of levodopa upon the metabolism of central amines can be in question, because levodopa has been observed to cause changes in the levels of cerebral amines (2, 3). On the other hand, it has been indicated that there is a central adrenergic neural system that inhibits ACTH-secretion (4–6). The effect of levodopa on hypothalamus-hypophysis and the adrenal cortex system has been studied very little. Werder *et al.* (7) observed that no significant change occurred in the urine steroid amounts of five Parkinson patients during 4 weeks of levodopa treatment. One patient did not respond to hypoglycemia.

We have studied the effect of chronic levodopa treatment upon plasma levels of 17-hydroxycorticosterone in dogs. Dose selection was based on what we considered corresponded to those doses administered to man in association with medical treatment. There were three groups, each consisting of six dogs. The first group acted as a control group, the second received levodopa *per os* 150 mg./kg./day, and the third group received 300 mg./kg./day for 3 months. Venous samples were taken without anesthesia from dogs that had been made accustomed to blood sample taking. The samples were taken in the same stage of the daily rhythm (between 10 and 11 a.m.); 17-hydroxycorticosterone was determined immediately from 0.1 ml. of plasma, using Sweat's method (8), by micromodification (9). The average determination was 12.7 ± 1.7 mcg./100 ml. (29 determinations) in the first group, 14.6 ± 1.3 mcg./100 ml. (30 determinations) in the second group, and 14.6 ± 1.6 mcg./100 ml. (24 determinations) in the third group. No significant differences were observed in the values. No remarkable differences occurred between sexes in the control group or the therapy groups. No significant fluctuations of the plasma levels of 17-hydroxycorticosterone were observed during the treatment. Further studies must be carried out to elucidate the effect of chronic levodopa treatment upon the reserves of the adrenal cortex.

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Nonspecific Intestinal Spasmolytic Actions of a Piperazine Antimalarial Drug

Keyphrases □ 1-Methyl-4-[4-(7-chloro-4-quinolylamino)benzoyl]-piperazine (WR 4809)—evaluation of spasmolytic activity □ Spasmolytic activity—1-methyl-4-[4-(7-chloro-4-quinolylamino)-benzoyl]piperazine on guinea pig ileum

Sir:

The quinolyl piperazine antimalarial drug 1-methyl-4-[4-(7-chloro-4-quinolylamino)benzoyl]piperazine, designated WR 4809, has been reported to antagonize the cardiovascular and pulmonary actions of adrenergic receptor agonists in the dog (1). Its effects on intestinal responses to nonadrenergic agonists have not been investigated. Since the related drug chloroquine is known to possess spasmolytic activity in the mammalian intestine (2), the actions of this piperazine derivative on guinea pig isolated ileum were studied in order to extend pharmacological characterization of this compound.

Segments of ileum, 3–4 cm. in length, were removed from guinea pigs and mounted in a conventional muscle bath. The tissue chamber (20-ml. volume) was filled with Krebs bicarbonate solution bubbled with 95% O_2–5% CO_2 and maintained at 37°. The chamber was washed by overflow with three volumes of warm, aerated Krebs solution. The longitudinal tension of the ileal segments, set initially at 0.5 g., was measured by a force transducer[1] and recorded on a dynograph recorder[2]. Agonist drugs were dissolved in saline and were added to the bath in volumes of 0.1–1.0 ml. Responses were measured as the total tension developed during exposure of the tissue to the agonist drugs. The agents used were bethanechol chloride[3], histamine diphosphate, 5-hydroxytryptamine (serotonin) creatinine sulfate, and potassium chloride. All doses listed refer to the salt forms. Statistical data were analyzed by analysis of variance, randomized complete block design, and parallel line bioassay (3).

Dose–response curves to bethanechol, histamine, potassium, and 5-hydroxytryptamine were shifted approximately three to fourfold to the right in the presence of the quinolyl piperazine in a bath concentration of 20 mcg./ml. (Fig. 1). Analysis of variance indicated in the case of each agonist that the dose–response regression lines were significant and showed no evidence for deviation from parallelism within each pair of lines. Recovery of ileal responsiveness to the agonists was usually complete after washing of the antagonist from the bath chamber. Three dose levels of the quinolyl piperazine were tested against 5-hydroxytryptamine and bethanechol, and the degree of spasmolytic activity observed was directly proportional to the dose in the concentrations employed (Fig. 2).

These data indicate that, in the isolated guinea pig ileum at least, this substituted piperazine exerts spas-

[1] Statham UC 2.
[2] Beckman RB.
[3] Urecholine, Merck.

