On this basis, it is difficult to account for inhibition of fat mobilization in animals that were restrained after cord section and for pronounced increase in fat mobilization in sham operated restrained animals. Neural excitation initiated by manipulation of intact cord seems aggravated by muscle tension produced by restraint. This cannot occur in lesioned animals where muscle tonus is eliminated. Alteration in fat mobilization has been produced by these procedures and chronic experiments are planned to elucidate mechanisms involved.

Summary. Male rats were subjected to spinal cord section and restraint during 24-hour fast. Both sham operation and cord section increased movement of fat from epididymal depots. Sham cord section plus restraint resulted in even greater rate of lipid movement; whereas, section plus restraint inhibited fat mobilization.

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Fluorinated Pyrimidines XII. Effects of Simple Nucleotides on Transplanted Tumors.* (25752)

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Previous work demonstrated potent tumor inhibitory properties(1,2) of 5-fluorouracil (FU)(3) and its nucleosides, 5-fluorouridine (FUR) and 5-fluoro-2′-deoxyuridine (FUDR). Although it seemed improbable (4) that nucleotides could enter cells without breakdown, nevertheless the finding that 5 - fluoro - 2′ - deoxyuridine - 5′ - monophosphate (FUDRP) is a potent inhibitor of thymidylate synthetase(5,6) pointed to the desirability of testing this compound, as well as corresponding ribonucleotide, 5-fluorouridine-5′-monophosphate (FURP), against transplanted mouse tumors. FURP was prepared enzymatically by Dahl *et al.*(7), and chemically by Farkas *et al.*(8). However, the method of Gilham and Tener(9) appeared more convenient, and we have prepared gram quantities of FURP and FUDRP by this procedure. The synthesis will be described elsewhere, and we are greatly indebted to Dr. Tener for making the details available to us prior to publication. The 2 nucleotides have been tested at various dosages against 3 transplanted mouse tumors, and compared with equimolar amounts of the corresponding nucleosides. We are not aware of any published reports on tumor-inhibitory activity of nucleotides of purine or pyrimidine analogs.

Methods. Nucleosides, FUR and FUDR, were kindly supplied by Dr. Robert Duschinsky of Hoffmann-LaRoche, and were converted chemically into nucleotides, FURP and FUDRP(9). Female Swiss mice were obtained from A. R. Schmidt Co., Madison, Wis., and used for Sarcoma-180 and EF Ehr-

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TABLE I Effect of Fluorinated Pyrimidine Nucleosides and Nucleotides on Growth of Sarcoma. Measurements are given for 14th day after transplantation. Dose administered intraperitoneally daily for 7 days, starting one day after transplantation.

Group	Dose, mg/kg/day	Wt change, g	Survivors, out of 6	T vol, mm³	T/C
Controls	0	-1.3	5	920	
FUDRP	200	-4.7	2	15	.02
"	150	-2.3	3	38	.04
"	100	+.5	6	54	.06
"	66.3	+2.6	6	257	.28
FUDR	50	-1.1	6	288	.31
FUDRP	30	+.4	6	461	.50
"	15	0	6	929	1.01
"	10	1.0	6	1240	1.35
"	5	-1.4	6	1850	2.02
Controls	0	1.9	6	1420	
FUDRP	150	-2.7	3	15	.01
"	66.3	+.3	6	50	.04
FUDR	50	-.6	6	21	.02
Controls	0	-1.4	6	967	
FURP	6	-5.6	4	954	.98
"	5	-5.5	5	936	.97
FUR	4.5	-7.8	5	781	.82
FURP	4	-5.1	6	914	.94
"	3	-4.6	6	644	.67

lich ascites carcinoma. L-1210 leukemia was carried in female BDF_1 mice from Cumberland View Farms, Clinton, Tenn. S-180 was transplanted bilaterally by trocar, and the 2 ascites tumors were transplanted intraperitoneally with suspensions of approximately 5 x 10^6 cells. Drugs were given once daily by intraperitoneal injection for 7 days, starting one day after transplantation. Survival of mice with ascites tumors was recorded, and in Sarcoma 180 experiments, tumors were measured periodically and volumes calculated(1). Because of limited supply of nucleotides, large numbers of mice or animals larger than mice could not be used.

Results. The effects of FUR, FURP, FUDR, and FUDRP against Sarcoma-180 are shown in Table I. Although there were only 6 mice in each group, there were actually 12 tumor measurements, since tumors were transplanted bilaterally. Although measurements were taken at various times, only data at 14 days after transplantation (one week after cessation of therapy) are shown here since they are representative also of other times. It is evident that FUDRP is a potent inhibitor of tumor growth from doses of about 30 to 150 mg/kg/day, although the latter dose is toxic. There are insufficient number of mice to justify calculation of a chemotherapeutic index. In 2 experiments 66.3 mg kg of FUDRP and 50 mg/kg of FUDR, which are equimolar equivalents, are not significantly different in tumor-inhibitory potencies. Thus, the nucleotide does not appear to offer chemotherapeutic advantage over the nucleoside. On the other hand FUR and FURP, although of much greater toxicity than the corresponding deoxy compounds, produced no significant inhibition of this tumor. Even severe weight loss of mice had no effect on growth rate of S-180.

