Exogenously Administered Prostaglandins Modulate Pulmonary Granulomas Induced by Schistosoma mansoni *Eggs*

STEPHEN W. CHENSUE, PhD, STEVEN L. KUNKEL, PhD, PETER A. WARD, MD, and GENE I. HIGASHI, MD

From the Department of Pathology, University of Michigan Medical School, and the School of Public Health, University of Michigan, Ann Arbor, Michigan

The inflammatory modulating activity of specific prostaglandins has been examined for both immune and foreign-body types of pulmonary granulomas. Lung granuloma formation generated in mice by embolization of *Schistosoma mansoni* eggs was markedly suppressed by treatment with the stable, functional analog of prostaglandin E, (PGE_1), (15-(S)-15-methyl PGE_1) while treatment with $PGF_{2\alpha}$ augmented the granulomatous response. Despite marked effects on egg-induced granuloma formation, PGs had no significant effect on the foreign body lesion induced by Sephadex beads. Likewise, PGs had no effect on the primary antibody response to schistosome egg antigens. However, notable derangements in splenic lymphoid populations occurred. While T-cell numbers appeared constant in face of PG treatment, B-cell populations were depressed by methyl-PGE_1 and augmented by $PGF_{2\alpha}$. Further analysis revealed that methyl-PGE_1 appeared to suppress both the induction and elicitation phases of the cell-mediated response to schistosome eggs. Cyclophosphamide treatment could partially reverse this suppression, but the induction of suppressor cell activity was not solely responsible for this effect. The possible role and mechanism of PGs as modulators of chronic inflammation is discussed. (Am J Pathol 1983, 111:78–87)

IT HAS BECOME APPARENT that prostaglandins (PGs) and related arachidonic acid derivatives take part in a multiplicity of physiologic events. With regard to inflammation, PGs have traditionally been assigned a purely phlogistic role. However, recent evidence has suggested that at least some types also have antiinflammatory properties. It has been shown that PGs or their precursors can suppress both acute and chronic inflammatory states, including reagin-mediated histamine release,[1] immune complex vasculitis,[2] adjuvant-induced arthritis,[3] and experimental autoimmune encephalomyelitis.[4] While it is known that nonspecific mediators such as PGs are present in chronic inflammatory foci, particularly granulomas,[5] their role as pro- or anti-granulomatous agents is not precisely known.

In the present study we examined the effect of systemically administered PGs on the development of pulmonary granulomas in mice induced by embolization of schistosome eggs. This is a well-established model of a highly active T-cell–mediated hypersensitivity lesion, whose development and regulation involve helper/effector ($Ly1^+$) and suppressor ($Ly2^+$) T-cell subsets.[6–8] The data delineate the effect of PGs on various aspects of the granulomatous immune response, including sizes of lesions, splenic lymphoid tissue composition, T-cell mitogen responsiveness, primary antibody formation, and cyclophosphamide-sensitive suppressor cell function. In addition, we used adoptive cell transfers to examine the influence of PGs on the induction and elicitation of granulomatous hypersensitivity. Our results showed that the response to schistosome eggs was significantly affected by PG treatment. PGE_1 dramatically suppressed schistosome egg granuloma formation, whereas $PGF_{2\alpha}$ appeared to augment the response. No significant effects were seen with the Sephadex bead (foreign body-type) granuloma. Both types of

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Address reprint requests to Steven L. Kunkel, PhD, Department of Pathology, University of Michigan Medical School, 1335 E. Catherine Street, Box 045, Pathology Building, Ann Arbor, MI 48109.

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PGs caused notable alterations in the composition of splenic lymphoid tissue without significantly affecting the primary antibody response to schistosome egg antigens (SEA). These data support the notion that PGs can potentially regulate granulomatous hypersensitivity and may offer a valuable approach to manipulating granulomatous diseases.

Materials and Methods

Animals

Female CBA/J mice (The Jackson Laboratory, Bar Harbor, Maine) were used in all experiments. The mice were maintained under standard care and given food and water *ad libitum*.

Isolation of Schistosome Eggs

Eggs were isolated aseptically from the livers of mice infected with >200 cercariae of the Puerto Rican strain of *Schistosoma mansoni* as described by Coker and von Lichtenberg.[9] Eggs were suspended to 4000/ml of sterile normal saline, and each mouse received 2000 eggs via a tail vein.

Preparation of Sephadex Beads

G-75 Superfine Sephadex (Pharmacia, Piscataway, NJ) was swollen and sieved over nylon mesh (Spectrum Medical Industries, Inc. Los Angeles, Calif.) for the removal of beads <40 μ in diameter. Final bead sizes ranged between 40 and 50 μ in diameter. The beads were autoclaved in suspension, and the concentration was adjusted to 1×10^4/ml in physiologic saline. Each mouse received 5000 beads by tail vein injection.

Prostaglandin Treatments

M-PGE (15-(S)-15-CH_3-PGE_1) and $PGF_{2\alpha}$ (PGF) were generously provided by Dr. J. Pike (Upjohn, Kalamazoo, Mich). Stock solutions of 10 mg/ml were prepared in absolute ethanol and stored at −20 C. PGs were diluted in normal saline to 100 μg/ml, and the mice were given subcutaneous injections of 1.5 μg/g body weight each day following embolization of eggs or beads. Control animals received daily injections of saline with diluted ethanol.

