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EDITORIAL

The Bone Marrow as a Metabolic Organ

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In the human organism, there are numerous regulatory mechanisms designed to cope with both rapid and insidious adverse changes in the environment. One such hemostatic mechanism involves the biochemical transformation of such endogenous compounds as steroidal hormones, catecholamines, and bilirubin, as well as a wide variety of xenobiotics including insecticides, food additives, and therapeutic drugs [1,2]. To this point in time, most studies of drug biotransformation have emphasized the role of the liver in drug metabolism (including drug activation and detoxification) with little attention having been devoted to the bone marrow as a possible drug-metabolizing organ. In fact, the available data on the mono-oxygenase drug-metabolizing system and enzymologic properties of bone marrow are astonishingly meager, and the literature provides only sporadic data in this area.

Bone marrow depression secondary to drugs and other environmental agents has been well documented by numerous investigators. Classic examples are seen in industrial workers exposed to benzene who often show development of a potentially fatal disorder of the blood-forming elements [3–5] that may be caused directly by benzene or its metabolites [6]. The apparent selectivity of benzene toxicity for hemopoietic tissue may be explained by selective benzene distribution in various tissues. Schrenk et al. [7] studied the distribution of benzene in dogs chemically exposed to benzene and found approximately 20 times more in the bone marrow as compared with liver and other tissues. Many other agents are capable of causing some form of bone marrow injury resulting in blood dyscrasias ranging from single cytopenias to complete bone marrow aplasia and pancytopenia. Among the various potential bone marrow toxins, chloramphenicol continues to head the list as a cause of aplastic anemia [8,9]. Aplasia has been reported after oral, intramuscular, intravenous, and topical chloramphenicol administration. In addition, idiosyncratic depression of marrow occurs and more often leads to irreversible marrow damage than does the depression seen after prolonged drug use. Small changes in structure may considerably alter a drug's effect on hematopoiesis by altering its rate of biotransformation. Thus, thiamphenicol produces dose-related marrow suppression, but idiosyncratic persistent marrow aplasia is rare as compared with that from chloramphenicol [9]. This may suggest that the bone marrow is able to metabolize thiamphenicol much faster than it metabolizes chloramphenicol. This would also indicate that persons with either a congenital or acquired marrow enzyme defect in drug biotransformation systems might be at greater risk for development of marrow dysfunction.

In the light of the adverse bone marrow reactions described for environmental agents and drugs, it would seem appropriate to investigate the presence and inducibility of the microsomal mixed function oxidase drug-metabolizing enzyme system in hematopoietic cells.

In an attempt to begin to investigate the capability of the bone marrow to metabolize drugs, we sought to examine the activity of aminopyrine N-demethylase, a cytochrome P-450-dependent enzyme, in marrow hematopoietic cells as an example of a phase I activation system of susceptible drugs, and uridine diphospho (UDP) glucuronyl transferase as an example of a phase II detoxification reaction for susceptible drugs. Basal levels of hematopoietic N-demethylase are extremely low and 3-methylcholanthrene, a known inducer of cytochrome P-450 [1,10] is capable of causing a twofold increase in enzyme levels. These studies have also shown that N-demethylase activity found in induced marrow microsomes has a high K_m and V_{max} [11]. This is compared with the activity found in 3-methylcho-

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lanthrene-induced rat liver microsomes in which there is a 20-fold increase in V_{max} of the enzyme activity without a significant change in K_m (the same affinity of enzyme for substrate as in uninduced liver microsomes). This result indicates that the bone marrow enzyme has a lower affinity for the substrate tested as compared with liver enzymes.

Studies in this laboratory have also been able to identify the presence of a UDP glucuronyl transferase system in bone marrow cells [12]. The enzyme activity of UDP glucuronyl transferase, using etiocholanolone as substrate, was detectable only after pretreatment of bone marrow cells with 3-methylcholanthrene. A kinetic study indicated a difference in the reaction rate and affinities of the hematopoietic enzyme compared with the liver enzymes [12]. The difference in affinities between liver and bone marrow organ enzyme for demethylation and glucuronidation reaction may be explained as follows. The liver has a well established role as a prime drug-biotransforming organ. Due to recent modern-day exposures to relatively new xenobiotics and environmental pollutants, various extrahepatic tissues such as bone marrow may just *now* (in evolutionary terms) be acquiring the ability to metabolize these agents.

The preliminary studies demonstrate that the bone marrow can play a role similar to that of the liver in the in situ biotransformation of compounds, both exogenous and endogenous. Furthermore, like the liver, bone marrow drug-metabolizing enzyme systems are inducible by conventional inducers, such as 3-methylcholanthrene.

As mentioned earlier, lipid-soluble environmental agents or drugs, such as benzene, may accumulate in the marrow at a concentration 20 times higher than that in the liver. Thus, the principal potential consequence is the prolonged exposure of the bone marrow to many drugs and their metabolites at elevated concentration and for prolonged duration. Taking into consideration a slower rate of basal metabolism in the marrow (10 to 20 percent of the liver enzyme activity), this provides a plausible mechanism whereby these drugs become highly toxic to marrow cells. On the other hand, the liver may readily metabolize various drugs to inactive metabolites or metabolites that have less effect on vital cellular function. In addition, most liver cells are in the G_0 stage and are not usually undergoing mitosis, whereas bone marrow stem cells proliferate and mature as part of their ongoing activity. Therefore, accumulation of drugs and their slow rate of metabolism in marrow cells suggests that these drugs may be toxic to proliferating cells by virtue of their ability to inhibit mitosis and with a resultant depletion of circulating blood cells. This is, of course, of great toxicologic importance and emphasizes the need to investigate further the cytochrome P-450-dependent drug-metabolizing enzyme and the role bone marrow might play as a metabolic organ.

We believe that in order to elucidate the role of drug metabolism in the cytotoxicity and carcinogenicity of various chemicals and drugs to the marrow, a basic understanding of the properties and mechanisms of action of the cytochrome P-450-dependent monooxygenase involved in the activation and inactivation of such agents is essential. Further information in this area would do much to explain the pathogenic mechanisms operative in such diverse entities as aplastic anemia, myelodysplastic syndromes, chemotherapeutic bone marrow suppression, environmentally induced carcinogenesis, and various idiosyncratic drug reactions.

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