Comparing all dosage levels over the 4 weeks of the experiment in regard to the 3 measurement parameters, Table I demonstrates that: 1. mecamylamine treatment exerted a depressant effect on the shuttlebox behavior of trained guinea-pigs, which reached significance at about 1.0 mg/kg, 2. considering each week separately, dose-dependant increases in response latencies were accompanied by corresponding drops in percent of avoidance response and in the number of intertrial responses, and 3. comparison of weeks 1 and 4, in which the same dose of mecamylamine was repeated, raised the question as to whether tolerance to the effect of mecamylamine might not possibly occur over a period of time and/or of continuous training.

Table II shows changes of shuttlebox performance when considered from the standpoint of blocks of 10 trials, with all treatment conditions included together. A rapid and pronounced performance decrement during each session can be seen with the response latencies parameter, but not with that of percent of avoidance response.

Discussion. The decrement in shuttlebox behavior, which was significant even during the 20- and 30-trial sessions utilized in this study, is characteristic only of the guinea-pig. Although a previous study measured only percent of avoidance responses[8], we have found in this study that the measurement of response latencies was more sensitive to the shorter sessions employed here in regard to monitoring this performance decrement. This test, refined and standardized, has been further applied to the stimulant effects of nicotine, where it was possible to quantitatively differentiate between doses of 0.075, 0.15 and 0.3 mg/kg of that substance[13], thus making this method with guinea-pigs comparable to the previously devised 'extinction procedure' method with rats, which also made use of the measurement of response latencies with that species[14].

The finding in this present study that mecamylamine, at doses of about 1.0 mg/kg and above, exerted a significantly depressant effect on the shuttlebox behavior of trained guinea-pigs agrees somewhat with the results of a study which showed that the learning of active avoidance in DBA inbred mice was inhibited by similar doses[3]. However, that study also found that mecamylamine at 5.0 mg/kg did not influence avoidance behavior in previously trained mice (measuring only % of avoidance responses). Furthermore, another experiment, using different methods and MF1 mice, found that 6.25 mg/kg or more of mecamylamine was necessary before active avoidance acquisition was impaired[4].

Experiments with smaller doses of mecamylamine have also yielded interesting results, with such variable findings as the impairment of shuttlebox behavior in guinea-pigs (this study), the facilitation of active avoidance and swimming endurance in rats[2], and the occasional similarity to or actual enhancement of the effects of nicotine in certain other tests with rats by mecamylamine[2,15,16], in addition to many other studies concerned with the anti-nicotinic effects of mecamylamine. The importance of conducting more experiments with small doses of mecamylamine can be clearly seen, especially in connection with its expanding use as a nicotine antagonist in many nicotine and tobacco smoke studies. The exact nature of the nicotine-mecamylamine interaction, as well as the comparative importance of mecamylamine itself in this interaction[17], are both questions which should be answered.

Zusammenfassung. Bei trainierten Meerschweinchen wurde der Prozentsatz von Vermeidungsreaktionen, deren Latenzzeiten, und die Spontanreaktionen zwischen den Reizen in einer «two-way shuttlebox» unter dem Einfluss von Mecamylamin gemessen. Unter Verwendung eines flexiblen Dosierungsplanes wurde für 1 mg/kg Mecamylamin eine signifikante Depression des «Shuttlebox»-Verhaltens beobachtet. Für die Verminderung der Vermeidungsleistung innerhalb einer Sitzung, die für diese Spezies charakteristisch ist, war die gemessene Reaktionslatenz der empfindlichste Indikator.

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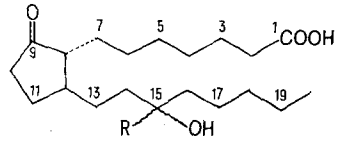
[12] Courtesy of Merck Sharp and Dohme, Zürich.
[13] P. Driscoll and K. Bättig, in preparation (1973).
[14] P. Driscoll and K. Bättig, Psychopharmacologia *18*, 305 (1970).
[15] C. F. Morrison, J. M. Goodyear and C. M. Sellers, Psychopharmacologia *15*, 341 (1969).
[16] M. Stitzer, J. Morrison and E. F. Domino, J. Pharmac. exp. Ther. *171*, 166 (1970).
[17] P. Driscoll, Z. Präventivmed. *17*, 211 (1972).

