Introduction

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The explosion of knowledge in the fields of biology and chemistry has not gone unnoticed by the toxicologist, pharmacologist, physiologist, or physician. Indeed, basic findings in biology and biochemistry have found extrapolation to man, and this symposium is concerned with how man is served through an understanding of basic factors of living organisms in general.

Two basic factors must be considered in relating how information derived from species other than man can be used in order to explain what goes on in man. These are simple, but they form an important part in the overall scheme of what is or is not useful to explain how man will respond to an insult emerging from the environment. These factors are: *1*) species differences in response to environment, and *2*) nutritional components and biochemical pathways directing responses in various species to environmental agents. One example may serve to illustrate both points.

Toxicologists have known for a very long time that the simplest of alcohols, methyl alcohol, is quite toxic to man. We have also known for a very long time that this alcohol is almost completely innocuous in the rat, in rabbits, and in guinea pigs (7) (Table 1). Recently, we have shown that, under certain conditions, it is possible to reproduce many of the findings reported in man in the monkey (5). At first glance some might be tempted to ask what relevance this has to us since methanol poisoning represents only a minor percentage of the poisonings reported in the United States. However, most everyone knows now that methanol is being proposed, and is in use already in certain areas, as a fuel and source of energy. Therefore, what seemed to be a problem of mere minor or academic interest turns out to be one of great potential importance.

TABLE 1. Sensitivity of methanol poisoning

Rat	–
Mouse	–
Guinea pig	–
Monkey	+
Man	+

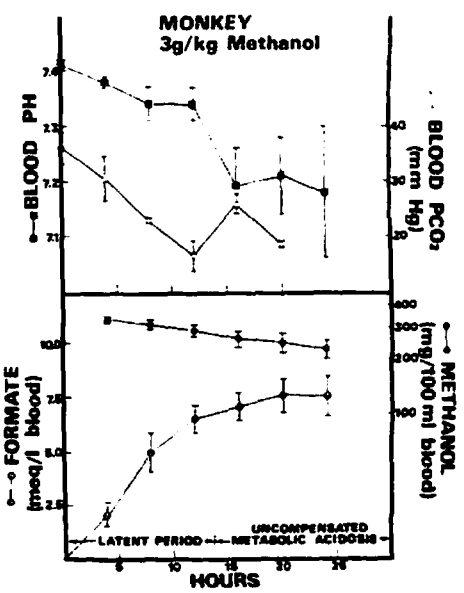
There are two pathways available in the mammalian organism for methanol oxidation, a catalase peroxidative pathway and an alcohol dehydrogenase system. Early studies of Mannering and Parks (3), and later by Mannering, Tephly, and their colleagues (2, 4, 8) have shown that in the rat, guinea pig and rabbit the major route of methanol oxidation is through a catalase dependent pathway, whereas in the monkey, and presumably in man, an alcohol dehydrogenase system functions in vivo (Table 2). The significance of these findings rests in how one selects, designs, and uses the appropriate inhibitor of methanol oxidation. This is because the toxicity of methanol

TABLE 2. Metabolic pathways for methanol

Species	Catalase—H_2O_2	Alcohol dehydrogenase
Rat	++	+
Guinea pig	++	?
Mouse	++	?
Monkey	–	+
Man	?	Probable

in monkey and man is not due to methanol per se but to metabolic products of methanol. In the monkey it is possible to trace the course of methanol conversion to formic acid and carbon dioxide and to show the coincidence between formic acid accumulation in the blood and metabolic acidosis (Fig. 1). Recently, we

Figure 1. Arterial blood, pH, P_{CO_2}, methanol, and formate in monkeys fed methanol. Each value represents the mean ± SEM of at least 3 animals.



