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# Decreased natural killer cell activity in atopic eczema

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**Summary.** We have studied NK cell activity in atopic and non-atopic subjects using a standard $^{51}Cr$-release assay and K562 target cells. In atopics (AT) with allergic rhinitis and/or asthma, NK cell activity was similar to that in non-atopic (N) subjects, whilst patients with severe atopic eczema (AE) had depressed NK cell activity compared to AT or N subjects. In addition, circulating T-cell numbers and Con A responsiveness was decreased in AE, although neither parameter was correlated with decreased NK cell activity. However, decreased NK cell activity in atopic eczema was positively correlated with decreased numbers of $Fc\gamma^+$ lymphocytes ($P=0{\cdot}01$) and decreased effector:target cell binding ($P=0{\cdot}05$), and negatively correlated with increased monocytes in AE ($P=0{\cdot}09$). AE NK cell activity was equally or more sensitive to the inhibitory effects of drugs such as dibutyryl cyclic AMP, prostaglandins (PG) $D_2$, $E_2$ and histamine. The relative percentage increase in NK cell activity by the interferon inducer poly I:C was similar in AE patients and controls.

The results suggest that reduced numbers of circulating NK cells and pre-NK cells account for the depressed level of NK cell activity in subjects with severe atopic eczema.

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## INTRODUCTION

Atopic excema (AE) is a chronic, pruritic inflammatory skin disorder often associated with a personal history of atopy, immunological abnormalities and increased susceptibility to cutaneous viral and bacterial infections (reviewed by Hanifin, 1981).

Immune abnormalities include elevated serum IgE levels (Hanifin, 1981) and decreased numbers of circulating T cells, particularly of the OKT8+/T gamma ($T\gamma$) subset (Schuster, 1980; Leung, Rhodes & Geha, 1981). *In vivo*, depressed cell-mediated immunity has been shown by hyporeactivity to common skin test antigens (McGeady & Buckley, 1975; Hanifin, 1981), and *in vitro*, depressed responses to T-cell mitogens and antigens are well documented (Thestrup-Pederson *et al.*, 1977; Elliott & Hanifin, 1979).

Natural killer (NK) activity in AE has been studied by several groups, with conflicting results. Leung *et al.* (1982) demonstrated increased cytotoxicity against fibroblasts in AE, but normal levels of cytotoxicity against K562. The majority of other reports found depressed NK cell activity against K562 in AE (Kusaimi & Trentin, 1982; Jensen *et al.*, 1984), and our results reported here support this view. It was suggested by Jensen *et al.* (1984) that depressed NK cell activity in AE may be due to decreased numbers of circulating NK cells. Our results confirm this view, and suggest that the $T\gamma$ cell population of NK cells—approximately 50% of the total (Herberman, 1981)—is decreased in AE patients.

## MATERIALS AND METHODS

*Patients*

Non-atopic and mild atopic laboratory personnel were used as control subjects in these experiments. Atopic subjects ($n=10$; mean age 31 yr; range 23–55 yr; 3F/7M) with seasonal or perennial allergic rhinitis ($n=7$) and/or allergic asthma ($n=3$, two using $\beta$-agonist therapy) were skin test positive to one or more common inhalant allergens. Non-atopics ($n=12$; mean age 30 yr; range 22–48 yr; 4F/8M) were skin test negative to common allergens and had no history of allergy.

Blood samples from severe AE in-patients ($n=14$; mean age 28 yr; range 16–54 yr; 5F/9M) were kindly collected by Drs Ian Coulson, Richard Rycroft and Mike Feher at St John's Hospital for Diseases of the Skin, London. All subjects had positive skin tests to common allergens, some having allergic rhinitis and/or asthma as well as severe AE involving the face, limbs and trunk. All AE subjects were using topical steroids at the time of study, and had an 'extent and severity' score factor $>10$ [i.e. severe disease as defined by Elliott & Hanifin (1979)].

All blood samples were collected into preservative-free heparin (10 U/ml) under sterile conditions.

