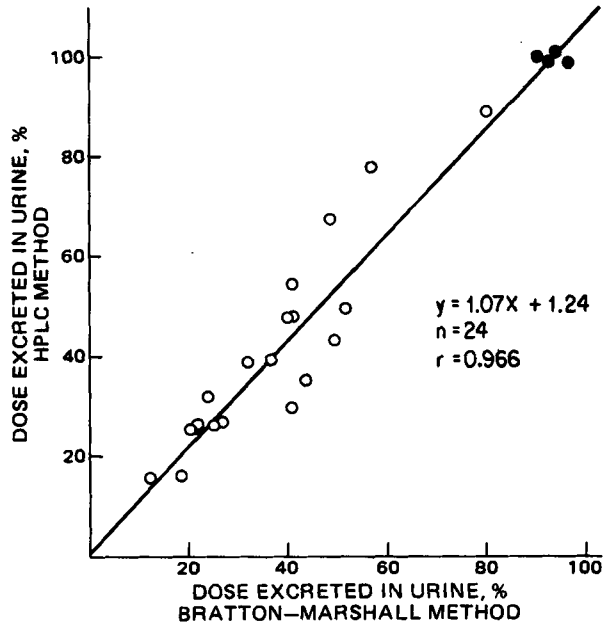

Figure 1—*Relationship between the percent of chlorothiazide dose excreted in the urine of four dogs as determined by HPLC and Bratton–Marshall methods. Key:* ○, *125–750 mg po; and* ●, *250 mg iv.*

administration of chlorothiazide (coefficient of variation of 26–50% for the various doses irrespective of analytical method) than after intravenous administration (coefficient of variation was 1.0% by the HPLC method and 2.5% by the Bratton–Marshall method).

These results clearly indicate that interferences by urinary constituents, which vary during the experimental period and with the extent of dilution of the urine specimen (3, 4, 8), can cause appreciable errors in chlorothiazide bioavailability estimates based on the colorimetric procedure and that HPLC should be the analytical method of choice in all future urinary excretion-based bioavailability studies on chlorothiazide and, perhaps, other thiazide diuretics.

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Localization of Isoproterenol-Induced Contractions of Canine Small Intestine

Keyphrases □ Isoproterenol—*in vivo* effects on small intestinal motor activities, dogs □ Motor activities *in vitro*—effect of isoproterenol on muscularis mucosa and muscularis externa motility

To the Editor:

The proposition is generally accepted that the catecholamines produce relaxation of the small intestinal musculature of a number of species *via* α- and β-receptor mechanisms. This acceptance was gained because exceptions to this rule were rarely noted and were usually inconsistent or segment related. These scattered observations have not been systematically analyzed to determine what possible common threads connected them.

For all practical purposes, most experimental evidence for the small intestinal relaxatory activities of the catecholamines has derived from *in vitro* and *in situ* studies involving dogs, cats, rats, rabbits, mice, and guinea pigs. The only serious disagreement arises with the canine ileum. Some years ago, it was reported (1, 2) that occasionally high dosages of isoproterenol produced marked stimulation of the ileum of the anesthetized dog *in situ*, but no explanation for this phenomenon was advanced. Since that time, we have observed similar anomalous effects of isoproterenol stimulation on the canine small intestine. Thus, the purpose of this communication is to propose a unifying theory with respect to the excitatory activities of catecholamines on the mammalian GI tract.

Kokas and Gordon (3) reported that the villi of the canine small intestine were specifically stimulated by β-adrenergic agents and that this effect was enhanced by α-adrenolytics. Later, we also observed that stimulatory effects of β-adrenergic agents on canine ileal segmenting activities in the chloralose–urethan anesthetized animal became predictably reproducible following pretreatment by α-adrenolytics. Intravenous doses of isoproterenol usually produced marked jejunal and ileal segmenting activity. Both bilateral vagotomy and atropine were ineffective in blocking this small intestinal response. Prior administration of the α-adrenolytic phenoxybenzamine potentiated the response (Fig. 1), which was blocked by dichloroisoproterenol (not depicted).

We subsequently decoupled the canine ileal tunica muscularis from the muscularis mucosa (4) and demonstrated that the β-excitatory effect upon the latter occurs *pari passu* with the inhibitory effect on the former. Again, the excitatory effects of the β-agonists are enhanced by pretreatment with α-adrenolytics. In experiments using the classical tissue bath technique, contractions of the circular and longitudinal components of the muscularis were recorded (Fig. 2). Isoproterenol had opposite effects in different parts of the ileum of the same animal. The tunica muscularis portion of the ileum exhibited a relaxation response to a fixed dose of isoproterenol, whereas the muscularis mucosa portion exhibited only a tonic contractile response to the same dose of the β-agonist. These observations using mechanically decoupled effector systems are identical to the results obtained by Kokas and Gordon (3) without decoupling but by specific observations of the motility of the villi.