Measurement of Granuloma Areas

The mice were sacrificed at 4, 8, and 16 days after egg or bead injection, and the lungs were inflated with buffered formalin, excised, and prepared for histologic sectioning. Granulomas in tissue sections were measured with the use of an Omicron Alpha Analyzer (Bausch and Lomb, Rochester, NY) with the data directly fed into an attached computer. A minimum of 20 granulomas were measured from each lung.

Assay for T and B Lymphocytes

T cells were identified by a two-stage cytotoxicity assay described by Schlesinger.[10] Briefly, spleen cells suspended to 1×10^7/ml RPMI-1640 (Grand Island Biological Co., Grand Island, NY) containing a 1:320 dilution of anti-Thy 1.2 monoconal antibodies (Miles Laboratories, Inc., Elkhart, Ind) or normal mouse serum were incubated for 20 minutes at 4 C. The cells were then washed twice and restored to their original volume in a 1:10 dilution of rabbit complement (Accurate Chemicals, Hicksville, NY) in RPMI. Suspensions were next incubated for 30 minutes at 37 C, washed, and suspended in RPMI. The numbers of killed cells were determined by trypan blue exclusion, and the net percentage of Thy 1-bearing cells was calculated as previously described.[11]

B cells were identified by direct immunofluorescence using the $F(ab')^2$ fragment of fluorosceinlabeled rabbit anti-mouse IgG (heavy and light chain specific) (RAMIg) (Cappel Labs, Cochranville, Pa). Spleen cells were suspended in a 1:80 dilution of RAMIg in cold RPMI. Following incubation for 30 minutes at 4 C, the cells were washed three times and suspended to original volume in RPMI containing 0.01% sodium azide to prevent capping. The percentage of fluorescent cells was determined with the use of a microscope with an ultraviolet light source. A minimum of 200 cells were counted, and each preparation was assayed in duplicate.

Mitogen Assay

Spleen cells were prepared aseptically in cold RPMI, then suspended to 2×10^6 cells/ml in RPMI supplemented with 5% fetal calf serum (KC Biological, Inc., Lenexa, Kansas) and 5 μg/ml gentamicin (Schering Pharmaceutical Corp., Kenilworth, NJ) (RPMI-FCS). One-tenth of a milliliter of cell suspension was distributed into each well of a 96-well microtiter culture plate (Costar, Cambridge, Mass). To each well was added graded doses of phytohemagglutinin (PHA) (Wellcome Reagents Ltd., Beckingham, England) in 0.05 ml of RPMI-FCS. Control wells received media only. The plates were then in-

cubated at 37 C in a 5% CO_2 humidified atmosphere. After 64 hours, the plates were removed, and 1.0 μCi of ^{3}H-thymidine (New England Nuclear, Boston, Mass) in 0.05 ml of RPMI-FCS was added to each well, and the dishes were reincubated for 8 hours. The cells were then harvested with the use of a multiwell harvester, and uptake of radioactive label was determined by scintillation spectrophotometry. Individual spleens were assayed in duplicate or triplicate, and stimulation ratios were calculated from the mean of each.

Measurement of Antibody to Soluble Egg Antigens (SEA)

SEA was prepared from eggs isolated from livers of infected mice. Serum anti-SEA antibody titers were determined by passive hemagglutination as previously described[12] All sera were absorbed with an equal volume of packed sheep erythrocytes for removal of Forssman antibodies.

Cell Transfer and Cyclophosphamide Treatment

Sensitized spleen cells were prepared aseptically from donor mice given 2000 schistosome eggs intraperitoneally 16 days previously. In some experiments mice were treated with PGs during this sensitization period. Cells were suspended to appropriate concentrations in RPMI, then injected via the tail vein in a 0.25-ml volume. Within 30 minutes recipients were given an intravenous injection of schistosome eggs. Subsequent granuloma formation was examined 8 days later.

In experiments using cyclophosphamide (Mead Johnson and Co., Evansville, Ind) mice were given 15 mg/kg intraperitoneally one day before egg injections. This dose has been shown to adequately eliminate suppressor function.[13]

Statistics

The Student t test was used for comparison of control and treated groups. Values of $P < 0.05$ were considered significant.

Results

Comparison of the Effect of PG Treatment on Schistosome Egg and Sephadex Bead Granuloma Formation

Granuloma size around the embolized schistosome eggs increased linearly over the 16-day study period

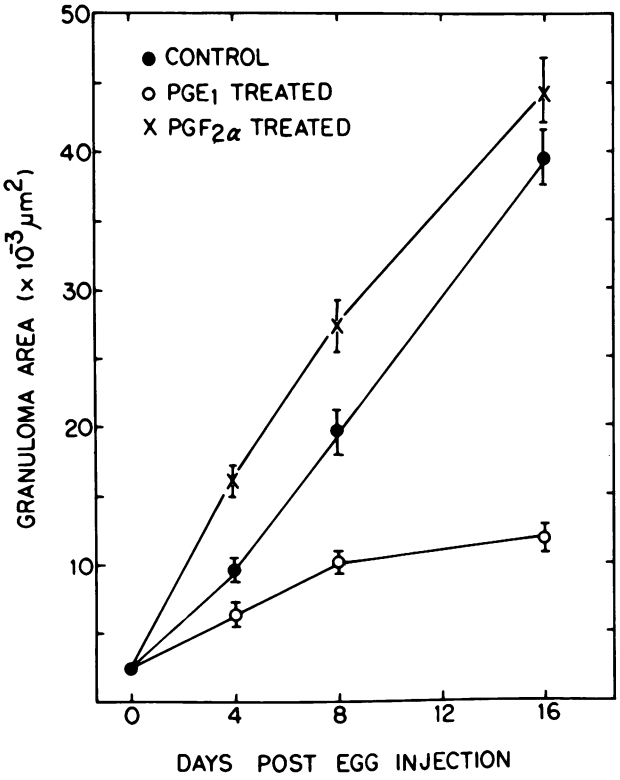

Figure 1—Effect of treatment with prostaglandins M-PGE$_1$ and PGF$_{2\alpha}$ on granuloma formation around schistosome eggs. Points represent the mean granuloma area ± SEM, 5-7 mice per point.

