prevent the complication of possible radiation damage, larger amounts should not be used. This is especially important in studies in which subsequent development or movement of the labeled cells is to be followed.

Summary. Tritiated thymidine, when given to young male rats 20 hours following partial hepatectomy in doses of 1.0 μc/g body weight or greater, causes a transient inhibition of regeneration as mirrored in rate of increase of residual liver mass, mitotic rate, and incidence of abnormal mitotic figures. The importance of this effect in tracer studies is obvious.

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Action of Angiotensin on Isolated Guinea Pig Ileum. (26175)

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Earlier studies(1,2) with angiotensin (hypertensin, angiotonin) indicated a direct spasmogenic action on smooth muscle. A recent report(3) suggests that on rabbit and guinea pig ileal strips, angiotensin may have an indirect action in producing contraction. The present study attempts to delineate the site of action of angiotensin in guinea pig ileum by use of pharmacologic blocking agents. The results suggest that angiotensin produces contraction by acting on the post-ganglionic cholinergic mechanism. They also indicate that care should be taken in interpreting such results and that a number of blocking agents of each class should be examined over a wide range of concentrations before conclusions are reached.

Materials and methods. Freshly prepared strips of guinea pig ileum were suspended in duplicate 10 ml baths of aerated Tyrode's solution maintained at 37°C. The responses were recorded on soot-paper by frontal writing levers. Maximal contractions were induced at 4-minute intervals by exposing the tissues to 0.05 γ/ml of angiotensin* for 60 seconds and to 1 γ/ml of nicotine for 30 seconds. The antagonists were added midway between contractions allowing 2-minute exposure of the tissue. Three or more concentrations of each antagonist were studied to obtain dose-response curves. The EC_{50}'s, concentration effecting a 50% inhibition of the contractions, were obtained from graphic plots. Each of the antagonists was studied on 6 ileal strips. The results are presented in Table I.

Results and discussion. The data establish that the spasmogenic actions of angiotensin and nicotine on the ileum are effectively blocked by low concentrations of atropine and morphine. Emmelin and Feldberg (4) have shown that atropine effectively blocked the action of nicotine on the gut while Schaumann(5) and Paton(6) have

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TABLE I. Effect of Autonomic Blocking Agents on Angiotensin and Nicotine-Induced Contractions of Guinea Pig Ileum.

	Spasmogen			
	Angiotensin		Nicotine	
Antagonist*	Avg EC_{50}	γ/ml range	Avg EC_{50}	γ/ml range
Atropine	.02	(.01 – .04)	.01	(.003– .03)
Morphine	.06	(.002– .16)	.19	(.004– .96)
Mecamylamine	28	(16 – 41)	.11	(.05 – .19)
Pempidine	306	(115 –320)	.10	(.06 – .14)
Pentolinium	>500		.33	(.11 – .68)
Hexamethonium	>500		.82	(.47 –1.3)

* As base or ion.

demonstrated that morphine blocks the effects of cholinergic stimulation by preventing release of acetylcholine. With only this information, one would be tempted to classify angiotensin with nicotine as having ganglion-stimulating properties. These results with atropine do not confirm those of Collins(7); however, his use of crude angiotensin may have resulted in spasmogenic impurities not affected by atropinization. When 4 ganglionic blocking agents were examined, it was shown that all blocked nicotine at low concentrations; however, only mecamylamine (3-methylaminoisocamphane) and pempidine (1:2:2:6:6-pentamethylpiperidine) exhibited blocking activity against angiotensin and then only at concentrations several hundred-fold higher than their nicotine EC_{50}'s. This indicates that the inhibition observed was probably not due to ganglionic blockade. The results obtained, however, may be related to a reported local anesthetic effect produced by mecamylamine on the isolated rabbit ileum (8).

The lack of blocking effect observed with high concentrations of hexamethonium (1,6-bis-[trimethylammonium]-hexane) and pentolinium (pentamethylene-1:5-[bis-1-methylpyrrolidinium]) causes angiotensin to resemble more closely the action of serotonin on the guinea pig ileum as reported by Rocha e Silva *et al.*(9). The inability of the latter 2 ganglionic blocking agents to penetrate intracellularly may be related to their inactivity. If this latter possibility is fact, it implies that angiotensin is acting at an intracellular site.

These results indicate that angiotensin is acting at some point on the post-ganglionic cholinergic mechanism to produce contraction of guinea pig ileal smooth muscle and confirm the earlier report(3) in which botulinium toxin was used to show an indirect effect of angiotensin. This proposed site of action is unique only for the guinea pig ileum since it is well established that angiotensin acts directly on vascular smooth muscle(1).

Conclusions. 1. Atropine and morphine effectively block angiotensin and nicotine-induced spasm on the isolated guinea pig ileum. 2. Mecamylamine, pempidine, pentolinium and hexamethonium blocked nicotine-induced spasms; however, only mecamylamine and pempidine blocked angiotensin spasms, but very high concentrations were required. 3. It is proposed that angiotensin acts on the post-ganglionic cholinergic mechanism of the ileum and that its site of action is probably peripheral to the ganglion.

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