tholytic and hypotensive effects are dependent upon a high blood level of the drug since slow rates of infusion at low dosage did not result in sympathetic inhibition. Even with large doses rapidly injected adrenergic inhibition was transient and disappeared at a rate similar to the observed disappearance of high concentrations of diethylaminoethanol from the blood. It was not possible to determine from the present experiments whether the site of sympathetic inhibition was central or peripheral.

Summary and conclusions. Doses of diethylaminoethanol sufficient to produce high blood concentrations resulted in a temporary inhibition of sympathetic vasoconstrictor reflexes in man. It is suggested that the effects of the drug on arterial pressure and ventricular tachycardias are secondary to its sympatholytic action.

Since preparation of this paper, Clark and Helpern (*Fed. Proc.*, 1949, **8**, 282) have reported on the ganglionic blocking action of diethylaminoethanol in dogs and cats. Their observations on the sympatholytic effects of the drug in animals are in essential agreement with the results of the present investigation in man.

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17171. Action of 1-Methyl-4-(3-Hydroxyphenyl)-4-Piperidyl Ethyl Ketone on the Gastrointestinal Tract.*

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One of the most active analgesic compounds reported by Kleiderer, Rice *et al.*[1] was 1-methyl-4-(3-hydroxyphenyl)-4-piperidyl ethyl ketone which will be referred to in this report as WIN 1539. This compound has the same basic phenyl-piperidine nucleus as Demerol (brand of isonipecaine), but contains a meta-hydroxy group on the phenyl ring and has a propionyl group in place of the carbethoxy substituent of Demerol. The analgesic activity of WIN 1539 is 5-10 times greater than that of Demerol.[1-4] Because of its high analgesic activity and its close chemical relationship to Demerol, the actions of WIN 1539 on the gastrointestinal tract have been investigated.

Results. A. *Effect on excised intestinal segments.* WIN 1539 and Demerol were compared for their activity against barium chloride and acetylcholine induced spasms of the rabbit ileum and against histamine induced spasms of the guinea pig ileum by the procedure described by Miller, Becker and Tainter.[5] The results are given in Table I. These data indicate that the spasmolytic activity of WIN 1539 is considerably greater than Demerol against all three spasmogenic agents.

B. *Effect on intestine in situ.* Kymographic recordings were made of a segment of the intact ileum of anesthetized dogs by a modification of the Barbour method as described by Jackson.[6] Aqueous solutions of the drugs

* This work is part of an investigation carried out under the supervision of Dr. M. H. Seevers and submitted in a dissertation to the Graduate School of the University of Michigan in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

1 Kleiderer, E. C., Rice, J. B., Conquest, V., and Williams, J. H., Report No. 981, Office of the Publication Board, Department of Commerce, Washington, D.C.

2 Scott, C. C., Kohlstaedt, K. G., and Chen, K. K., *Anesth. and Analges.*, 1947, **26**, 12.

3 Lewis, J. R., Dissertation, University of Michigan, 1949.

4 Cahen, R. L., Epstein, H. J., and Dramentz, C. S., *J. Pharmacol.*, 1948, **94**, 328.

5 Miller, L. C., Becker, T. S., and Tainter, M. L., *J. Pharmacol.*, 1948, **92**, 260.

6 Jackson, D. E., *Experimental Pharmacology and Materia Medica*, 1939, C. V. Mosby Co., St. Louis, Mo.

TABLE I.
Relative *in vitro* Spasmolytic Properties of WIN 1539 and Demerol.

Compound	Barium chloride induced spasms		Acetylcholine induced spasms		Histamine induced spasms	
	Effective dilution*	Relative activity % papaverine	Effective dilution*	Relative activity % atropine SO_4	Effective dilution*	Relative activity % papaverine
WIN 1539	1:1,000,000	630	1:3,200,000	2.5	1:1,000,000	475
Demerol	1:300,000	200	1:98,000	0.08	1:205,000	98

* Values are averages from intestinal strips of 6 animals.

were injected into the exposed femoral vein. A total of 6 dogs was used in these experiments. The most marked effect on the intestine following the administration of WIN 1539 was a decrease in tonus. There was no significant change in amplitude or frequency of the contractions. Doses of WIN 1539 as low as 0.01 mg/kg produced a definite decrease in tonus. These small doses had no effect on blood pressure, heart rate or respiration. Larger doses (1-2 mg/kg) did not cause stimulation of the intestine but only a relaxation of longer duration. The results obtained in a representative experiment are shown in Fig. 1.

