d]	4.78 ± 0.53[d]
Hydroxy-acid oxidase	12.4 ± 0.92	10.2 ± 0.69	6.79 ± 0.13[c]	6.67 ± 0.17[b]	6.77 ± 0.39[b]

[a] N = 10 for day 0, 5 for days 1-5

[b] $p < 0.001$

[c] $p < 0.01$

[d] $p < 0.05$

TABLE 3. PHYSIOLOGIC AND METABOLIC RESPONSES IN NAFENOPIN-FED RATS FOLLOWING TURPENTINE INJECTION

Parameter	Mean ± S.E. by days post-turpentine injection[a]				
	0	1	2	3	5
Body temperature °C.	37.1 ± 0.2	39.5 ± 0.2[b]	38.1 ± 0.2[c]	37.5 ± 1	37.7 ± 0.2
WBC (x 10^{-3}/mm.^{3})	6.94 ± 0.47	3.52 ± 0.31[b]	3.92 ± 0.23[b]	6.14 ± 0.64	6.20 ± 0.66
PMN (%)	16.2 ± 3.1	12.0 ± 2.7	3.1 ± 1.8[c]	12.0 ± 0.6	16.1 ± 1.6
Plasma Fe (ug./dl.)	314 ± 12	159 ± 18[b]	225 ± 18[d]	227 ± 16	302 ± 17
Plasma Zn (ug./dl.)	116 ± 3	70 ± 2[b]	89 ± 2[b]	89 ± 4[b]	91 ± 3[b]
Plasma α_2-MFP (mg./ml.)	0.5 ± 0.3	13.0 ± 1.8[b]	22.6 ± 5.3[b]	25.2 ± 4.1[b]	8.0 ± 3.0[c]
Plasma lysozyme (ug./ml.)	2.5 ± 0.1	3.2 ± 0.1[b]	4.2 ± 0.3[b]	4.4 ± 0.3[b]	4.0 ± 0.2[b]
Plasma β-Glucuronidase (U/dl.)	72.7 ± 7.1	115.8 ± 8.5[c]	107.2 ± 4.7[c]	73.0 ± 7	75.0 ± 12.3
Catalase (mU)	1573 ± 28	1125 ± 79[c]	991 ± 106[b]	869 ± 35[b]	1160 ± 118[b]
Carnitine acetyltransferase (U/mg. protein)	60.9 ± 5.3	42.7 ± 4.4	35.0 ± 0.3[c]	37.3 ± 9.3[d]	41.5 ± 4.4[d]

[a] N = 10 for day 0, N = 5 for days 1-5.

[b] $p < 0.001$

[c] $p < 0.05$

[d] $p < 0.05$

TABLE 4. CALCULATED RATES FOR CATALASE DESTRUCTION AND SYNTHESIS FOLLOWING TURPENTINE INOCULATION.

Hours Post-turpentine	Rate of destruction (K_d)	Rate of synthesis (K_s)	Corresponding curve in Fig. 2
	% per hour	mU per hour	
CONTROL	2.20	17.5	A
10 - 65	3.04	7.0	B
65+	2.20	17.5	C

TABLE 5. METABOLISM OF FATTY ACIDS BY ISOLATED HEPATOCYTES FROM CONTROL AND TURPENTINE-TREATED RATS.

Fatty acid		nmol. substrate converted converted/hour/5 x 10^6 cells ± S.E. (N)	
Substrate	Metabolic parameter	Control rats	Turpentine-treated rats
Oleate	$^{14}CO_2$ Production	7.31 ± 0.41 (9)	3.74 ± 0.29 (9)[a]
Palmitate		6.13 ± 1.09 (9)	3.53 ± 0.28 (9)[a]
Octanoate		2.06 ± 0.19 (9)	1.61 ± 0.70 (9)[a]
Oleate	^{14}C-esterified cell lipid	11.24 ± 1.00 (21)	15.65 ± 1.40 (18)[b]
Palmitate		4.52 ± 0.31 (21)	6.73 ± 0.37 (18)[a]
Octanoate		0.80 ± 0.06 (18)	1.31 ± 0.05 (21)[a]

Substrate consisted of 2 μCi. of [1- ^{14}C] labeled fatty acid and 2mM unlabeled fatty acid complexed at a molar ratio of 2:1 with bovine serum albumin.

[a] $p < 0.01$ [b] $p < 0.025$

TABLE 6. MODULATION OF HEPATIC AND BLOOD PARAMETERS IN RESPONSE TO TISSUE INJURY (INFECTION OR INFLAMMATION) OR TREATMENT WITH ANTI-HYPERLIPIDEMIC DRUGS.