*Preparation of effector and $^{51}Cr$-labelled target cells*

Peripheral blood mononuclear cells (PBMC) were obtained by Ficoll–Hypaque centrifugation as previously described (Hall *et al.*, 1983a). The effector cells were washed twice and resuspended at the appropriate concentration in RPMI-1640 supplemented with 10% FCS (complete medium).

K562, an erythroid cell line susceptible to human NK cell activity, was obtained from Dr M. F. Greaves (ICRF, London) and maintained in culture until required. The target cells ($5\times10^6$) were washed twice, pelleted and resuspended in 300 $\mu$l of $^{51}$Cr-labelled sodium chromate in 0·9% saline (Amersham International Ltd, Amersham, Bucks; specific activity 250–500 $\mu$Ci/$\mu$g chromium). After incubation at 37° for 1 hr, the labelled target cells were washed four times in BSS + 5% FCS before resuspending in RPMI + 10% FCS at $1\times10^5$/ml for use in the NK cell assay. Viability of both effector and labelled target cells was routinely 95% as judged by u.v. microscopy using acridine orange/ethidium bromide (AO/EB) staining.

*Assay for natural killer (NK) cell activity*

NK cell activity was assessed as previously described (Hall *et al.*, 1983a). Briefly, $^{51}$Cr-labelled K562 target cells ($1\times10^4$ in 0·1 ml) were incubated with or without drugs and an appropriate number of effector cells in a total volume of 0·2 ml in 96-well round-bottomed microtitre plates (Sterilin Ltd, Teddington, Middlesex). The plates were centrifuged for 5 min at 150 *g* and then incubated for 4 hr, when 0·1 ml of supernatant was removed for counting. The percentage specific cytotoxicity was calculated by the formula:

$$\frac{\text{supernatant c.p.m.} - \text{spontaneous release c.p.m.}}{\text{total c.p.m.} - \text{spontaneous release c.p.m.}} \times 100.$$

Spontaneous chromium release was between 8% and 15%, and was not significantly altered by any drugs used in these experiments. Lysis of labelled target cells with 5% decon produced total release of radiolabel. The variability among at least triplicate wells was less than 10%.

*Pharmacological mediators*

$PGD_2$ and $PGE_2$ (Sigma Chemical Co., Poole, Dorset) were dissolved in ethanol at $4\times10^{-3}$ M. Indomethacin (Sigma) was dissolved in ethanol at 4 mg/ml and stored diluted in RPMI at a concentration of 100 $\mu$g/ml. Ethanol at concentrations of 0·1% and 0·025% (control for PGs and indomethacin, respectively) did not affect NK cell activity (Hall *et al.*, 1983a).

Histamine dihydrochloride and $N^6$, 2′-dibutyryl adenosine 3, 5 cyclic monophosphate (DiBcAMP) (Sigma) were dissolved in RPMI-1640.

All drug solutions were stored at −20° until use. Drugs were added at the start and included throughout the 4-hr assay. None of the drugs at the highest concentrations used significantly altered the viability of effector or target cells as judged by AO/EB staining.

*Measurement of effector–target cell binding*

The method used was as previously described (Hall *et al.*, 1983a).

*Poly I:C induction of NK cells*

This was as described by Koren *et al.* (1981). PBMC in complete medium were incubated for 18 hr in round-bottomed microtitre plates ($1\times10$/well) in the presence or absence of indomethacin and/or 0·1 mg/ml of the interferon inducer poly I:C (Polyinosinate: Polycytidylate, Miles Laboratories, Elkhart, IN). After 18 hr incubation, the effector cells were washed twice and the NK assay performed as described above.

*Con A dose response*

PBMC from AE patients and N and AT control subjects were cultured with various concentrations of Con A (Sigma) as previously described (Hall, Hudspith & Brostoff, 1983b).

