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GI Drug Absorption in Rats Exposed to Cobalt-60 γ-Radiation I: Extent of Absorption

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Abstract □ The extent of absorption of sulfanilamide, bretylium tosylate, sulfisoxazole acetyl, and riboflavin was determined in rats exposed to 850 rad of cobalt-60 γ-radiation or sham irradiated. The drugs were administered orally at 1 or 5 days postirradiation, and the amount of drug excreted in the urine was used as the measure of absorption. Following intravenous drug administration, there was no difference between irradiated and control animals in the amount of drug excreted in the urine. At 1 day postirradiation, the absorption of sulfanilamide and bretylium was not affected by radiation; the absorption of sulfisoxazole acetyl and riboflavin was increased. The fraction of sulfanilamide excreted in the urine as N^4-conjugate was increased at 1 day postirradiation. At 5 days postirradiation, there was no detectable difference between irradiated and control animals in the extent of drug absorption. The effects of radiation on the extent of absorption of orally administered drugs were most pronounced immediately following irradiation. Irradiation apparently does not affect the absorption of drugs that are normally well absorbed or poorly absorbed due to slow transport across the GI mucosa. Following irradiation, there may be an increase in the extent of absorption of drugs that are poorly absorbed due to low aqueous solubility or that are absorbed by a saturable transport mechanism.

Keyphrases □ Absorption, GI—various drugs, effect of cobalt-60 γ-radiation, rats □ Radiation, gamma—effect on GI absorption of various drugs, rats □ Sulfanilamide—GI absorption, effect of cobalt-60 γ-radiation, rats □ Bretylium tosylate—GI absorption, effect of cobalt-60 γ-radiation, rats □ Sulfisoxazole acetyl—GI absorption, effect of cobalt-60 γ-radiation, rats □ Riboflavin—GI absorption, effect of cobalt-60 γ-radiation, rats

Patients exposed to ionizing radiation for the treatment of cancer commonly receive drugs during or following radiation therapy. When the GI tract is involved in radiation therapy, its structure and function may be altered for several days. Such alterations may affect the bioavailability of orally administered drugs.

The potential mechanisms by which radiation may alter drug absorption were explored by studying the absorption of several drugs in rats that were exposed to cobalt-60 γ-radiation. The drugs used were chosen so that the absorption rate of each drug was controlled by a different step in the overall process of absorption (Table I). Experiments were performed to assess the effects of radiation on the rate and extent of absorption of each drug and on the permeability of the intestinal mucosa. The studies on the extent of drug absorption are presented here; the other studies are reported elsewhere (1, 2).

BACKGROUND

Following oral administration, the rate and extent of absorption of many drugs are determined by one or more of the following steps: dissolution in the lumen of the GI tract, transport across the GI epithelium, and gastric emptying (3, 4). The primary rate-controlling step (or steps) in the absorption of a particular drug depends on dosage formulation and on the physicochemical properties of the drug; *e.g.*, the solubility in water affects the rate of solution, and the oil/water partition coefficient affects epithelial permeability. Since drugs with low solubility in water tend to dissolve slowly following oral administration, dissolution is usually the step that controls the absorption rate of poorly water-soluble drugs. As water solubility increases, the dissolution rate increases, but the permeability of the intestinal epithelium tends to decrease due to the lipophilic nature of this barrier. The rate-controlling step in the absorption of very polar drugs is the transport of the dissolved drug across the intestinal epithelium.