Oral Anti-Ulcer Activity of a Synthetic Prostaglandin Analogue (9-Oxoprostanoic Acid: AY-22,469)

As has been observed with the natural prostaglandins, various synthetic prostaglandin analogues have been shown to be regulators of gastric acid secretion. In the rat, synthetic PGE analogues (i.e. 11-deoxyprostaglandins and their analogues) inhibit gastric acid secretion when given subcutaneously; PGF analogues exhibit weak activity[1,3]. A synthetic PGE analogue (AY-22, 093, Figure),



	R
AY-22,093	H
AY-22,469	CH_3

which is a relatively potent inhibitor of basal gastric acid secretion, prevents the increase in gastric acid secretion caused by pentagastrin[2]. Another PGE analogue (AY-22, 469, Figure) exhibits a more prolonged inhibition of basal gastric acid secretion than AY-22, 093[4]. In contrast to AY-22, 093, AY-22, 469 is also an effective inhibitor when given perorally[4]. A natural PGE, in addition to inhibiting gastric acid secretion, also prevents ulcer formation when given parenterally[5]. As AY-22, 469 inhibits gastric acid secretion when given perorally, the effects of the synthetic

[1] W. Lippmann, J. Pharm. Pharmac. *21*, 335 (1969).
[2] W. Lippmann, J. Pharm. Pharmac. *22*, 65 (1970).
[3] W. Lippmann, Ann. N.Y. Acad. Sci. *180*, 332 (1971).
[4] W. Lippmann, attached manuscript.
[5] A. Robert, J. E. Nezamis and J. P. Phillips, Gastroenterology *55*, 481 (1968).

Table I. Inhibition of pylorus ligation-induced ulcer formation by perorally-administered AY-22,469 and imipramine

Drug	Dose (mg/kg, p.o.)	Ulcer formation		ED_{50}
		Score ± S.E.	Inhibition (%)	
Vehicle	—	8.1 ± 0.5	—	
AY-22,469[a]	30	0.4 ± 0.1[c]	95	
	10	1.1 ± 0.7[c]	86	
	3	0.3 ± 0.3[c]	96	
Imipramine[a]	40	5.9 ± 1.4	27	
	20	8.6 ± 0.6	0	
	10	7.6 ± 1.0	6	
Vehicle	—	7.7 ± 1.5	—	
Imipramine[a]	40	5.9 ± 1.0	23	
	20	6.5 ± 1.5	16	
	10	7.1 ± 1.0	8	
Vehicle	—	10.4 ± 2.0	—	
Imipramine[b]	40	3.5 ± 0.8[d]	66	16
	20	4.6 ± 1.1[e]	56	
	10	6.2 ± 0.9	40	

[a] Drug was administered immediately after pylorus ligation. [b] Drug was administered 30 min before pylorus ligation. There were 6–17 animals per group. [c] $P < 0.001$, [d] < 0.01, [e] < 0.05.

Table II. Inhibition of pylorus ligation-induced ulcer formation by perorally-administered AY-22,469 and perorally- and parenterally-administered imipramine

Drug	Dose (mg/kg)	Ulcer formation		ED_{50}
		Score ± S.E.	Inhibition (%)	
Vehicle	—	5.8 ± 1.7	—	
AY-22,469[a]	4	0.1 ± 0.1[d]	98	1
	2	2.8 ± 1.0	53	
	1	3.4 ± 0.7	43	
Imipramine[b]	40	0.3 ± 0.2[d]	95	25
	20	4.7 ± 1.0	20	
	10	4.5 ± 1.3	23	
Vehicle	—	6.3 ± 0.6	—	
AY-22,469[a]	2	0.7 ± 0.2[d]	89	0.7
	1	3.1 ± 0.6[d]	51	
	0.5	3.6 ± 0.9[f]	43	
Vehicle	—	7.4 ± 0.8	—	
AY-22,469[c]	2	1.4 ± 0.5[d]	81	0.9
	1	4.0 ± 0.7[e]	46	
	0.5	5.1 ± 0.9	31	
Vehicle	—	7.7 ± 1.4	—	
Imipramine[a]	40	5.1 ± 0.7	34	
	20	5.8 ± 1.4	25	
	10	5.8 ± 1.2	25	
Vehicle	—	5.3 ± 1.2	—	
Imipramine[b]	40	1.3 ± 0.7[g]	75	27
	20	3.6 ± 0.6	32	
	10	6.3 ± 1.0	0	

[a] Drug was administered perorally immediately after pylorus ligation; there were 9–21 animals per group. [b] Drug was administered i.p. after pylorus ligation; there were 9–13 animals per group. [c] Drug was administered perorally in 0.2% carboxymethyl cellulose immediately after pylorus ligation; there were 10–20 animals per group. [d] $P < 0.001$, [e] < 0.01, [f] < 0.02, [g] < 0.05.

PGE analogue, i.e. when administered perorally, on ulcer formation were determined.

Materials and methods. The determination of the effects on ulcer formation induced by pylorus ligation was made essentially according to the method of SHAY et al.[6]. Female albino rats (Sprague Dawley, Canadian Breeding Laboratories, 170–190 g), caged individually, were fasted for 48 h and pylorus-ligated under ether anesthesia. Drugs (0.2 ml perorally or 0.5 ml i.p. of an aqueous suspension containing 2 drops of Tween 80 per 14 ml, except where indicated) were administered and the animals were sacrificed 19 h after ligation.

