Br. J. Pharmac. (1976), **58**, 573–581

THE LOCAL ANTINOCICEPTIVE AND TOPICAL ANTI-INFLAMMATORY EFFECTS OF PROPYL GALLATE IN RODENTS

WENDY J. McDONALD-GIBSON, S.A. SAEED & C. SCHNEIDER
Research Division, Miles Laboratories Ltd, Stoke Court, Stoke Poges, Slough, SL2 4LY

1 In common with several anti-inflammatory, analgesic, local anaesthetic and antioxidant drugs, propyl gallate *in vitro* inhibited the biosynthesis of prostaglandin E_2 and $F_{2\alpha}$ from arachidonic acid by a prostaglandin synthetase from bull seminal vesicles.

2 In common with analgesic drugs, propyl gallate reduced the ability of arachidonic acid, acetylcholine or acetic acid to cause abdominal constrictions in mice.

3 Using a new method of evaluating anti-inflammatory activity, we demonstrated the effectiveness of aspirin or indomethacin given subcutaneously before u.v. irradiation of guinea-pig ears, the prophylactic action of topically applied sunscreen agents and the therapeutic value of bufexamac and propyl gallate applied after irradiation.

Introduction

Propyl gallate is used as an antioxidant to stabilize oils, fats and cosmetics against oxidative deterioration. Previous studies (Tappel, Lundberg & Boyer, 1953 and Saeed, S.A., unpublished) have shown that propyl gallate inhibits hydroperoxidation of several polyunsaturated fatty acids. It has also been reported (Nugteren, Beerthuis & Van Dorp, 1966) that propyl gallate inhibits the conversion of di-homo-γ-linolenic acid to prostaglandin E_1 by microsomal particles of sheep vesicular glands. Otomo & Fujihira (1970) suggested that several non-steroidal anti-inflammatory drugs (NSAID) stabilize erythrocyte membranes against hydrogen peroxide-induced lipid peroxidation by 'mopping up' free radicals or peroxides. Subsequently, Vane and co-workers (Ferreira, Moncada & Vane, 1971; Smith & Willis, 1971; Vane, 1971; Flower, Gryglewski, Herbaczynska-Cedro & Vane, 1972) showed that clinically attainable plasma concentrations of NSAID inhibit prostaglandin biosynthesis. Since lipid peroxides and prostaglandins are important in the inflammatory process, we compared inhibition of prostaglandin biosynthesis by propyl gallate with several anti-inflammatory drugs. These experiments with bull seminal vesicle prostaglandin synthetase showed that propyl gallate was seven times as potent as aspirin. We also investigated the antinociceptive and topical anti-inflammatory activity of propyl gallate in laboratory rodents.

Methods

Inhibition of prostaglandin synthetase

The effects of propyl gallate and several other classes of drugs on prostaglandin biosynthesis *in vitro* were measured against prostaglandin synthetase of bull seminal vesicles (BSV) prepared as described previously (Collier, McDonald-Gibson & Saeed, 1974). Experiments were performed by incubation of an appropriate amount of the test substance in a standard assay mixture (2.0 ml) containing 50 mM phosphate buffer pH 7.4, 0.66 mM reduced glutathione, 0.09 mM hydroquinone, 5.25 mM disodium edetate (EDTA) and 500 µl of the BSV prostaglandin synthetase preparation. The reaction was started by the addition of sodium arachidonate (final concentration 0.061 mM) and the tubes aerated at 37°C with gentle shaking. After 12 min, the reaction was terminated by adding 2.0 ml of 0.2 M citric acid and the mixture was extracted with 16 ml ethyl acetate. After evaporation of ethyl acetate, the residue was re-dissolved in Krebs solution and assayed on rat stomach strip in the presence of antagonists of acetylcholine, catecholamines, histamine and 5-hydroxytryptamine. All experiments were carried out in duplicate with appropriate controls.