The rate of gastric emptying may determine the rate of drug absorption since most drugs tend to be absorbed more rapidly from the intestine than from the stomach. For drugs that are absorbed by a saturable transport process in the intestine, slowed gastric emptying may enhance absorption by maintaining a low concentration of drug at the site of absorption for

Table I—Drugs Selected for Study

Drug and Dosage Form	Physicochemical and Biological Properties	Probable Rate-Limiting Step in Absorption
Sulfanilamide suspension	Relatively high aqueous solubility, high oil/water partition coefficient, normally well absorbed	Gastric emptying
Bretylium tosylate solution	Ionized, high aqueous solubility, low oil/water partition coefficient, not well absorbed due to low mucosal permeability	Mucosal permeability
Sulfisoxazole acetyl suspension	Low aqueous solubility, high oil/water partition coefficient, not well absorbed due to slow dissolution	Dissolution
Riboflavin solution	Low aqueous solubility, low oil/water partition coefficient, may be absorbed in part by a capacity-limited mechanism	Mucosal permeability

a prolonged time. In addition, changes in intestinal motility may affect the absorption of drugs that dissolve slowly or are absorbed slowly by altering the time available for dissolution or absorption.

Exposure of the GI tract to ionizing radiation could alter bioavailability by altering the normal rates of the primary rate-controlling steps, particularly transfer across the GI epithelium, and GI motility. The normally rapid rate of cell division in the intestinal epithelium is slowed following irradiation, resulting in villi that are abnormal in size and shape (5). In addition, the mass of the epithelium decreases following irradiation, *e.g.*, 50% in mice exposed to 600 rad (6). In rodents, the maximal change in the structure of the epithelium occurs 4–6 days postirradiation (5, 7). A decrease in the surface area of the intestinal mucosa could significantly reduce the absorption of drugs that slowly cross the normal intestinal epithelium. The impaired absorption of digoxin in a human (8) and slowed absorption of diazepam and aminobenzoic acid in rats[1] following irradiation may have resulted from a reduction in the capacity of the intestinal epithelium to absorb these drugs.

Both gastric emptying and intestinal motility are altered following irradiation of the gut. Radiation-induced changes in GI motility depend on the dose of radiation and are greatest immediately following irradiation. Slowed gastric emptying was shown to be the major cause of the reduced rate of absorption of sulfadiazine and quinine observed in irradiated mice and rats (9). Following irradiation, both an increase and a decrease in the motility of the rat small intestine, as reflected by the rate of intestinal transit of a nonabsorbed marker, have been reported. The intestinal transit rate increased in irradiated animals following intraduodenal administration of the marker (10) but decreased following intragastric administration. The greatest reduction in transit rate occurred in the middle segment of the intestine (11).

Other mechanisms by which irradiation of the GI tract could alter absorption include an alteration in blood flow to the intestine (12, 13) and inactivation of carriers associated with transport across the intestinal epithelium (14–16).

EXPERIMENTAL

Materials—Sulfisoxazole acetyl[2], bretylium tosylate[3], riboflavin[4], and sulfanilamide[5] were used as received. ^{14}C-Riboflavin[6] was dissolved in a pH 5.0 aqueous buffer and stored at 5° in an opaque container. The labeled radiochemical purity of ^{14}C-riboflavin was 99%; it was verified periodically by TLC on silica gel G-coated plates developed with either methanol–benzene–acetone–acetic acid (20:70:5:5) or pyridine–acetic acid–water (20:2:80). Methylcellulose 4000, polyethylene glycol 400[7], 2,2′,4,4′,6,6′-hexanitrodiphenylamine[8] (dipicrylamine), sodium nitrite[9], sulfamic acid[9], and *N*-(1-naphthyl)ethylenediamine dihydrochloride[4] were used as received. All other reagents and solvents were reagent grade.

Irradiation Procedure—A 7000-Ci cobalt-60 source, stored in a lead chamber at the bottom of a bulk shielding reactor pool, was used to irradiate rats. Animals were placed in a Plexiglas restraining cage, rotated at 20 rpm, and lowered down a watertight sample tube to a position near the source of radiation. To irradiate animals, the source was elevated automatically from its storage chamber.

The dose of radiation was checked regularly with an ionization-type dosimeter[10], and the sample-to-source distance was adjusted to maintain a dose of 850 ± 42 rad delivered over 5.0 min. Sham-irradiated animals were manipulated as were irradiated animals, except that the source of radiation remained in its storage chamber.