The effects of the drugs on the development of gastric lesions caused by reserpine were determined according to REILLY et al.[7] using male albino rats (170–190 g). The animals were fasted 24 h and then were pretreated with the test drug or vehicle before reserpine. 6 h after reserpine administration the animals were sacrificed by cervical dislocation.

For the assessment of the effects of the drugs on the gastric lesions induced by cold-restraint, a method based

[6] H. SHAY, S. A. KOMAROV, S. S. FELS, D. MERANZE, M. GRUENSTEIN and H. SIPLET, Gastroenterology *5*, 43 (1945).

[7] J. F. REILLY, A. P. AHLSTROM, J. S. WATTS, P. S. CASSIDY and L. M. LUSKY, Toxic app. Pharmac. *15*, 97 (1969).

Table III. Effect of perorally-administered AY-22,469 and imipramine on reserpine-induced and cold-restraint induced ulcer formation

Reserpine-induced

Drug	Dose (mg/kg, p.o.)	Ulcer formation		ED_{50}
		Score ± S.E.	Inhibition (%)	
Vehicle	—	4.6 ± 0.4	—	
AY-22,469	30	3.9 ± 0.6	15	
	10	4.5 ± 0.5	2	
Imipramine	25	2.0 ± 0.5[a]	57	20
	12.5	2.8 ± 0.4[a]	39	

Reserpine, 5 mg/kg, i.p., was administered 6 h prior to sacrifice of the animals. Drugs were administered perorally 30 min prior to reserpine. There were 10 animals per group. [a] $P < 0.01$.

Cold-restraint induced

Drug	Dose (mg/kg, p.o.)	Ulcer formation	
		No. of rats with ulcers	Inhibition (%)
Vehicle	—	21/22	—
AY-22,469	30	8/16	47
	10	10/16	34
	3	10/12	13
Imipramine	20	2/8	74
	10	6/18	65
	5	5/14	63
	2.5	10/12	13

Drugs were administered perorally immediately before restraint.

on that of BRODIE and VALITSKI[8] was employed. Male rats (180–200 g) were starved for 24 h; drugs were injected immediately before the restraint. The rats were restrained by placing each in a prone position and taping the paws and head to the board. The animals were then placed in a cold room (4–7 °C) for 2 h.

AY-22,469 (15–hydroxy–15–methyl–9–oxoprostanoic acid) was prepared by Dr. J. F. BAGLI of Ayerst Laboratories; imipramine (Tofranil) was a gift from Geigy Ltd.

Results and discussion. AY-22,469 administered in the range of 30–3 mg/kg, p.o., immediately following the ligation caused essentially complete prevention of pylorus ligation-induced ulcer formation (Table I). Imipramine, a known inhibitor when administered parenterally[9,11], was relatively ineffective at 10–40 mg/kg, p.o.

In contrast to lacking activity when given after the pylorus ligation, imipramine (40–10 mg/kg, p.o.) was effective when given 30 min before the pylorus ligation; the ED_{50} was 16 mg/kg (Table I). Thus, the time of peroral administration of imipramine was of importance.

AY-22,469, when given perorally after the pylorus ligation, inhibited the ulcer formation exhibiting an ED_{50} of 1 mg/kg (Table II). Imipramine, administered i.p. at this time, exhibited an ED_{50} of 25 mg/kg, while not showing appreciable activity even at 40 mg/kg when given perorally. With AY-22,469 similar activity was also obtained when the vehicle employed was carboxymethyl cellulose. AY-22,469 is thus relatively a very potent inhibitor of this type of induced-ulcer when given perorally.

AY-22,469 (10–30 mg/kg, p.o.) did not prevent the gastric lesion formation produced by reserpine (Table III). Imipramine exhibited an ED_{50} of 20 mg/kg. Therefore, in contrast to imipramine, AY-22,469 is ineffective in preventing the formation of this type of gastric lesion under the conditions examined.

AY-22,469 (p.o.), like imipramine, antagonized the ulcer formation caused by cold-restraint (Table III). The level of activity of AY-22,469 was, however, much less than that of imipramine as a dose of 30 mg/kg of AY-22,469 caused a 47% decrease in the number of animals exhibiting ulcers while at 5 mg/kg imipramine caused 63%.

The present findings demonstrate that the synthetic PGE analogue AY-22,469 administered perorally inhibits ulcer formation. As AY-22,469 is a racemate with four possible optical isomers, the activities of the isomers are of interest. In the present studies AY-22,469 has been compared to imipramine, which given parenterally, inhibits ulcer formation caused by pylorus ligation[12], reserpine administration[13,14] and restraint and cold-restraint[12,15]. Imipramine has been shown to be of interest in humans in this respect, as it reduces gastric acidity and relieves pain in ulcer patients[16].

