endotoxin by papain does not appear, from these findings, to conflict with previous observations on the lack of correlation of biological potency of the endotoxin with its content of protein, peptide, or fatty acid. However, all endotoxins may not be affected by papain in a like manner; therefore we do not attempt to generalize beyond the data presented here.

Summary. The pyrogenicity of endotoxin which had been diminished by incubation with papain was restored by treatment of the inactive complex with pronase and ethanol, indicating that a hydrolytic cleavage of the endotoxin molecule had not occurred. In addition, it was shown that the reduction of the second fever peak in papain-inactivated endotoxin could be explained on the basis of a normal dose-response phenomenon. These findings suggest that there is no disagreement between the inactivation of a purified endotoxin by papain and the observed correlation of the biological activity of endotoxin with the polysaccharide portion of the molecule.

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Vinblastine Effect on Nucleic Acids and Ribonuclease of Lymphoid Tissue.* (30113)

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Vinblastine, one of the periwinkle alkaloids, has found limited clinical usefulness in the management of certain tumors. Studies on the mechanism of action of the drug have revealed that it inhibits mitosis in early metaphase in tissues studied(1,2,3). Biochemical studies do not reveal any effect of the agent on cellular respiration, glycolysis, protein or nucleic acid synthesis(4). Beer(5) investigated the effect of the drug on the incorporation of ^{14}C-labeled formate into the nucleic acids of the liver of intact and partially hepatectomized rats. In both cases he found that vinblastine treated animals incorporated more of the label into RNA than did controls. Enhanced liver RNA synthesis has also been obtained with corticosteroids by Lowe(6), and by Feigelson *et al*(7). These studies, and the fact that vinblastine is clinically most useful in the management of tumors of lymphoid origin make it desirable to know the influence of the drug on RNA and ribonuclease activity in normal and neoplastic lymphoid tissue, parameters which we have recently shown to be affected by corticosteroids(8,9).

Materials and methods. Sprague-Dawley rats weighing approximately 125 g and obtained from Camm Research Institute were injected subcutaneously with 1.0 mg vinblastine sulfate (Velban†) and sacrificed by decapitation 22 hour later. The thymus was removed and assayed for RNA and DNA content by the methods of Ceriotti(10) and Seibert(11), respectively. RNase in 10% thymus homogenates was assayed at pH 5.9 by a method previously reported by us(8).

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† Trademark, Eli Lilly and Co.

TABLE I. Nucleic Acid Concentration in the Thymus of Untreated and Vinblastine Treated Male Rats.

Hr after vinblastine	Thymus wt (mg)	μg RNA/ mg thymus	μg DNA/ mg thymus	RNA/DNA
0 (4)	453 ± 23	5.06 ± .18	113.55 ± 3.22	.044 ± .003
22 (4)	214 ± 27	3.69 ± .14	127.16 ± 4.72	.029 ± .004

Entries represent means ± standard error of mean. No. of animals studied indicated in parentheses.

Protein was measured by the method of Lowry *et al*(12). BALB/c mice, obtained from Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine were inoculated with either the corticoid-sensitive or corticoid-resistant strain of lymphosarcoma P1798 by the subcutaneous injection of a 30% tumor mince into the inguinal region as previously described(8). After 10 days' growth the animals were used for experimentation. Three-tenths mg of vinblastine was injected into the animals subcutaneously and they were sacrificed by decapitation 4 and 22 hours later. Tumor nucleic acid content, RNase activity, and protein were assayed as described above.

TABLE II. Ribonuclease Activity in Thymus Homogenates from Control and Vinblastine Treated Male Rats.

Hr after vinblastine	RNase activity*
0 (4)	216.16 ± 16.60
22 (4)	106.04 ± 5.16

* △ O.D. measured at 260 mμ/mg protein/hr.
Entries represent means ± standard errors of mean. No of animals studied indicated in parentheses.