The level of radiation in the sample tube when the source was shielded was less than 1 rad/hr.

Bioavailability Studies—Experiments were conducted on the 1st and 5th days postirradiation to maximize the potential effects of radiation on gastric emptying (9, 17, 18) and intestinal epithelial permeability (19–21), respectively. Equal numbers of irradiated and sham-irradiated male Sprague–Dawley rats (170–250 g) were fasted for 16–20 hr prior to and for 3 hr following drug administration. Drug was administered at the same time of day either intravenously *via* the penile vein or orally by gastric intubation. Animals were anesthetized lightly with ether to facilitate drug administration.

After drug administration, animals were housed individually in metabolism cages[11] which permitted quantitative separation of urine and feces. The room in which the animals were housed was maintained at 16° and lighted 9 hr followed by 15 hr of darkness per day. Urine was collected until the drug and metabolites were no longer excreted. Each urine sample was combined with a distilled water rinse of the lower section of the metabolism cage and was stored at −20° until assayed.

Sulfanilamide, 200 mg/kg, and sulfisoxazole acetyl, 100 mg/kg, were administered orally suspended in 8.0 ml of 0.5% methylcellulose solution/kg. Identical doses of the sulfonamides were dissolved in 2.0 ml of polyethylene glycol 400–water (9:1)/kg and administered intravenously. Prior to administration, suspensions were agitated for 24 hr at room temperature and sonicated. Riboflavin, 0.8 and 4.0 mg/kg, was given orally and intravenously in 12.0- and 1.6-ml/kg doses, respectively; the intravenous solutions contained 200 mg of niacinamide[12]/ml. ^{14}C-Riboflavin was diluted with unlabeled riboflavin to a specific activity of approximately 0.5 mCi/g. Bretylium tosylate was administered orally, 30 mg/kg, and intravenously, 5 mg/kg, dissolved in 8.0 and 2.0 ml of water/kg, respectively.

Analytical Methods—Free (unconjugated) and total (free + N^4-conjugated) sulfanilamide and sulfisoxazole acetyl were determined in urine by a colorimetric method[13] involving extraction of the free drug with ethyl acetate and acid hydrolysis for total drug (22). Sulfisoxazole acetyl was measured as sulfisoxazole and converted on a molar basis to equivalent amounts of sulfisoxazole acetyl. Radioactivity was determined by liquid scintillation spectrometry[14]; ^{14}C-toluene was used as an internal standard to correct for quenching. Bretylium was analyzed by a spectrophotometric method[13] involving ion-pair extraction of drug from urine (23).

Recovery of sulfanilamide and sulfisoxazole acetyl from urine was greater than 95%; urine blanks of free and total sulfonamides were 0.25 and 0.31 mg/day, respectively. Recovery of bretylium and ^{14}C-riboflavin from urine was 101 and 97%, respectively; urine blanks of both were negligible.

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[3] Donated by Burroughs Wellcome Co., Research Triangle Park, N.C.
[4] Eastman Organic Chemicals, Rochester, N.Y.
[5] Sigma Chemical Co., St. Louis, Mo.
[6] Amersham/Searle, Arlington Heights, Ill.
[7] Ruger Chemical Co., Irvington, N.Y.
[8] Aldrich Chemical Co., Milwaukee, Wis.
[9] J. T. Baker Chemical Co., Phillipsburg, N.J.
[10] Landsverk Roentgen meter, Landsverk Co., Glendale, Calif.
[11] Model HB-11M with HB-66 food tunnel, Hoeltge, Inc., Cincinnati, Ohio.
[12] Riboflavin and niacinamide 1-ml ampul, Eli Lilly and Co., Indianapolis, Ind.
[13] Beckman DU (Beckman Instruments, Fullerton, Calif.) with a Gilford model 2000 multiple sample recorder (Gilford Instrument Laboratories, Oberlin, Ohio).
[14] Packard Tri-Carb model 3320, Packard Instrument Co., Downers Grove, Ill.

