diglycolaldehyde (DGA). For these six agents, the negative correlation between the ratio and anticancer activity was good. Of the other agents where adequate negative tumor data exist and there are B/P ratios of > 0.8, some pharmacokinetic points usually can be evoked to explain the discrepancy. For example, the high ratios for 6-mercaptopurine (6-MP), nitrogen mustard (HN_2) and 5-fluorouracil (5-FU) are known to represent radiolabeled metabolites and not parent material. Very poor correlations exist for tritylcystine, pseudourea, guanazole and diethylstilbesterol (DES), but no explanation can be offered at the present time because adequate metabolic data are not yet available for these drugs. Regarding the agents for which the experimental therapeutics data are incomplete, colchicine and coralynsulfoacetate, one could speculate, on the strength of the high B/P ratios, that the anticancer activity would be good. For the three compounds with the highest B/P ratios, alanosine, ellipticine, and hycanthone, the tumor testing was positive. Other time points for B/P ratios and other studies of CSF levels, gave essentially the same results as for 24 hr B/P ratios.

In summary, the correlation between drug concentration at 24 hrs in nonmalignant brain tissue and drug effectiveness against the model tumor system showed a fairly good correlation for the effective drugs; however, a significant number of the ineffective drugs achieved relatively high levels in the normal brain tissue and CSF, and several effective drugs occurred at relatively low levels in the normal brain tissue. Adequate delivery of the drug to the tumor is considered to be necessary for the effective treatment of brain tumors. In addition to this correlation with drug distribution to normal brain tissue, attempts should now be considered to correlate effectiveness in this solid brain tumor model with other pharmacological and biochemical factors.

DISTRIBUTION AND TOXICITY OF SELECTED WATER POLLUTANTS IN THE SPINY DOGFISH, *Squalus acanthias*

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There is inadequate information for marine fish about the pharmacologic disposition and toxicology of water pollutants, including those resulting from oil spills. We studied in detail two known components of crude oil, octane and phenol, as well as a detergent which occurs in many natural bodies of water, sodium lauryl sulfate (SLS). The general procedures used here for administration of compounds, tissue handling and pharmacokinetic modeling in the spiny dogfish were described previously (Guarino et al., MDIBL Bull., 15, in press, 1976). ^{14}C-Octane, ^{14}C-phenol and ^{35}S-SLS were available commercially and were administered in dogfish saline (3%) except that for octane, ethanol:emulfor:dogfish saline (1:1:8) was used as a suspending agent. Nonisotopic compounds were all commercially available and except where indicated were administered in the emulfor system.

First considering the data in Table 1, the shortest plasma $t_{½}$'s (time required for plasma levels to decrease to one-half the initial level; Co is designation for initial plasma levels) were for octane (37 min) and phenol (44 min) while SLS was longer (61 min). SLS had an apparent volume of distribution (V_D) closest to that of plasma indicating very little early metabolism, binding and excretion, while the higher values for the oil pollutants indicate moderate increases in V_D for octane and large increases for phenol. Plasma binding was the highest for octane (99.6%) and the lowest for SLS (25.5%). Data in Table 2 demonstrate that SLS was excreted extensively in the

TABLE 1

Pharmacokinetic Parameters for Selected Water Pollutants in the Spiny Dogfish, *Squalus acanthias*

	^{14}C-Octane	^{14}C-Phenol	^{35}S-Sodium Lauryl Sulfate
Plasma			
$t_{½}$ (min)	37.0	44.4	60.5
V_D (% B.W.)	17.6	71.9	8.2
C_0 (μg/ml)	80.6	14.8	12.7
Plasma Binding (%)	99.6	54.5	25.5

urine (65%) in 24 hours while only 4% of the phenol dose appeared in urine in 24 hrs (Table 2). By 6 days after dosing, less than 1% of the radioactivity of octane was in urine. Only 1-2% of any of the three pollutants appeared in dogfish bile, thus ruling out this route as a major pathway for removal of these xenobiotics. It is interesting to note that while plasma levels of SLS and phenol decayed in a usual manner, the rise in plasma octane-derived radioactivity by day 6 suggested mobilization from a tissue storage site. The liver appears to be a likely organ to explain this phenomenon since it initially contained about 80% of the administered dose and had only 16% of the dose by day 6. Note that the kidney showed this same profile in terms of concentrations of ^{14}C-octaine. Muscle tissue had initial levels of octane equal to those in plasma and had virtually cleared all the radioactivity by day 6. The only other interesting compartment for this compound was the brain (data not shown) where the 2 hr brain/plasma ratio was about 2.7, which is consistent with the known CNS depressant actions of this class of aliphatic hydrocarbons. The overall recovery of radioactivity was high for octane (bottom Table 2).