Antinociceptive tests

Generally, methods were as described by Collier, Dinneen, Johnson & Schneider (1968) and Collier, Saeed, Schneider & Warren (1973). Arachidonic acid (100 µg/ml) was incubated with propyl gallate (0–2 mg/ml). The incubate was tested intraperitoneally for its ability to induce abdominal constrictions in mice. Also, mice were pretreated with propyl gallate 1 to 4 mg/kg intraperitoneally 5 min before challenge with arachidonic acid (1 mg/kg) close to the site of the first injection, propyl gallate being

injected into the midline of the abdomen, arachidonic acid given slightly lower and to the right of this site. In a second batch of experiments, the mice were treated with propyl gallate (40 mg/kg intraperitoneally or subcutaneously) 5 min before intraperitoneal challenge with acetylcholine bromide (3.2 mg base/kg). Third, propyl gallate (10 or 40 mg/kg) intraperitoneally was given 5 min before a solution of acetic acid (75 mg/kg, i.p.) or acetylcholine bromide respectively. Fourth, sodium aspirin (40 mg as aspirin)/kg was given subcutaneously 10 min before challenge and propyl gallate (40 mg/kg) given intraperitoneally 2 min before challenge by acetylcholine or acetic acid.

In these abdominal constriction tests, solutions for injection were coded so that the observer of the abdominal constriction responses was unaware of the drug treatment given. The appropriate vehicles were always given as controls. The statistical significance of results was found using 2×2 Contingency Tables (Finney, Latscha, Bennett & Hsu, 1963).

Topical anti-inflammatory test

A preliminary account of the method was given by McDonald-Gibson & Schneider (1974). Individually marked Hartley strain male albino guinea-pigs weighing 200–300 g were used. The dorsal surfaces of both ears were depilated by Nair cream, and the cream removed by washing in tap water. Twenty hours later, a group of 4 guinea-pigs was placed in a cage 40 cm long × 15 cm wide × 10 cm high, separated from each other by wire mesh barriers. Test substances were applied to one ear using 100–150 mg of water miscible cream (Acid Mantle cream or occasionally Carbowax cream). The other ear received vehicle alone. In each experiment involving four guinea-pigs, two right ears and two left ears were treated with the test substance. Twenty min after each application, all four guinea-pigs were placed for 30 min under a 20 W u.v. strip-light (57 cm long; 8 cm above their heads). The lamp was switched on for 30 min before irradiating the animals. In unprotected animals, irradiation caused a marked increase in ear temperature, erythema, delayed oedema and blister formation. Food and water were withheld until observations on ear temperatures were complete (usually 4 h after irradiation). In other experiments test substances were applied immediately following irradiation or injected subcutaneously 20 min before irradiation. In one experiment sodium aspirin was injected 2 h and 6 h after irradiation.

Estimates of erythema were made subjectively by two independent observers, each usually comparing the test and control ear. When drugs were given subcutaneously, comparisons were made between test and control guinea-pigs. From 5–280 min after irradiation, ear temperature was monitored with a thermistor probe set in plasticine firmly on the dorsal surface of each ear in turn for 2.5 minutes. Temperature was measured via a Wheatstone bridge and a twin-channel Devices polygraph with a DC2-D pre-amplifier.

Ear thickness was measured by a micrometer screw gauge immediately before application of test substance and 24 h after irradiation. Oedema was taken as being proportional to the increase in ear thickness. Blister formation was assessed subjectively 5–7 days after irradiation by two independent observers.

In experiments in which ear temperature was measured, the animals were kept at a laboratory temperature of 24–26°C; in others they were kept at 20–23°C. In most experiments, the guinea-pigs were returned to their home cages immediately after irradiation and removed for measurement of ear temperature or ear-lobe thickness.

Statistical analyses of the results of the experiments in guinea-pigs were carried out by Mr L.C. Dinneen in this department using conventional methods.

