the glandular and rumenal segments of the stomach wall; rumenal mucosal counts were omitted because of the inconsistent presence of a few cells in this region[8–10]. Data were analyzed using Student's t-test.

Results. Nonstressed (table 1, A) or reserpine vehicle-injected (table 2, A) groups pretreated with either dexamethasone vehicle or dexamethasone showed low ulcer indices due to occasional petechiae found only in the gastric glandular mucosa. Dexamethasone pretreatment markedly depleted the mast cell population only in the mucosal layer of the stomach glandular wall of both nonstressed and reserpine vehicle-injected rats; the magnitude of dexamethasone-induced mast cell depletion was statistically comparable in the 2 groups.

Stress (table 1, B) or reserpine (table 2, B) produced a high ulcer index in dexamethasone vehicle-treated animals; the lesions in either group presented as grossly hemorrhagic ulcers confined to the glandular mucosa. Dexamethasone pretreatment effectively reduced both types of ulceration, but the mean ulcer index after stress (0.83 mm) was significantly smaller than that following reserpine (2.10 mm). Residual stress lesions were mainly petechiae, whereas those after reserpine were largely hemorrhagic ulcers. In the controls pretreated with dexamethasone vehicle, stress or reserpine significantly decreased the mast cell count only in the glandular mucosal layer of the stomach. Neither ulcer-producing method lowered dexamethasone-reduced mucosal mast cell counts much further.

Discussion. The etiology of stress- or reserpine-induced gastric glandular ulcer formation, primarily related to vagal overactivity, which mainly provokes mast cell degranulation in the mucosal layer of the stomach glandular wall to release ulcerogenic agents, has been discussed elsewhere[3,5,6,8–13].

The present comparative study revealed that, although both ulcer-inducing methods produced statistically similar reductions in mast cell counts in the glandular mucosal layer (stress, 43%; reserpine, 49%), glandular ulceration by reserpine was greater. A difference was also seen in the dexamethasone-pretreated rats, where the glandular mucosal mast cell population was almost completely depleted before ulcer induction. The significantly larger residual ulceration after reserpine appears, therefore, not to result from stomach mast cell degranulation. Since 5-hydroxytryptamine receptor blockade with methysergide in rats prevents reserpine-evoked gastric ulcers more strongly than those induced by stress (unpublished findings), it is possible that the residual lesions are chiefly produced by a nonvagal-mediated action of reserpine which releases 5-hydroxytryptamine directly from stomach storage sites[14,15].

These results indicate that reserpine, in contrast to stress, activates an additional mechanism which plays a small but significant role in its gastric ulcerogenicity in rats.

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A selective concentration-dependent dysrhythmogenic and antidysrhythmic action of prostaglandins E_2, $F_{2\alpha}$ and I_2 (prostacyclin) on isolated rat hearts

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Summary. Prostaglandins (PGs) E_2, $F_{2\alpha}$ and I_2 were examined for their effects on the electrical and mechanical activities of isolated rat, rabbit and guinea-pig hearts. All PGs produced dysrhythmias in rat hearts at low concentrations only, while higher concentrations were antiarrhythmic. Guinea-pig hearts were less responsive while rabbit hearts were completely resistant.

PG release from myocardium, particularly that subjected to hypoxic stress, has been demonstrated by various workers[2,3]. In man the primary PGs released are I_2, E_2 and $F_{2\alpha}$[4]. Although these substances are known to influence various parameters of cardiac activity there is substantial uncertainty regarding their exact function.

PGs have been described as endogenous antiarrhythmic factors released by the hypoxic or ischemic myocardium[5]. They have been demonstrated to have antiarrhythmic properties in a variety of experimental situations[5–8]. Some protection against ventricular arrhythmias has been demonstrated with $PGF_{2\alpha}$ in man[8]. It has however been suggested that PGs released by the myocardium may be contributing factors for arrhythmogenesis[9] and some PGs have been shown to cause rhythm disturbances in clinical and experimental situations[10–12]. We therefore examined the effects of PGE_2, $PGF_{2\alpha}$ and PGI_2 on the electrocardiogram (EKG) of isolated rat, rabbit and guinea-pig hearts and report that these PGs cause EKG disturbances in rat hearts at low concentrations while demonstrating antiarrhythmic properties at high levels.

