that the preliminary injection of insulin greatly increased the susceptibility of mice to endotoxin shock.

Eighteen hours after the administration of either insulin or up to 800 μg of endotoxin there were no deaths. Significant mortality was found, however, among mice pretreated with insulin and challenged with either 200 or 400 μg of endotoxin (70% and 90% mortality, respectively).

Insulin is capable of heightening the sensitivity of experimental animals to the vasoactive amines, histamine and serotonin[7], to immediate and delayed-type hypersensitivity states[4], as well as to anaphylactoid agents such as dextran and peptone[4,6]. The present experiment suggests that insulin-induced hypoglycemia can also exacerbate endotoxin shock in mice. This result is consistent with the thesis that there is a reciprocal relationship between the glycemic state of a host and its susceptibility to a wide variety of stressor agents[4-6]. If the enhanced susceptibility of insulin-pretreated animals to endotoxin shock is a result of the compounding of the hypoglycemic effects of both of these agents, one might expect that glucose would exert a protective effect against endotoxin shock. Recently, it has been demonstrated that glucose is capable of prolonging the survival time of adrenalectomized rats challenged with endotoxin[8]. We are currently investigating this phenomenon in intact animals.

Effect of insulin on susceptibility of CFW mice to *Salmonella typhosa* endotoxin

Sensitizing agent	Dose IU	Challenge agent[a]	Dose μg	Dead/ total[b]
–	–	Endotoxin	200	0/10
–	–	Endotoxin	400	0/9
–	–	Endotoxin	800	0/10
Insulin	0.5	–	–	0/8
Insulin	0.5	Endotoxin	200	7/10
Insulin	0.5	Endotoxin	400	9/10

[a] Challenge agent injected 10 min after sensitizing agent. All injections i.p. [b] Deaths tabulated 18 h after challenge.

Résumé. Nous avons constaté que les souris traitées à l'insuline possèdent une sensibilité élevée à l'endotoxine de bactéries à gram négatif. Ce résultat concorde avec l'hypothèse d'une relation inverse entre la quantité de glucose dans le sang et la sensibilité d'un hôte à une grande variété de «stressors».

R. E. Pieroni and L. Levine

Division of Biologic Laboratories, State Laboratory Institute, Massachusetts Department of Public Health, and the Department of Microbiology, Harvard School of Public Health, Boston (Massachusetts 02130, USA), 6 January 1969.

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Ethanol Blood Levels Following Acute i.v. Administration in Mice

The rate of metabolism of ethanol in vivo is generally accepted as being linear and independent of blood concentration. The principal rate controlling factors are thought to be the amount of liver alcohol dehydrogenase and the availability of NAD[1]. In the present study the rate of disappearance of blood alcohol has been measured after a single i.v. injection and has been found to be both concentration dependent and, at high concentrations, nonlinear.

Materials and methods. Adult, male, DBA/2 mice, *20–25* g, were injected with ethanol in physiological saline into the tail vein. Doses of 0.33, 0.67 and 2.67 g/kg were used. The duration of the injection was 1 min and blood samples were withdrawn at 5, 20, 35 and 50 min after the injection was complete. Samples were taken from the retro-orbital sinus directly into a 50 μl disposable micropipette and the ethanol concentration determined by the method previously described[2].

Results. The results are shown in the Figure. At the lowest dose level (0.33 g/kg) the blood ethanol concentration decreases at a rate of 17.3 μg/ml/min during the first period and falls to less than half this rate during the second interval. For the 0.67 g/kg dose the rate during the first 2 periods is constant and equal to the initial rate at the lower dose level. In the final 15 min period the rate decreases slightly but not significantly. After the 2.67 g/kg dose the initial decline of blood alcohol is more than twice that seen after the lower doses ($P < 0.002$). During the second interval the rate is somewhat greater than that after the smaller doses but in the final 15 min is very significantly smaller ($P < 0.01$).

Discussion. The results obtained here with the 2 lower doses (0.33 and 0.67 g/kg) conform with the idea that the rate of ethanol metabolism is linear and independent of concentration provided that the concentration exceeds that required to saturate the available alcohol dehydrogenase. Below this concentration blood alcohol levels are known to fall exponentially[3] and this explains the fall off in rate seen here at the lowest dose. The results obtained with the highest dose (2.67 g/kg) do not, however, fit this concept. The total metabolism over the whole 50 min period is substantially the same as that seen after the lower doses but this is made up of a very rapid initial rate balanced by a small or negligable final rate. The large increase in rate in the initial period