Materials

Drugs were obtained from various pharmaceutical manufacturers (as indicated) and were prepared in aqueous solution either as the free acid or base or as the sodium or hydrochloride salt respectively. All drugs were of analytical grade; acetic acid (BDH), acetylcholine bromide (Sigma), Acid Mantle cream (Dome), amidopyrine (BDH), arachidonic acid (99% pure, Sigma), benzocaine (Sigma), benzydamine (Angelini Franchesco), bufexamac (butoxyphenyl-acetyl-hydroxamic acid; Lederle), butylated hydroxy-anisole (BHA; Sigma), Carbowax cream (Dome), citric acid (BDH), ethyl acetate (BDH), ethyl-enediamine tetra-acetate sodium (EDTA; Hopkin & Williams), flufenamic acid (Parke-Davis), glutathione (reduced form; Sigma), hyoscine hydrobromide (BDH), hydroquinone (Koch-Light), ibuprofen (Boots), indomethacin (Merck, Sharp & Dohme), meclofenamic acid (Parke-Davis), mefenamic acid (Parke-Davis), mepyramine maleate (May & Baker), methysergide bimaleate (Sandoz), Nair cream (Carter Wallace), nordihydroguaiaretic acid (NDGA; Fluka, A.G.), oxyphenbutazone (Geigy), para amino benzoic acid (PABA; Sigma), paracetamol (Koch-Light), phenazone (L. Light & Co.), phenoxybenzamine (Menley & James), phenylbutazone (Geigy), procaine hydrochloride (Sigma), propranalol hydrochloride (ICI), propyl gallate (Sigma), prostaglandin E_2 (Ono), prostaglandin $F_{2\alpha}$ (Ono), sodium acetylsalicylate (Miles), sodium chloride (BDH), sodium phosphate (BDH), Uval (2-hydroxy-4-methoxy-benzophenone-5-sulphonic acid; Dome), Vitamin E (Sigma).

Results

Inhibition of prostaglandin synthetase

As incubation of arachidonic acid with bull seminal vesicle homogenate (plus co-factors glutathione and hydroquinone) produced an average of 44 times more prostaglandin E_2 than $F_{2\alpha}$ results are expressed in terms of prostaglandin E_2 equivalents. Rank order of potency inhibiting prostaglandin biosynthesis *in vitro* correlated well with known analgesic activity in man and antinociceptive activity in mice (for references see Collier *et al.*, 1968). Results are shown in Table 1. Each of the 19 drugs incubated with arachidonic acid, bovine seminal vesicle prostaglandin synthetase preparation plus co-factors glutathione and hydroquinone reduced prostaglandin biosynthesis in a dose-related manner. Meclofenamate was the most potent drug tested, and although propyl gallate was 1000 times less potent, it was approximately 7 times more potent than aspirin and only slightly less potent than oxyphenbutazone in this system. Some substances other than the well known anti-inflammatory agents inhibited prostaglandin biosynthesis. These included the antioxidants butylated hydroxyanisole and nordihydroguaiaretic acid and the sunscreen agent 2-hydroxy-4-methoxy-benzo-phenone-5-sulphonic acid.

Antinociceptive activity

Table 2 shows that the ability of arachidonic acid (100 μg/ml) to induce abdominal constrictions in mice was significantly ($P < 0.01$) less after it had been incubated with 2 mg/ml of propyl gallate. Also, pretreatment of mice with 4 mg/kg propyl gallate intraperitoneally, significantly ($P < 0.005$) inhibited abdominal constrictions to a subsequent intraperitoneal challenge with arachidonic acid (Table 3). Furthermore, treatment of mice with propyl gallate, 40 mg/kg intraperitoneally 5 min before challenge, reduced abdominal constrictions in response to acetylcholine ($P < 0.01$). Propyl gallate, 10 mg/kg intraperitoneally 5 min before challenge, reduced abdominal constrictions induced by intraperitoneal acetic acid. In addition, propyl gallate 10 or 40 mg/kg significantly reduced diarrhoea ($P < 0.05$) after arachidonic acid or

Table 1 Inhibition of prostaglandin biosynthesis *in vitro*

Drug	IC_{50} (μM)
Non-steroidal anti-inflammatory	
Meclofenamate	0.11
Flufenamate	0.5
Indomethacin	1.2
Mefenamate	2.2
Ibuprofen	6.8
Phenylbutazone	13.0
Oxyphenbutazone	41.0
Benzydamine	410
Amidopyrine	518
Phenazone	637
Aspirin	692
Paracetamol	2516
Local anaesthetic and sunscreens	
Uval (2-hydroxy-4-methoxy-benzophenone-5-sulphonic acid)	227
Benzocaine	569
Para amino benzoic acid (PABA)	2828
Antioxidants	
Nordihydroguaiaretic acid	42
Butylated hydroxyanisole	52
Propyl gallate	103
Vitamin E	5804