*Enumeration of monocytes, T lymphocytes and cells bearing Fc receptors for IgG*

Monocytes were enumerated by carbonyl iron ingestion (10 mg/ml) as described by Rumpold *et al.* (1979). Total T cells were measured by E-rosetting with neuraminidase-treated sheep red blood cells (N-SRBC) as previously described (Hall, Lydyard & Brostoff, 1982). Cells bearing Fc receptors for IgG are enumerated by rosetting with IgG-coated ox red blood cells, following the method of Campbell (1981). Washed ox RBC were sensitized with a subagglutinating concentration of rabbit IgG anti-ox RBC antibody (kindly provided by Dr P. M. Lydyard). Thirty $\mu$l of PBMC suspension ($1 \times 10^6$/ml in RPMI without FCS) were incubated with 30 $\mu$l of 1% IgG-coated ox RBC for 10 min at room temperature, pelleted by centrifugation at 150 ***g*** for 6 min, and incubated on ice for 15 min before counting rosettes using AO/EB staining and u.v. microsopy.

*Statistics*

Statistical significance was determined using the Students' paired and unpaired *t*-tests, and the rank correlation test, where appropriate.

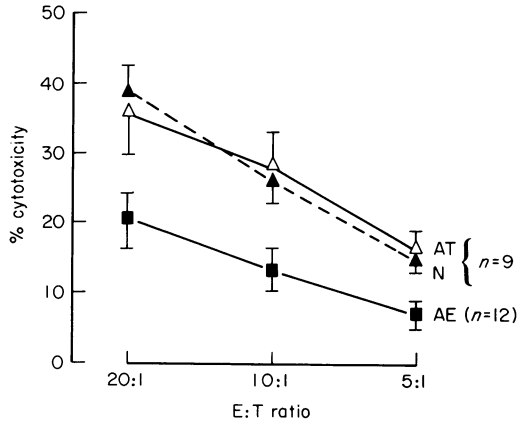


**Figure 1.** NK cell activity is depressed in the AE group when compared to that of the AT and N subjects at all E:T ratios used (each point represents the mean ± SE for each group of subjects). Lytic unit/$10^7$ cells (where 1 LU is the number of effector cells required to produce 30% lysis of target cells; Goto *et al.*, 1983): N = 73·0, AT = 70·4, AE = 36·5 LU/10 cells. Unpaired *t*-test: N *vs* AT, *P* = NS at all E:T ratios; AE *vs* N/AT, $P < 0{\cdot}001$ at all E:T ratios.

## RESULTS

### NK cell activity in atopics and non-atopics

NK cell activity measured at various E:T ratios was similar in atopics with rhinitis and/or asthma and non-atopics, but was significantly depressed in AE patients at all E:T ratios used (Fig. 1). The mean lytic activity of AE PBMC was approximately half that of the AT or N subjects (Fig. 1 legend). As shown in Fig. 2, whilst there is considerable overlap between the individual AE, AT or N subjects, only 3/12 AE patients have NK cell activity within AT or N means ± 2 SE. Similar results were obtained at ET = 5·1 and 20·1 (data not shown). Since the AT and N subjects showed no significant difference in NK cell activity, AT and N subjects were used as controls in all experiments.

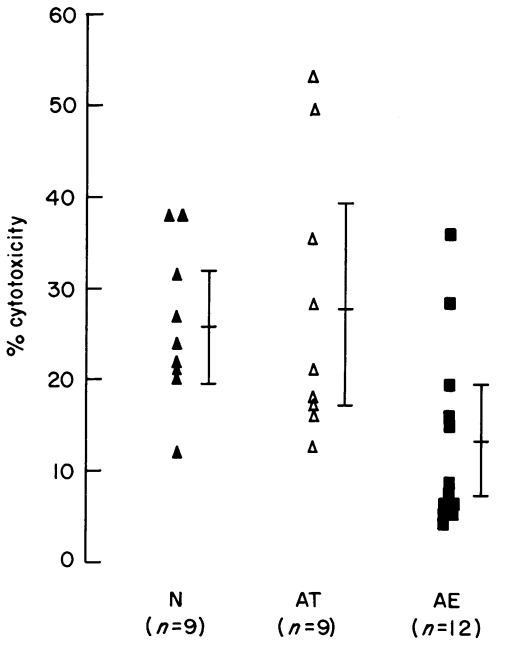


**Figure 2.** The NK cell activity of individual normal (N), mild atopic (AT) and severe AE patients (shown as group means in Fig. 1) is shown. The vertical bars represent the mean ± 2 SE for each group (E:T = 10:1). It is clear from the individual data that not all AE subjects have depressed NK cell activity, although this is the case for the majority of subjects (9/12). Unpaired *t*-test: N *vs* AT, *P* = NS; AE *vs* N/AT, $P < 0{\cdot}001$.

