fering with production of high energy phosphate compounds in key cells within the glomerulus. This hypothesis raises a question concerning enzymatic activity and metabolic requirements of the normally functioning glomerulus. Experiments to explore this question are underway.

Summary. Production of acid-labile phosphate by crude brewer's yeast system, in the presence of adenosine and inorganic phosphate, has been demonstrated. This acid-labile phosphate has been identified as adenosine triphosphate. The nucleoside, 6-dimethylaminopurine-3-amino-d-riboside inhibits adenosine triphosphate formation in this system. The possible relationship of this inhibitory action to ability of the nucleoside to produce nephrosis in rats is discussed.

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Received June 9, 1958. P.S.E.B.M., 1958, v98.

Effects of 5-Flurouracil on Human Bronchogenic Carcinoma Grown in Hamster Cheek Pouch.* (24179)

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It has been shown that pyrimidine analogue 5-flurouracil has appreciable tumor-inhibitory activity against a variety of transplantable rat and mouse tumors(1). The work described here is a preliminary study of the efficacy of this drug on heterologously grown human bronchogenic carcinoma transplanted in the hamster cheek pouch.

Materials and methods. The tumor was the Skiff Bronchogenic Carcinoma obtained from Sloan-Kettering Institute for Cancer Research, N.Y. City. The host animal used was the golden hamster (*Mesocricetus auratus*), and site of tumor growth was the left cheek pouch. Experimental animals 40 to 80 g were obtained from National Pet Shops, St. Louis, Mo. Animals of both sexes were used. The tumor transplant was introduced into the cheek pouch under light ether anesthesia with a No. 14 trocar, by the method of Lutz, *et al.*(2) as modified by Toolan(3), Patterson, *et al.*(4) and Palm, *et al.* (unpublished). Microscopic examination of a hematoxylin eosin stained section at time of transplantation revealed that the tumor was composed of fairly uniform cells of moderate size with hyperchromic nuclei and fairly large amounts of deeply staining cytoplasm. The cells tended to be spindle-shaped and elongated in many areas. Only rare giant nuclei were present and multi-nucleated forms were not seen. A bronchogenic tumor in man with these morphologic characteristics would usually be classified as an undifferentiated carcinoma of the "large cell" type. The tumor specimen used for transplantation was harvested from the cheek pouch of a maintenance animal, in which it had grown for 14

* This investigation was supported in part by research grant from Nat. Cancer Inst., U. S. P. H. S.

TABLE I. Treatment with 25-30 mg/kg/Day of 5-Flurouracil for 7 Days.

Control		Treated	
Wt of		Wt of	
Host (g)	Tumor (mg)	Host (g)	Tumor (mg)
59	789	56	709
66	375	82	1054
64	182	57	338
64	178	54	928
49	260	65	363
63	466	56	383
		65	179
61 ± 1.2	375 ± 95	62 ± 6.1	565 ± 126*

* Mean ± stand. error of mean.

days. The animals were placed under light ether anesthesia 5 days after implantation of tumor. Animals in which tumors did not take were discarded and tumor bearing animals were divided randomly into treated and control groups. All animals were given cortisone: 50 mg/kg, injected subcutaneously into nape of neck, every 4 days throughout experiment (Cortone Acetate, Merck, Sharp and Dohme). 5-Flurouracil treatment was begun on fifth day after transplantation (animals had received 2 cortisone injections), and was continued for 7 days or until the drug proved to be too toxic (as indicated by marked weight loss). 5-Flurouracil in crystalline form was obtained from Dr. Charles Heidelberger (Univ. of Wisconsin Medical School). 5-Flurouracil was dissolved at concentration of 4 mg/ml of distilled water and stored at 5°C. Control animals were given 0.45% saline solution prepared by dilution of physiological saline with distilled water. 5-Flurouracil and saline control solutions were administered intraperitoneally. At termination of each experiment, animals were weighed and autopsied. Tumors of treated and control animals were weighed. In addition, gross toxic effects on various organisms were noted, and histologic sections of treated and control tumors were made. The possible anti-tumor action of 5-flurouracil was tested at 2 dosage levels: 25-30 mg/kg/day and 50-60 mg/kg/day. The lower level was the optimal dosage used by other workers with homologously grown rat and mouse tumors(1).