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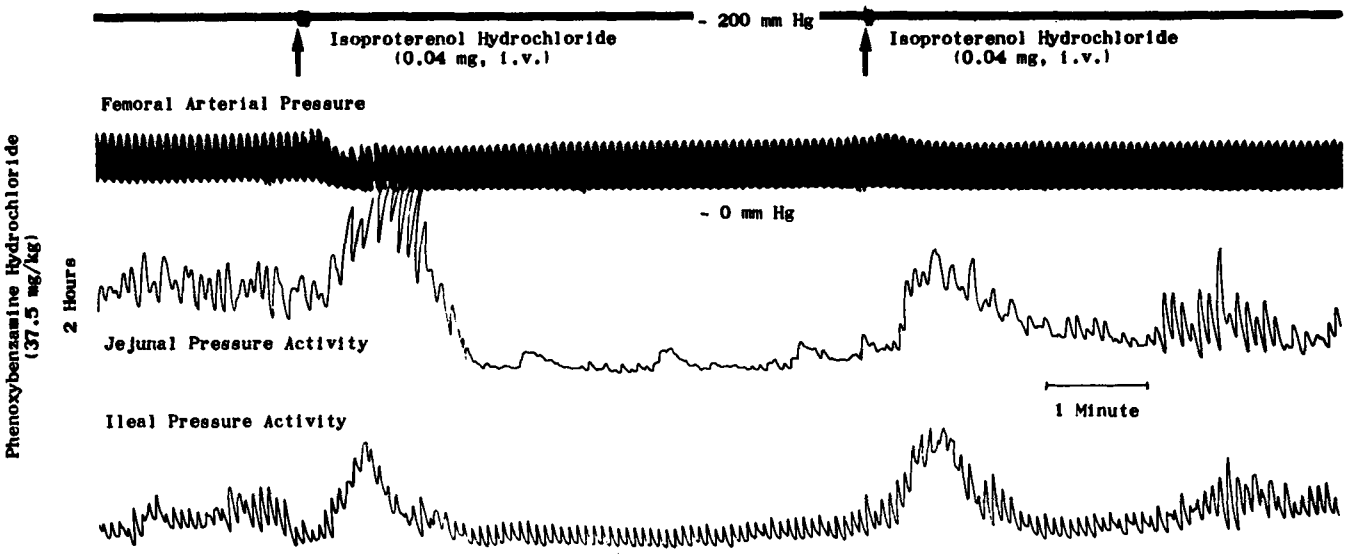

Figure 1—*Polygram showing the effect of intravenous isoproterenol, repeated once, on a phenoxybenzamine background on femoral arterial blood pressure and jejunal and ileal intraluminal pressure activities.*

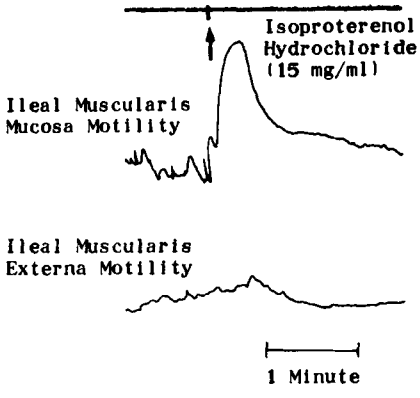

Figure 2—*Polygram showing* in vitro *effects of isoproterenol on the muscular components of the canine ileum.*

A systematic review of the literature indicates that, insofar as gross organ motility is concerned, the canine ileum is the one system observed *in vitro* or *in situ* in which the adrenergic effect is not always inhibitory. Basic histology also tells us that this is the only system that exists in the aforementioned species, from the cardia to the rectum, in which the muscularis mucosa forms a physically significant effector layer (similar to humans) in terms of the ratio of layer thickness to inner layer radius.

Therefore, we advance the general proposition that β-adrenergic agents in high doses are usually stimulatory to the muscularis mucosa and that they are potentiated by α-adrenolytics. We also support the proposition that the β-agents are inhibitory of the motility of the tunica muscularis. In terms of gross organ motility, we believe that the net effect of any agent will be primarily determined by its effect on the more physically significant of the coupled effector systems.

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Bioavailability under Variable Renal Clearance Conditions

Keyphrases □ Bioavailability—method for assessment under variable renal clearance conditions □ Renal clearance conditions, variable—effect on bioavailability □ Pharmacokinetics—bioavailability under variable renal clearance conditions

To the Editor:

Several methods are used to calculate the bioavailability of a drug, *i.e.*, the fraction of the administered dose that reaches the general circulation. Bioavailability can be determined from single (1–4) or multiple (5) doses, as well as at steady state (6).

The most popular methods for assessing bioavailability involve single test and reference doses. A comparison determination of the total area under the plasma concentration *versus* time curve, AUC_0^∞, or the total amount excreted unchanged in urine from time = 0 to time = ∞, A_R^∞, between the test dose and a reference dose is made. The assumptions in these methods are:

1. Total plasma clearance is the same in the test dose and reference studies when the areas are used for bioavailability assessment.
2. The fraction excreted unchanged in the urine, f_e, is

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