Parameter	Tissue Injury	Ref.	Anti Hyperlipidemic Drugs	Ref.
Peroxisome density	-[a]	(8)	+	(43, 44)
Catalase synthesis	-	(b)	+	(45)
Carnitine acetyl-transferase activity	-	(b)	+	(13, 31)
Fatty acid oxidation	-	(32)	+	(9, c)
In vitro peroxisomal fatty acid oxidation			+	(25)
Blood ketone bodies	-	(32)	+	(30)
Cholesterol synthesis	+	(5)	-	(21)
Fatty acid esterification	+	(5, b)	- +	(10, 22) (9, 14)
Bound/free ribosome ratio	+	(47)	-	(39)
Synthesis of serum proteins	+	(40)	-	(39)
Susceptibility to *S. pneumoniae* infection	Uniformly lethal	(38)	Increased resistance	(38)

[a] -, decreased; +, increased

[b] This report

[c] Unpublished observation

LEGEND TO FIGURES

Fig. 1. Kinetics of liver catalase destruction. Semilogarithmic plot of catalase activity vs. time in control and turpentine-treated rats given 20 mg. AIA per 100 gm. body weight twice daily. Turpentine was given 12 hours after the first injection of AIA.

Fig. 2. Return of liver catalase activity after injection of 3 amino-1, 2, 4-triazole. Open and closed circles represent experimental data. Solid lines are theoretical curves to fit equation 1 (in text) on assuming rates of synthesis and destruction as given in Table 5. Stippled bar represents average catalase activity $\pm$ S.E. of rats not given aminotriazole.

Fig. 3. Theoretical curve showing the expected change in catalase activity with respect to time due to changes in the rate of synthesis (K_s) and/or destruction (K_d). Curve A, steady state value where K_s = 17.5 units/hour and K_d = 2.20 per cent/hour; Curve B, K_d = 3.04 per cent/hour; Curve C, K_s = 7 units/hours; Curve D, sum of curves B and C. Solid squares represent experimental observations as reported in Table 1.