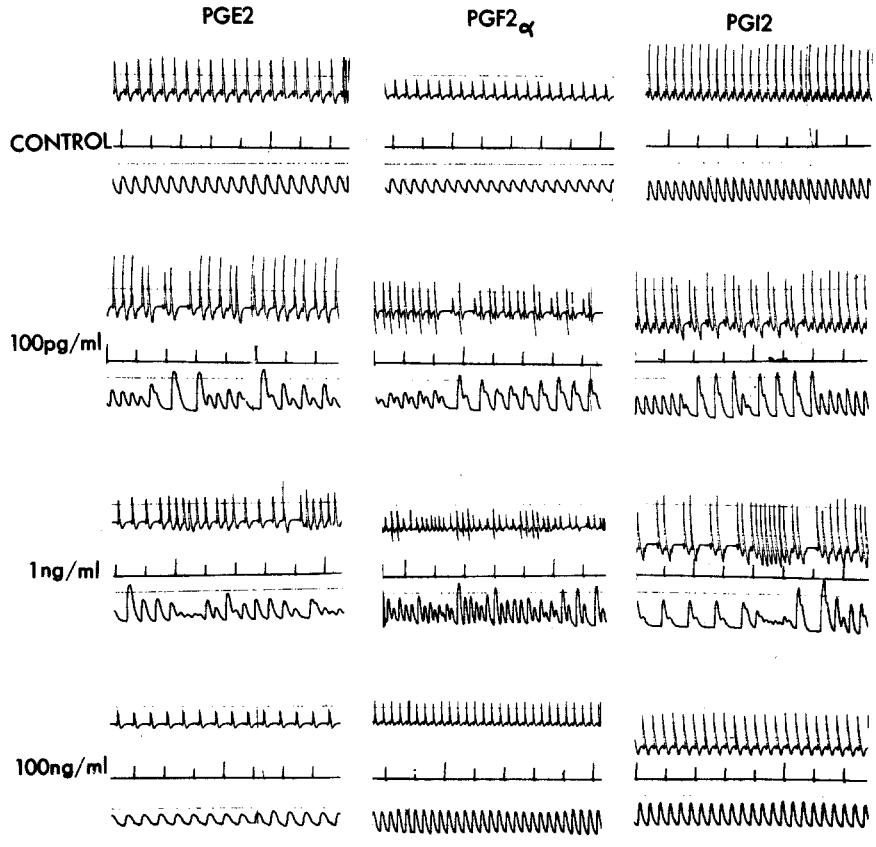
Methods. Male Sprague-Dawley rats (average weight 250 g), albino guinea-pigs (500 g) and New Zealand rabbits (2.5 kg) were utilized in this investigation. The animals were sacrificed either by decapitation or cervical dislocation (rabbits) and their hearts were rapidly excised and placed in ice-cold buffer until contractions ceased. They were then mounted by the aorta and perfused at a constant

pressure of 70 mm Hg (9.31 kPa) with Krebs-Henseleit buffer containing (mmoles): 120 NaCl, 20 $NaHCO_3$, 4.63 KCl, 1.17 KH_2PO_4, 1.25 $CaCl_2$, 1.20 $MgCl_2$ and 8 glucose. The buffer was continuously gassed with a 95% 0_2/5% CO_2 mixture, pH 7.4, at 37 °C. The EKG was obtained by inserting a fine-gauge needle electrode into the left-ventricular epicardium while a 2nd electrode was placed around the steel perfusion cannula. The mechanical activity was obtained by attaching the apex of the heart to a Grass FT.03 force displacement transducer and all recordings were made on a Grass polygraph. PGE_2 and $PGF_{2\alpha}$ were stored in ethanol at −5 °C. They were diluted to the desired concentration in buffer on the day of the experiment and kept on ice. PGI_2 was stored in crystalline form at −5 °C and the desired amount was dissolved in 1 M Tris buffer (pH 9.3) on the day of the experiment and kept on ice. Dilutions were prepared in buffer immediately before adding to the perfusion medium. In control experiments equimolar concentrations of 6 keto-$PGF_{1\alpha}$, the stable prostacyclin metabolite, were tested.

