Table I

Pharmacokinetic Parameters for Antineoplastic Agents in *Squalus acanthias*
Mean Tissue or Fluid Concentration (ug/g or ml)*

NSC No.	Compound	Dose mg/kg	Plasma 4 hr.	Plasma 24 hr.	Liver 4 hr.	Liver 24 hr.	Bile 4 hr.	Bile 24 hr.	Kidney 4 hr.	Kidney 24 hr.	Urine 4 hr.	Urine 24 hr.	Plasma t½ (min.)	Volume of Distribution (% of Body Weight)
762	Nitrogen Mustard ^{14}C	1.0	0.1	0.0	0.1	0.0	0.2	3.1	2.5	1.8	7.7	2.6	2	76.6
3,055	Puromycin ^{3}H	1.0	0.3	0.3	1.4	1.5	2.6	56.7	5.2	2.8	34.6	12.8	15	16.3
71,795	Ellipticine ^{14}C	10.0	0.3	0.1	13.7	36.1	0.8	53.8	219.7	203.4	3.9	2.5	18	233.0
740	Methotrexate ^{3}H	10.0	0.5	0.2	2.9	1.9	0.9	440.5	4.1	0.8	117.4	23.9	31	6.9
755	Mercaptopurine ^{14}C	5.0	6.2	2.2	3.1	4.1	3.6	44.1	14.9	5.9	166.9	62.4	50	17.5
757	Colchicine ^{3}H	1.0	0.5	0.3	4.3	5.7	55.9	98.8	2.2	1.6	24.3	9.8	38	16.9
3,053	Actinomycin D ^{3}H	1.0	2.1	0.5	0.5	0.1	0.2	13.1	3.1	1.5	12.2	3.7	37	7.4
19,893	5-Fluorouracil ^{14}C	10.0	6.8	3.0	3.7	0.4	1.2	10.1	9.1	3.2	56.1	18.5	55	13.7
56,054	Pseudourea ^{14}C	10.0	8.4	2.2	17.0	25.6	2.1	89.9	321.9	602.6	25.2	10.4	55	8.6
102,627	Propanol-iminodi-dimethanesulfonate ^{14}C	10.0	8.7	10.8	3.9	2.3	0.9	7.2	61.3	27.9	715.6	309.5	51	13.2
142,982	Hycanthone ^{3}H	10.0	1.3	0.7	22.5	22.4	10.6	1009.6	157.6	93.7	65.3	23.5	47	117.0
1,895	Guanazole ^{14}C	10.0	22.1	15.1	5.1	4.4	1.0	7.5	24.1	16.0	121.8	81.9	96	11.1
26,271	Cytoxan ^{14}C	10.0	12.0	9.3	12.4	4.8	49.2	420.8	38.8	31.9	208.9	74.9	68	17.2
45,338	Imidazole-4-Carboxamide ^{14}C	10.0	9.8	7.2	3.3	2.5	1.2	34.9	20.8	17.1	173.7	178.5	83	31.2
63,878	Cytosine Arabinoside ^{14}C	50.0	82.7	59.9	17.3	15.0	4.1	137.0	119.7	95.8	1281.3	594.7	93	14.2
94,100	Dibromomannitol ^{14}C	10.0	16.3	10.4	6.8	6.0	48.6	266.3	80.6	40.7	190.9	67.4	79	15.3
102,816	5-Azacytidine ^{14}C	40.0	68.0	–	27.5	–	1.6	–	322.3	–	4023.5	--	84	9.6
104,801	Cytembena ^{14}C	10.0	10.1	0.3	10.1	2.2	293.0	186.6	119.8	5.8	400.9	21.4	100	18.0
118,994	Diglycolaldehyde ^{14}C	10.0	25.3	15.3	3.5	4.4	19.1	245.5	42.9	26.7	201.1	96.0	127	9.9
119,875	*Cis*-diamminedichloro Platinum**	1.0	1.0	0.5	0.2	0.2	0.0	1.2	3.1	2.0	1.6	0.8	115	20.1

*Means are for 4-6 fish per time point
**Assay by atomic absorption spectroscopy

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Pharmacokinetic Studies of Antineoplastic Agents in the Dogfish, *Squalus acanthias*

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Sine the pioneer work of Zaharko *et a* (*Comp. Biochem. Physiol. 42A:* 183, 197 on the pharmacologic disposition of metho trexate in stingrays, and the challenges Dedrick (*J. Pharmacokinetics and Biopha maceutics 1;* 435, 1973) concerning the ap plication of pharmacokinetics to lower anim species, we have been interested in furthe testing the concept that such studies can b effectively done on the more abundant dog fish shark. The hypothesis that the utilizatio of realistic physiological compartments an parameters can be extended from *higher* t *lower* species (e.g., rodents to fish) is in nee of rigorous testing by the utilization of man other drugs and model compounds.

The procedures utilized in these studie were as described previously (Guarino, Anderson, *Xenobiotica,* in press 1975). With th points which were reviewed above in mind let us examine Table 1. In this study, th plasma half-times could be divided into thre time categories. The rapid t½'s (20 min. top panel) are reflected further by the ver low levels of material, 0.3 g/ml, present i the plasma at either 4 or 24 hour time points Nitrogen mustard (HN_2) has a V_d of almos 80% and this is consistent with the well established point that it is rapidly metabolized For puromycin the V_d is 16% which suggest that some metabolism and/or tissue penetration has begun to occur. The high V_d c 233% for ellipticine suggests avid tissue binding, rapid metabolism or rapid excretion. Th next category of t½'s (Table 1, middle pane are in an intermediate range (20-60 min. The V_d for methotrexate (MTX), actinomyci D (Act D), and pseudourea are very close t that of plasma volume of the dogfish suggesting that at t_0 all of the drug is in the pla ma compartment. The slightly higher value are suggestive of metabolism in general. Mercaptopurine (6-MP) is known to be h droxylated while 5-flourouracil (5-FU) known to be both reduced and oxidized b non-microsomal enzymes. Metabolic info mation on propanol-iminodi-dimethanesulf nate (PIDMS) is unavailable. The volume distribution for hycanthone is greater tha 100% and this value, along with other info mation available regarding this compou suggests multiple processes are contributin to this figure. Together, the liver and kidne at either 4 or 24 hours, have approximate-