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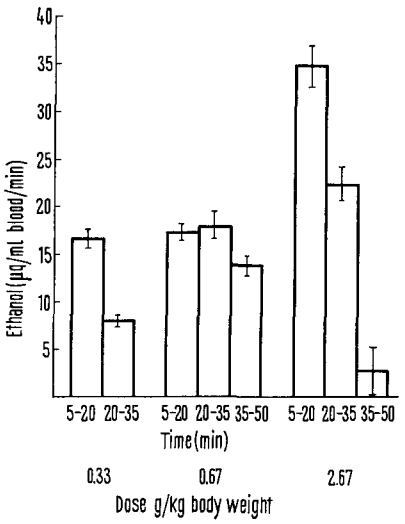
(5–20 min) compared with the rate seen after the lower doses suggests that an alternate metabolic pathway which requires a high concentration of ethanol is coming into play since the lower doses must be presumed to give a concentration of ethanol sufficient to saturate the available alcohol dehydrogenase. Preliminary results from this laboratory indicate that the microsomal mixed function oxidase system which has been reported to oxidize ethanol[4] is such a possible pathway. The final period (35–50 min) after this dose is characterized by a very slow rate of ethanol metabolism. This biphasic effect may be explained by assuming that following a large dose of ethanol the limiting factor after the initial period of rapid metabolism becomes the rate of reoxidation of $NADH_2$. It seems from the results that this reoxidation is slower after a large than after smaller doses which would suggest that the oxidation of $NADH_2$ can be depressed by rapid ethanol metabolism leading to alternating periods of fast and slow metabolism. Preliminary experiments in the monkey, a species which allows for repeated samples to be taken over a period of hours, have confirmed this pattern after a high (2.67 g/kg) but not after a lower (1.33 g/kg) dose of ethanol[5]. These effects are being investigated[6].



Decline in blood ethanol after i.v. dosage. Mice received 0.33, 0.67 and 2.67 g/kg body wt. i.v. into the tail vein. The rate of disappearance of ethanol from the blood for the periods 5–20, 20–35 and 35–50 min is shown (± S.E.M.) for the 3 doses.

Zusammenfassung. Nach einer einzelnen intravenösen Dosis von 0,33, 0,67 und 2,67 g/kg Äthanol wurde der Stoffwechsel in Mäusen untersucht. Es wurden dosenabhängige Geschwindigkeiten des Stoffwechsels gefunden.

MARY K. ROACH and P. J. CREAVEN

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Die Wirkung von Na_3[Ca-DTPA] auf den Glykogengehalt von Niere und Leber der Ratte

Bei der systematischen Untersuchung der Pathogenese von Nierenschädigungen bei Ratten durch den Chelatbildner Na_2[Ca-ÄDTA] (Äthylendiamintetraazetat) konnten wir den in der Literatur[1–7] nicht beschriebenen Befund erheben, dass ÄDTA neben der hydropischen Degeneration auch zu einer auffallenden Zunahme von histochemisch darstellbarem Glykogen in bestimmten Nephronabschnitten führt[8]. Diese Feststellung gab Anlass, bei der vorliegenden Arbeit über die Wirkungen des dem ÄDTA verwandten Na_3[Ca-DTPA] (Diäthylentriaminpentaazetat) neben den Nieren auch Leber und Darm – als möglicherweise mitbeeinflusste Organe – zu untersuchen. DTPA ist insofern von Interesse, als es jetzt allgemein als Antidot der Wahl bei Vergiftungen mit bestimmten stabilen und radioaktiven Metallionen angesehen wird[9], was eine weiterführende Analyse (vgl. [2, 10, 11]) der allgemeinen toxischen Wirkungen wünschenswert macht.

Versuchstiere waren männliche Ratten des Heiligenberg-Stammes, denen 1, 2, 4 bzw. 8 mmol Na_3[Ca-DTPA] kg^{-1}/d^{-1} i.p. oder s.c. injiziert wurde. Kontrolltiere erhielten äquimolare Kochsalzlösung. Jeweils 24 h nach einer vorgegebenen Zahl von Injektionen wurden je 5 Tiere durch Äther getötet. Die Fixierung einer 2 mm dicken Querscheibe einer Niere, eines Stückes Duodenum und Leber erfolgte in eiskalter Rossmanscher Lösung. An 7 µ dicken Schnitten wurde die PJS-Reaktion nach Mac-Manus – zur Glykogenkontrolle nach Diastasebehandlung – durchgeführt; Kernfärbung nach Weigert.

Bereits 24 h nach 1 mm kg^{-1}/d^{-1} lässt sich in den Zellen der Marksammelrohre eine Glykogenvermehrung nachweisen (Figur 1). Sie nimmt mit den weiteren Injektionen zunächst noch zu, dann wieder ab, wobei dann in der ganzen Henleschen Schleife Glykogen auftritt (Figuren 2 und 3).

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