(Figure 1). In PGF-treated animals, granulomas were augmented by 60% at Day 4 and 39% at Day 8, but by Day 16 the areas were not significantly different from those of controls. In contrast, granulomas of M-PGE-treated mice were dramatically suppressed, attaining a mean area only 30% of the control area by Day 16. Figure 2 shows the histologic appearance of representative lesions from the treated and control groups. We next tested the effect of PGs on the granulomatous response to the less immunogenic polysaccharide bead, Sephadex. As shown in Figure 3, neither PGF nor M-PGE affected this less active foreign-body lesion after 8 days of treatment.

Effect of PG Treatment on Splenic Lymphoid Tissue During Granuloma Formation

Since relatively small subcutaneous doses of PGs seemed to have a profound effect on the development of the granulomatous immune response, it was important to determine whether any gross alterations of lymphoid tissue composition or function had occurred. The spleen, an easily accessible lymphoid organ, was chosen for study. Total cell yield, as well as T- and B-cell composition, was quantified. Table 1

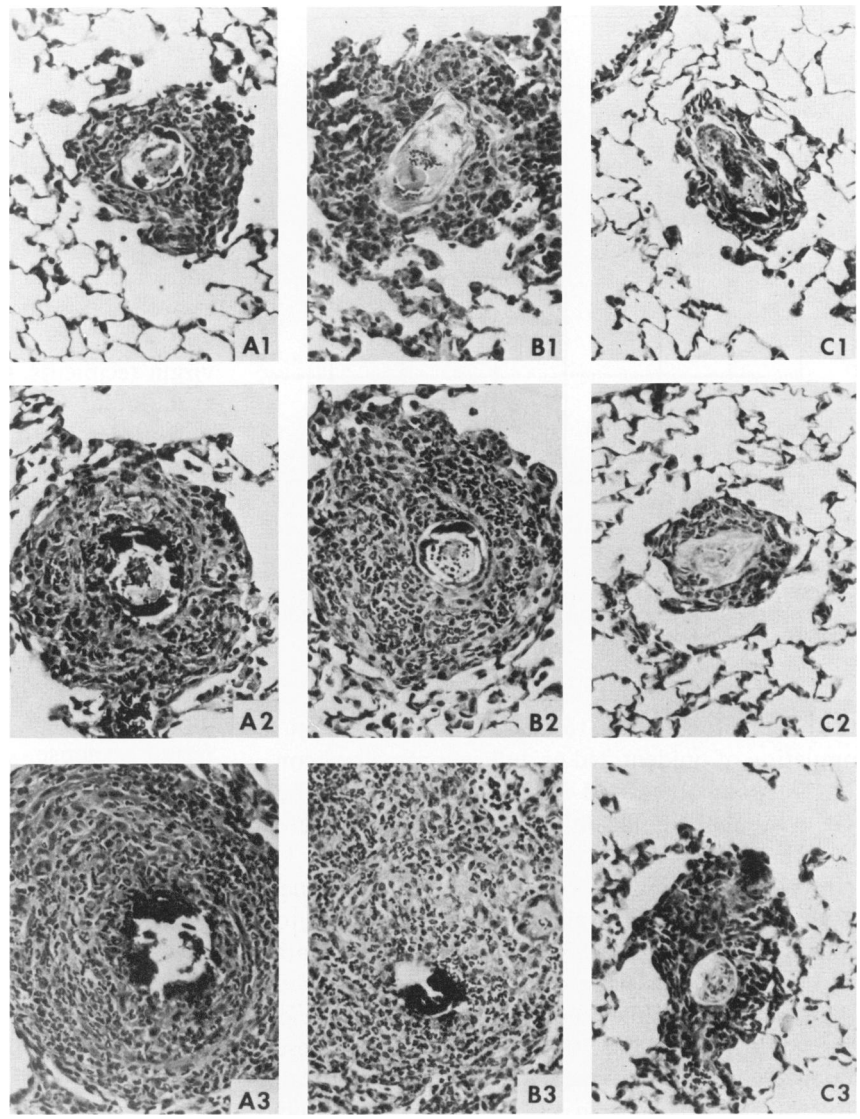

Figure 2— Photomicrographic appearance of pulmonary granuloma formation around schistosome eggs in mice treated with prostaglandins. Series **A** shows normal (control) granuloma development at 4 (**A1**), 8 (**A2**), and 16 (**A3**) days. Series **B** shows granuloma formation in $PGF_{2\alpha}$-treated mice at 4 (**B1**), 8 (**B2**), and 16 (**B3**) days. Series **C** shows granuloma formation in M-PGE_1-treated mice at 4 (**C1**), 8 (**C2**) and 16 (**C3**) days. (H&E, ×400)

