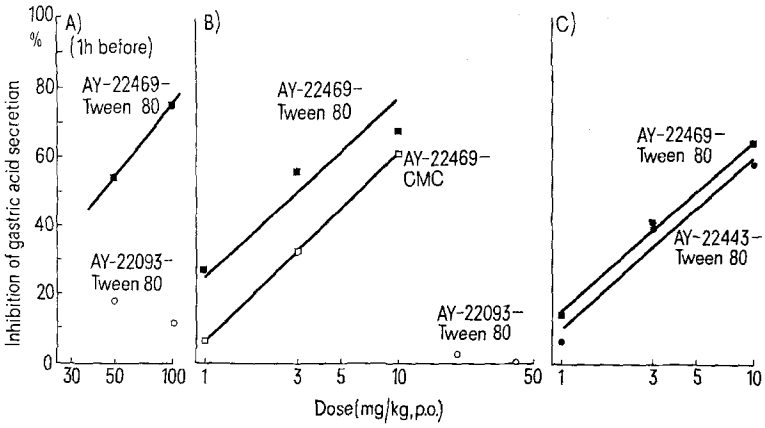

Fig. 3. Effects of peroral administration of synthetic prostaglandin analogues on basal gastric acid secretion.

at the $\Delta 13$ double bond, two steps of β oxidation and ω oxidation[10,11]. As AY-22,469 is a racemate with 4 possible optical isomers, the activities of the isomers are of interest.

The findings of oral activity with the synthetic PGE analogues is also of interest in regard to studies on the oral activity of PGE_1 in the human. PGE_1 increases the propulsive activity of the gut and it was suggested that metabolites of PGE_1 might be of importance with respect to the effects observed[12]. PGE_1 is ineffective in inhibiting gastric acid secretion induced by pentagastrin in doses exhibiting effects on gastrointestinal motility[13]. Use of a higher level of PGE_1 or a different prostaglandin might have resulted in a demonstration of antisecretory activity, the latter in view of the findings[14] that human gastric mucosa contains PGE_2. In this connection PGA_1, infused intravenously, decreases gastric acid secretion induced by histamine[15].

Résumé. L'analogue synthétique de la prostaglandine, AY-22,093, exerce moins d'inhibition sur la sécrétion basale de l'acide gastrique chez le rat lorsque administré en dose unique plutôt qu'en dose divisée, par voie sous-cutanée. Par contre, l'analogue AY-22,469 contenant un groupe méthylé en C-15, montre des effets semblables. AY-22,469 et son ester méthylique AY-22,443 sont efficaces lorsque administrés par voie orale, tandis que le composé AY-22,093 ne l'est pas.

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The Effect of Small Doses of Mecamylamine on Shuttlebox Behavior in the Guinea-Pig[1]

Although mecamylamine has found wide application in recent years as an anti-nicotinic agent in various studies with different species, its influence on animal behavior has not been extensively studied, especially in the lower dose ranges. Preliminary experiments with rats at this laboratory have indicated that mecamylamine in small doses (up to 0.3 mg/kg) facilitates both swimming endurance and shuttlebox performance in that species[2]. On the other hand, an impairment of active avoidance learning in mice has been demonstrated with higher doses of this substance. Whereas Oliverio[3] obtained this effect with doses ranging between 1.2 and 5.0 mg/kg, however, Goldberg et al.[4] reported that doses of mecamylamine in excess of 6.25 mg/kg were necessary to impair active avoidance learning. These and other differences in results between and within species and various tests, in addition to the increasing importance of mecamylamine in nicotine and tobacco smoke studies, prompted this initial investigation into the effects of mecamylamine on guinea-pig behavior. Since the earliest reports concerned with the pharmacological properties of mecamylamine[5], there has been no mention in the literature of its use in any behavioral testing situations with guinea-pigs.

The guinea-pig has, however, found increasing use in shuttlebox-avoidance experiments in recent years, having been so tested in relation to the effects of various brain lesions[6,7], and of different drugs, such as amphetamine[8],

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benzodiazepines[9] and thymoleptics[10]. A principal advantage in using this species, apart from very unique training characteristics, is the fact that previously trained guinea pigs display a rapid and pronounced avoidance decrement during the course of each session. This characteristic has been utilized only by SANSONE and BOVET[8] in demonstrating the stimulant effect of amphetamine during sessions of 100 or 300 trials, measuring the percent of avoidance response only. In this present experiment we have also measured response latencies and intertrial responses. It was reasoned that the addition of one or both of these parameters might prove to be more sensitive than the measurement of percent of avoidance responses alone, thereby making the detection of drug effects on this test possible over a shorter time span, in addition to being otherwise more informative.