Results and discussion. 3 PG concentrations (100 pg/ml, 1 ng/ml and 100 ng/ml) were investigated either in cumulative dose-response studies or as single additions. There was a dramatic and consistent response of isolated rat hearts in that the 2 lower PG concentrations studied produced severe dysrhythmic activity as demonstrated by the mechanical and electrical responses illustrated in the figure. It should be noted that the term 'dysrhythmic' refers to any aberration observed in the surface EKG recordings irrespective of the exact mechanism. Within minutes after the addition of either PGE_2, $PGF_{2\alpha}$ or PGI_2 at the highest concentrations, the disturbances were reversed and the hearts resumed normal electrical and mechanical activity (figure). 5 hearts were examined in the dose-response studies and the results were continuously reproducible. In a 2nd series of experiments (n = 4) we examined the effects of a single infusion of each concentration of the PG in separate hearts. In all hearts either 100 pg/ml or 1 ng/ml of each PG produced dysrhythmic activity within minutes after addition, and these disturbances persisted for the duration of the 1-h perfusion period. This observation was particularly surprising with respect to PGI_2, since, given the labile properties of this substance (+ ½ 10 min at 37 °C) and the failure to observe any dysrhythmogenic actions of 6 keto-$PGF_{1\alpha}$ in 3 experiments we expected a shortlasting effect of this PG. The dysrhythmic activity persisted after reperfusing the hearts with control (PG-free) buffer but they were immediately terminated or reduced in severity by the addition of 100 ng/ml of any of the 3 PGs.

In contrast to the consistent dysrhythmogenic influence of the 3 PGs on the rat hearts we were unable to observe severe electrical disturbances after PG addition to either guinea-pig or rabbit hearts. $PGF_{2\alpha}$ was effective in producing premature ventricular contractions (PVCs) at 100 pg/ml and 1 ng/ml in either dose-response studies (2 of 5 hearts) or after single concentration infusions (2 of 4 hearts). These PVCs occurred randomly during the perfusion period and did not follow any appreciable pattern. They persisted as long as the low $PGF_{2\alpha}$ concentration was present in the buffer, and as previously described with the rat hearts, after reperfusing with normal buffer. 100 ng/ml $PGF_{2\alpha}$ however terminated the occurrence of PVCs. Rabbit hearts were highly resistant to the dysrhythmogenic actions of the PGs with no appreciable alterations in electrical activity being observed after PG addition.

We believe that these results may partly explain the diverse effects of PGs on heart electrical rhythm. Thus it is clear from this report that low PG concentrations cause electrical disturbances, particularly in rat hearts, while high PG levels



EKG (top panel) and mechanical activity (bottom panel) of the isolated rat heart either in the control situation or 5 min after the addition of different concentrations of prostaglandins E_2, $F_{2\alpha}$ and I_2. Note the disappearance of electrical and mechanical disturbances with 100 ng/ml of the PG. These effects were continuously reproducible. Markers indicate 1-sec intervals.

demonstrate antiarrhythmic properties. Most studies demonstrating antiarrhythmic properties of PGs have used relatively high concentrations. However, endogenous myocardial PG production which would be expected to be at a low level may actually contribute to dysrhythmogenesis under various situations such as hypoxia or ischemia.