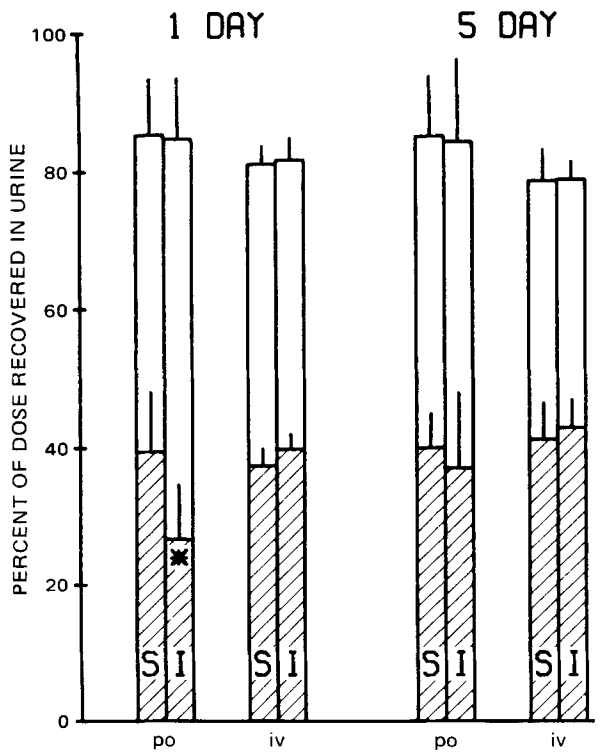

Figure 1—*Recovery of sulfanilamide in the urine of rats exposed to 850 rad of γ-radiation (I) or sham irradiated (S) 1 or 5 days before administration of 200 mg/kg. Each bar represents the mean of five or more animals, the vertical line in the center of each bar indicates 1* SD, *and the * indicates that recovery was significantly different (p < 0.01) from the corresponding S group. The hatched and open portions of each bar represent non-*N^4*-conjugated and* N^4*-conjugated sulfanilamide, respectively.*

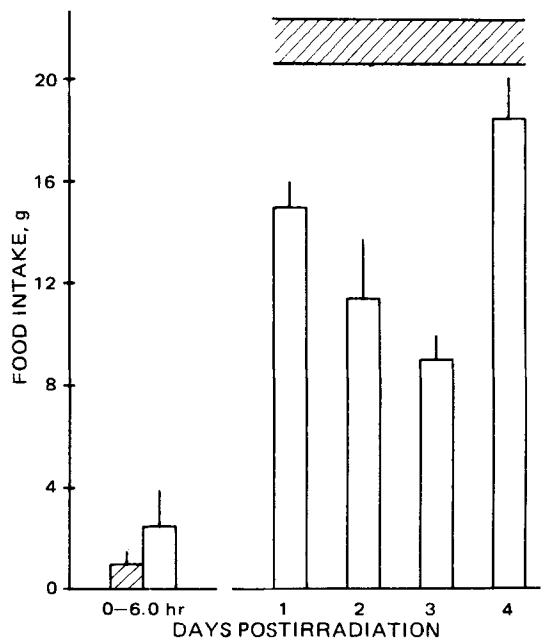

Figure 2—*Food intake in rats following exposure to 850 rad of γ-radiation (open bars) or sham irradiation (hatched bars). Each vertical bar represents the mean of 10 or more animals, and the vertical line in the center of each bar indicates 1* SD. *The horizontal bar represents the mean daily food intake of 10 or more sham-irradiated animals* ± SE.