shows that cell yield in control animals increased by approximately 30×10^6 by Day 16. In contrast, splenic lymphocytes from M-PGE–treated mice displayed no increase but were significantly decreased, compared with controls at Day 8, showing only a partial recovery by Day 16. PGF treatment gave a distinctly opposite result, causing increases above controls by Day 8, then falling below by Day 16. The percentage of T- and B-cells in these spleens is shown in Table 2. In controls, T-cell percentages remained constant over the 16-day study period, and B cells showed a modest increase. No significant differences were seen between any of the groups at 4 days other than a moderate increase of B-cell percentages in PGF-treated mice. However, at Day 8 and 16, M-PGE–treated mice showed significant increases in T-cell and decreases in B-cell percentages. PGF tended to have the opposite effect, causing a decrease in the percentage of T cells on Day 8, with a return to normal range by Day 16, while B-cell percentages in the latter were increased.

To obtain a clearer concept of T- and B-cell population changes in face of a changing total yield, absolute numbers of T and B cells were calculated and plotted in Figure 4. It can be seen that splenic T-cell numbers were similar among the treated and control groups. In contrast, splenic B-cell numbers of controls appeared to steadily increase following egg embolization. Treatment with M-PGE caused a notable loss of B cells on Day 8, with a return to normal baseline at 16 days. PGF treatment seemed to accelerate the expansion of B cells at 4 and 8 days but leveled

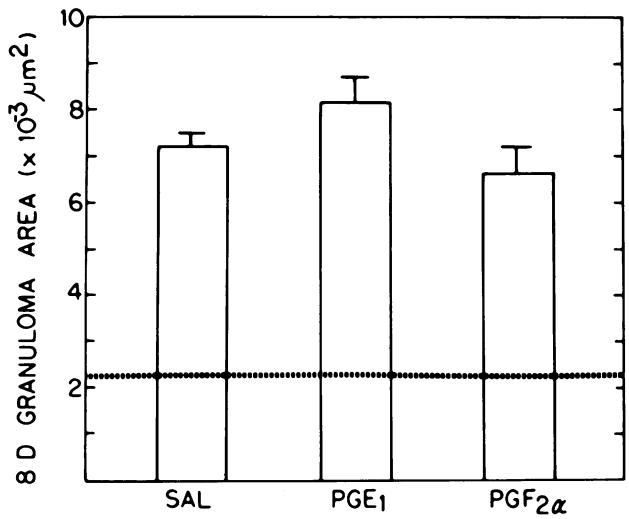

Figure 3—Effect of treatment with prostaglandins M-PGE$_1$ and PGF$_{2\alpha}$ on granuloma formation around Sephadex beads. Bars show the mean granuloma area ± SEM after 8 days of treatment with prostaglandins, 5 mice per group. The *dotted line* represents the mean area of the embolized Sephadex beads only.

off to control values by 16 days. It is notable that a population of unidentified or null cells remained constant in control and M-PGE–treated groups, but PGF treatment significantly increased null cells at 8 days; these returned to baseline by Day 16.

In order to evaluate T-cell function, we examined responses of splenic lymphocytes to the T-cell mitogen PHA. As shown in Figure 5, both experimental and control groups were optimally stimulated with 0.1 μg/ml PHA. While there was a trend of increased E/C ratios following egg injection, no shifts in dose-response curves were observed. The only significant effect of PG was seen in PGF-treated mice, which showed a clearly depressed stimulation at 8 days. It is noteworthy that this depression corresponds with the decreased percentage of T cells observed in PGF-treated mice.

Effect of PG Treatment on Anti-SEA Antibody Levels

Since mice with embolized schistosome eggs develop both cell-mediated and humoral immunity to soluble schistosome egg antigens (SEA),[14] it was of interest to determine the effect of PGs on B-cell function by measuring antibody levels during the 16-day study period. Therefore, serum samples were collected at the various times of sacrifice, and anti-SEA titers were determined. As shown in Table 3, while there was a trend to higher titers at 16 days in the PGF group, no significant differences in the antibody response were observed at any of the time points. These results indicated that the primary antibody response was unaffected by PG treatment.

Effect of PG Treatment on the Induction and Elicitation of Granulomatous Hypersensitivity

We next determined whether PG treatment was affecting granuloma formation via the induction and/or elicitation arm of the immune response. To approach this question, spleen cells from donor mice sensitized with schistosome eggs were transferred to virgin recipients. On the day of transfer, pulmonary granulomas were induced by intravenous egg injection as described in Materials and Methods. Subsequently, mice received daily treatments with PG and were sacrificed on Day 8 for examination of granuloma size. As shown in Figure 6, sensitized spleen cells indeed transferred an augmented (secondary) granulomatous response, compared with normal spleen. The elicited response of primed spleen cells was clearly suppressed by M-PGE to a level even less than seen in normal cell transfer controls. Interestingly, PGF had no significant effect on the transferred response.

In order to test the effect of PG treatment on the induction of immunoreactive lymphocytes, mice were treated with PG as usual during a 16-day sensitization with schistosome eggs. Spleen cells of such mice were then transferred to virgin recipients and tested for their capacity to generate a secondary granulomatous response to an egg challenge. The results are shown in Figure 7. As expected, spleen cells from sensitized untreated donors gave a strong secondary response, compared with controls. In contrast, cells of M-PGE–treated donors showed a significantly reduced capacity to transfer granulomatous hypersensitivity. Furthermore, cells of PGF-treated donors showed a trend to smaller lesions, but these were not significantly different from those of recipients of sensitized spleen cells.

