Amifostine is a prodrug in which selectivity is largely determined by the preferential formation and uptake of its cytoprotective metabolite, WR-1065, in normal tissues as a result of differences in membrane-bound alkaline phosphatase activity. In this study, we characterized the sites and extent of organ-specific activation by the liver, gastrointestinal tract, lungs, and kidneys after systemic administrations of amifostine. A total of 10 dogs were infused via the cephalic vein using sequential dose rates of drug at 0.125, 0.500, and 1.00 μmol/min/kg. Infusion of each dose rate lasted 2 h, at which time steady-state plasma concentrations were obtained (i.e., portal vein, carotid artery, hepatic vein, pulmonary artery, and renal vein). The hepatic arterial, portal venous, and renal arterial blood flows, and cardiac output, were measured. The hepatic and splanchnic extraction of amifostine remained high at 90%, whereas gastrointestinal extraction decreased from 43 to 12 to 15% with increasing dose. Pulmonary extraction of amifostine was low at 7%, whereas renal extraction was intermediate at 57%. Because blood flow measurements were relatively constant during the drug infusions, clearance parameters paralleled that of organ extraction. As a result, saturability was observed in the gastrointestinal blood clearance (i.e., from 9.8 to 2.8–3.3 ml/min/kg) and total body plasma clearance of amifostine (i.e., from 52.6 to about 37.3 ml/min/kg), as the doses increased. Due to the drug's high activation in liver, these findings suggest that amifostine may offer good protection of this organ against the toxicities of chemotherapy and radiation.
and lung). A secondary objective of the study was to probe the potential for saturable kinetics in these organs.

Materials and Methods

Chemicals. Amifostine and WR-1065 were obtained from MedImmune, Inc. (Gaithersburg, MD). The aminothiol analogs (WR-80855 and WR-251833), used as internal standards, were a generous gift from the Walter Reed Army Institute for Research (Washington, DC). Amifostine aqueous solutions were prepared immediately before use by dissolving the powder in saline solution. All other chemical and solvents were reagent grade or better.

Experimental Methods. A total of 10 mixed breed male and female dogs (20.9 ± 3.3 kg) were used in these acute pharmacokinetic studies. The surgical design was adapted from studies performed previously by our group in dogs (Kuan et al., 1996, 1998), with minor modifications. Briefly, after an overnight fast, each dog was administered a preanesthetic mixture consisting of acepromazine maleate (1.1 mg/kg i.m.) and atropine sulfate (0.04 mg/kg i.m.). Anesthesia was then induced with sodium pentobarbital (35 mg/kg i.v.). Supplemental doses of the anesthetic agent were provided on an as-needed basis, and respiration was maintained on a volume-controlled ventilator (Harvard Apparatus, South Natick, MA). In five dogs, catheters for serial blood sampling were placed by laparotomy into the portal and hepatic veins, by thoracotomy into the pulmonary artery, and by cutdown into the carotid artery. Perivascular ultrasonic transit time flow probes (Transonic Systems, Inc., Ithaca, NY) were placed for blood flow measurements around the common hepatic artery, portal vein, and ascending aorta. This allowed regional pharmacokinetic parameters to be determined for the liver, gastrointestinal tract, splanchnic area (i.e., combined liver, gastrointestinal tract, spleen, and pancreas), lungs, and total body. In another five dogs, catheters for serial blood sampling were placed by laparotomy into the hepatic and renal veins, by thoracotomy into the pulmonary artery, and by cutdown into the carotid artery. Perivascular ultrasonic transit time flow probes were placed for blood flow measurements around the common hepatic artery, portal vein, ascending aorta, and renal artery. This allowed regional pharmacokinetic parameters to be determined specifically for the kidneys, along with the splanchnic area, lungs, and total body. For all dogs, the gastrointestinal artery was ligated to eliminate any extrahepatic blood flow from contributing to the measurement of blood flow in the hepatic artery. Catheters and flow probe wires were tunneled subcutaneously to exit the skin, and the abdomen and chest were closed (Fig. 1). In our studies, flow probes were factory tested and precalibrated upon arrival. The probes were also tested/validated before and after experimentation, according to the manufacturer’s directions (Transonic Systems, Inc.).