RESULTS AND DISCUSSION

Sulfanilamide—Similar recoveries of sulfanilamide in the urine following oral and intravenous administration (Fig. 1) indicate that the orally administered drug was absorbed completely, as reported by others (24, 25). Following intravenous administration, neither the total recovery of the drug in the urine nor the fraction excreted in the urine as N^4-conjugate was affected significantly by prior irradiation of the animals (Fig. 1). Other studies in mice and rats found that serum and whole blood levels following intravenous or intraperitoneal administration of certain sulfonamides were not affected by prior irradiation (9, 26). Thus, the differences between irradiated and sham-irradiated animals in the urinary recovery of sulfanilamide administered orally reflect the effects of radiation on the absorption of sulfanilamide rather than on the distribution or elimination of the drug.

The lack of effect of radiation on the extent of metabolism of sulfanilamide *in vivo* is interesting in view of *in vitro* drug metabolism studies with homogenates of liver from irradiated rats. In these studies, prior whole-body exposure to γ-radiation induced a subsequent decrease in microsomal enzyme activity at 3–5 days postirradiation for several drugs (27, 28), including sulfanilamide (29). Recent pharmacokinetic analyses showed that *in vitro* studies of drug metabolism do not necessarily provide information about the intrinsic capacity of liver tissue to metabolize drugs (30, 31). Apparently, the *in vivo* rate of metabolism of sulfanilamide

Table II—Recovery of Sulfanilamide in Urine following Oral Administration[a] of 200 mg/kg to Rats Fasted Postirradiation

	Percent of Dose Recovered[c]	
Treatment[b]	Unconjugated	Total
Sham	40.9 ± 4.84	80.3 ± 6.29
850 rad	29.5 ± 10.2[d]	78.7 ± 11.1

[a] Administered as a suspension in 0.5% aqueous methylcellulose. [b] Rats were exposed to 850 rad of cobalt-60 γ-radiation or sham irradiated 1 day before sulfanilamide administration. Following irradiation, animals were not allowed food. [c] Mean of five animals ± *SD*. [d] Significantly different from sham ($p < 0.05$).

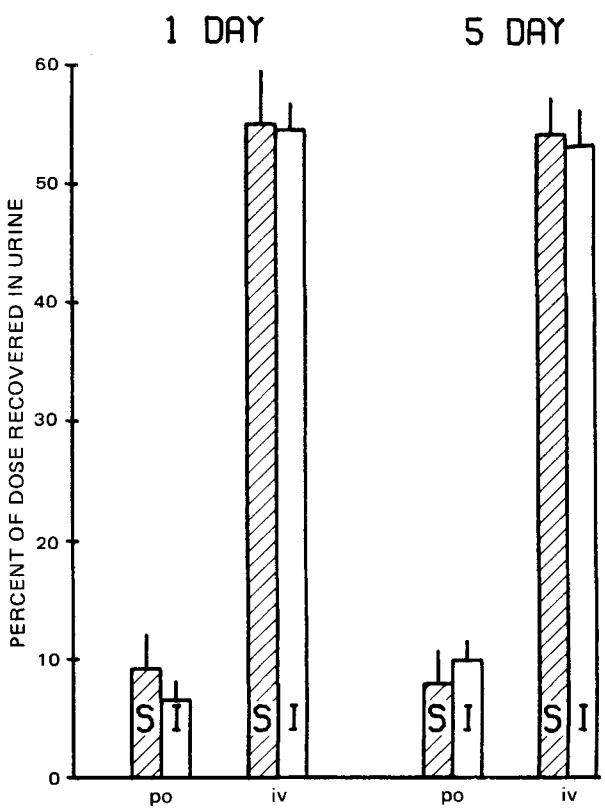

Figure 3—*Recovery of bretylium in the urine of rats exposed to 850 rad of γ-radiation (I) or sham irradiated (S) 1 or 5 days before administration of 30 mg/kg po or 5 mg/kg iv of bretylium tosylate. Each bar represents the mean of five animals, and the vertical line in the center of each bar indicates 1* SD.