Taken together, the above results showed that M-PGE can suppress the elicitation of granuloma for-

Table 1—Spleen Cell Yields During Egg Granuloma Formation and PG Treatment

Group	Total yield (cell numbers × 10^{-7})			
	Day 0	Day 4	Day 8	Day 16
Control	5.4 ± .43*	7.4 ± 2.2	7.1 ± 1.3	8.0 ± .68
M-PGE$_1$	–	5.8 ± 2.6	4.7 ± 1.2†	5.9 ± 1.2†
PGF$_{2\alpha}$	–	7.3 ± 1.1	9.8 ± 2.2†	6.9 ± 1.2†

* Values represent mean ± SD of 5–8 mice.
† $P < 0.05$.

Table 2—Proportion of T and B Cells in Spleens During Egg Granuloma Formation and PG Treatment

	Time after egg injection							
	Day 0		Day 4		Day 8		Day 16	
Group	T	B	T	B	T	B	T	B
Control	26.7 ± 1.8*	57.0 ± 2.6	28.9 ± 1.6	57.2 ± 2.1	27.0 ± 3.0	59.0 ± 3.2	25.0 ± 2.0	62.6 ± 1.9
M-PGE_1	–	–	31.4 ± 2.6	60.1 ± 3.3	34.4 ± 1.8†	46.0 ± 2.0†	35.2 ± 3.0†	51.0 ± 4.5†
$PGF_{2\alpha}$	–	–	24.7 ± 2.6	62.7 ± 1.5†	17.2 ± 2.4†	52.4 ± 4.7	21.1 ± 2.2	69.1 ± 1.2†

* Values represent mean percentage ± SEM of 4-5 mice sampled from each group shown in Table 1. Each mouse was assayed in duplicate or triplicate.
† $P < 0.05$.

mation by a primed induced T-cell population as well as block the induction of functional primed T cells during immunization.

Role of PG in the Generation of Cyclophosphamide-Sensitive Suppressor Cell Activity

It has been suggested that PGE may stimulate suppressor T-cell (T_S) activity.[15,16] Since suppressor T cells take part in regulating the schistosome egg granuloma, it was important to determine whether the suppression mediated by PGE was the result of augmented T_S activity. To ascertain this, we utilized low-dose cyclophosphamide (CY) treatment, which has previously been shown to eliminate T_S activity during schistosome egg granuloma formation.[7] One day before egg challenge and PG treatment, we gave the mice CY to eliminate T_S cell precursors. If PGE recruited T cells from this T_S pool, then its suppressive effect would be negated by CY. As shown in Figure 8, CY treatment significantly augmented the normal progression of granuloma formation. Furthermore, the suppressive effect of M-PGE was restored to the level of a normal primary granuloma. However, M-PGE prevented the full augmentation by CY, suggesting that T_S cells are not the sole mechanism by which M-PGE exerts its suppressive effect.

Discussion

Prostaglandins (PGs) are among several types of mediators, such as kinins, complement, lymphokines, etc., which take part in the inflammatory process. While various classes of PGs have been identified within granulomatous lesions,[5] their precise role is not understood. However, recent evidence suggests they may be important modulators of chronic inflammation. The studies of Bonta and Parnham[17] showed that PGE_1 has a time-dependent effect on the generation of the granulomatous response to carrageenan-impregnated sponges, augmenting the early infiltrative phase and suppressing the later proliferative phase. The latter effect was modest and achieved by the local administration of PGE_1. Other studies have suggested that PGs have a beneficial effect in chronic inflammation. It has been shown that orally or systemically administered E-type PGs suppress adjuvant-induced arthritis in rats.[18] Such studies have lent support to the model proposed by Morley[19] that PGs act as feedback signals which down-regulate chronic inflammation.

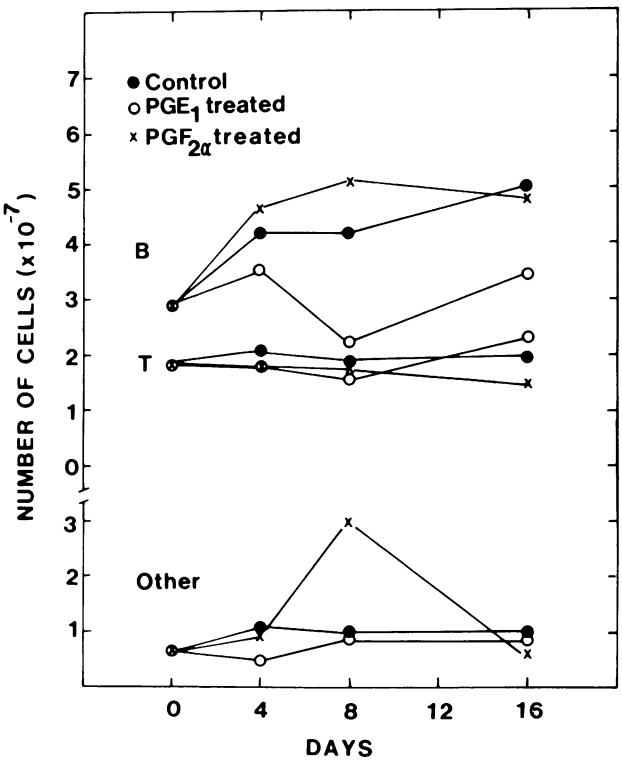

Figure 4—The effect of prostaglandin treatment on the absolute yield of splenic T and B cells during schistosome egg granuloma formation. The values were obtained by multiplying total spleen cell numbers by the percentage of T or B cells. ●, control; O, M-PGE_1-treated; X, $PGF_{2\alpha}$-treated.

