TABLE I. Local Reactions to Intramuscular Injection.

% of 26 patients with	Time of examination: 1 hr	Days: 1	2	3	7
	Digoxin preparation				
Severe pain	50	15	0	0	0
Erythema	0	8	12	8	0
Induration	0	42	4	4	0
	Propylene glycol				
Severe pain	4	0	0	0	0
Erythema	0	0	0	0	0
Induration	0	23	8	4	4

each of the 14 individual ventricular rate curves. The deepest depression of rate sustained for at least 3 hours was read from each curve. That depression fell lower after intravenous injection in 4 patients, after intramuscular in 3. The mean effects for the routes were not different; standard errors were 2.5 beats per minute for intravenous and 3.6 for intramuscular. No systemic toxicity was encountered.

Table I summarizes the local reactions and their time of onset. Within 1 hour of intramuscular digoxin half of the patients developed severe pain, and most of these showed tissue reactions the following day. In the parallel test, propylene glycol caused little pain and less frequent tissue response. Twenty additional patients served in a final "double-blind" comparison between reactions to the solvent (40% propylene glycol and 10% ethanol) and to physiological saline. In these 20 patients there was neither tissue reaction nor severe pain, although 9 of them mentioned fleeting pain after the solvent and 3 did so after saline.

Discussion. Absorption from an intramuscular depot of digoxin is not fast enough to serve an emergency that demands rapid digitalization. This preparation might act as a convenient substitute for oral digoxin in patients temporarily unable to take regular digoxin tablets. Since only two-thirds of the activity of oral digoxin is detected on the heart(3), a shift from oral to intramuscular digoxin should include reduction in dosage.

Summary. Digoxin in 40% propylene glycol and 10% ethanol was injected intramuscularly in 7 patients with auricular fibrillation. Its full cardiac effect was reached in 8 hours, while intravenous digoxin in the same patients reached full effect in 2 hours. Intensity and persistence of action were the same for both routes. Additional intramuscular injections in 26 patients revealed pain but no permanent tissue damage.

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Intestinal Absorption of Pyrimidines in the Rat.* (23218)

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Continuing interest in the metabolism and pharmacology of pyrimidines and pyrimidine derivatives(1,2) prompted us to make a study of the intestinal absorption of a number of 2-thiopyrimidines and of 3 natural pyrimidines. Compounds of this type have frequently been studied by oral administration to animals, although it has not been determined which of them is adequately absorbed from the gastrointestinal tract. We wished

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to obtain information on this point, and to determine whether any consistent changes in absorption were produced by various substituents in the ring. Since a number of 2-thiopyrimidines have antithyroid activity, it was possible in some instances to correlate rate of absorption with presence or absence of antithyroid activity.

Procedures. Sprague-Dawley rats, fasted 24 hours, and weighing 200-250 g were used for all tests. Compounds were prepared as 5 mM solutions in 0.154 M phosphate buffer at pH 6.6, and 2 ml, containing 10 μM of compound (*e.g.*, 1.28 mg thiouracil), administered intragastrically by means of a #10 soft rubber catheter attached to a hypodermic syringe. Although 6.6 is considered to be the normal average pH of the rat intestine(3), it was necessary to test a few compounds at pH 8 because of their poor solubility at pH 6.6. After 30 minutes, the test animal was killed, the stomach and small intestine removed and washed out with enough phosphate buffer at pH 6.6 to give a total volume of 50 ml. The combined washings were filtered, and recovered thiopyrimidine determined colorimetrically with Grote reagent(4). Natural pyrimidines were determined by the lithium arseno-tungstate method of Soodak *et al.*(5). Since phosphate interferes in this test, physiological saline was used for washing out the tract. All readings were corrected for blank, and the fraction of dosage not recovered was calculated as % disappeared. Disappearance by loss into the cecum was excluded since administered compounds seldom traversed more than ⅔ the length of the intestine in 30 minutes. Disappearance by enzymatic destruction prior to absorption was also excluded, since incubation tests *in vitro* showed that digestive enzymes do not attack pyrimidines. Adsorption of pyrimidines on proteins does occur at the normal pH of the intestine(6), but attempts to recover adsorbed material by acid washes did not give good results. An estimate of adsorption was obtained by placing 2 ml of pyrimidine solution in the duodenum of the intestine from a freshly-killed rat, and washing through immediately. Recovered compound was determined as before, and the % adsorption calculated. The difference between % disappeared and % adsorbed was taken as % absorbed. When the animal was anesthetized and the stomach ligated at the pyloric end, administered pyrimidine was recovered almost completely. Hence, the stomach was not used in measuring adsorption, since any material bound in this way was apparently removed by acidic secretions during the 30-minute disappearance tests. *Antithyroid tests.* Thiopyrimidines were prepared as olive oil mulls, and 50 μM/day injected subcutaneously into 30-day-old Sprague-Dawley rats. After 6 days, 5 μC of I^{131} sodium iodide was injected intraperitoneally, and the 24-hour accumulation of isotope in the thyroids measured. In other tests, thiopyrimidines were injected for 13 days, then the thyroids analyzed for total iodine.

