muscles. Although ethanol is considered to be a central nervous system depressant[7], it can depolarize neurons[7]. In addition, it has been demonstrated that low concentrations of ethanol can increase activity of afferent nerves from primary and secondary endings in the muscle spindles and tendon organs of in situ rat caudal muscle[8] as well as cause singly excited cat soleus motor nerve terminals to fire repetitively[9]. Collectively, such reports suggest that ethanol may have both excitatory and depressant effects on other excitable tissues, in addition to vascular muscles.

An attractive hypothesis to explain ethanol enhancement and inhibition of $PGF_{2\alpha}$ responses might be related to the effects of this alcohol on the intracellular availability of free, ionized calcium (Ca^{++}). Ethanol has been demonstrated to affect the movement of Ca^{++} in several excitable tissues[10], including those used here[4]. Ethanol-induced enhanced uptake, or release, of intracellular Ca^{++} could result in a potentiation of PG contractions, since the action of all vasoactive stimulants, including $PGF_{2\alpha}$, are dependent on availability of Ca^{++}[11]. High concentrations of ethanol could inhibit PG responses by simply reducing the availability of free, ionized Ca^{++}. Interestingly, these latter high concentrations of ethanol, which are associated with anesthesia, death and coma[7], can inhibit the contractile effect of Ca^{++} in potassium-depolarized rat aortic and portal vein segments[4].

Although the differential effects of ethanol observed here may be linked to actions on cellular Ca^{++}[4], further work will be required to corroborate this tenet since other explanations for the observed differences could be invoked[12].

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Phenobarbital and SKF-525A on Vinblastine and Vincristine Toxicity in Mice[1]

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Summary. The effect of SKF-525A and phenobarbital on the LD_{50} values of vinblastine and vincristine suggests that the toxicity of these agents in mice does not arise from a toxic metabolite.

The vinca alkaloids, vinblastine (VLB) and vincristine (VCR) are clinically useful antitumor agents, yet little is known of their mechanism of action or mode of metabolism[3]. Interestingly, VLB and VCR exhibit different antitumor spectra and different toxic symptoms despite a high degree of structural similarity between the two compounds. Among the hypotheses suggested for these differences is the possibility that VLB and VCR may have different metabolic fates and give rise to different toxicities and/or antitumor activities[4,5]. It was therefore of interest to observe the effect of the metabolic stimulator, phenobarbital, and the metabolic inhibitor, SKF-525A, on the toxicities of these two antitumor agents.

Six-week-old DBA/2 male mice were given aqueous solutions of the drug i.p. One group received only VLB or VCR. A 2nd group was treated twice daily with 50 mg/kg sodium phenobarbital solution for 3 days prior to administration of VLB or VCR. A 3rd group of mice was treated with a single 50 mg/kg dose of SKF-525A 1 h before giving VLB or VCR. All deaths occurring within 1 week of drug administration were counted. LD_{50} values were calculated using a maximum likelihood probit analysis method programmed for digital computation. The results are displayed in the Table.

Pretreatment of the animals with phenobarbital increased the LD_{50} to more than double that of VLB alone but, in contrast, had considerably less effect on the LD_{50} of VCR. When the animals were pretreated with SKF-525A a much greater decrease was seen in the LD_{50} of VLB than in the LD_{50} of VCR.

These results suggest that the lethal toxicity of VLB and VCR in these animals is due primarily to the parent drugs and not to the formation of toxic metabolites. If toxic metabolites were responsible for the toxic lethal effects, then pretreatment with phenobarbital would be expected to decrease the LD_{50} of the drugs, while pre-

Effect of phenobarbital and SKF-525A pretreatment on vinblastine and vincristine toxicity in DBA/2 mice

	LD_{50} (mg/kg ± SE)		
	Alone	Pretreatment	
		Phenobarbital	SKF 525A
VLB	9.85 ± 1.38	26.5 ± 3.8	2.80 ± 0.97
VCR	1.83 ± 0.17	2.38 ± 0.69	1.23 ± 0.23

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treatment with SKF-525A would be expected to increase the LD_{50} values. In fact, the opposite effects were observed with both phenobarbital and SKF-525A.