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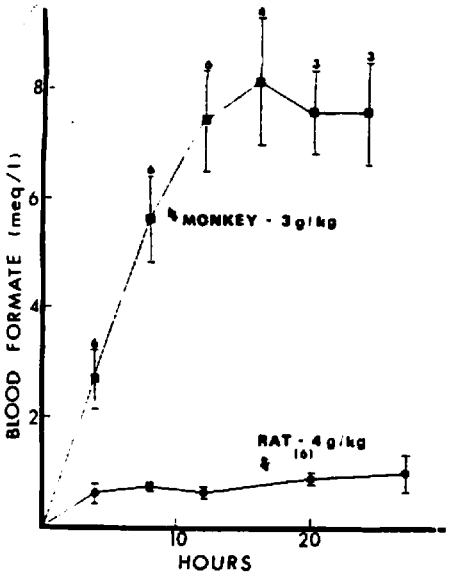


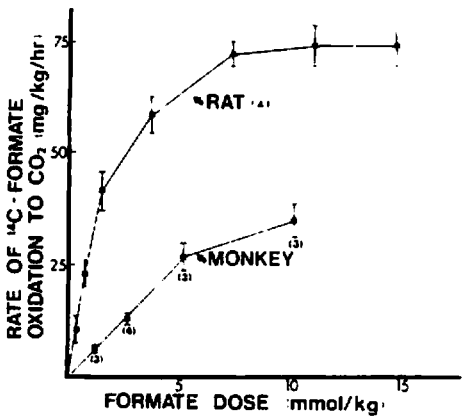
Figure 2. Accumulation of formate in the blood of rats and monkeys after methanol. Numerals indicate the numbers of animals used to compute the values. Dose is indicated beside the species.

have also been able to produce ocular toxicity in the monkey, a finding which also occurs in man and apparently not in lower species.

The second factor mentioned previously leads to a possible explanation of why man and monkey may be susceptible and not the rat. After a large dose of methanol the rat neither accumulates formic acid in the blood nor gets acidotic, but the monkey does (Fig. 2). It has recently been shown that the major route for formate metabolism in the rat in vivo is through the folate-dependent one-carbon pool (6). The only pathway suggested for formate metabolism other than the one-carbon pool has been the catalase peroxidative system and, as mentioned previously, this is not operative in the monkey. Therefore, the folate-dependent one-carbon pool operates for formate oxidation to CO_2 in the monkey but does so with far less capacity in this species than it does in the rat (Fig. 3).

The rat can be made to exhibit methanol poisoning by producing in this species a folate deficiency (Fig. 4). This is the first demonstration of marked and obvious metabolic acidosis in the rat (1). Thus, we believe that the monkey, and probably man, accumulates formic acid because of a relative deficit in formate metabolism and that this is due to a relative deficit in tissue folate concentrations or to an enzymatic deficiency in the folate-dependent one-carbon pool system.

Figure 3. Metabolism of formate to CO_2 in the rat and monkey. Numerals indicate the number of animals employed to compute the values. Rates were determined during periods of linear $^{14}CO_2$ formation with time.



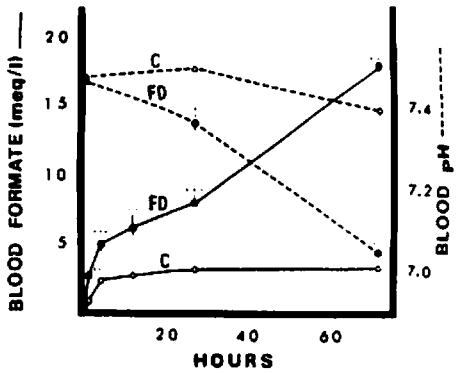


Figure 4. Acidosis after methanol injection in folate-deficient (FD) or control (C) rats. Folate-deficient diets were fed to adult male Sprague Dawley rats for 6 weeks prior to study. Control rats were given the same diet with folate added. Methanol (4 g/kg) was administered intraperitoneally.

This knowledge helps us explain why there is a species difference in sensitivity to methanol and certainly helps us to be able to predict many potential ways of treating, preventing, or intensifying the toxicity in man.

Other work to follow will explore other key factors in the way the organism responds, and will point out ways from which we will be able to understand mechanisms of sensitivity or insensitivity to a hostile factor in the environment. FP

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