IC_{50}: concentration which inhibits prostaglandin biosynthesis by 50%. The test drugs in aqueous solution were incubated with sodium arachidonate, glutathione, hydroquinone, EDTA and bull seminal vesicle homogenate in sodium phosphate buffer (see text for details). After extraction and re-constitution in Krebs solution the prostaglandins were assayed against prostaglandin E_2 on rat stomach strip using methods described by Collier *et al.* (1974).

Table 2 Inhibition by propyl gallate of the abdominal constriction response induced by arachidonic acid in the mouse

Concentration of propyl gallate in incubate (mg/ml)	*No. of mice*	*No. of mice responding within min*			*No. of responses by min*		
		0–0.5	*0.5–2*	*2–10*	*0–0.5*	*0.5–2*	*2–10*
None	50	12	16	20	20	37	84
0.25	35	2*	5	9**	2	7	17
0.40	5	1	2	5	1	8	38
0.50	10	0	0*	0**	0	0	0
1.00	45	0**	1**	8	0	1	23
2.00	5	0	0	4	0	0	6

Abdominal constrictions were induced by intraperitoneal injection of an incubate containing arachidonic acid (100 μg/ml), mouse peritoneal exudate (0.2 ml), propyl gallate (0–2 mg/ml), in 50 mM phosphate buffer containing ethanol (5% v/v), glutathione (50 μg/ml) and hydroquinone (10 μg/ml).
* $P < 0.05$; ** $P < 0.01$.

Table 3 Inhibition by propyl gallate of abdominal constrictions induced by arachidonic acid, acetylcholine or acetic acid in the mouse

Intraperitoneal treatment	*No. of mice*	*% of mice responding within*		
		0–0.5 min	*0.5–2 min*	*2–10 min*
AA + control vehicle	40	10	25	55
AA + propyl gallate (25 μg/ml)	35	6	5	23**
AA + propyl gallate (100 μg/ml)	35	0	3*	6**
AA 5 min after control vehicle	25	44	48	N.T.
AA 5 min after propyl gallate (1 mg/kg)	25	41	20*	N.T.
AA 5 min after propyl gallate (4 mg/kg)	20	0***	0*	N.T.
ACh 5 min after control vehicle	20	5	85	6/10
ACh 5 min after propyl gallate (40 mg/kg)	20	0	10***	1/10*
Acac 5 min after control vehicle	40	0	3	48
Acac 5 min after propyl gallate (10 mg/kg)	30	0	0	10**

Methods were those described by Collier *et al.* (1968).
AA = arachidonic acid, 1 mg 10 ml^{-1} kg^{-1}; ACh = acetylcholine bromide, 3.2 mg base 10 ml^{-1} kg^{-1}; Acac = acetic acid, 75 mg 10 ml^{-1} kg^{-1}. Propyl gallate was dissolved in sodium phosphate buffer, 0.05 M, pH 7.0. NT = not tested.
* $P < 0.05$; ** $P < 0.01$: *** $P < 0.005$.

acetylcholine challenge respectively, and also appeared to protect some mice from the immobilizing effect of arachidonic acid. Results in Table 4 show that sodium aspirin and propyl gallate together reduced abdominal constrictions to acetylcholine more effectively than did either drug alone.

In contrast, propyl gallate 10 or 40 mg/kg orally or subcutaneously in 4 groups of 10 mice had no anti-nociceptive activity against arachidonic acid.

Topical anti-inflammatory activity

Using the method of Tonelli, Thibault & Ringler (1965), B.M. Phillips (Miles Laboratories Inc., Elkhart, Indiana, USA, personal communication) found that propyl gallate showed significant topical anti-inflammatory activity, having a potency 0.03 relative to hydrocortisone.