Considering that VLB and VCR are responsible for their own observed toxic effects, the results obtained in the present work are consistent with the findings that 50–65% of a dose of tritiated VCR in rats is excreted unchanged (urine and bile)[6], but only 2–5% of a dose of tritiated VLB is excreted unchanged under similar conditions[5]. That is, agents which affect the metabolism of a drug have a greater effect on the toxicity of those drugs which are more extensively metabolized.

Whether similar relationships hold for the antitumor effects of these drugs is not known.

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Elevation of Serum Xanthine Oxidase Following Halothane Anesthesia in the Rat

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Summary. Halothane anesthesia was found to be hepatotoxic in the rat, as demonstrated by a significant elevation of serum xanthine oxidase (SXO) level. SXO appeared to be a more sensitive marker of liver damage than serum glutamic oxalacetic transaminase. SXO was found to be elevated also following exposure to relative hypoxia.

In man, halothane anesthesia has been occasionally associated with hepatic damage, as evidenced clinically, histologically or biochemically[1–3]. Various animal species are believed to be less prone than man to halothane-induced liver damage, as for instance the dog[4–7], the monkey[4,7,8], the mouse[9,10] and the rat[9,11,12] in which administration of halothane by inhalation failed to produce elevation in the serum level of hepatocellular enzymes or histologically detectable abnormality. Only in the guinea-pig halothane has been found to cause early focal diffuse hepatitis, which, however, was not associated with a detectable release of the hepatocellular enzymes, glutamic oxalacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT) or lactic dehydrogenase (LDH)[13].

It has recently been shown by several investigators[14,15], and confirmed in our laboratory[16], that in the human as well as in several animal species, including the rat[17], serum xanthine oxidase activity (SXO) is a highly sensitive indicator of hepatocellular damage. It was the aim of the present study to reevaluate the possible hepatotoxicity of halothane in the rat by utilizing SXO as a marker.

Materials and methods. 70 Wistar rats of either sex between 100 and 120 g, were randomly divided into 7 groups of 10 animals each, as shown in the Table; one group of 10 rats served as non-anesthetized control. The rats, 2 at a time, were placed in a 6-liter glass chamber. The anesthetic agents, nitrous oxide (N_2O) oxygen and halothane, were delivered from an Fluotec Mark III vaporizer at a flow rate of 7 l/min. The oxygen concentration in the delivered gas mixture was regulated by an Oxygen Analyzer IL 406. The non-anesthetized control rats were kept in cages in the room.

Rats selected for reexposure were removed from the anesthetic chamber after the first exposure and kept in cages for 1 week following which the same anesthetic procedure was repeated. Blood samples obtained immediately following anesthesia by cardiac puncture, were allowed to clot, centrifuged, and the separated sera were assayed for SXO and for SGOT.

SXO was assayed radiochemically, as described by OLIVER and SPERLING[18] by measuring the enzymatic conversion of ^{14}C-labelled hypoxanthine to uric acid. The activity of the enzyme is expressed in units/l, a unit being the amount of enzyme catalyzing the oxidation of 1 nmole of hypoxanthine to uric acid in 1 min at 37 °C. SGOT was measured according to FURUNO and SHEEMA[19].

Results and comment. The mean SXO and SGOT values in the non-anesthetized rats, 5062 ± 572 and 96.4 ± 14.05 units/l, respectively (see Table), were markedly higher than the serum levels of these enzymes found in healthy human subjects in our laboratory, 1.3 ± 2.1 and 21 ± 8.4 units/l, respectively[16]. This finding is in accordance with reports of other investigators[20–22]. The strikingly high

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