Results. Table I shows the rat thymus weight and nucleic acid concentration 22 hours after *in vivo* vinblastine administration. Decreased thymus weight and RNA concentration was noted in thymi from treated animals. An apparent increase in DNA concentration was noted in thymi from treated animals. RNA/DNA ratios reflected the loss of RNA. Table II shows the rat thymus RNase specific activity 22 hours after *in vivo* vinblastine administration. Diminished specific activity of ribonuclease from thymi of treated rats was observed. Table III shows mouse lymphosarcoma P1798 weight and nucleic acid concentration 4 and 22 hours after *in vivo* vinblastine administration to tumor-bearing mice. No change in tumor weight was observed after 4 hours, but a significant decrease in weight of both tumor strains was observed at 22 hours post treatment. Decreased RNA concentration in both tumor strains was noted after 4 hours, and a further decrease was observed after 22 hours. RNA/DNA ratios changed accordingly. An apparent increase in DNA concentration was noted in the corticoid-sensitive tumor strain 4 and 22 hours after treatment. No such increase was observed in corticoid-resistant tumors. The results of RNase activity assays in lymphosarcoma P1798 4 and 22 hours after vinblastine administration to tumor-bearing mice are shown in Table IV. Decreased RNase activity was noted after 4 hours in both tumor strains.

TABLE III. Lymphosarcoma P1798 Weight and Nucleic Acid Concentration 4 and 22 Hours After Treatment of Host Mice with Vinblastine.

Hr after corticoid	Tumor wt (mg)	μg RNA/ mg tumor	μg DNA/ mg tumor	RNA/DNA
I. Corticoid-sensitive tumor				
0 (10)	1870 ± 20	6.91 ± .10	39.71 ± 1.98	.180 ± .012
4 (5)	1815 ± 27	5.23 ± .08	55.81 ± 2.37	.093 ± .011
22 (5)	102 ± 24	3.47 ± .15	65.35 ± 3.43	.053 ± .019
II. Corticoid-resistant tumor				
0 (10)	1225 ± 260	8.19 ± .04	38.99 ± 1.63	.208 ± .012
4 (5)	1301 ± 187	5.33 ± .11	38.88 ± .93	.137 ± .013
22 (5)	614 ± 139	3.77 ± .10	38.29 ± 1.78	.096 ± .015

TABLE IV. Lymphosarcoma P1798 RNase Specific Activity 4 and 22 Hours After Vinblastine Administration to Host Mice.

Hr after vinblastine	RNase activity*
I. Corticoid-sensitive tumor	
0 (10)	.261 ± .021
4 (5)	.200 ± .010
22 (5)	.077 ± .010
II. Corticoid-resistant tumor	
0 (10)	.319 ± .009
4 (5)	.200 ± .011
22 (5)	.098 ± .019

* △ O.D. measured at 260 mμ/mg protein/hour. Entries represent means ± standard error of mean. No. of animals studied indicated in parentheses.

A further decrease was observed after 22 hours.

Discussion. Sugár(13) studying nucleic acid synthesis in 2 types of ascites tumor cells by means of the polarization and fluorescence microscope concluded that vinblastine administered to host animals resulted in a loss of tumor cellular RNA. Creasey *et al*(14) found uptake of tritiated uridine into the soluble RNA of Enrlich ascites cells derived from mice treated with vinblastine depressed about 60% as compared with that of controls. In the present study a decrease in RNA concentration was observed in thymus and lymphosarcoma P1798 derived from vinblastine treated animals. This effect is not the result of increased RNase activity as occurs after corticosteroid administration in thymus (9) and corticoid-sensitive lymphosarcoma P1798(8), since RNase activity in the tissues studied was lower than control values. It appears that vinblastine causes deterioration of the RNA-RNase system in rat thymus and both strains of lymphosarcoma P1798.

There is an apparent increase in DNA concentration in the thymus of vinblastine treated rats. This phenomenon has also been noted by the authors in thymi from corticosteroid treated rats(9). An apparent increase in DNA concentration is also noted in corticoid-sensitive but not corticoid-resistant P1798 from vinblastine treated mice. These results have also been obtained after treating such mice with corticosteroid(8).

Summary. The RNA concentration and ribonuclease activity in rat thymus were decreased by injection of vinblastine. The same results were noted in both the corticoid sensitive and resistant strains of mouse lymphosarcoma P1798. An apparent increase in DNA concentration was noted in rat thymus and corticoid-sensitive P1798. No change in DNA concentration was noted in the corticoid-resistant tumor.

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