Immediately after surgery, amifostine was administered through a cephalic vein via a syringe infusion pump (Harvard Apparatus) set at 0.167 ml/min. The dogs were studied at three sequentially escalated dose rates of 0.125, 0.500, and 1.00 μmol/min/kg (i.e., 8-fold range). Each infusion lasted 2 h, and steady-state blood samples (5 ml) were obtained from the catheters at 105 and 120 min after initiation of each infusion (Fig. 2). No significant differences were observed in amifostine concentrations at the 105 and 120 min sampling times, assuring that steady-state levels had been achieved. This is consistent with the 16-min terminal half-life of amifostine in dogs (Swynnerton et al., 1985). Normal saline was administered intravenously, as needed, to maintain blood pressure during the surgery and drug infusions. Systolic blood pressure was monitored throughout the study period using an ultrasonic Doppler flow detector.

Aliquots of blood were collected in prechilled EDTA-containing tubes and immediately placed on ice. Samples were then centrifuged (0°C) and the plasma harvested and frozen at −80°C until analysis of amifostine and total radioactivity. A second aliquot of blood was placed in a prechilled tube containing ice-cold 1.0 M perchloric acid and 2.7 mM EDTA (1:1, v/v), immediately after sampling. The mixture was vortexed vigorously and centrifuged at 100g for 10 min (0°C). The supernatant (of blood) was stored at −80°C until analysis of WR-1065.

Analytical Methods. Amifostine and WR-1065 concentrations were determined using the method of Shaw et al. (1984, 1986a, 1994b) with minor modifications. Analyses were performed using high-performance liquid chromatography coupled to an electrochemical detector, with chemical analogs as the internal standards. Amifostine, WR-1065, and internal standard were determined using the method of Shaw et al. (1984, 1986a, 1994b) with minor modifications. Analyses were performed using high-performance liquid chromatography coupled to an electrochemical detector, with chemical analogs as the internal standards. Amifostine, WR-1065, and internal standard were detected using a BAS (West Lafayette, IN) LC-4C amperometric detector equipped with a thin film mercury-gold amalgam electrode. The Hg/Au electrode working potential was set at +0.15 V with respect to the Ag/AgCl reference electrode. The column (100 × 3 mm, 3-μm particle size, ODS; BAS) was operated at room temperature. The amifostine chromatography used an isocratic mobile phase consisting of 0.1 M monochloracetic acid and 3 mM sodium octyl sulfate, pH 3.0, at a flow rate of 1.0 ml/min. The WR-1065
chromatography used an isocratic mobile phase consisting of 0.1 M monochloric acetic acid, 3 mM sodium octyl sulfate, pH 3.0, and 30% methanol at a flow rate of 0.6 ml/min. Peak identification was confirmed by comparing retention times in samples with authentic standards. Quantification was based on the peak area ratio of the compound and the appropriate internal standard (i.e., WR-80855 for amifostine and WR-251833 for the active free thiol). Validation assays were performed for amifostine (0.5, 1, 10, and 40 μM) and WR-1065 (1, 4, 10, and 50 μM), and the interday variability (precision) and accuracy (bias) were less than 12% for all methods.

**Pharmacokinetic Calculations.** The regional kinetics of amifostine, after extended drug infusions, were based on clearance concepts across an eliminating organ (Gibaldi and Perrier, 1982; Wilkinson, 1987). Thus, the extraction ratios by the liver (Eₕ), gastrointestinal tract (E₆), splanchnic region (E₈), lungs (E₉), and kidneys (Eₚ) were determined for each infusion as follows:

\[
E_H = \frac{C_{av} - C_{HV}}{C_{ave}} \\
E_{GI} = \frac{C_{ave} - C_{PV}}{C_{ave}} \\
E_{Spl} = \frac{C_{ave} - C_{HV}}{C_{ave}} \\
E_{Lu} = \frac{C_{ave} - C_{PA}}{C_{ave}} \\
E_p = \frac{C_{ave} - C_{RV}}{C_{ave}}
\]

where \(C_{ave}\) was the average plasma concentration of drug entering the liver, \(C_{HV}\), \(C_{CA}\), \(C_{PA}\), \(C_{PV}\), and \(C_{RV}\) were the respective plasma concentrations in the hepatic vein, carotid artery, portal vein, pulmonary artery, and renal vein. Because the liver receives drug from two sources, namely, the hepatic artery and portal vein, \(C_{ave}\) was estimated as follows:

\[
C_{ave} = \frac{Q_{HA} \cdot C_{CA} + Q_{PV} \cdot C_{PV}}{Q_{HI}}
\]

in which \(Q_{HA}\) is the hepatic arterial blood flow, \(Q_{PV}\) the portal venous blood flow, and \(Q_{HI}\) the total blood flow to liver. The fraction of drug escaping extraction on each pass through the liver (\(F_{IH}\)), gastrointestinal tract (\(F_{GI}\)), splanchnic region (\(F_{Spl}\)), lungs (\(F_{Lu}\)), and kidneys (\(F_{p}\)) were calculated as follows:

\[
F_{IH} = 1 - E_H \\
F_{GI} = 1 - E_{GI} \\
F_{Spl} = 1 - E_{Spl} \\
F_{Lu} = 1 - E_{Lu} \\
F_{p} = 1 - E_p
\]

Blood clearances by the liver (\(CL_{b,H}\)), gastrointestinal tract (\(CL_{b,GI}\)), splanchnic region (\(CL_{b,Spl}\)), lungs (\(CL_{b,Lu}\)), and kidneys (\(CL_{b,R}\)) were then determined as follows:

\[
CL_{b,H} = \frac{R_o \cdot E_H}{Q_H} \\
CL_{b,GI} = \frac{Q_{PV} \cdot E_{GI}}{Q_H} \\
CL_{b,Spl} = \frac{Q_{RV} \cdot E_{Spl}}{Q_H} \\
CL_{b,Lu} = \frac{Q_{Lu} \cdot E_{Lu}}{Q_H} \\
CL_{b,R} = \frac{Q_{RA} \cdot E_p \cdot 2}{Q_H}
\]

where \(Q_{CO}\) was the cardiac output and \(Q_{RA}\) was the renal arterial blood flow (one kidney). Finally, the total body plasma clearance of drug (\(CL_{p,TB}\)) was calculated as follows:

\[
CL_{p,TB} = \frac{R_o}{C_{CA}}
\]

in which \(R_o\) is the infusion rate of drug in the cephalic vein.

**Statistics.** Data were reported as mean ± S.D., unless otherwise indicated. To test for parameter differences among treatment groups, an ANOVA was performed with repeated measures. When the F ratio showed that there were significant differences among groups, Tukey’s test was used to determine which groups differed (\(\alpha = 0.05\)). Means that were significantly different have the same capital letters in Tables 1 to 3. All statistical computations were performed using SYSTAT version 8.0 (SPSS Inc., Chicago, IL).

**Results**

The extraction ratios of amifostine across specific organs are shown in Table 1. As observed, hepatic extraction of amifostine remained unchanged at about 90%, whereas gastrointestinal extraction decreased significantly from 43 to 12 to 15% as the dose rates increased. Taken as a whole region, the splanchnic area had a constant extraction ratio for amifostine of about 88%. Pulmonary extraction of amifostine was low at 7%, whereas renal extraction was intermediate at 57%.

Table 2 shows the fraction of amifostine that escaped regional extraction by each organ. In agreement with the extraction data, hepatic and splanchnic availabilities were low but constant, averaging about 10 to 12%. In contrast, the fraction of amifostine surviving elimination by the gastrointestinal tract increased from 57 to 85 to 88% as the dose rate increased. The pulmonary availability remained high at 93% and the fraction of drug surviving renal elimination was 43%.

Blood clearances by the liver, gastrointestinal tract, splanchnic region, lungs, and kidneys, as well as the total body plasma clearance of amifostine are summarized in Table 3. As the dose rate increased, hepatic and splanchnic clearances did not change significantly, maintaining values on the order of 21.6 to 25.6 ml/min/kg. Clearance by
were measured, as well as the cardiac output, during amifostine
conversion of amifostine to WR-1065, it seems that the total body
clearance (CLR, TB) after three sequentially escalated intravenous
infusions of amifostine (Table 3).