Tables 5, 6 and 7 show results of tests of anti-inflammatory activity. Topically, propyl gallate at 10% w/w before and immediately after irradiation of guinea-pig ears significantly reduced ($P<0.05$) the heat and erythema observed for up to 4 h, the oedema that develops by 24 h and the blister formation that develops within 5 days. Lower concentrations of propyl gallate had progressively less effect, but even 1.25% w/w significantly ($P<0.01$) reduced ear heat. Propyl gallate 5 or 10% w/w was also significantly effective ($P<0.01$) when applied only after irradiation; at 10% w/w it reduced ear heat, erythema, oedema and blister formation.

Other substances which reduced inflammatory responses when applied before and after u.v. irradiation were the sunscreen Uval, the antioxidants butylated hydroxyanisole (BHA) and nordihydroguaiaretic acid (NDGA), each being less effective than propyl gallate. Mixtures of propyl gallate with NDGA or with PABA were also effective. Soluble buffered aspirin given subcutaneously also reduced ear heat, erythema and oedema.

Discussion

Although there is a good rank order correlation between inhibition of prostaglandin synthetase and analgesic potency of non-steroidal anti-inflammatory drugs, absolute potencies against prostaglandin synthetase from bovine seminal vesicles do not correlate well with absolute potency of NSAID in the treatment of inflammatory conditions such as rheumatoid arthritis in man. Therapeutic doses of aspirin for example are not 567 × those of indomethacin. Several antioxidants also inhibited, in a dose-related manner, prostaglandin biosynthesis.

The expected antinociceptive activity of propyl gallate was confirmed in mice. High concentrations of propyl gallate when incubated *in vitro* with arachidonic acid lessened the ability of arachidonic acid to induce abdominal constrictions. Simultaneous or prior administration of propyl gallate also inhibited abdominal constrictions induced by arachidonic acid. Responses to acetylcholine or to acetic acid were inhibited by high doses of propyl gallate. When administered with sodium aspirin there was an apparent additive antinociceptive effect, which would be expected if the drugs had similar modes of action.

The antinociceptive actions of propyl gallate in the mouse might be due at least in part to a local anaesthetic action. Hendershot & Forsaith (1959) thought that procaine given intraperitoneally exerted a local anaesthetic effect when blocking abdominal con-

Table 4 Inhibition by propyl gallate plus sodium aspirin of abdominal constrictions induced by acetylcholine or by acetic acid in the mouse

Subcutaneous treatment 10 min before challenge	*Intraperitoneal treatment 2 min before challenge*	*Intraperitoneal challenge*	*No. of mice*	*No. of mice responding within 0–30 s*	*0.5–2 min*	*2–10 min*
NAS	Propyl gallate	ACh	15	0	0***	NT
Control	Control	ACh	15	4	12	NT
NAS	Propyl gallate	ACh	15	0	0***	NT
NAS	Control	ACh	10	0	9	NT
NAS	Propyl gallate	ACh	10	0	0***	NT
Control	Propyl gallate	ACh	10	1	7	NT
NAS	Propyl gallate	Acac	5	0	0	4
NAS	Control	Acac	15	0	0*	2
NAS	Propyl gallate	Acac	5	0	0	4
Control	Propyl gallate	Acac	5	0	0	5

NAS; sodium aspirin 40 mg (as acetylsalicylic acid)/kg; Propyl gallate 40 mg/kg. Other details as in Table 3.

Table 5 Inhibition by drugs of heat, erythema and oedema of guinea-pig ears irradiated by ultra-violet light