The mechanism for the dysrhythmogenic actions of PGs as well as the reason for the resistance observed with guinea-pig and rabbit hearts is difficult to suggest at this time. The rat heart is resistant to dysrhythmias[13] and therefore the increased sensitivity observed in this investigation is surprising. It would be unwise to extrapolate these results to the human situation although the possibility that locally synthesized PGs may be contributing arrhythmogenic factors in ischemic heart disease should be considered. Recent reports have in fact strenghtened such a possibility. Thus Moschos et al.[14] reported an antiarrhythmic property of aspirin, a PG synthesis inhibitor after coronary artery occlusion in the dog which would perhaps suggest an involvement of endogenous PGs in the generation of cardiac arrhythmias. Furthermore, Dix et al.[12] demonstrated an arrhythmogenic and cardio-deleterious influence of prostacyclin, the main cardiac PG after infusion into cats subjected to coronary artery ligation.

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Insect antifeedant properties of withanolides and related steroids from Solanaceae

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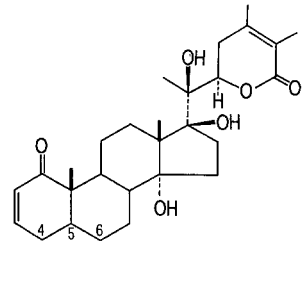
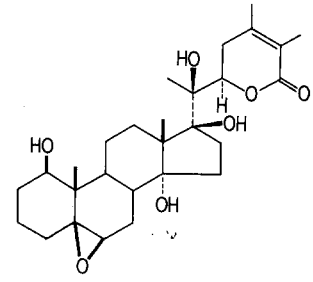
Summary. Physalis peruviana shrubs were not attacked by larvae of *Spodoptera littoralis.* It was demonstrated that withanolide E, a steroid isolated from *P. peruviana,* as well as several related steroids, have insect antifeedant properties.

For our studies on the steroidal constituents of solanaceous plants[1], we have maintained for several years small field plots of various *Physalis* and *Nicandra* spp. During an infestation by larvae of the Egyptian cotton leafworm, *Spodoptera littoralis* (Boisd.), in the summer of 1978, it was noted that *Physalis peruviana* L. (cape gooseberry) shrubs were not attacked, whereas other *Physalis* and *Nicandra* spp. suffered heavy damage. Laboratory experiments conducted at 27 °C were therefore initiated with *S. littoralis* larvae obtained from a culture on alfalfa. At first, 80–100 and 170–190 mg larvae kept singly in large petri dishes were allowed to feed on leaves of either *P. peruviana* or *P. ixocarpa* Brot. (tomatillo) and on alfalfa. The results (table 1) indicated that P. peruviana deterred the larvae from feeding to such an extent that their weight loss was nearly the same as that of starved larvae.

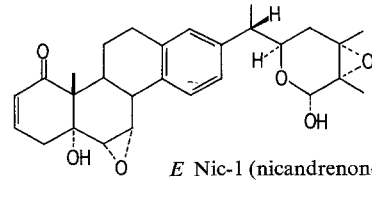
In subsequent experiments (table 2) an attempt was made to grow larvae of 3 weight ranges on leaves of *P. peruviana* in mass cultures in large enamel basins. No feeding and no mortality occurred after 1 day; heavy mortality began after 3 days and was practically complete after 7 days. In order to detect the antifeedant[2] principle(s), methanolic *P. peruviana* leaf extracts, and aqueous-methanolic (2:1) solutions obtained from them after removal of pigments, were prepared, and the latter diluted stepwise with the same solvent mixture; 5% sucrose was dissolved in each test concentration. To assess antifeeding activity, the 'Styropor method'[3] was employed: lamellae (6×4 cm) of 'Styropor' (foamed polystyrene) of density 0.016 (P_{16}) were dipped into the solutions, left to dry for 24 h, then weighed individually. They were then offered singly, in large petri dishes, to *S. littoralis* larvae weighing 170–190 mg, together with



A 5β,6β-epoxy (withanolide E)[4,5]
B 4β-hydroxy-5β,6β-epoxy (4β-hydroxywithanolide E)[5]
C 5α,6β-dihydroxy (withanolide S)[4]



D 5β,6β-epoxy-1β,14α,17β,20-tetrahydroxywith-24-enolide[4]



E Nic-1 (nicandrenone)[6]