The effect of indomethacin and depletion of complement on cell migration and prostaglandin levels in carrageenin-induced air bleb inflammation

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Prostaglandins (PG), including PGE_1, are produced during phagocytosis *in vitro* by rabbit polymorphonuclear leucocytes (PMNL), in the absence of plasma, in amounts chemotactic for other PMNL (Higgs & Youlten, 1972; McCall & Youlten, 1973). Since phagocytosing PMNL also release enzymes which can activate complement to give chemotactic fragments (Ward, Cochrane & Müller-Eberhard, 1965), we have investigated the relative contribution made to the PMNL invasion in acute inflammation by PG and activated complement factors, by the separate and combined administration of indomethacin to inhibit PG synthesis and heat aggregated human-γ-globulin (HAGG) to deplete complement.

Inflammation was induced by the carrageenin air bleb technique (Willis, 1969) in adult male Wistar rats. Groups of 3 to 6 animals were treated with either indomethacin (3 mg/kg body weight) i.p. or HAGG (100 mg/kg body weight) i.v., or both, 1 h before induction of the inflammation under ether anaesthesia. The animals were killed at 4, 8, 12, 18 or 24 h and the fluid in the air bleb removed, its volume and cell count estimated and its PG-like activity determined by extraction and bioassay as previously described (Higgs & Youlten, 1972).

The volume of exudate was unaffected by any treatment. Cell counts, predominantly PMNL, were significantly reduced in the indomethacin and in the HAGG treated groups at all times from 8 h onwards. Indomethacin reduced the prostaglandin content of the fluid at all times. The HAGG treated group had raised PG levels at 4 and 12 h, and a decrease at 24 hours. Combined treatment with indomethacin and HAGG reduced the cell counts to a greater extent than either treatment alone at all times from 4 h to 24 h (Table 1).

Table 1 Mean cell counts and PG concentrations in fluid from air blebs at different times after carrageenin injection. Tests of significance were performed of the differences between the treated and control (no indomethacin or HAGG) groups. In the case of the combined treatment, WBC and PG were compared with the more effective of the two separate treatments at that time

		Control	*Indomethacin (3 mg/kg)*	*HAGG (100 mg/kg)*	*Indomethacin + HAGG*
4 h	WBC ($\times 10^{-6}$/ml)	1.5	1.3	1.6	0.5***
	PG (ng/ml)	7.4	2.7**	20.9**	5.6**
8 h	WBC	20.0	5.4***	7.9**	1.8*
	PG	23.9	3.1***	18.8	2.7
12 h	WBC	51.9	36.0**	30.0***	5.8***
	PG	11.2	1.5***	18.3**	3.6***
18 h	WBC	95.9	68.3***	63.9***	36.1**
	PG	10.9	4.3***	7.5	1.5
24 h	WBC	140.6	108.5*	82.0***	69.8
	PG	10.8	2.3***	1.1***	3.3

* $P < 0.10$; ** $P < 0.05$; *** $P < 0.01$.

These findings suggest that a PG-mediated chemotactic mechanism may operate in carrageenin inflammation, causing a significant reinforcement of the complement-mediated mechanism.

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