C. *Roentgenographic study of the rate of movement of a barium meal through the gastrointestinal tract.* The method used was a modification of the one described by Gershon-Cohen and Shay.[7] Adult male albino rats were starved for approximately 24 hours. They were then given orally a 50% suspension of barium sulfate in 0.5% gum tragacanth, by intubation in a dose of 0.5 cc/100 g of body weight. The analgesic compounds were injected subcutaneously as aqueous solutions immediately preceding the barium meal. The doses used are indicated in Table II. These doses had been found to produce approximately the same degree of analgesia in rats. Roentgenograms were made at 1, 2, 3 and 4 hours following the administration of the barium meal. The results are summarized in Table II. The time for complete evacuation was not determined, but the data obtained indicate that there is a delay in the emptying time of the stomach due to the action of each of the analgesic drugs. Morphine caused the greatest and Demerol the least delay. The delay resulting from WIN 1539 was almost as great as from morphine. Morphine appears to act somewhat longer than WIN 1539 on the gastrointestinal tract which is also true of its analgesic effect. Karr[8] reported that morphine slowed the passage of a carbon suspension in the intestine of rats and that Demerol was much less active in this respect. This is undoubtedly related to

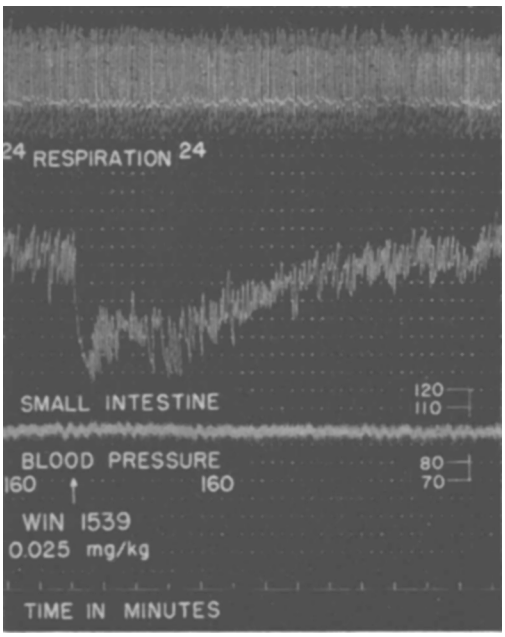

FIG. 1.
Action of WIN 1539 in an anesthetized dog. Upper figures are respiratory rates. Lower figures are heart rates. Scale at right represents mm Hg pressure.

[7] Gershon-Cohen, J., and Shay, H., The Rat in Laboratory Investigation, 1942, p. 371, J. B. Lippincott Company, Philadelphia.

[8] Karr, N. W., *Fed. Proc.*, 1947, **6**, 343.

TABLE II.
Rate of Movement of a Barium Meal Through the Gastrointestinal Tract of Albino Rats.

Drug	No. of animals	Approximate % barium meal remaining in stomach Hr after administration 1	2	3	4	Location of remainder of barium meal 4 hr after administration
Untreated controls:	7					
Mean		15	9	7	4	Cecum and feces.
Range		2-50*	2-25	0-25	0-15	
Morphine (10 mg/kg):	5					
Mean		100	96	86	49	Jejunum and ileum.
Range		—	90-100	75-95	25-95	
Demerol (30 mg/kg):	9					
Mean		58	46	34	26	Lower ileum and cecum.
Range		20-100	10-95	2-95	2-90	
WIN 1539 (3 mg/kg):	10					
Mean		89	70	46	44	Jejunum, ileum and some
Range		80-100	20-95	10-80	5-80	in cecum of 4 animals.

* 2% indicates a visible trace—other values are estimates of percentage of total volume as determined from area and density of barium meal.

the emptying time of the stomach as shown by our results.

D. *Effect on stomach in situ.* Since the roentgenographic study showed that the analgesic drugs retarded the emptying of the stomach, the effect of these drugs on the motility and tone of the intact stomach was investigated. Jackson's method[6] of recording contractions of the dog's stomach was modified for use with rats. The rats were anesthetized with sodium pentobarbital and the apparatus attached so that recordings of the pyloric portion of the stomach were obtained. The drugs were injected into an exposed saphenous vein.