TABLE I. Intestinal Absorption and Adsorption of Pyrimidines in Rats.

Derivative	No. of animals	% absorbed		% adsorbed	Oral antithyroid activity in rats(7)	
(Thiouracil)	14	41	2.2	23	1	
5-Methyl	5	41	3.5	27	.7	
6-Methyl	8	41	2.6	22	1	
5-Propyl	5	40	4.0	33	2	
5-Iodo	9	38	3.0	35	.5	*
3-Methyl	9	33	2.2	33	.5	
6-Propyl	10	30	1.6	33	11	
5,6-Dihydro	5	43	3.5	17	0	
5-Carboxy	10	20	2.0	16	0	†
4-Amino	7	16	3.8	31	.001	
6-Carboxy	10	11	1.2	24	.001	
4-Amino-5-carboxy	8	0		25	0	
Thiobarbituric acid	10	4	.9	25	.003	
6-Methyl-5-iodo‡	9	47	2.4	32	0	*
1,6-Dimethyl‡	10	40	1.5	22	.3	†
6-Butyl‡	9	36	1.8	32	3	
5-Cyano‡	15	9	3.9	26	.001	
Uracil	6	Complete		67		
Cytosine	5	46	2.1	10		
Orotic acid	5	19	2.6	10		

* By thyroid iodine analysis(8).
† Determined for this paper.
‡ At pH 8.

Results. Table I shows the results of the absorption studies as % absorbed ± mean standard error, and as % adsorbed. These figures may be converted directly to micromols by dividing by 10. Thiopyrimidines are named as derivatives of 2-thiouracil, and the ring is numbered in accord with IUC nomen-

TABLE II. Antithyroid Activity of Injected Thiopyrimidines.

Thiouracil derivative	Thyroid I^{131}, μg/100 mg	Antithyroid rating	Thyroid I^{131}, 24 hr., % of dose*	Antithyroid rating
Controls	68		12.3	
(Thiouracil)	15	1	3.28	1
3-Methyl	12	1	1.31	2.5
5-Carboxy	27	.55		
1,6-Dimethyl	32	.5	5.22	.6
6-Methyl-5-iodo	35	.43	.79	4
5-Cyano	55			
Thiobarbituric	53			
4-Amino	60			
4-Amino-5-carboxy	58		8.17	.4
5-Iodo	33	.5	.67	5
6-Carboxy			10.8	
5,6-Dihydro	70			

* Probable error of counting <5%.

clature. The number of animals refers to the absorption figure. Adsorption was measured with 3-5 animals, and all measurements were within 3% of the mean. In addition to the compounds shown in the Table, thiobarbituric acid and the carboxy derivatives were also tested at pH 8, and showed some improvement in absorption. Absorption of uracil was so rapid that none could be recovered from the intestine after 30 minutes even when the dosage was increased to 15 μM.