### The effect of drugs on NK cell activity in AE and control subjects

As shown in Fig. 3, inhibition of NK cell activity by DiBcAMP was similar in AE and control subjects; however, AE NK cell activity was significantly more inhibited than that of controls by $PGD_2$ over a wide dose range, and by $PGE_2$ and histamine used at maximal inhibitory non-toxic concentrations (Hall *et al.*, 1983a). Inhibition of NK cell activity by H-1 and H-2 receptor-specific agonists (2 and 4 methyl histamine, respectively) was similar in both AE and control subjects (data not shown), whilst indomethalin (1 μg/ml) had no significant effect in either group of subjects.

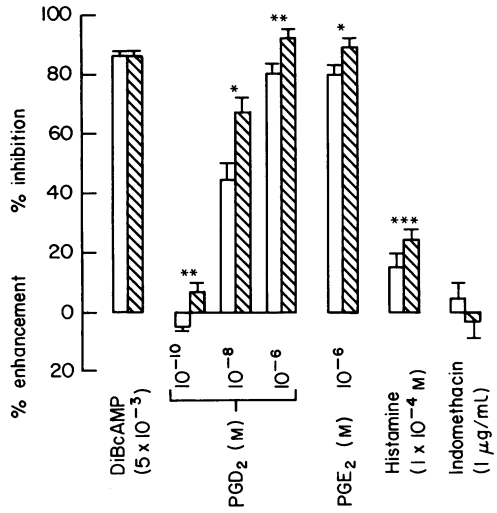


**Figure 3.** The effect of drugs on NK cell activity in AE and control subjects. Mean percentage cytotoxicity: E:T 10:1; control subjects = 31·5 ± 5·7% ($x \pm$SE, $n = 6$, open columns); AE patients = 17·2 ± 4·4% ($x \pm$SE, $n = 7$, hatched columns). AE *vs* controls: * $P = 0.002$; ** $P < 0.001$; *** $P = 0.05$.

### Correlation of NK cell activity with other immunological parameters

As shown in Table 1, there was a weak negative correlation between monocyte numbers and NK cell activity ($P = 0.09$), monocyte numbers being significantly higher in AE PBMC than controls ($P < 0.01$), whilst NK cell activity was significantly lower ($P < 0.001$). There was no correlation between NK cell activity and total T-cell numbers, although both parameters were decreased in AE compared to control subjects. Similarly, although the response of AE PBMC to Con A was significantly depressed (the majority of AE responses < control mean − 2 SE), particularly at suboptimal mitogen doses, depressed Con A responsiveness was not correlated with decreased NK cell activity at any Con A concentration used (data not shown).

However, there was a significant correlation between NK cell activity and FcγR + PBMC ($P < 0.01$, Table 1, Fig. 4). Both parameters were significantly decreased in AE compared to control subjects (FcγR + PBLs, $P < 0.001$ *vs* controls), as shown in Fig. 4. Since T-cell numbers, FcγR + PBMCs and NK cell activity are all decreased in AE patients, and the T-cell population includes approximately 50% of NK cells

**Table 1.** Correlation of NK cell activity with other immunological parameters in severe AE patients and control (AT and N) subjects

| | Normal/atopic controls (N/AT) ($n = 8$) | | Severe atopic eczema (AE) ($n = 8$) |
|---|---|---|---|
| Mean % cytotoxicity | 28·1 ± 5·3 | ($P < 0.001$ | 15·7 ± 4·4** |
| % monocytes | 5 ± 1 | ($r = -0.45$) ($P = 0.09$) | 8 ± 1* |
| % total T cells | 71·6 ± 1·7 | ($r = 0.04$) ($P > > 0.1$) | 62·0 ± 1·8* |
| % FcγR + PBLs† | 11 ± 1 | ($r = 0.63$) ($P = 0.01$) | 5 ± 1** |

Correlation coefficients were calculated by the Rank correlation test. Since the two groups of subjects were considered together ($n = 16$), then df = $n - 2$. Figures shown are mean ± SE for each subject group.