In addition to being an orally active, anti-ulcer agent AY-22,469 also exhibits oral antigastric acid secretory activity[4]. These findings are of interest in relation to the activities of the natural prostaglandins in humans. Parenterally, PGA_1 reduces histamine-induced gastric acid secretion[17]. PGE_1 inhibits basal[18] and pentagastrin stimulated[19] gastric acid secretion. However, perorally PGE_1 is ineffective in inhibiting gastric acid secretion induced by pentagastrin in doses exhibiting effects on gastrointenstinal motility[20].

Résumé. AY-22,469, un analogue synthétique de la prostaglandine, inhibe les différents types d'ulcère développé chez le rat lorsqu'il est administré par voie orale.

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Biochemical Pharmacology Department, Ayerst Laboratories, P.O. Box 6115, Montreal (Quebec, Canada), 28 November 1972.

[8] D. A. BRODIE and L. S. VALITSKI, Proc. Soc. exp. Biol. Med. *113*, 998 (1963).
[9] S. BONFILS, M. DUBRASQUET and A. LAMBLING, J. appl. Physiol. *17*, 299 (1962).
[10] P. BASS and M. A. PATTERSON, J. Pharmac. exp. Ther. *156*, 142 (1967).
[11] W. LIPPMANN, Biochem. Pharmac. *18*, 2517 (1969).
[12] W. LIPPMANN, J. Pharm. Pharmac. *22*, 568 (1970).
[13] S. GARATTINI, A. GIACHETTI, A. JORI, L. PIERI and L. VALZELLI, J. Pharm. Pharmac. *14*, 509 (1962).
[14] W. LIPPMANN, Archs int. Pharmacodyn. Ther. *193*, 340 (1971).
[15] S. BONFILS, N. DUBRASQUET, A. DRY-LAVALLEE and A. LAMBLING, C.r. Séanc. Soc. Biol. *154*, 924 (1960).
[16] A. VARAY, J. BERTHELDT, J. BILLIOTET, G. VITERBO and B. GRAF, Bull. Mém. Soc. méd. Hôp. Paris *76*, 228 (1960).
[17] D. E. WILSON, C. PHILLIPS and R. A. LEVINE, Gastroenterology *58*, 1007 (1970).
[18] M. CLASSEN, H. KOCH, P. DEYHLE, S. WEIDENHILLER and L. DEMLING, Klin. Wschr. *48*, 876 (1970).
[19] M. CLASSEN, H. KOCH, J. BICKHARDT, G. TOPF and L. DEMLING, Digestion *4*, 333 (1971).
[20] E. W. HORTON, I. H. M. MAIN, C. J. TOMPSON and P. M. WRIGHT, Gut *9*, 655 (1968).
[21] Acknowledgments. The authors acknowledge the technical assistance of Miss A. TOM, Mrs. E. SCHWARTZ and Mr. J. LACASSE.

Effect of Chemical Sympathectomy on Pressor Responses to Norepinephrine, Angiotensin and Tyramine[1]

6-Hydroxy dopamine (6-OH DA) is a catecholamine analogue which produces anatomic and functional sympathetic denervation[2–5]. The hearts of animals pretreated with 6-OH DA demonstrate enhanced responsiveness to infused norepinephrine and nearly absent responses to sympathetic nerve stimulation or tyramine comparable to the changes seen with surgical sympathetic denervation[4,5]. In the cat 6-OH DA treatment is followed by enhanced arterial pressure responses to norepinephrine and reduced responses to tyramine[4], suggesting a role for sympathetic nerves in inactivating circulating norepinephrine throughout the systemic circulation. However, 6-OH DA administration reduces vasoconstrictor responses to norepinephrine in rat mesenteric arteries[6].

In view of the increasing use of chemical sympathectomy with 6-OH DA as a tool for investigating arterial pressure

[1] Supported by U.S.P.H.S. Grant No. HL-13479.
[2] J. P. TRANZER and H. THOENEN, Experientia *24*, 122 (1968).
[3] J. DE CHAMPLAIN and R. NADEAU, Fedn Proc. *30*, 877 (1971).
[4] G. HAEUSLER, W. HAEFELY and H. THOENEN, *170*, 50 (1969).
[5] R. A. NADEAU, J. DE CHAMPLAIN and G. M. TREMBLAY, Can. J. Physiol. Pharmac. *49*, 36 (1971).
[6] G. HAEUSLER, in *6-Hydroxydopamine and Catecholamine neurons*, (Eds. T. MALMFORS and H. THOENEN; American Elsevier Co., New York 1971), p. 193.