In marked contrast, as shown in Table II, FURP produced a significant prolongation of survival time of mice bearing Ehrlich ascites carcinoma. At doses of 3 and 4.5 mg/kg/day

TABLE II. Effects of Fluorinated Pyrimidine Nucleosides and Nucleotides on Survival of Mice Bearing Ehrlich Ascites Carcinoma. Dose conditions as before.

Group	Dose, mg/kg/day	No. mice	Avg survival, days	Extremes, days	100 day negatives	T/C
Controls	0	18	15.9	8- 19	0	
FUDRP	150	8	23.7	8- 35	0	1.5 Toxic
"	66.3	8	49.0*	18-100	2	3.1*
FUDR	50	8	33.5	11- 47	0	2.1
FUDRP	66.3(14 days)	8	56.0*	19-100	2	3.5*
FUDR	50 (")	8	41.0*	12-100	2	2.6*
FURP	4.5	10	50.9*	23-100	3	3.2*
FUR	4	10	9.8	8- 10	0	.6 Toxic
FURP	3	10	54.7*	16-100	3	3.4*
"	2	10	25.9	12- 85	0	1.6
"	1	10	18.6	12- 22	0	1.2

* Mice that survived 100 days were sacrificed, autopsied, and no tumors observed. Since it is impossible to calculate avg survival and T/C values under these conditions, values above were calculated as if the mice had died on 100th day. Thus these values are low.

TABLE III. Effects of Fluorinated Pyrimidine Nucleosides and Nucleotides on the Survival of Mice Bearing L-1210 Leukemia. Dose conditions as before.

Group	Dose, mg/kg/day	No. mice	Avg survival, days	Extremes, days	T/C
Controls	0	28	11.0	9-14	
FUDRP	150	8	11.2	10-13	1.0*
"	66.3	8	16.2	11-22	1.5
FUDR	50	8	15.6	9-22	1.4
FURP	6	20	15.3	9-21	1.4
"	5	20	15.2	9-28	1.4
FUR	4.5	20	12.2	9-20	1.1
FURP	3	20	20.1	12-48	1.8

* Toxic.

of FURP, 3 mice survived tumor-free for 100 days. At higher doses toxicity was prohibitive. It is interesting to note the very high toxicity of the nucleoside, FUR at dose, 4 mg/kg, equimolar to the highly therapeutic level of 4.5 mg/kg of FURP.

In Ehrlich ascites carcinoma, FUDRP appeared slightly more effective than FUDR at equivalent doses, and toxicity was low enough to allow treatment for 14 days, resulting in somewhat improved survivals.

In L-1210 leukemia (Table III) all compounds produced a moderate effect. FUDR and FUDRP appear of equivalent activity, and there is a suggestion that FURP may be somewhat more effective and less toxic than FUR.

Discussion. Although the number of mice in above experiments was small, necessitated by limitation in supply of nucleotides, some conclusions can be reached. In Sarcoma-180 and L-1210 leukemia FUDR and FUDRP had comparable activities, with the latter possibly more active in Ehrlich ascites tumor. On the other hand, in the 2 ascites tumors, FURP appeared less toxic and more effective than FUR, although neither compound exerted an effect on S-180. Further screening of FURP against other tumors is indicated. Whether possible advantage of FURP or FUDRP reflects penetration into cells or merely a different rate of excretion or body distribution is under investigation with suitably labeled compounds. In deoxy compounds the nucleotide provided no advantage over nucleoside. In practical terms, it would appear that before large-scale trials could be justified, a nucleotide would have to offer very significant therapeutic advantages over the corresponding nucleoside, which itself is expensive and difficult to obtain.

Summary. Tumor inhibitory activity of 5-fluorouridine-5′-monophosphate (FURP) and 5 - fluoro - 2′ - deoxyuridine - 5′ - monophosphate (FUDRP) have been studied in mice bearing Sarcoma-180, Ehrlich ascites carcinoma, and L-1210 leukemia. Comparisons have been made with equimolar equivalents of corresponding nucleosides, 5-fluorouridine (FUR) and 5 - fluoro - 2′ - deoxyuridine (FUDR). FUDR and FUDRP were inhibitors of S-180 of not strikingly different potency. FUR and FURP were inactive against this tumor. However, FURP at lower dose was as active as FUDRP against Ehrlich ascites carcinoma, producing about 30% 100 day survivors. FUR was extremely toxic. In L-1210 leukemia the compounds were of moderate and equivalent activity.

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