AE *vs* controls: * $P = 0.01$, ** $P < 0.001$.

† Individual data shown in Fig. 4.

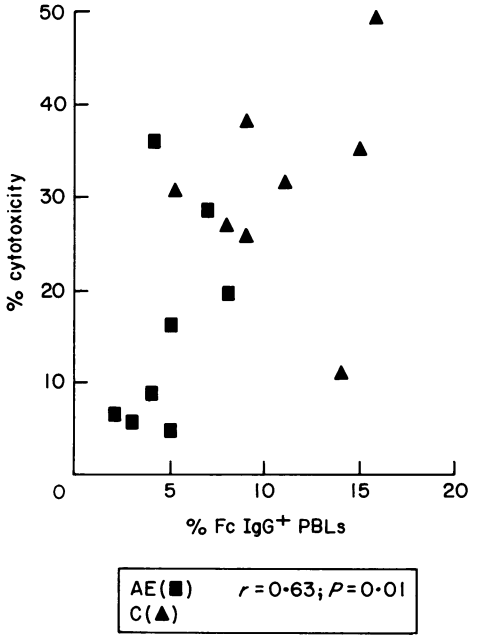


**Figure 4.** Correlation between FcγR+ PBL and NK cell activity: (■) points for AE patients; (▲) points for control subjects. Percentage cytotoxicity at E:T = 10:1 for all subjects. Correlation coefficient, $r = 0{\cdot}63$, $n = 16$ (df = 14 for two subject groups), $P = 0{\cdot}01$.

(Herberman, 1981), these results suggest that circulating NK cell numbers are depressed in AE and this may account for the depressed NK cell activity in AE PBMC. In support of this concept, effector:target cell binding (E:TCB) was significantly reduced in AE ($P < 0{\cdot}001$ *vs* control subjects) and was also significantly correlated with NK cell activity ($r = 0{\cdot}54$, $P = 0{\cdot}05$; Table 2).

**Table 2.** Effector:target cell binding in AE and control subjects

| Subjects | % cytotoxicity (E:T ± 10:1) | % E:T cell binding (E:T ± 1:1) |
|---|---|---|
| Controls ($n = 7$) | 27·9 ± 4·8* (Range: 15·9 – 52·8) | 9·5 ± 1·0* (Range: 6·0 – 13·2) |
| AE patients ($n = 7$) | 12·7 ± 3·4 (Range: 5·2 – 28·6) | 7·9 ± 0·6 (Range: 5·6 – 9·7) |

Figures shown are mean ± SE for each subject group.
* Controls *vs* AE patients: unpaired *t*-test, $P < 0{\cdot}001$.
Correlation between percentage cytotoxicity and percentage E:T cell binding: $r = 0{\cdot}54$, df = 12 ($n - 2$), $P = 0{\cdot}05$.

Sera from four AE patients with low NK cell activity (8·5 ± 2·4%) and sera from four controls with high NK cell activity (32·3 ± 3·6%) were found to contain similar, normal levels (< 50 μg/ml) of immune complexes. Direct addition of AE or control sera (final concentration = 10%) had no effect on the NK cell activity of two different control donors (data not shown). These results indicate that serum factors do not account for the reduced NK cell activity observed in AE patients.

**Table 3.** Induction of NK cell activity by poly I:C and the effect of indomethacin on cultured PBMC from severe AE and control subjects

| | % cytotoxicity on: | | % cytotoxicity after overnight incubation with: | | |
|---|---|---|---|---|---|
| | Day 0 | Day 1 | Indomethacin | Poly I:C | Indomethacin + poly I:C |
| Controls ($n = 4$) | 20·6 ± 1·9 (20% decrease overnight) | 16·5 ± 3·3 | 20·8 ± 1·7 (126 ± 8) | 22·9 ± 2·5 (139 ± 11) | 25·7 ± 2·8 (156 ± 11) |
| AE patients ($n = 4$) | 8·5 ± 2·5 (21% decrease overnight) | 6·7 ± 1·8 | 9·3 ± 1·0 (139 ± 11) | 9·1 ± 0·8 (136 ± 9 ) | 11·3 ± 1·8 (169 ± 10) |

NK cell activity is decreased to a similar extent in AE and control subjects after overnight incubation (Day 1). The presence of indomethacin or poly I:C abrogates this decrease but by different mechanisms, as shown by their additive effect. Figures in parentheses show the percentage increase in Day 1 control cytotoxicity (= 100%) when drugs were present during the overnight incubation period. E:T = 10:1; indomethacin = 1 μg/ml; poly (I:C = 0·1 mg/ml. All figures are mean ± SE.