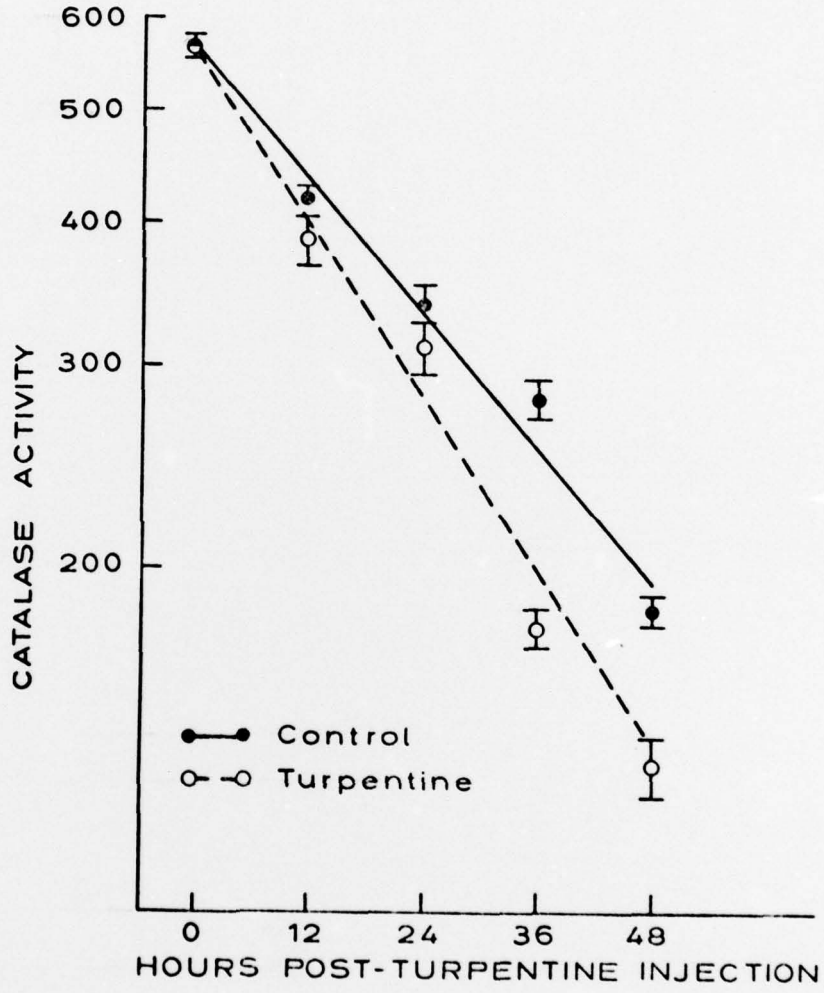


Fig 1 Canonico et al

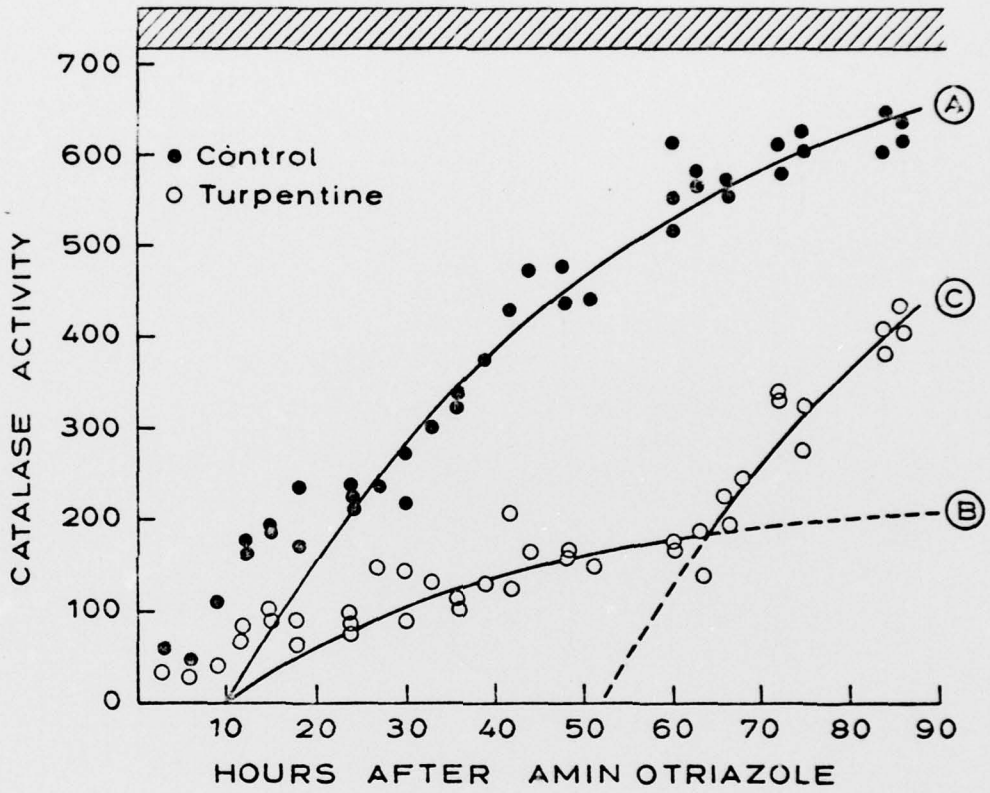
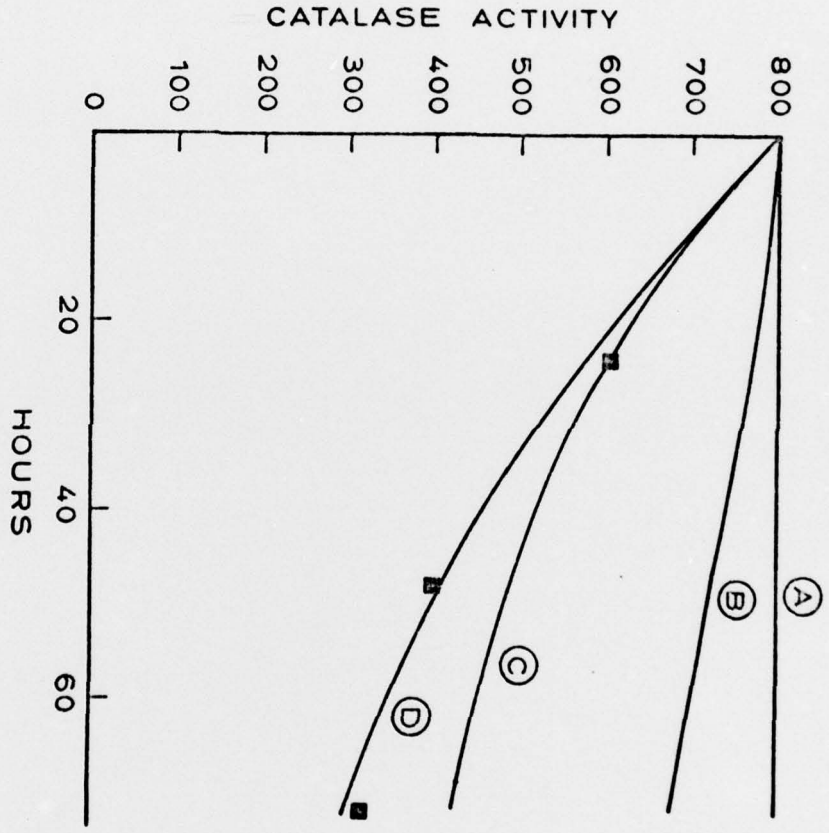


Fig 2 Corrected



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