Treatment	*Concentration of propyl gallate or other test drug*	*Note*	*Mean increase in temperature (°C) of control ears compared with treated ears at times after exposure to u.v. light* 20–40 min	41–60 min	100–120 min	200–240 min	*Proportion of treated ears with less erythema than controls*	*Proportion of treated ears with less oedema than controls*
Propyl gallate	10%		4.59***	5.33***	5.94***	4.01***	NT	4/4
Propyl gallate	10%	a	3.72**	3.25*	5.10*	4.80***	4/4	5/5
Propyl gallate	10%	b	2.30**	2.40**	1.28**	2.25**	4/4	4/4
Propyl gallate	10%	c	3.03***	3.48***	3.32***	1.00***	12/12	11/12
Propyl gallate	10%	a,c	1.90	2.23	3.73	1.30	4/4	4/4
Propyl gallate	5%	a	3.86***	3.96***	5.10***	2.36*	5/5	5/5
Propyl gallate	2.5%	a	3.62**	3.86**	3.42**	1.28***	4/4	1/1
Propyl gallate	1.25%	a	1.54	1.68	2.80***	0.88	4/4	4/4
Propyl gallate	0.625%		0.08	0.38[d]	0.38	0.28	0/4	1/4
Propyl gallate	0.5%		0.15[d]	1.05	NT	0.30	0/2	0/2
Propyl gallate	10%	e	4.85*	5.80***	5.88***	NT	4/4	4/4
Propyl gallate	5%	c	3.40**	4.40***	4.47***	0.93*	3/3	NT
Uval	10%		5.81***	6.19***	6.70***	8.20***	4/4	4/4
Uval	10%	c	0.33*[d]	0.14**	0.07	0.07	0/7	1/7
BHA	10%		0.76***	1.08***	1.24**	0.98**	12/12	7/8
NDGA	10%		0.73	0.70*	0.03	0.10[d]	0/4	2/4
Propyl gallate and NDGA	0.5% 9.5%	f	2.83*	3.80***	3.70	1.78*	4/4	4/4
Sodium aspirin	150 mg/kg	g	3.90***	4.50**	4.30**	1.00	4/4	2/2

Uval contains 2-hydroxy-4-methoxy-benzophenone-5-sulphonic acid; BHA is butylated hydroxyanisole; NDGA is nordihydroguaiaretic acid; PABA is para amino benzoic acid. NT indicates not tested. Concentration refers to % w/w applied to test ear.

Notes (a) Propyl gallate was added to warmed vehicle. When the cream had cooled to room temperature it was applied to the guinea-pig ears. (b) Drug was applied 10 min before irradiation. (c) Cream applied only after irradiation. (No pretreatment). (d) Increased temperature of treated ears compared with controls. (e) Carbowax cream was used, instead of Acid Mantle cream. (f) Mixture of two substances. (g) Solution of sodium acetylsalicylate (150 mg aspirin/kg) given subcutaneously 30 min before irradiation.

* $P \leqslant 0.05$; ** $P \leqslant 0.02$; *** $P \leqslant 0.01$.

Table 6 Inhibition by topically-applied drugs of oedema of guinea-pig ears irradiated by ultra-violet light

Treatment	*Concentration % w/w*	*Note*	*Mean difference in thickness (μm) between treated and control ears 24 h after exposure to u.v. light*	*Statistical significance*	*Proportion of treated ears with less oedema* than controls*
Propyl gallate	10		+165.1[i]	NS	3/4
Propyl gallate	10	c	−162.1	$P<0.05$	7/8
Propyl gallate	10	e	−393.7	$P<0.002$	4/4
Propyl gallate	0.5		+114.3[i]	NS	0/2
Propyl gallate	0.625		−19.05	NS	2/4
Uval	10	c	+127.0[i]	$P<0.05$	5/7[i]
BHA	10		−251.0	$P<0.05$	8/8
NDGA	10		−6.35	NS	2/4
Propyl gallate + NDGA	0.5 9.5	f	−254.0	NS	4/4
PABA	10		−355.6	$P<0.02$	4/4

* Difference between control and treated ears 24 h after irradiation. The figures in column 5 analysed statistically have used measurements taken both before and after 24 h irradiation. i = more oedema in treated ear. NS = not significant.
Other details as in Table 5.

strictions elicited by phenylbenzoquinone. Modak & Rao (1971) found that in the frog, rabbit and guinea-pig, propyl gallate is as potent a local anaesthetic agent as procaine. Although we found benzocaine to inhibit prostaglandin biosynthesis, procaine had little activity.