**Effect of poly I:C and indomethacin on the induction of NK cell activity**

As shown in Table 3, NK cell activity of PBMC cultured in complete medium alone shows decreases by 20% in AE patients and controls after overnight incubation (16 hr). The original (Day 0) level of cytotoxicity is maintained on Day 1 if the cells are cultured in the presence of indomethacin or poly I:C alone, the enhancing effects of the two drugs being additive, indicating separate mechanisms of action. since depressed NK cell activity in AE is not increased to control levels by poly I:C, these results suggest that 'pre-NK' cell levels are decreased in AE patients, and that decreased 'mature' NK cell activity is not due to dysfunctional maturation of 'pre-NK' cells *in vivo*.

## DISCUSSION

The results of this study show that NK cell activity is depressed in the majority of patients with severe atopic exzema, but not in atopics with rhinitis and/or asthma, compared to healthy age- and sex-matched non-atopic subjects. The decreased NK cell activity in AE patients was seen at all E:T ratios used, the level of lytic activity in AE PBMC being approximately half that of atopic or non-atopic control subjects (Fig. 1). It is unlikely that the use of topical steroids by all the AE patients studied affected NK cell activity since, in a separate study, we have found elevated NK cell activity in patients with sarcoidosis, regardless of oral steroid therapy (2–30 mg predisone/day) (T.J. Hall, N. McI. Johnson, B. N. Hudspith and J. Brostoff, manuscript submitted). Thus, depressed NK cell activity in atopic eczema represents another immunological deficiency associated with this disease.

It is well known that circulating T cells and T-cell mitogen responses are decreased in AE (Leung *et al.*, 1981; Elliott & Hanifin, 1979), and these observations were confirmed in this study. However, whilst the decreased numbers of E-rosetting cells and depressed Con A responses did not correlate with NK cell activity in individual AE patients, there was a weak inverse correlation between monocyte numbers and NK cell activity in AE and control subjects (Table 1). The possibility that increased numbers of monocytes in AE patients were producing prostaglandins (i.e. $PGE_2$) which inhibited NK cell activity (Hall *et al.*, 1983a; Goto *et al.*, 1983) was ruled out by the observation that addition of indomethacin during the 4-hr cytotoxicity assay had no significant effect on NK cell activity in AE (or control) subjects (Fig. 3). However, it is interesting that in a similar study showing depressed NK cell activity in atopic eczema, Jensen *et al.* (1984) found that the addition of autologous monocytes to AE cytotoxicity assays reduced NK cell activity. They suggested that a suppressive *in vivo* interaction between NK cells and monocytes, or low numbers of circulating NK cells, may account for the observed decreased NK cell activity in AE. A significant positive correlation was found between lymphocytes bearing Fc receptors for IgG and NK cell activity, both parameters being decreased in AE patients (Fig. 4). Although not proven, it is tempting to suggest that it is cells of the T subset that are decreased in number in AE (as shown by Canonica *et al.*, 1979), since total T-cell numbers are also reduced in AE, and T cells form a substantial proportion (approximately 50%) of the NK cell population (Herberman, 1981). Decreased NK cell activity in AE does not appear to be due to increased levels of immune complexes or other serum factors in AE subjects, since serum from AE subjects with low NK cell activity did not inhibit the NK cell activity of normal subjects. In addition, the lytic activity of a given number of AE PBMC was approximately half that of control subjects, indicating the absence of roughly half the NK cell population.

