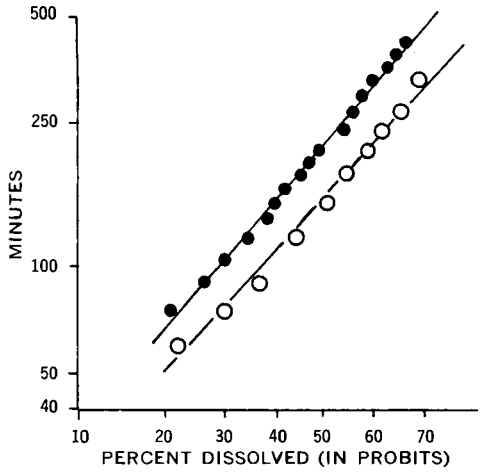

Figure 3—*Representative log-normal probability plots of dissolution rate data for nitrofurantoin from a commercial capsule at 37°. Key: ●, pH 1.12; and ○, pH 7.20.*

form was introduced into the pH 7.20 medium, it displayed poor disintegration properties, produced relatively large granules, and maintained most of its shape during the greater portion of the dissolution run.

Hailey and Glascock (5) demonstrated, in patients with known intolerance to nitrofurantoin, that the incidence of undesirable side effects is markedly reduced upon oral administration of a commercial capsule containing macrocrystalline drug particles[3] as compared to a commercial tablet containing microcrystalline drug particles[2]. In view of these findings, the lack of official recognition for this larger particle-size fraction of drug or its capsule dosage form seems surprising. When dissolution rate experiments were conducted at pH 7.2, the pH suggested by the USP (6), the dissolution rate of macrocrystalline nitrofurantoin from the commercial capsule was identical to that of microcrystalline drug from the tablet dosage form (Table I). These results are inconsistent with the anticipated slower dissolution rate of nitrofurantoin from the macrocrystalline drug capsule (1) and its lower toxicity (5). However, when the same two dosage forms were exposed to simulated gastric fluid (pH 1.12), an interrelationship was found to exist among the particle size of drug contained within the dosage form, its dissolution rate (Table I), and its reported toxicity (5).

The results of the present investigation provide evidence that the dissolution rate of nitrofurantoin from three different pharmaceutical dosage forms can be markedly affected by pH. The dissolution medium (pH 7.2 phosphate buffer) recommended by the USP (6) is unable to discern inherent, particle-size-dependent differences in the rate of solution and incidence of side effects of nitrofurantoin from commercial, microcrystalline drug tablet and macrocrystalline drug capsule dosage forms. The dissolution rate characteristics of nitrofurantoin from these two dosage forms in simulated gastric fluid (pH 1.12) and the existence of a relationship between these *in vitro* results and reported toxicity data suggest that the USP XVIII dissolution rate specification for nitrofurantoin products should be modified.

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COMMUNICATIONS

Effect of γ-Radiation on Intestinal Absorption of Sulfanilamide

Keyphrases □ Radiation, gamma—effect on intestinal absorption of sulfanilamide, rats □ Sulfanilamide—effect of γ-radiation on intestinal absorption, rats □ Absorption, intestinal—effect of γ-radiation on rate of sulfanilamide absorption, rats

To the Editor:

Following sublethal irradiation of the mammalian small intestine, cell division in the intestinal epithelium slows. The mass of the epithelium declines temporarily and then becomes abnormally large before the intestine appears histologically normal again (1). Since the barrier characteristics of the intestinal epithelium are thought to control the absorption of many orally administered drugs, exposure of the intestine to ionizing radiation could affect drug absorption.

Although the results of a number of studies on the influence of radiation on the intestinal absorption of vitamins, minerals, water, and nutrients have been reported (1, 2, and references cited therein), there is very little published information on the effects of ra-

Table I—Effect of 850 Rad of ^{60}Co γ-Radiation on Absorption of Sulfanilamide from Rat Intestine

	Sham[a]	850 Rad[a]	p
Absorption half-life, min	17.1 (2.24)	26.8 (5.49)	<0.01
pH of drug solution[b]	6.3 (0.12)	6.4 (0.15)	>0.30
Gut length, cm	90 (6.3)	87 (4.9)	>0.30

[a] Mean of six animals; standard deviation in parentheses. [b] Measured at the end of the experiment; initial pH was 6.5.

diation on drug absorption. The results of studies on the effects of 700 rad of ^{60}Co whole-body γ-radiation on the transfer of drugs across the *in vitro* rat small intestine were recently reported (3). Four days following irradiation, the transfer of salicylate and ethionamide was increased, the transfer of mecamylamine, aminopyrine, and isoniazid was unchanged, the transfer of phenobarbital and diphenylhydantoin was decreased slightly, and the transfer of butylscopolamine was completely blocked (3, 4). Since the GI tract is exposed to radiation during the treatment of some cancers, it is important to know how such exposure affects the absorption of orally administered drugs.

This preliminary communication describes the effect of whole-body ionizing radiation on the absorption of sulfanilamide from the *in situ* small intestine of the rat. Male Sprague–Dawley rats, weighing 180–250 g, were either exposed to 850 rad of ^{60}Co γ-radiation delivered over 5 min or sham irradiated (5). Irradiated and sham-irradiated animals underwent identical manipulation, except the sham-irradiated animals were shielded from the radiation. The animals were housed in cages with wide-mesh floors and had access to food and water *ad libitum* prior to and following the irradiation procedure. Food was withdrawn on the 3rd day after irradiation, and on the 4th day[1] the animals were prepared as described previously (6) for measuring the rate of drug absorption from solution by the *in situ* small intestine. The rectal temperature of each animal was monitored throughout the absorption experiment and maintained at 37° with a rheostatically controlled heating pad placed under the animal. Seven milliliters of 0.4 m*M* sulfanilamide dissolved in 67 m*M* sodium phosphate buffer made isotonic with sodium chloride was placed in the intestine, and 0.2-ml samples were removed at 5-min intervals for 30 min. The volume of the drug solution was maintained constant by adding 0.9% NaCl solution immediately prior to sample removal. The concentration of sulfanilamide in each sample was determined by the colorimetric procedure of Bratton and Marshall (7). Plots of log sulfanilamide concentration *versus* time appeared linear for both irradiated and sham-irradiated rats. Absorption rate constants were determined from the slopes of lines fitted to the plots by least squares. The rate constants were corrected for drug removed due to sampling by subtracting 0.0057 min^{-1} and were converted to half-lives. At the conclusion of each experiment, the pH of the intestinal perfusate and the length of the intestine lying between the cannulas were measured.

The absorption rate of sulfanilamide was significantly reduced in irradiated animals compared to the sham-irradiated controls (Table I). The data in Table I also indicate that the radiation-induced reduction in absorption rate cannot be attributed to differences between irradiated and control animals in the pH of the drug solution nor to differences in the length of intestine used in the absorption experiment.

Although the reduced rate of sulfanilamide absorption in irradiated animals could result from a decrease in the surface area of the intestinal mucosa, other mechanisms may be involved. For example, irradiation of the intestine could directly alter the permeability of the intestinal mucosa and it could alter blood flow to the mucosa. Additional experiments are underway to determine the effects of radiation on the absorption of other drugs and the mechanisms by which radiation alters drug absorption.

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[1] Preliminary experiments and the results of Mattila *et al.* (3) indicate that the acute effect of radiation on the rate of intestinal drug absorption in the rat is greatest 4 days following whole-body irradiation.