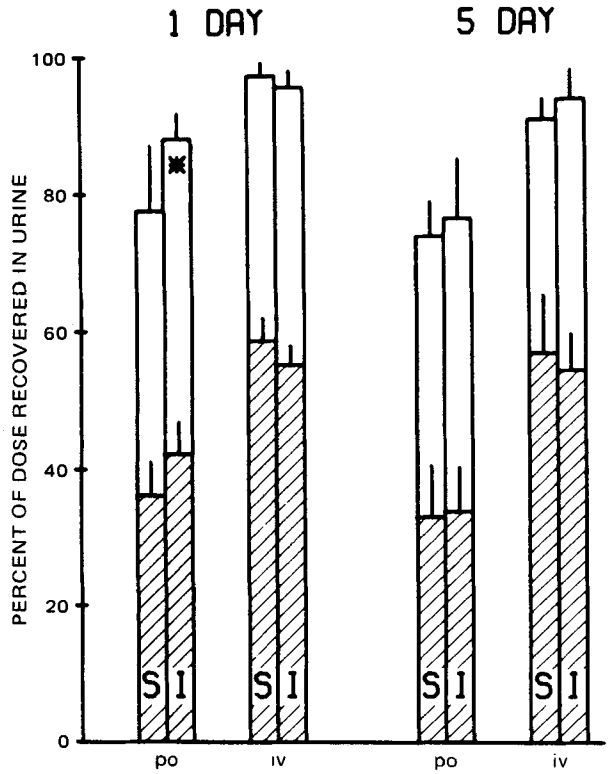

Figure 4—*Recovery of sulfisoxazole acetyl in the urine of rats exposed to 850 rad of γ-radiation (I) or sham irradiated (S) 1 or 5 days before administration of 100 mg/kg. Each bar represents the mean of five animals, the vertical line in the center of each bar indicates 1* SD, *and the * indicates that recovery was significantly different ($p < 0.05$) from the corresponding S group. The hatched and open portions of each bar represent non- N^4-conjugated and N^4-conjugated sulfisoxazole acetyl, respectively.*

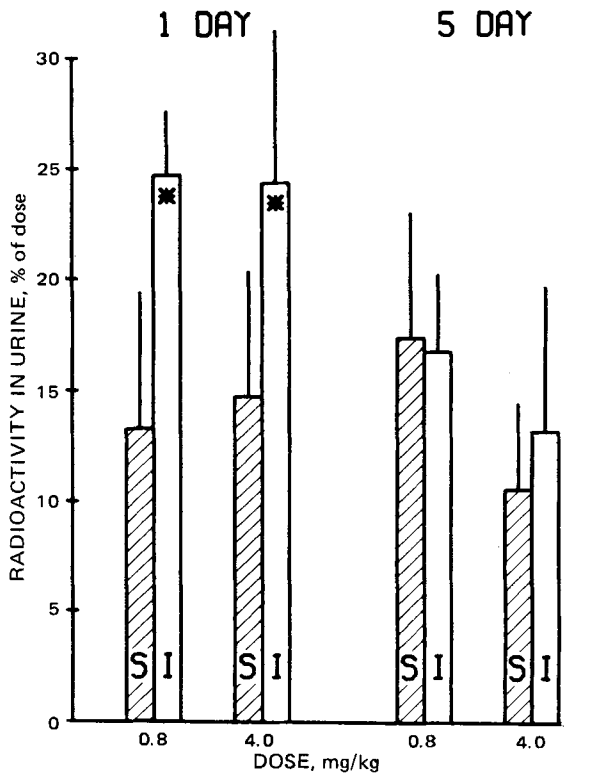

Figure 5—*Recovery of radioactivity in the urine of rats exposed to 850 rad of γ-radiation (I) or sham irradiated (S) 1 or 5 days before oral administration of 0.8 or 4.0 mg of ^{14}C-riboflavin/kg. Each bar represents the mean of six animals, the vertical line in the center of each bar indicates 1* SD, *and the * indicates that recovery was significantly different ($p < 0.05$) from the corresponding S group.*

is not controlled by the intrinsic metabolic capacity of the liver; changes in this capacity, as indicated by *in vitro* microsomal enzyme studies, do not result in changes in the *in vivo* rate of elimination or extent of metabolism of the drug.