The major compartments for SLS were the liver and the urine. At 4 hrs most of this detergent was in the liver (61%) while by 24 hrs most of it had been excreted (65%) in the urine. There were no other unique features of the disposition of this compound by the dogfish except that while the biliary compartment accounted for only 2% of the administered dose, the 24 hr bile/plasma ratio of about 50, is suggestive of active biliary transport of SLS. The total recovery of SLS was quite high at each time point studied.

Perhaps the most interesting oil pollutant of this study was phenol. First, its high V_D suggested multiple processes such as metabolism, sequestration and excretion. The plasma clearance was prompt and the plasma binding was only modest. The liver and muscle were the primary tissues localizing this xenobiotic; 58% of the dose was in liver in four hr. and this value had halved by 24 hrs. Meanwhile, the muscle values at these same times had declined from 11 to 3%. As was the case with SLS, phenol-derived radioactivity concentrated in the bile yielding a bile/plasma ratio of about 70. The 4 hr recovery of ^{14}C-phenol was about 70% while only about 30% of the administered pollutant could be recovered in 24 hr fish. While direct evidence is lacking it would appear that since the lipid partition coefficient ($K_{heptane}$) for phenol is greater than for antipyrine (0.15 vs 0.005) and since antipyrine was shown by Maren et al. (Comp. Biochem. Physiol. 26:853, 1968) to be cleared by the gills of the dogfish at a moderate rate, then according to the Maren Hypothesis, phenol should be rapidly cleared by this mechanism.

Table 2 Distribution of Water Pollutants in the Spiny Dogfish, *Squalus acanthias**

	Time After Injection (hrs or days)	Octane C^{14}	Time After Injection (hrs)	Phenol C^{14}	Time After Injection (hrs)	Sodium Lauryl Sulfate S^{35}
Plasma	2	8.5±5.4 (4.2)	4	3.0±0.8 (1.5)	4	1.8±0.8 (9.0)
	24	1.1±0.1 (0.6)	24	1.5±0.2 (0.7)	24	0.5±0.4 (2.7)
	6 days	5.6±0.3 (2.8)				
Liver	2	71.1±5.0 (81.7)	4	59.8±12.3 (58.5)	4	5.4±1.8 (61.0)
	24	74.5±16.6 (78.6)	24	21.3±5.8 (24.5)	24	1.2±0.4 (16.9)
	6 days	14.0±2.2 (16.2)				
Bile	2	2.8±0.3 (0)	4	2.9±2.3 (0)	4	0.4±0.4 (0)
	24	1.9±0.6 (0)	24	103.8±62.0 (0.9)	24	27.4±2.3 (2.1)
	6 days	42.2±15.0 (0.6)				
Kidney	2	19.6±1.0 (0.5)	4	12.9±6.2 (0.4)	4	7.5±1.2 (1.5)
	24	4.1±0.4 (0.6)	24	4.0±1.2 (0.1)	24	1.7±0.7 (0.4)
	6 days	23.2±5.5 (0.8)				
Urine	2	1.4±0.6 (0)	4	83±60 (1.7)	4	195.9±58.11 (28.4)
	24	0.2±0.1 (0)	24	42.3±15.5 (4.2)	24	39.3±7.6 (65.1)
	6 days	4.9±1.4 (1.6)				
Muscle	2	8.2±3.2 (37.0)	4	2.5±1.4 (11.4)	4	0.4±0.1 (19.3)
	24	8.3±2.9 (37.0)	24	0.7±0.2 (3.2)	24	0.2±0.1 (7.0)
	6 days	0.2±0.1 (0.9)				
Total	2	123.0±25.1	4	73.4±10.6	4	132.3±14.8
	24	116.0±2.3	24	33.4±10.5	24	98.7±12.8
	6 days	23.1±2.3				

*Values are mean µg/g or ml ± S.D. for 2-6 fish at each time point. Values in parenthesis are mean percent of the administered dose in the indicated tissue or fluid. Urine values are cumulative to the designated time point. The dose for SLS was 1 mg/kg body weight and for the other two pollutants was 10 mg/kg.