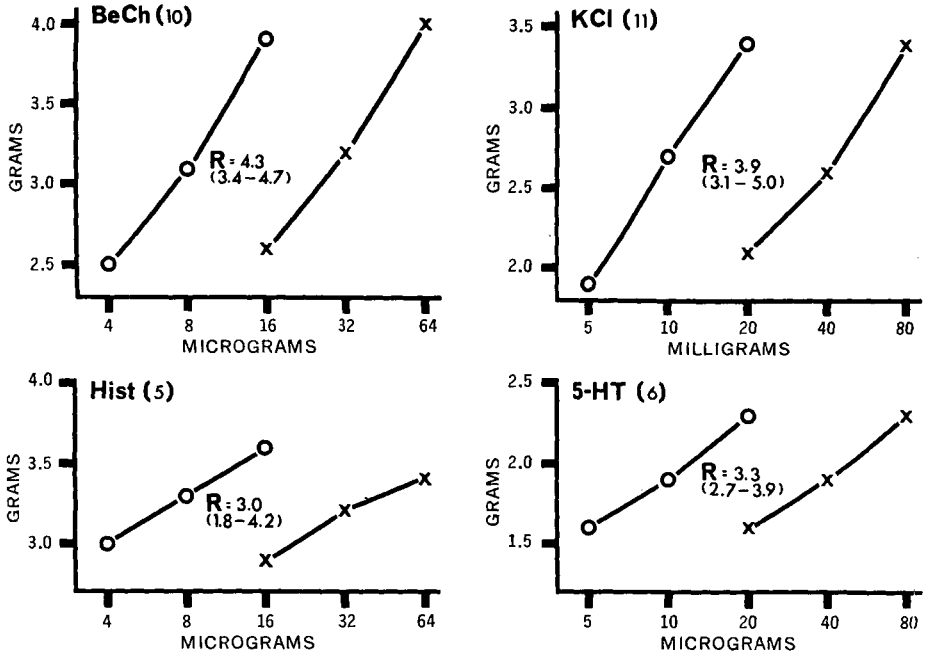

Figure 1—*Dose–response curves to bethanechol (BeCh, preparations from 10 animals), potassium ion (KCl), histamine (Hist), and 5-hydroxytryptamine (5-HT) in the isolated guinea pig ileum in the absence (O—O) and in the presence (×—×) of 20 mcg./ml. of the quinolyl piperazine. Agonist doses represent amount/20 ml. bath volume. The potency ratio (R), with its 95% confidence limits, is given for each agonist in the presence of the quinolyl piperazine as compared to the control response.*

molytic actions against a variety of spasmogens. Histamine, bethanechol, 5-hydroxytryptamine, and potassium cause contraction of the intestine by several direct and indirect interactions with different nerve and smooth muscle receptor mechanisms. Histamine and 5-hydroxytryptamine produce significant indirect spasmogenic action involving neural components (4–6); potassium ion and probably bethanechol act directly upon the intestinal smooth muscle (5, 6). While complete dose–response curves were not obtained, it can be speculated that since all agonists tested, including potassium ion, were affected to approximately the same extent by the piperazine derivative, its spasmolytic activity most likely reflects a nonspecific depression of the smooth muscle rather than specific receptor blockade. Agarwal and Deshmankar (2) observed that the antimalarial drug chloroquine antagonizes the spasmogenic actions of histamine, acetylcholine, and 5-hydroxytryptamine. Olatunde (7) concluded that chloroquine exerts direct spasmolytic actions on smooth muscle rather than specific antagonism of these agents. Additional experiments will be required to establish the mechanism of action of this substituted piperazine on intestinal smooth muscle.

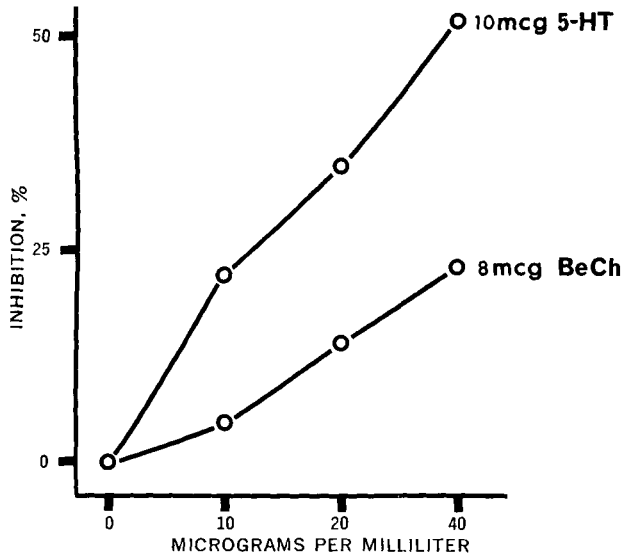

Figure 2—*Inhibition of contractor responses of the guinea pig ileum to 10 mcg. 5-hydroxytryptamine (5-HT) or to 8 mcg. bethanechol (BeCh) produced by the quinolyl piperazine in concentrations of 10, 20, and 40 mcg./ml. Each point is the mean of preparations from five animals. Percent inhibition was calculated as control − experimental response/control × 100.*

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