Results. Data in Table I show that with dosage level of 25-30 mg/kg/day of 5-flurouracil for 7 days there was no inhibition of growth of the Skiff Human Bronchogenic Carcinoma grown in the hamster cheek pouch. The average weight of treated tumors at end of 7 days was 565 mg, the control tumors weighed 375 mg; the difference of these values was not statistically different. There was also no significant difference in weights of treated and control animals, indicating that the drug had no toxic effects by this criterion. Gross examination of spleens, livers and gastrointestinal tracts of treated animals revealed no abnormalities. Microscopic examination of treated and control tumors revealed no difference in histological appearance.

Data in Table II show that with higher dosage level of 5-flurouracil, 50-60 mg/kg/day, for 3 days there was marked inhibition of the heterologously grown human bronchogenic carcinoma. The average weight of treated tumors was 74.5 mg; that of control tumors was 358.0 mg. The weights of necrotic tumors were not included in the final tabulation nor were the weights of tumors in animals who died prior to termination of experiment.

There was also a marked and significant loss of weight in the treated group of animals indicating extremely toxic effects of the drug at dose given. The data in Table III show that treated animals dropped from average weight of 60 g, on day that treatment was

TABLE II. Treatment with 50-60 mg/kg/Day of 5-Flurouracil for 3 Days.

Control		Treated	
Wt of		Wt of	
Host (g)	Tumor (mg)	Host (g)	Tumor (mg)
63	350	52	30
80	81	50	29
68	91	64	180
60	114	40	59
48	457	55	59 (necrotic)
52	742	38	28 (")
52	666	39*	
58	Necrotic	48*	
54	"	44*	
68	"	50*	
		49*	
60 ± 3.3	358 ± 104.5	46.9 ± 2.2	74.5 ± 35.0 †

* Died after 3 days of treatment.
† Mean ± stand. error of mean.
Weights of necrotic tumors not averaged.

TABLE III. Summary of Effects of 5-Flurouracil on Host Animals.

Experiment	Group	Wt of host (g) Prior to treatment	Wt of host (g) After treatment	Animals surviving/animals treated
Exp. 1—25-30 mg/kg/day of 5-flurouracil for 7 days	Control	61.9 ± 4.3	61.0 ± 2.8	6/6
	Treated	64.9 ± 4.2	62.0 ± 3.7	7/7
Exp. 2—50-60 mg/kg/day of 5-flurouracil for 3 days	Control	59.3 ± 4.8	60.3 ± 3.3	10/10
	Treated	60.0 ± 2.9	46.9 ± 2.2	5/11

begun, to average weight of 46.9 g after 3 days of treatment with drug at higher dosage level. In the control group in the 3-day period there was no decrease of average weight. Five of 11 animals died after 3 days of treatment. Further indications of the toxicity of the drug were that 50% of treated animals showed infection and necroses of the stomach, small and large intestine and pallor of liver on gross examination. The average weight of spleens of treated animals was 45.8 mg (= .098% body weight) that of controls 102 mg (= .168% body weight). In addition, all treated animals showed a marked loss of fur, not noted in the control group.

Histological examination of the treated tumor revealed no morphological difference from control tumors.

Discussion. It is interesting to note that 5-flurouracil when administered at dosage level of 25-30 mg/kg/day for 7 days showed no incidence of cytotoxic effect on either host or tumor, while double this dose for 3 days had a very drastic effect on both. These effects are summarized in Table III. Future work with this drug will be aimed at determining whether there is any dosage level between the apparently ineffective 25-30 mg/kg and the highly toxic 30-60 mg/kg at which a specific toxic effect on the tumor can be demonstrated.

Summary. 5-flurouracil at dosage level of 50-60 mg/kg/day produced a marked tumor inhibitory effect on human bronchogenic carcinoma grown in the hamster cheek pouch but was very toxic to the host. A dose of 25-30 mg/kg/day had no apparent effect on either tumor or host.

We are indebted to Dr. Valentina Suntzeff of the Wernse Cancer Research Laboratory, Washington University, St. Louis, Mo., for the tumor maintained in her laboratory, and to Dr. Joy Palm of Sloan-Kettering Institute for Cancer Research, N. Y. City, who made the tumor available to Wernse Laboratory. We also thank Dr. Morris Friedkin of Washington Univ. Dept. of Pharmacology for his technical assistance, and Dr. Robert O'Neal, Dept. of Pathology, and Dr. Suntzeff for help in histologic studies.

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Received June 9, 1958. P.S.E.B.M., 1958, v98.