<table>
<thead>
<tr>
<th>Dose Rate</th>
<th>Fmax</th>
<th>Fmax</th>
<th>Fmax</th>
<th>Fmax</th>
<th>Fmax</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>µg/min/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.125</td>
<td>0.111 ± 0.056</td>
<td>0.567 ± 0.024</td>
<td>0.165 ± 0.109</td>
<td>0.931 ± 0.089</td>
<td>0.435 ± 0.110</td>
</tr>
<tr>
<td>0.500</td>
<td>0.117 ± 0.066</td>
<td>0.877 ± 0.040</td>
<td>0.111 ± 0.061</td>
<td>0.922 ± 0.072</td>
<td>0.427 ± 0.051</td>
</tr>
<tr>
<td>1.00</td>
<td>0.084 ± 0.027</td>
<td>0.849 ± 0.109</td>
<td>0.094 ± 0.041</td>
<td>0.936 ± 0.068</td>
<td>0.432 ± 0.047</td>
</tr>
</tbody>
</table>

Significance (n) 0.590 (5) <0.001 (5) 0.138 (10) 0.926 (10) 0.987 (5)

Data are reported as mean ± S.D. (n = 5–10 dogs).

a P values were determined by ANOVA with repeated measures. For a given parameter, mean values with the same capital letter are significantly different (Tukey’s test; α = 0.05).

TABLE 3
Blood clearances by the liver (CLL, H), gastrointestinal tract (CLL, GI), splanchnic region (CLL, Spl), lungs (CLL, Lu), and kidneys (CLL, R) for all dose rates.

<table>
<thead>
<tr>
<th>Dose Rate</th>
<th>CLH</th>
<th>CIG</th>
<th>CLSpl</th>
<th>CLLu</th>
<th>CLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg/min/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.125</td>
<td>22.6 ± 4.9</td>
<td>9.85 ± 2.57</td>
<td>18.9 ± 5.6</td>
<td>5.71 ± 6.43</td>
<td>6.03 ± 2.14</td>
</tr>
<tr>
<td>0.500</td>
<td>25.2 ± 10.1</td>
<td>2.78 ± 1.42</td>
<td>21.9 ± 8.2</td>
<td>6.93 ± 5.85</td>
<td>6.10 ± 1.73</td>
</tr>
<tr>
<td>1.00</td>
<td>29.0 ± 8.5</td>
<td>3.29 ± 2.45</td>
<td>24.1 ± 8.3</td>
<td>6.04 ± 6.60</td>
<td>6.11 ± 1.52</td>
</tr>
</tbody>
</table>

Significance (n) 0.584 (5) 0.002 (5) 0.370 (10) 0.910 (10) 0.000 (5)

Data are reported as mean ± S.D. (n = 5–10 dogs).

a P values were determined by ANOVA with repeated measures. For a given parameter, mean values with the same capital letter are significantly different (Tukey’s test; α = 0.05).

The gastrointestinal tract, on the other hand, showed a significant decrease from 9.8 ml/min/kg to 2.8 to 3.3 ml/min/kg at the higher doses. Values for the pulmonary and renal clearance were steady at 8.3 ml/min/kg for cardiac output. These blood flows compared well with values found in the literature (Altman and Dittmer, 1974) except for that of the kidney, which was about 40% lower. The reason for a lower renal blood flow is unclear, although it might represent normal variability among animals or, perhaps, vasoconstriction of the renal artery as a result of contact with the flow probe. Importantly, there were no time-dependent changes (i.e., from 0 to 2, 2 to 4, and 4 to 6 h) in flow for the hepatic artery (P = 0.880), portal vein (P = 0.841), total liver (P = 0.935), renal artery (P = 0.963), or cardiac output (P = 0.371). The systemic blood pressure was also measured during the amifostine infusion studies, as displayed in Fig. 4. The mean blood pressure during the infusion was 122 ± 18 mm Hg. As observed, amifostine infusion did not cause a dose-dependent hypotension under conditions used in these experiments. The volume of normal saline administered during the 10 h of surgical and drug experiments was 4.0 ± 0.5 liters.