% of the administered dose and the brain contained and 7% at 4 and 24 hours, respectively. The final agory (Table 1, lower panel) of agents has high t½'s -130 min.) associated with generally higher values in plasma than were for the other two catagories of nts mentioned above. None of the agents in this class V_d's which are suggestive of either moderate tissue trances or slow metabolism the following were drugs nd to have no unusually high T/P ratio (Table 1): nazole, cytoxan, imidazole-4-carboxamide (I-4-C), osine arabinoside (Ara C), and diglycoaldehyde. In this ss of drugs, very high bile to plasma (B/P) ratios were n for cytoxan, Ara C, dibromomannitol (DBM), and lycoaldehyde, while the highest B/P ratios seen in this dy occurred for cytembena (622) and MTX (2200) at 24 urs. The kidney to plasma ratios seen for DBM, zacytidine (5-AC), and Ara C were 1.

Other pharmacokinetic parameters can be measured the excretory pathways, and urinary and biliary asurements are reported as percentages of the total ount excreted compared to the total dose administered. The following compounds were excreted at least % in 24 hours in the urine (values in parantheses are actual amount excreted): puromycin (20), MTX (35), MP (21), PIDMS (44), I-4-C (24), cytembena (28), and AC (20). An intermediary (7-17%) range of urinary cretion was observed for the following compounds: Act (7), colchicine (9), guanazole (15), cytoxan (12), Ara C 7), DBM (12), and diglycoaldehyde (12). The lowest nounts of urinary excretion were seen for HN_2 (4), pticine (1.4), 5-FU (3), pseudourea (4.4), hycanthone 6) and CDDP (2.9). Only seven compounds were creted in the bile in quanities greater than 1% of the ministered dose: MTX (32), cytembena (16), hycanne (9.6), puromycin ')5.6), cytoxan (3.5), DBM (2), diglycoaldehyde (2). While the total "bookkeeping" adioactivity of most of the agents above is good nsidering the number of organs sampled, the possibility excretion via the gills is likely (*Maren, et al., Comp. iochem. Physiol. 26, 853, 1968*) and should be vestigated further.

For 14 of these drugs there are t½'s available for a ammal (usually the human) and the dogfish shark. For TX, 6-MP, colchicine, HN_2 and 5-FU, the t½'s were mparable within a few minutes of each other. Slightly eater differences were seen for the following drugs here dogfish and mammalian t½'s respectively, are ven in parentheses: guanazole (96 vs. 120 min.); Act D .7 vs. 17 min.); cytoxan (68 vs. 20 min.); I-4-C (83 vs. 10 min.); Ara C (93 vs. 25 min); DBM (1.3 vs. 8 hr.); 5-AC (1.5 vs. 3.5 hr); cytembena (1.6 vs. 4 hr.); and CDDP (115 vs. 40 min.). Note that t½ values are higher for the dogfish in four of nine cases, reflecting the expected slower tissue uptake and metabolism. Hence, it would seem that the dogfish is suitable specie upon which to conduct preliminary fate and disposition experiments for xenobiotics.

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Absence Of The "Rehm Effect" In The Gastric Mucosa Of *Squalus acanthius*

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The gastric mucosae of several bony vertebrates respond to depolarization and hyperpolarization by respectively decreasing and increasing the rate of H^+ secretion ("Rehm effect"). In the following, the H^+ secretory rate of the dogfish mucosa proved to be remarkably refractory to a considerable displacement of the transepithelial potential difference in either direction.

Mucosae were mounted as previously described (*Hogben, Science 129: 1224, '59*) in flux chambers at 14°C and bathed by electrolyte solutions (urea-trimethylamine-free), whose ionic composition resembles the extracellular fluid of *Squalus*. The serosal solution had 30 mM of HCO_3 and was gassed by 5% CO_2, 95% O_2, while that at the mucosal surface lacked HCO_3^- and was gassed by 100% O_2. The spontaneous H^+ secretory rate was augmented by 5 carbachol added to the serosalsolution before the first test period. At the end of a 45 minute test period the solution before the first test period. At the end of a 45 minute test period the solution bathing the mucosal surface was removed and titrated automatically to pH 6.85. Paired portions of mucosa were alternately at their spontaneous PD (OmV) and then voltage clamped at 60 mV with one portion being polarized and the other depolarized, for a total of seven 45 minute periods (315').

The results are summarized in Table 1. (The paired differences were corrected for a minor time bias).

Thus, in spite of a substasntial degree of hypo- and hyper- polarization, the H^+ secretory rate was not significantly degreased or increased. In other vertebrates, the H^+ is markedly dependent on the transepithelial PD, prompting the assertion that the H^+ "pump" is "electrogenic". An equally plausible explanation for those vertebrates where the H^+ secretory rate responds to the

Table I

H^+ SECRETION

$\mu Eq.hr^{-1}cm^{-2}$

	Spontaneous potential (~OmV)	Voltage clamped (60mV)	Paired Differences ±95% Conf. Limits
Hypo-polarization (+)	1.35±.21	1.59±.22	0.206±0.382
Hyper-polarization (-)	1.35±.24	1.51±.27	0.108±0.110

(Reference = serosal surface; x±SE, n=6)