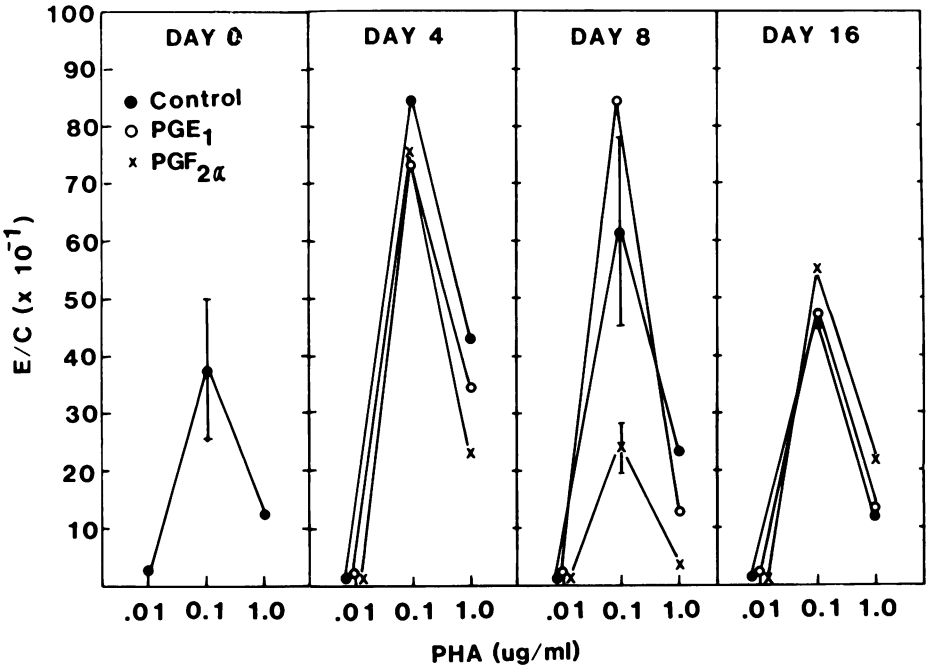

Figure 5—The effect of prostaglandin treatment on the mitogenic response of spleen cells to phytohemagglutinin during schistosome egg granuloma formation. Points represent the mean stimulation ratio ± SEM of 5–7 individual spleen cultures at graded doses of PHA. Stimulation ratios were calculated by dividing the average CPM (counts per minute) of ^{3}H-thymidine uptake in PHA-stimulated cultures (*E*) by that of the unstimulated cultures (*C*). ●, control, ○, M-PGE_1-treated, X, $PGF_{2\alpha}$-treated.

In the present study, we demonstrated that systemically administered PGs can have dramatic effects on granuloma formation, depending upon the character of the irritating nidus and the specific type of PG employed. Our finding, that the hypersensitivity-type granuloma (schistosome egg) was markedly affected while the nonspecific foreign-body lesion (Sephadex bead) was not, is probably related to the differing degrees of lymphoid involvement. The *S mansoni* egg is a natural granulomagenic nidus that induces a highly active, T-cell–mediated response to soluble protein antigens secreted by the larva (SEA).[20] This response involves at least two phases: 1) the induction and proliferation of reactive T cells and 2) the elicitation of a local cellular infiltration. Previous *in vitro* experiments showing that PGs can regulate lymphocyte transformation,[21] cell-mediated cytotoxicity,[22] and lymphokine production[23] indicate that both of these phases could be affected by systemically administered PGs. Conversely, the Sephadex bead granuloma represents a less active, low-turnover lesion, probably lacking specific T-cell involvement[24]; and it may therefore be more resistant to the effects of PGs. This might explain the modest suppression previously reported with the carrageenan-sponge granuloma, which more closely resembles a low-turnover lesion.

The finding that PGF augmented while M-PGE suppressed the egg granuloma suggests that these types of PGs have antagonistic effects on inflammatory events. This may be related to the opposing effects these PGs have on levels of cyclic AMP and GMP within inflammatory cells.[25] Thus, the functional balance of the inflammatory response may be the sum of opposing stimuli. The dynamic nature of this state is reflected by our observation that the pro-inflammatory effect of PGF was lost by 16 days, possibly because of the induction of counterbalancing mechanisms. As yet, it is not known whether the suppressive effect of M-PGE can eventually be overcome or whether preformed lesions will regress with prolonged treatment. Studies are under way to explore these possibilities.