A total of 12 animals were used in these experiments. Fig. 2 is a record obtained in a representative experiment. It was observed that WIN 1539 in a dose of 0.1 mg/kg caused a marked decrease in the motility of the stomach. In contrast, 1.0 mg/kg of Demerol produced an increase in tone and in some experiments also an increase in frequency of contraction. In two experiments morphine caused a response similar to that obtained with WIN 1539 in that the peristaltic waves were abolished.

The marked decrease in the motility of the stomach caused by WIN 1539 or morphine could account for the delay in the emptying time which is an important factor in the constipating action of morphine. Gruber, Hart and Gruber[9] reported that Demerol produced a stimulation of the stomach and pylorus in anesthetized dogs. We obtained similar results in rats. In clinical use Demerol does not have a constipating effect. Even though morphine has an inhibitory action on the stomach of some species of animals (Krueger, *et al.*[10]), Veach[11] found that it is predominantly motor to the human stomach. Because of species differences in the digestive processes it cannot be stated that the actions obtained with WIN 1539 in these experiments would be the same for men.

Summary. WIN 1539, a new potent synthetic analgesic related chemically to Demerol, was found to have a stronger spasmolytic action than Demerol on the stimulated isolated intestinal strip. A decrease in tone of the intact small intestine of the dog was observed. WIN 1539 caused a greater delay than Demerol in the emptying time of the rat's stomach

9 Gruber, C. M., Hart, E. R., and Gruber, C. M., Jr., *J. Pharmacol.*, 1941, **73**, 319.

10 Krueger, H., Eddy, N. B., and Sumwalt, M., The Pharmacology of the Opium Alkaloids, U. S. Public Health Reports, Supplement No. 165, Part 1.

11 Veach, H. O., *J. Pharmacol.*, 1937, **61**, 230.

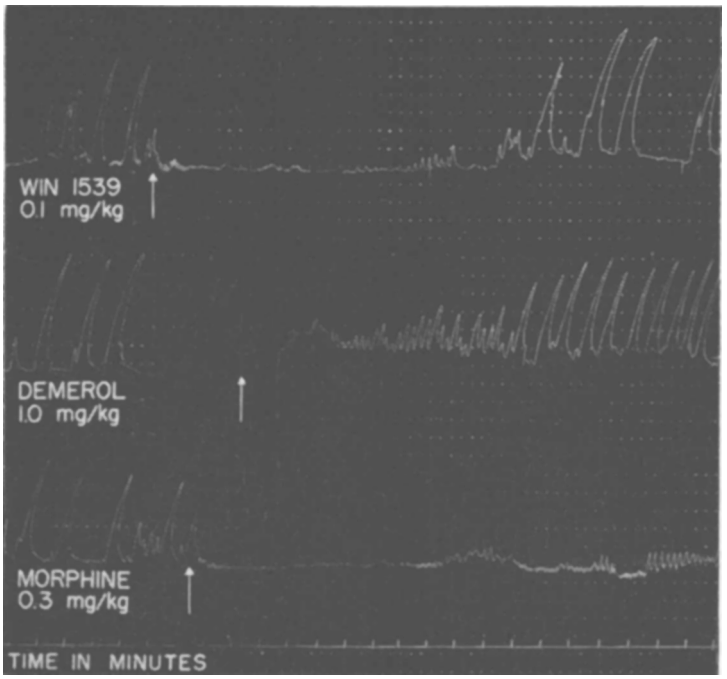

FIG. 2.
Kymographic recordings of intact stomach of anesthetized rat.

but morphine retarded emptying more than either of these drugs. Demerol caused a stimulation of the intact rat's stomach whereas WIN 1539 and morphine decreased the motility of this organ.

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17172. Some Relationships of Folic Acid to Structurally Similar Metabolites.*

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Jacobson and Good[1] observed that if folic acid (pteroylglutamic acid) is incubated with milk xanthopterin oxidase a material producing a greater response in cases of pernicious anemia than folic acid itself was obtained. At nearly the same time Kalckar and Klenow[2] demonstrated that xanthopterin is converted to leucopterin by milk xanthopterin oxidase and that this reaction is strongly inhibited by

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1 Jacobson, W., and Good, P. M., International Physiol. Congress, *Abstracts*, 1947, July.

2 Kalckar, H. M., and Klenow, H., *J. Biol. Chem.*, 1948, **172**, 349.