Discussion

Amifostine (previously known as WR-2721) has been shown to protect almost all normal tissues from the cytotoxic effects of radiation and some chemotherapeutic agents (Spencer and Goa, 1995; Capizzi, 1996; Foster-Nora and Siden, 1997). To accomplish this, amifostine must be dephosphorylated to the active metabolite WR-1065 at its site of action in tissue and be preferentially taken up by normal as opposed to tumor cells. At present, amifostine is used to protect the kidney against cisplatin toxicity and the parotid gland against radiation treatment for head and neck cancer. However, depending on the outcome of numerous ongoing clinical trials, amifostine may find broader clinical applications, both as a chemos- and radioprotectant (Culy and Spencer, 2001). In this regard, we believe that a systematic examination of the sites and extent of organ-specific activation will facilitate the development of other cancer treatments and novel routes of drug delivery for amifostine.

In the present study, we have demonstrated that amifostine is...
Amifostine may exhibit dose-dependent kinetics as suggested by a study (Shaw et al., 1994a) in which cancer patients were administered a P/H11005 dose of amifostine to patients (infused over 15 min), the free WR-1065 levels were reported as being similar to that of amifostine, with area under the plasma concentration-time profiles (AUCs) of both chemical species being about 1/10 that of the disulfides. Although the reason for undetectable blood levels of WR-1065 in our study is not clear, it probably reflects the use of much lower amifostine infusion rates (8- to 64-fold). Still, the effect of animal species and disease differences cannot be ruled out. It is also possible that organ blood flow and organ uptake of drug in an awake, free-moving dog may be markedly different compared with an anesthetized animal. Notwithstanding this uncertainty, maximal plasma concentrations of 16 to 17 μM were reported for amifostine and protein-bound WR-1065 after a 500-mg s.c. dose of drug to healthy subjects (Bonner and Shaw, 2002). Moreover, the AUC of free WR-1065 was less than 12% of the AUC for total WR-1065. These results after s.c. dosing in subjects are strikingly similar to our findings in dogs and may reflect the use of more congruous input rates of drug into the systemic circulation (assuming the s.c. dose of amifostine is released over 30 min or longer).

Amifostine may exhibit dose-dependent kinetics as suggested by a study (Shaw et al., 1994a) in which cancer patients were administered a 15-min i.v. infusions of drug at 910 or 740 mg/m². In the high-versus low-dose groups, mean values were reported for volume of distribution (7.4 versus 8.7 liters), half-life (2.7 versus 1.5 min), and plasma clearance (2.1 versus 4.3 l/min). Thus, a significant increase in clearance was observed when less amifostine was administered intrave-

### TABLE 4

<table>
<thead>
<tr>
<th>Dose Rate</th>
<th>C_{CA} μM</th>
<th>C_{PA} μM</th>
<th>C_{ave} μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.125</td>
<td>2.7 ± 1.0</td>
<td>2.9 ± 1.2</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>0.500</td>
<td>14.7 ± 4.2</td>
<td>15.8 ± 4.6</td>
<td>14.2 ± 4.2</td>
</tr>
<tr>
<td>1.00</td>
<td>27.8 ± 8.2</td>
<td>29.2 ± 8.8</td>
<td>29.0 ± 8.5</td>
</tr>
</tbody>
</table>

Data are reported as mean ± S.D. (n = 5-10 dogs).

### TABLE 5

<table>
<thead>
<tr>
<th>Dose Rate</th>
<th>C_{p,total WR-1065} μM</th>
<th>C_{p,total WR-1065}/Dose Rate bμM/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.125</td>
<td>3.5 ± 2.8</td>
<td>28.1 ± 22.2</td>
</tr>
<tr>
<td>0.500</td>
<td>11.3 ± 4.2</td>
<td>22.5 ± 8.4</td>
</tr>
<tr>
<td>1.00</td>
<td>29.5 ± 11.7</td>
<td>29.5 ± 11.7</td>
</tr>
</tbody>
</table>

Data are reported as mean ± S.D. (n = 10 dogs).

*p value was determined by ANOVA with repeated measures.

**Fig. 3.** Blood flow versus time profiles for hepatic artery (Q_{HA}; solid circles), portal vein (Q_{PV}; solid squares), total hepatic stream (Q_{H}; open diamonds), cardiac output (Q_{CO}; solid triangles), and renal artery (Q_{RA}; open triangles, one kidney) during three sequentially escalated intravenous infusions of amifostine.