In order to further evaluate the effects of PG treatment on lymphoid tissue and lymphocyte function, we quantitated splenic T- and B-cell populations, T-mitogen (PHA) response, and anti-SEA antibody titers. This survey revealed a number of interesting findings. Firstly, PG treatment indeed caused significant changes in splenic T- and B-cell populations: M-PGE suppressed the normal expansion of B cells, whereas PGF augmented it, paralleling the changes

Table 3—Anti-SEA Antibody Titers During Egg Granuloma Formation and PG Treatment

Group	Log_2 antibody titer			
	Day 0	Day 4	Day 8	Day 16
Control	1.6 ± 1.1*	5.4 ± .89	6.5 ± .84	5.8 ± 1.1
M-PGE_1	–	4.8 ± 1.4	6.5 ± 1.2	5.0 ± 1.4
PGF	–	5.2 ± 1.2	5.8 ± 1.3	6.6 ± .55

* Values represent mean ± SD of 5–9 mice.

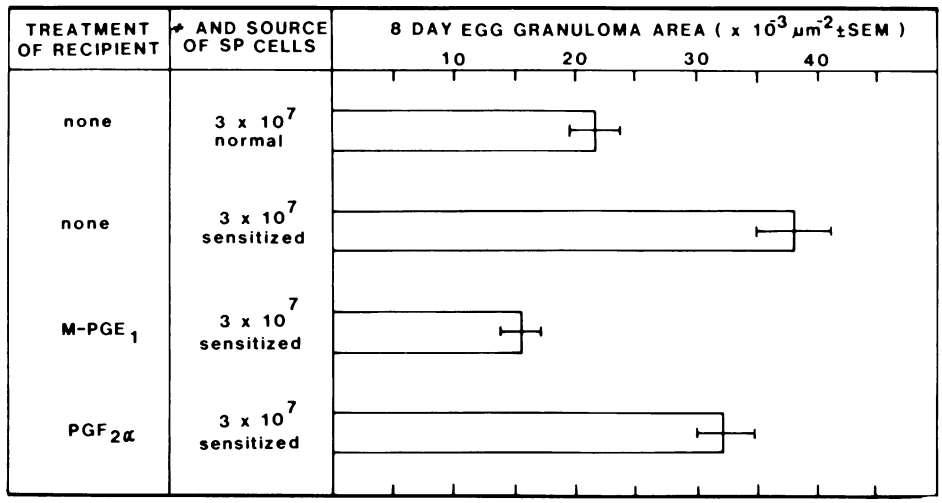

Figure 6—The effect of prostaglandin treatment on the capacity of adoptively transferred, primed spleen cells to elicit granuloma formation around schistosome eggs. Virgin recipients were each given 3 × 10^7 primed spleen cells, followed by 2000 schistosome eggs intravenously. Recipients were then treated daily with PGs, and granulomas were measured at 8 days. *Bars* represent the mean granuloma area ± SEM, 5 mice per group.

seen in granuloma formation. On the other hand, T cells tended to maintain stable numbers in all groups. Secondly, PHA responses of splenic T cells were identical in all groups except on Day 8, when PGF-treated mice appeared to have a depressed response. However, this could largely be attributed to the decreased T-cell percentages of this group. Hence, when corrected for the derangement of T/B ratios, PHA responses were essentially intact in all groups.

The finding that of T-cell numbers and function (PHA response) were essentially unchanged despite significant effects on the T-cell–mediated granulomatous response is presently without explanation. Such cells may function normally when placed *in vitro*, where they are no longer exposed to daily pulses of PG. In any event, there was no innate change in T-cell responsiveness or generation of suppressor cells, which can function *in vitro*, as suggested by Webb and Nowowiejski.[16] However, a more detailed analysis of T-cell populations in terms of Ly phenotype will help ascertain PG-induced changes in various functional subpopulations. Specifically, it will be of interest to determine whether M-PGE and PGF stimulate suppressor or helper cell differentiation. It should be added that our data also showed that PGF induced a population of "null cells," whose significance is currently unknown. Further studies employing fluorocytometry and tumor-cell cytotoxicity can determine whether this population has natural killer function or represents a cell population with low-density Thy 1.

Our result that the anti-SEA antibody titers were unchanged despite the significant effects on B-cell populations, suggests that the primary antibody response is resistant to PG treatment. This result agrees with the findings of Quagliata et al,[26] who found that PGE could suppress cell-mediated immunity and depress B-cell numbers without affecting antibody titers. It should be added that antibody titer is only one measure of B-cell function. Further studies are

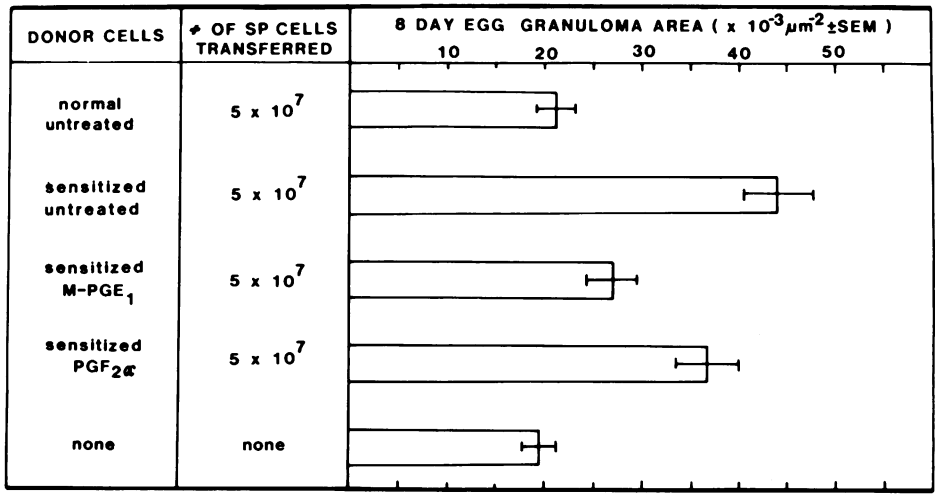

Figure 7—The effect of prostaglandin treatment on the induction of effector cells active in the adoptive transfer of the granulomatous response to schistosome eggs. Spleen cells were harvested from mice given daily PG treatment during 16 days of egg sensitization. Virgin recipients were each given 5 × 10^7 of the spleen cells, followed by 2000 schistosome eggs intravenously. Granulomas were measured 8 days later. *Bars* represent the mean granuloma area ± SEM, 5 mice per group.