Our results in mice suggest that propyl gallate has little clinical potential as a subcutaneous or oral drug in man. However, its topical application to skin may prove useful in preventing inflammation caused by sunburn (Saeed, Schneider & Phillips, 1974) as suggested by the guinea-pig erythema test. The modifications that we made in this test have several advantages. Heat and oedema can be quantified objectively, and blister formation can also be assessed. Each animal may be used as its own control, drugs can be given parenterally or applied topically in various vehicles, and the animals do not need to be restrained manually during irradiation. Furthermore, hyperalgesia could probably also be measured, if necessary.

The reduction of heat, oedema, erythema and blister formation of the ears was not due solely to absorption of u.v. light by propyl gallate, since protection also occurred when the drug was applied after irradiation.

In man, erythema is induced most by u.v. radiation of 296.7 nm (Giese, Christensen & Jeppson, 1950; Knox, Guin & Cockerell, 1957). If this wavelength is as damaging to guinea-pigs as it is to man, the apparent anti-inflammatory activity of Uval, BHA, NDGA and PABA may be due only to absorption of u.v. light; Uval was not effective when applied only after irradiation. Clinically it is applied as a sunscreen before exposure to sunlight.

The anti-inflammatory activity of parenterally administered aspirin or indomethacin and of bufexamac (a new non-steroidal topical anti-inflammatory drug (Grigoriu, 1972)) indicates that the new method is useful for assessing anti-inflammatory activity of aspirin-like drugs.

Snyder & Eaglstein (1974) found that a single application of a 2.5% solution of indomethacin decreased the redness, warmth and tenderness of sunburned human skin (Kesten, 1956) for 24 h or longer, and was more effective than a corticosteroid cream. However, they did not state whether the indomethacin was applied before or after u.v. radiation.

Kahn & Curry (1974) reported that propyl gallate was an extremely effective sunscreen. They found, however, that it was a strong contact sensitizer, in agreement with the findings of B.M. Phillips (personal communication). Recently, Lewis (1976) showed that propyl gallate has topical anti-inflammatory activity in the rat, thus confirming our results in the guinea-pig (McDonald-Gibson & Schneider, 1974).

The use of propyl gallate might be justified in the treatment of painful burns, in view of the report by Jelenko & Wheeler (1972) that various antioxidants, when mixed with ethyl linoleate, prolonged its efficacy and appeared to act as oxygen acceptors. These investigators claimed that the antioxidants had potential use in burn therapy as topical agents to control excessive post-burn evaporative water loss and perhaps hypermetabolism after burns.

Propyl gallate may also potentiate the effect of adrenaline which reduces erythema partly by vasoconstrictor activity. Grunwaldt (1972) showed that alkyl gallates effectively prevented the catabolism of adrenaline and noradrenaline which were used in the treatment of glaucoma. Greengard & Petrack (1972) claimed that alkyl gallates plus adrenaline or noradrenaline in a preparation suitable for inhalation, were useful for treating bronchospasms. Also, Cash, Petrack & Weiner (1971) claimed that propyl gallate increased the anti-Parkinson activity of L-DOPA.

Table 7 Inhibition by topically applied propyl gallate of blister formation of guinea-pig ears irradiated by ultra-violet light

Treatment with propyl gallate		*Concentration*	*Proportion of control ears with greater* blister formation than treated ears 4 or 5 days after exposure to u.v. light*
Before u.v.	*After u.v.*	*% w/w*	
+	+	0.625	1/4
+	+	10	4/4
+	+	10[e]	4/4
−	+	10	4/4 slight protection

* Determined subjectively by two observers; e=in Carbowax cream; +=propyl gallate applied; −=propyl gallate not applied.
Other details as in Table 5.

Propyl gallate may exert some of its anti-inflammatory action by inhibiting the effects of bradykinin as demonstrated on the guinea-pig ileum by Posati, Fox & Pollansch (1970).

We thank Mr L.C. Dinneen for statistical help; Miss J.L. Copas, Miss P. Boyle and Mr R.D. Elliott for technical assistance and Dr A. Bennett for some suggested alterations to the text.

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(Received April 8, 1976. Revised June 11, 1976.)