Data are reported as mean ± S.E. of 10 dogs (except for Q_{RA}, 5 dogs).
nously and reduced peak plasma concentrations were obtained (235 versus 100 μM). As also noted, in vitro K_{av} values for amifostine in human kidney (100 μM) and placenta (80 μM) alkaline phosphatase preparations were well within the range of plasma concentrations achieved during infusions of drug to cancer patients. Preclinical studies also support a concentration- and route-dependent disposition of amifostine (Mangold et al., 1989), in which 150 mg/kg amifostine was administered to monkeys by intravenous and portal venous infusions of 10- and 120-min duration. In comparing equivalent intravenous doses, the AUC of amifostine was 3 times greater during the 10-versus 120-min infusion. After equivalent portal venous doses, the AUC of amifostine was 7 times greater during the 10-min infusion compared with the 120-min infusion. This finding lends strong support to the argument that amifostine exhibits saturable kinetics, particularly after regional dosing to the liver.

In the present study, the gastrointestinal tract displayed a concentration-dependent extraction, first-pass availability and clearance at amifostine plasma concentrations of 15 μM and greater. In contrast, the liver, splanchnic region, lungs, and kidneys did not demonstrate a saturation. However, this does not preclude the liver (or other tissues) from exhibiting capacity-limited metabolism when higher concentrations of amifostine are present in the circulating blood. In fact, this is likely to occur during the first hour after clinical doses (or dose rates) of amifostine or, more dramatically, if drug were infused regionally. Given the known clearances of amifostine in the splanchnic region, lungs, and kidneys, one can also estimate the extent of drug elimination by other organs and/or tissues. Because the blood-to-plasma partitioning of amifostine is 0.5 (Souid et al., 1998), the total body clearance of drug, based on blood levels, would be twice that of its total body plasma clearance (i.e., CL_{p,TB} = CL_{p,T} + CL_{p,R}). Therefore, drug elimination by other processes would be determined as CL_{p,R} = CL_{p,TB} - (CL_{p,Spl} + CL_{p,Lung} + CL_{k,R}). Thus, the contribution (percentage) of amifostine elimination by CL_{p,R} was estimated at 70% for the low-dose rate and at 50% for the middle- and high-dose rates. Taken as a whole, a substantial portion of amifostine is eliminated by other clearance mechanisms. It should be appreciated that alkaline phosphatase is ubiquitous within the body (McComb et al., 1979). Although speculative, amifostine could be metabolized by many other tissues such as the muscle, brain, bone, adrenal glands, and vascular endothelium. It is also possible that these tissues may be contributing to the nonlinear total body clearance that is observed for amifostine.

A high extraction of amifostine by the liver suggests that it might serve as a protective agent to normal hepatocytes during hepatic radiotherapy or radiochemotherapy. The role of radiotherapy in the management of patients with diffuse intrahepatic cancer has been limited by radiation-induced liver disease. An agent that would protect the normal liver from the effects of ionizing radiation, without compromising tumor cell kill, would be very valuable. Previous studies in rats have demonstrated that systemic administration of amifostine protects irradiated hepatocytes from reproductive cell death with a radiation dose modification factor of 2 (Jirtle et al., 1985) and that the liver is protected from radiation fibrosis with a dose modification factor that is greater than two (Jirtle et al., 1990). In a subsequent study (Symon et al., 2001), either systemic or portal venous administration of amifostine effectively protected hepatocytes from ionizing radiation without compromising tumor cell kill in a rat liver tumor model. In addition, a higher liver/tumor ratio of free WR-1065 was achieved after portal venous administration of amifostine, compared with systemic dosing. These findings suggest that amifostine may be a selective normal tissue radioprotectant in liver cancer and that regional/portal infusions may be preferable to systemic dosing. Our dog data, exhibiting a high activation/extraction of amifostine by the liver, support this contention.

It has been documented that the major source of blood flow to macroscopic hepatic cancers is by way of the hepatic artery (Sigurdson et al., 1987). In contrast, the delivery of nutrients to normal liver tissue is primarily a function of the portal circulation (Ridge et al., 1987). Thus, amifostine selectivity in liver may not only be enhanced by differences between normal tissue and tumor in alkaline phosphatase activity, but also by differences in the drug’s regional route of delivery (i.e., portal vein is favored). We are currently investigating the use of systemic and regional amifostine, as a radiation protector of normal liver, in patients with cancer.

References