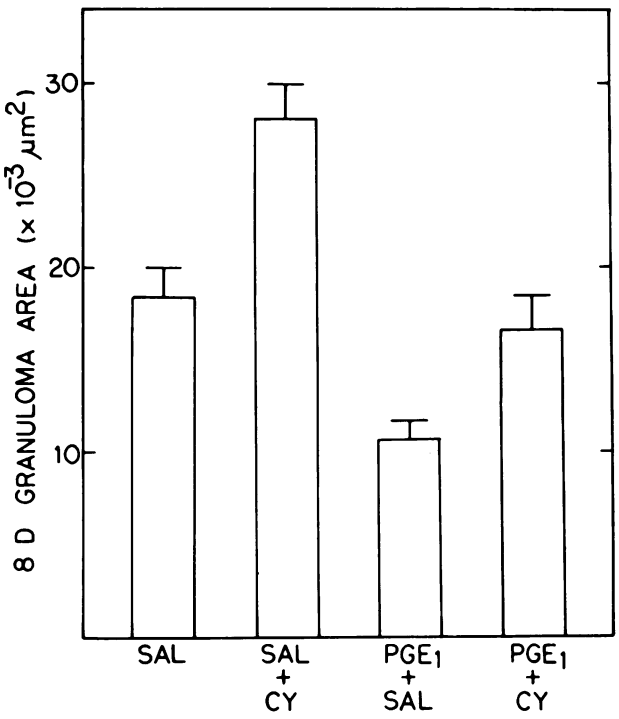

Figure 8—Effect of cyclophosphamide treatment on M-PGE_1-mediated suppression of schistosome egg granuloma formation. One day before egg injection the mice were given 15 mg/kg cyclophosphamide intraperitoneally. M-PGE_1 was administered daily, and granulomas were measured at 8 days. *Bars* represent the mean granuloma area ± SEM, 5 mice per group.

necessary to determine whether PGs alter immunoglobulin isotype, affinity, or B-cell memory. Based on their opposing effects on B-cell populations it would be predicted that M-PGE would depress and PGF would augment the secondary antibody response.

An initial analysis of the mechanism by which PG treatment influences granuloma formation revealed that PGF had no significant effect on the induction or elicitation of the granulomatous response when tested by adoptive cell transfer. The lack of expected amplification effects by PGF may be related to the time at which spleen cells were harvested, 16 days. At this point both granulomas and spleen cell populations had nearly normalized, possibly because of induced regulatory mechanisms. If helper cells are stimulated by PGF, there is a potential for feedback-induced regulation, as described by Eardley et al.[27] It has been shown that such a mechanism may operate in the modulation of granuloma formation.[7] In contrast to PGF, M-PGE suppressed both elicitation and induction of the response. It is known that PGE_1 has a suppressive effect on lymphokine production,[23] PMN degranulation,[28] and vasopermeability.[29] All of these events appear to take part in eliciting granuloma formation.[30] M-PGE can potentially have multiple effects also at the induction level. *In vitro* studies have demonstrated direct suppression of T-lymphocyte transformation,[21] an event that would be required for the generation of reactive T cells. More recently, it has been shown that PGs may inhibit the expression of I-region-associated antigens on macrophages.[31] This would tend to reduce the amount of antigen presented to T cells in a recognizable form, thus inhibiting the T-cell activation necessary for both induction and elicitation. In fact, we have recently demonstrated that macrophages from M-PGE-suppressed granulomas indeed have a reduced expression of I-region antigens (data not published).

We also tested the possibility that M-PGE may function via the selective recruitment of T_S cells. Cyclophosphamide treatment, which eliminates T_S cell precursors,[13] was able to partially reverse the suppressive effect of M-PGE. While this provided indirect evidence for the induction of some T_S activity, it could not account for all of the observed suppression. Thus, it appeared that M-PGE suppressed granuloma formation at multiple sites in the inflammatory process.

In conclusion, the present study lends further support to the theory that PGs may play a regulatory role in chronic inflammation. We have demonstrated that systemically administered PGs can promote or suppress hypersensitivity-type (*S mansoni* egg) granulomas but have little effect on nonspecific foreign-body responses. PGs apparently may set the tone of the immune response by modulating central lymphoid cell proliferation and local cellular infiltration. Certainly, macrophage populations within granulomas and lymphoid tissue may produce adequate PGs to act as endogenous immunoregulators, especially if activated by lymphokines.[32,33] Further analysis using cyclooxygenase inhibitors and measurement of PG production *in situ* will undoubtedly provide valuable information regarding this question. Finally, it is clear that systemically administered PGs can be used to manipulate a florid inflammatory response and may have eventual therapeutic benefit.

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