Therefore, decreased numbers of circulating NK cells, rather than, for example, a defect in the lytic activity of normal numbers of NK cells in AE patients, might be expected. This view is supported by the observation that both NK cell activity and E:T cell binding are significantly reduced in AE patients compared to controls ($P < 0{\cdot}001$; Table 2). The relatively weak correlation between E:T cell binding and NK cell activity ($r = 0{\cdot}54$) is probably due to the fact that not all the 'effector' cells binding to target cells are mature NK cells, capable of binding and killing target cells (Timonen, Ortaldo & Herberman, 1981). In this respect, pre-NK cells are able to bind but not kill target cells, and although E:T cell binding was significantly lower in AE than controls ($P < 0{\cdot}001$), the actual difference was not great: $7{\cdot}9 \pm 0{\cdot}6\%$ in AE *vs* $9{\cdot}5 \pm 1{\cdot}0\%$ in controls (Table 2). A defect in the maturation of pre-NK cells to mature NK cells *in vivo* could explain the decreased NK cell activity in AE.

Poly I:C was therefore used to stimulate AE and control PBLs to produce interferon, which in turn induces/matures pre-NK cells *in vitro*. The percentage increase in NK cell activity induced by poly I:C was

similar in AE and control subjects, but the total NK cell activity was still much lower in the AE group (Table 3). Indeed, the absolute increase in NK cell activity induced by poly I:C was greater in control than AE subjects, suggesting that pre-NK cell numbers are also decreased in AE and/or that interferon production is decreased in AE. In this context, it is interesting that increased susceptibility to viral infections in AE subjects has been reported (reviewed by Hanifin, 1981). This may be the result of depressed mature NK cell activity and decreased induction of pre-NK cells by depressed levels of virally induced interferon in AE subjects.

It was also found that, after overnight incubation without indomethacin or poly I:C, Day 1 PBMC had reduced NK cell activity compared to Day 0 cells in both AE and control subjects. This was probably due to the production of NK cell inhibitory prostaglandins by monocytes present in the PBMC preparations, since indomethacin present during the overnight culture period maintained Day 0 NK cell activity at the same level on Day 1. The presence of poly I:C overnight also increased Day 1 NK cell activity, but by inducing pre-NK cells to become mature NK cells capable of killing target cells. The different modes of action of the two drugs were demonstrated by their additive enhancing effect on NK cell activity (Table 3), these results confirming those of Koren *et al.* (1981).

Since a proportion of NK cells are T cells, and autoacoids such as histamine and $PGE_2$ have been shown to modulate T-cell responses in various *in vitro* systems (reviewed by Melmon, Rocklin & Rosenkranz, 1981) and NK cell activity (Hall *et al.*, 1983a; Goto *et al.*, 1983), it was of interest to determine the effects of autacoids on NK cell activity in AE and control subjects.

Strannegard & Strannegard (1980) have previously shown that NK cells from atopic subjects are more inhibited by histamine than those of normals, and this result is partially confirmed here, in that NK cell activity in severe AE patients was significantly more inhibited by histamine ($P=0{\cdot}05$) than in control subjects. The inhibition produced by the H-1 and H-2 receptor-specific agonists was not significantly different in AE or control subjects (data not shown).

Inhibition of NK cell activity by DiBcAMP was similar in AE and control subjects, but NK cell activity in AE subjects was slightly, but significantly, more inhibited by $PGD_2$ and $PGE_2$. This is surprising, since we have shown that these prostaglandins act via cAMP (Hall *et al.*, 1983a, Hall & Brostoff, 1983). Therefore, these results suggest that NK cells from AE patients may express more autacoid receptors than those from control subjects, accounting for their increased sensitivity to autacoids.

Reduced numbers of circulating NK cells in severe AE patients could be the result of decreased production of NK cells or due to migration of these cells to the tissues. In this respect, Jensen *et al.* (1984) showed that reduced NK cell activity in AE was related to the severity and extent of skin disease. In addition, Leung *et al.* (1982) demonstrated increased NK cell-like activity against autologous and allogeneic skin fibroblasts by AE PBMC (although this group found that NK cell activity against K562 was similar in AE patients and controls).

Braathen *et al.* (1979) have shown a predominance of T cells in the mononuclear cell infiltrate of skin lesions in AE, and these results, taken together with the data presented here, suggest a role for NK cell-mediated skin damage in atopic eczema.

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