Exposure of rats to 850 rad of γ-radiation 1 or 5 days prior to oral administration of sulfanilamide did not affect the total urinary recovery of the drug and its metabolites (Fig. 1). At 1 day postirradiation, however, the fraction of sulfanilamide excreted as metabolite increased significantly; this increase was not evident at 5 days postirradiation. Since the extent of metabolism of intravenously administered sulfanilamide was not affected by prior irradiation of the animals, the observed increase in the extent of metabolism of orally administered sulfanilamide apparently occurs before the drug reaches the systemic circulation. Whole-body irradiation is known to cause a subsequent transient reduction in the rate of gastric emptying (1, 32). The increased residence time of sulfanilamide in the stomachs of irradiated animals compared to controls may have resulted in metabolism of part of the dose prior to absorption. Both the gastric emptying rate (1) and the extent of metabolism of sulfanilamide (Fig. 1) returned to control values by 5 days postirradiation.

Following irradiation, rats alter their pattern of food consumption (6). In this study, food consumption was increased immediately following irradiation but reduced on Days 1–4 postirradiation (Fig. 2). In addition, the stomach at 1 day postirradiation was markedly distended by food following an overnight fast. By 5 days postirradiation, both food intake and the amount of food in the stomach were similar in irradiated and control animals.

To determine whether differences in food consumption between irradiated and control animals affected sulfanilamide absorption, the experiment was repeated with animals that were fasted from the time of irradiation or sham irradiation to 3 hr after drug administration. The results (Table II) were similar to the results of the study shown in Fig. 1. Thus, the effect of radiation on sulfanilamide absorption at 1 day postirradiation is apparently not due to a radiation-induced alteration in food consumption.

Bretylium—Following oral administration, the urinary recovery of bretylium was less than 20% of the recovery following intravenous administration (Fig. 3). This comparatively low recovery indicates that bretylium was poorly absorbed, probably due to low permeability of the GI epithelium to this ionized compound. The urinary recovery of intravenously administered bretylium was not affected by prior irradiation of the animals (Fig. 3). Thus, differences between irradiated and sham-irradiated animals in the urinary recovery of bretylium indicate the effect of prior irradiation on the absorption of orally administered bretylium.

Because bretylium is poorly absorbed following oral administration, the extent of drug absorption was anticipated to be sensitive to radiation-induced alterations in the permeability of the GI mucosa. At both 1 and 5 days postirradiation, the absorption of bretylium by irradiated rats was not significantly different from drug absorption by sham-irradiated animals (Fig. 3). There is evidence that the rate of small intestinal transit is increased in rats at 1 day postirradiation (10). Such an increase would reduce the time available for bretylium absorption, possibly explaining the tendency toward decreased absorption at 1 day postirradiation (Fig. 3). The extensive histological changes occurring in the small intestinal epithelium following irradiation (5, 33) probably do not affect significantly the capacity of the intestine to absorb bretylium.

Sulfisoxazole Acetyl—Following intravenous administration of sulfisoxazole acetyl, neither the total urinary recovery of the drug nor the fraction excreted unchanged was affected by prior irradiation of the animals (Fig. 4). In addition, irradiation did not affect significantly the extent of metabolism of sulfisoxazole acetyl (Fig. 4). As shown previously (34), the urinary recovery of orally administered sulfisoxazole acetyl was significantly lower than after intravenous administration, indicating incomplete absorption (Fig. 4). The low oral bioavailability was presumably due to the low aqueous solubility of the drug.

At 1 day postirradiation, the extent of sulfisoxazole acetyl absorption was significantly greater in irradiated animals than in sham-irradiated controls (Fig. 4). Since the sulfisoxazole acetyl absorption is dissolution rate limited (1, 34), the reduced rate of gastric emptying in irradiated animals apparently allows additional time for dissolution of sulfisoxazole acetyl and, therefore, increases absorption. At 5 days postirradiation, both the gastric emptying rate (1) and the extent of sulfisoxazole acetyl absorption (Fig. 4) were not significantly different from control values.