Results of the antithyroid studies are shown in Table II. Ten animals were used in each group, and an antithyroid rating calculated when the mean difference from the controls was significant at the 5% level or less. In previous work, the 6-methyl-5-iodo derivative was found to be inactive as an oral antithyroid compound(8). Present results indicate that the oral inactivity was due to low solubility, and consequent poor absorption, at the normal pH of the intestine.

Discussion. With the possible exception of uracil, intestinal absorption of the pyrimidines studied was undoubtedly passive. Very small quantities were absorbed in 30 minutes (*e.g.*, 0.52 mg thiouracil), and absorption of 4 different thiopyrimidines was unchanged when the solutions were made 10^{-3} M in phlorhizin. The pyrimidines most poorly absorbed are fairly strong organic acids, and extensively ionized at pH 6.6. Improved absorption of these compounds at pH 8 was most probably due to increased solubility, since they are difficultly soluble in neutral aqueous media, and may have partly precipitated in the stomach when administered at the lower pH. Aside from strongly ionic groups, comparison of different derivatives shows that any substituent that increased polarity of the molecule decreased intestinal absorption, while non-polar substituents (small alkyl groups) had no effect so long as the molecule remained soluble at the pH used. The position of the substituent in the ring was relatively unimportant.

It has been reported that intestinal absorption of both D- and L-amino acids is also inhibited by ionization or by presence of polar side-chains(9,10) despite active absorption of the L-isomers. Further examples of this same relationship as reported in the general biological literature(11) suggest that in any series of similar, water-soluble compounds, the rate of intestinal absorption is inversely related to polarity. Since strongly polar thiopyrimidines generally lacked antithyroid properties when injected, polarity may also inhibit penetration of compounds into the thyroid. Without further information on disposition of these compounds in other tissues, this possibility is only speculative. However, the results convince us that 6-butylthiouracil for instance, is indeed slowly absorbed from the intestine because of low solubility, but exhibits antithyroid potency because of favorable handling in the tissues.

Summary. The intestinal absorption of 3 natural pyrimidines and of 17 2-thiopyrimidines was studied in intact rats, and the antithyroid activity of 12 of the latter compounds tested by subcutaneous injection. With the possible exception of uracil, all compounds tested were passively absorbed. No relation was found between intestinal absorption and adsorption, and among compounds showing oral antithyroid activity, no relation was found between this activity and absorption. Both absorption and antithyroid activity were decreased by ionization or by polar groups, while small, non-polar groups had little or no effect on absorption. The position of the groups was of minor importance. It is sug-

gested that the rate of intestinal absorption, for any series of similar, water-soluble compounds, is inversely related to polarity.

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Effect of Distillers Dried Solubles and Molybdenum on the Growing Chick.* (23219)

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The role of molybdenum in animal nutrition has been ably reviewed by Dick(1) and the association of this element with xanthine oxidase in the rat by Westerfeld and Richert (2). The first indication of a possible requirement for molybdenum by the chick and poult fed a purified type diet was reported by Reid *et al.*(3). The addition of 0.0254 ppm of molybdenum to a purified diet has been subsequently shown by the same group of workers to stimulate the growth of poults and the activity of both intestinal and liver xanthine dehydrogenase(4). Furthermore, a portion of the growth promoting activity of the ash of distillers dried solubles(5,6) was reported by Reid *et al.*(4) to be due to the molybdenum content of this unidentified nutrient source.

The present study was initiated to determine the effect of feeding distillers dried solubles ash, after the molybdenum has been removed from this substance, on the growth, bone ash, molybdenum distribution in tissues and on xanthine dehydrogenase activity of chicks.

Method. New Hampshire chicks, from dams fed an all vegetable protein diet containing no added unidentified growth factors (5), were distributed at random into groups of 12 birds each. Each treatment was replicated once. The basal diet (Extracted soybean protein and Cerelose supplemented to meet the requirements of the chick) and the care and management of the birds was the same as previously reported by Reid *et al.*(3). At the close of the experiment, the chicks were sacrificed; the liver and a portion of the

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