An important body of information is emerging from excretion and distribution studies of xenobiotics in the spiny dogfish. For example, this species has more ways of "protecting" itself from the acute toxicity of xenobiotics than do most terrestrial animals since in addition to urinary and biliary excretion, the shark can excrete via the gills or can sequester enormous amounts of chemicals in their livers since: (1) it is very large, ca. 10% of the body weight, and (2) most (ca. 60%) of the wet weight of the liver is fat. We have administered the following maximum doses in mg/kg (in parenthesis) of xenobiotics (in EtOH: emulfor:saline as indicated above) with no significant mortality within 72 hr to groups of 2-6 fish per dose: DDT (4), PCB (Arochlor 1254) (50), ethylhexylphthalate (100), 2,4,5-T (15), 2,4-D (20), chlordane (10), heptachlorepoxide (5), lindane (5), malathion (10), phenol (in saline) (50), SLS (in saline) (10), and octane (10). Therefore, the spiny dogfish was able to survive doses of many xenobiotics which are quite toxic to terrestrial mammals.

ACTION OF HISTAMINE$_2$-INHIBITORS ON ACID SECRETION BY THE ISOLATED GASTRIC MUCOSA OF *Squalus acanthias*

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Since the discovery of histamine, its possible physiological role in regulation of acid secretion by the stomach has been the subject of heated controversy. Just as arguments against such a role became more compelling, a new class of histamine inhibitors, H_2-inhibitors, were introduced some four years ago. These inhibitors in vitro block H^+ secretion of amphibian and mammalian gastric mucosae not only when such secretion is elicited by histamine itself but also when stimulated by cholinergic agents such as carabachol as well as gastrin or its analogue pentagastrin.

The relative insensitivity of the isolated dogfish gastric mucosa to all three classes of chemo-transmitters prompted study of the inhibitors in *Squalus acanthias*. In this species, even considering this insensitivity to chemotransmitters, we find that H_2 inhibitors metiamide or cimetidine (2 mM) do not block transmission. At higher concentrations of the several transmitters a small but significant augmentation by cimetidine occurred. The effect, if any, on spontaneous secretion as well as with lower concentrations of excitants was obscured by the secretory rate's relatively large variance even though experiments were paired.

Experiments were conducted as previously (Hogben, Proc. Soc. Exp. Biol. Med. 124:890-893, 1967) except that (a) the secretory rate was obtained by "stat" titration in situ to a pH of 6.75, (b) mucosae were initially isolated and dissected in the HCO_3^--buffered saline, (c) mucosae were mounted after being impaled on pins embedded in the chamber wall about the 2 apertures, and (d) the ratio of surface area to volume of bathing solution was 2.95 cm^2:30 ml. No electrical measurements were made. Chambers, similar to those used previously, allow a section of mucosa to be placed over two adjacent apertures. Upon apposition of the two halves of the chamber we now have two adjacent segments which can be studied in tandem. For the present study, one segment serving as a control was not exposed to inhibitor during the third hour while the other member of the pair was exposed to inhibitor during the third hour. After about one-half hour for adjustment, the rate of spontaneous H^+ secretion was followed over 0-60'. Each of the adjacent segments of mucosa was exposed to a chemo-excitant beginning at 50' and its secretion measured during the interval 60'-120'. Until 110' each of the 2 segments had been treated alike. At 110' one member of the pair was treated with an H_2-inhibitor and the secretory rate of both segments was measured over the final hour, 120'-180'. In about half of the experiments, measurement continued for a 4th hour and in a few instances for a fifth hour. While the reduction of *n* of each subset precluded useful statistical analysis of the latter 2 hours, no unexpected changes were encountered. In one set of experiments, Spontaneous