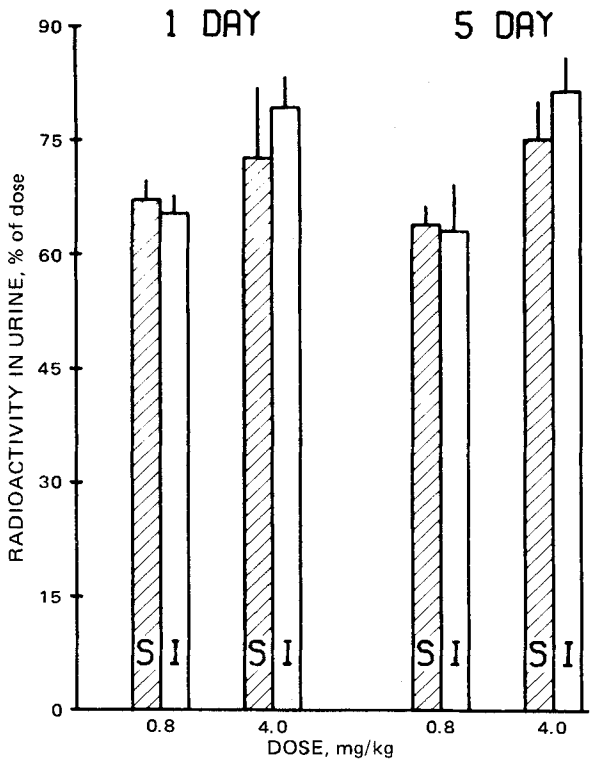

Figure 6—*Recovery of radioactivity in the urine of rats exposed to 850 rad of γ-radiation (I) or sham irradiated (S) 1 or 5 days before intravenous administration of 0.8 or 4.0 mg of ^{14}C-riboflavin/kg. Each bar represents the mean of six animals, and the vertical line in the center of each bar indicates 1* SD.

Riboflavin—The low recovery of radioactivity in the urine following oral administration of ^{14}C-riboflavin (Fig. 5) compared to intravenous administration (Fig. 6) indicates that riboflavin was not completely absorbed. The absorption of the vitamin in rats is probably limited by its low oil/water partition coefficient and low solubility in water.

Irradiation had a negligible effect on the excretion of riboflavin following intravenous administration of either 0.8 or 4.0 mg/kg (Fig. 6). However, irradiated animals receiving riboflavin orally at 1 day postirradiation excreted 70–85% more radioactivity than controls (Fig. 5). A similar increase in the bioavailability of orally administered riboflavin was reported in humans pretreated with propantheline to reduce the rate of gastric emptying (35). Delayed gastric emptying in humans apparently increased absorption by prolonging the contact of the vitamin with a capacity-limited mechanism for absorption. Although capacity-limited absorption of riboflavin has not been found in rats (36 and references therein), a reduction in the gastric emptying rate could increase the bioavailability of a passively absorbed drug as was reported for phenolsulfonphthalein (37).

The recovery of radioactivity (percent of dose) in urine following intravenous administration of riboflavin increased with dose (Fig. 6). This dose-dependent increase may be due to saturable tubular reabsorption in the kidney (38) or to saturable tissue binding (36). The urinary recovery of riboflavin following oral and intraperitoneal administration decreases as the dose is increased, apparently because of a nonlinear biliary excretion mechanism (36, 39).

In summary, there was no detectable difference between irradiated and sham-irradiated animals in the extent of drug absorption at 5 days postirradiation. At 1 day postirradiation, the extent of sulfisoxazole acetyl and riboflavin absorption was increased significantly while sulfanilamide and bretylium tosylate absorption was not affected. The extent of metabolism of sulfanilamide was increased at 1 day postirradiation.

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