Materials and method. The shuttlebox was divided into two $27 \times 27 \times 27$ cm compartments connected by an opening of 9.5×9.5 cm. The CS was a 5W lamp located on the ceiling of each compartment about 5 cm from the dividing wall, and the US was a scrambled shock of 1.0 ma delivered through stainless steel rods spaced 1.6 cm apart, which comprised the floor. One side of the shuttlebox consisted of a transparent plastic wall which could be raised or lowered to admit or remove the animal. The shuttlebox was placed in a large wooden box containing a loud speaker through which a steady background noise, at a level just discernible outside the box when it was closed, was emitted. The side of the box next to the transparent wall of the shuttlebox contained a glass window measuring 24×49 cm, allowing observation of the animal at all times. All sessions were conducted during the morning in a completely darkened room, into which the animals were brought and placed in the shuttlebox about 5 min before testing. The only illumination was provided by a shaded 60W red lamp directed so as to permit writing and observation of the guinea pig without the observer being seen by the subject. The switch activating either side of the shuttlebox was hand-controlled, and was connected to a digital stopwatch which automatically registered the response times, the intertrial intervals being determined with a separate stopwatch. The number of avoidance failures, intertrial responses (unpunished) and the response latencies for all trials were recorded throughout all training and experimental sessions.

Six male albino guinea-pigs, weighing between 225 and 245 g on the first day of training, were used. The animals were trained on a schedule closely approximating that of SANSONE and BOVET[11], being subjected to 5 consecutive daily sessions of 10 trials each, with intertrial intervals of 75 sec. The CS-US interval was 12 sec for all trials, the CS (and US) being discontinued upon completion of the response into the adjacent compartment. Following the completion of these 5 sessions, training was continued for 2 more sessions under the following conditions: 20 trials per session, 45 sec intertrial interval and 15 sec CS-US interval.

After the conclusion of training, the experiment proper was conducted every Monday, Wednesday and Friday over a period of 4 weeks. The CS-US interval was 15 sec throughout, with an intertrial interval of 30 sec. The first week consisted of sessions of 20 trials each and weeks 2, 3 and 4 of sessions of 30 trials each. All injections were given s.c. 30 min before testing in the shuttlebox, and the doses of mecamylamine HCl[12] for all weeks (as shown in Table I), were expressed in terms of the base. All animals received all dosages and the control condition (physiological NaCl solution) in a latin-square sequence. The flexible dosage schedule used was primarily designed to gradually increase the treatment until a clear-cut effect in either direction was obtained, following which a lower dose was repeated. A statistical analysis was conducted on the results for each separate week, relative to the treatments and sessions, the latter of which were divided into 10-trial blocks for each animal, with evaluation (Duncan multiple-*t*-test) of the partial averages being subsequently performed.

Results. The results of the first 5 training sessions were virtually identical to those previously noted under comparable conditions[11], in that no performance increments occurred within sessions, with comparable improvements occurring (in regard to % of avoidance responses) between sessions. During the 6th and 7th (20 trial) training sessions, all guinea-pigs avoided the shock at a rate of over 90%, showing average response latencies of 5.9 and 6.0 sec for the 2 sessions, respectively.

Table I. Shuttlebox behavior-interactions among the 4 experimental weeks, the different doses of mecamylamine employed, and the 3 parameters of measurement

Week	Mecamylamine dose (mg/kg)	Avoidance responses (%)	Intertrial responses (average/10 trials)	Average response latency/ trial (sec)
1	–	84	2.7	7.5
	0.2	74	1.5	9.1
	0.4	77	1.2	9.1
2	–[a]	91	2.6	7.0
	0.6	84	2.2	8.7
	1.2[c]	79	0.8	9.4
3	–[b]	98	3.0	5.6
	0.8[c]	93	1.7	6.2
	2.4[b, c]	76	0.4	10.0
4	–	97	2.4	5.5
	0.4	95	2.4	5.7

– = control injection (NaCl solution). [a] vs a, [b] vs b, and [c] vs c = $p < 0.01$ significance.

Table II. Comparison of 2 parameters of measurement in relation to the intra-session performance decrement

Week	Trials	Avoidance responses (%)	Average response latency/trial (sec)
1	1–10	83	7.4[a]
	11–20	74	9.8[a]
2	1–10	85	7.6
	11–20	84	8.6
	21–30	84	9.0
3	1–10	90	6.3[b]
	11–20	91	7.5
	21–30	87	8.0[b]
4	1–10	98	4.6[c]
	11–20	97	5.4
	21–30	94	6.6[c]

[a] vs a, [b] vs b, and [c] vs c = $p < 0.05$ significance.

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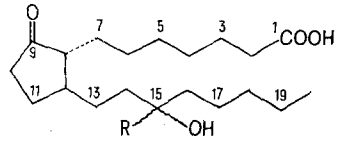
Oral Anti-Ulcer Activity of a Synthetic Prostaglandin Analogue (9-Oxoprostanoic Acid: AY-22,469)

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

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