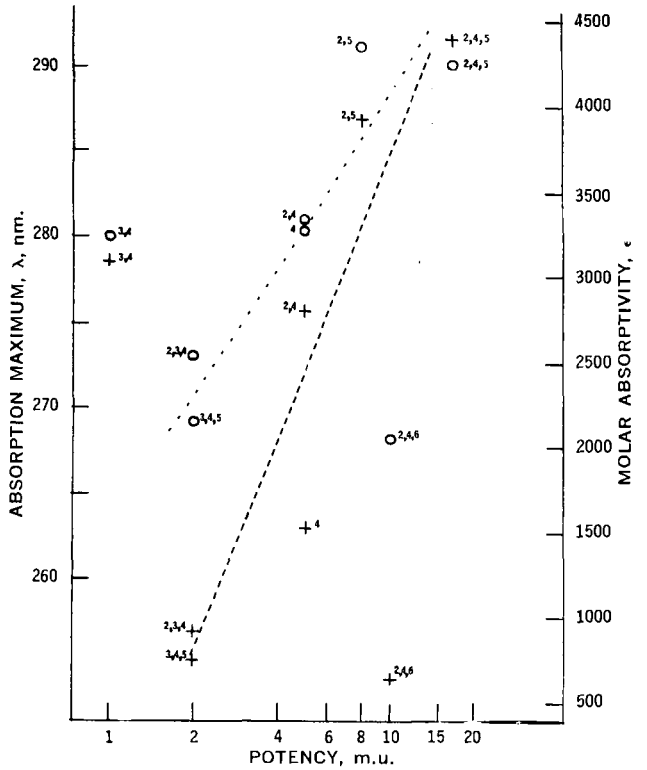

Figure 1—*Log potency (m.u.) in humans* versus *UV absorption maximum,* λ *(nm.)* (- - -○- - -), *and log potency* versus *molar absorptivity,* ε (- - -+- - -). *The numbers adjacent to the points show the positions of methoxy group substitution on the benzene ring of amphetamine. Spectra were determined on the methoxyamphetamine hydrochloride in ethanol. If the 3,4-dimethoxyamphetamines and 2,4,6-trimethoxyamphetamines are neglected, the linear regression equations are expressed by:*

$$\text{log potency} = -9.96 + 0.0380\,\lambda \quad (r = 0.94,\ F = 28.15,\ p < 0.01)$$
$$\text{log potency} = 0.176 + 0.000213\,\epsilon \quad (r = 0.94,\ F = 27.92,\ p < 0.01)$$

A significant correlation is not obtained if these apparently anomalous compounds are included in the regression analysis:

$$\text{log potency} = -4.99 + 0.020\,\lambda \quad (r = 0.42,\ F = 1.32,\ 0.1 < p < 0.5)$$
$$\text{log potency} = 0.434 + 0.000091\,\epsilon \quad (r = 0.33,\ F = 0.75,\ 0.1 < p < 0.5)$$

interactions could resemble those proposed in explaining the benzene-induced solvent shifts in the PMR spectra of polar solutes, where it is generally considered that the π-bonds of the aromatic ring interact with an electron-deficient region of the solute, perhaps forming a low energy 1:1 complex ($-\Delta H$ about 1–2 kcal./mole) (5).

Antun *et al.* (6) recently demonstrated a correlation between the degree of native fluorescence of methoxylated amphetamines and their hallucinogenic potency but they noted that the activities of the 3,4-dimethoxyamphetamine and 2,4,6-trimethoxyamphetamine appeared to be anomalously low and high, respectively. Appropriate bands in the UV spectra of aromatic compounds are functions of the energy of the π-electrons. The π–π^* or local excitation band (7) of substituted benzenes results from the perturbation of the π-electrons to a more polar state. It seemed possible that a correlation between this electronic transition and the ease of formation of the excited π-state involved in the π-receptor complex might exist (despite the differences in the mechanisms involved), since the energy differences of the two processes for a series of structurally similar compounds could well be different functions of the same variables.

Figure 1 shows our results for the UV spectra of eight methoxylated amphetamine hydrochlorides which we prepared and for which hallucinogenic activity data (expressed in the figure as log potency in mescaline units, m.u.) are available (8). The $\lambda_{max.}$ of the 4-methoxy and dimethoxy compounds is given as the center of a shallow trough in the absorption maximum, about 4 nm. wide. The relationship between $\lambda_{max.}$ and potency and between the molar absorptivity (ε) and potency are indicated by the graph lines. The lower energy of the π–π^* transition and the increased probability of it occurring (7) ($\lambda_{max.}$ correlates with ε for this series) appear to correlate positively with hallucinogenic potency. However, the activities of 3,4-dimethoxyamphetamine and 2,4,6-trimethoxyamphetamine are anomalous in the sense observed by Antun *et al.* (6), the degree of agreement in our work being similar to that presented by them.

The results seem to offer supporting evidence for the substrate-receptor model proposed (2).

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Effect of Levodopa upon Plasma Levels of 17-Hydroxycorticosterone

Keyphrases □ Levodopa—chronic treatment, effect on plasma levels of 17-hydroxycorticosterone, dogs □ 17-Hydroxycorticosterone plasma levels—effect of chronic levodopa treatment, dogs □ Plasma levels, 17-hydroxycorticosterone—effect of chronic levodopa treatment, dogs

Sir:

It has been observed that an intravenous single dose of levodopa (50 mg./kg.) inhibits the increase of 17-hydroxy corticosteroid in the adrenal vein of the dog in association with surgical stress (1). An effect mechanism

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.