

Genetic control of eosinophilia in guinea pig strains inbred for high or low bronchial allergic reactivity

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Development of eosinophilia was studied in four strains of guinea pigs (gp), selectively bred for either high or low respiratory anaphylactic reactivity. One high-asthma strain (IMM/S 209) and one low-asthma strain (IMM/R 203) developed spontaneous high blood eosinophilia. The 2 other gp strains – one high-asthma strain (IMM/S 740) and one low-asthma strain (IMM/R 201-16) – maintained normal low levels of eosinophilic granulocytes (eos). The levels of eos in various tissues showed similar differences between the gp strains. Following immunization with ovalbumin/Al(OH)₃ the levels of blood eos increased significantly only in gp of strain 209. The blood eos levels in gp of all 4 strains decreased significantly following immunization with ovalbumin in Freund's complete adjuvant (FCA).

Clinical aspects

In humans, eosinophilia of varying degree is a usual correlate to allergic disorders. Circulatory eosinophilia has been described in human atopies to be particularly correlated to the late asthmatic reaction (LAR). In our animal model the development of blood eosinophilia is a genetic trait that depends on the gp strain but is not correlated with the immediate type asthmatic reactions (IAR).

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The eosinophilic granulocyte (eos) is in several respects a unique leukocyte. In humans and rodents eos normally accounts for 0–2% of all blood leukocytes ($0\text{--}0.1 \times 10^9/\text{l}$), but under certain pathological conditions an increase of up to 20% may occur (17, 24, 26).

In humans, circulatory hypereosinophilia is connected particularly with one of the following pathological conditions: 1) allergic disorders; 2) parasitic infestations; 3) certain neoplastic disorders and 4) an "idiopathic" syndrome of unknown etiology (2, 10). In animals, models for hypereosinophilia provoked by parasites or induced by special immunization programs have been described with evidence of genetic control of the eos response (18, 27, 28, 31, 33).

There is some evidence that the eos may have a role in regulating the immediate type allergic reaction by dampening mast cell activity (15). However, large amounts of eos that are attracted to areas of anaphylactic reactions may cause tissue injury. Eosinophilia may therefore be considered as a potential,

injurious hyperreaction like other forms of allergic response (5, 6, 7, 9, 13, 16, 20, 32, 34).

On this background it was considered of value to study the occurrence of eosinophilia in 4 inbred strains of gp genetically different with regard to their respiratory anaphylactic response.

The genetic homogeneity obtained within each of these gp-strains has already been documented (23, 29). In the present study the background levels of eos of the 4 strains were estimated. We investigated the incidence of eos in blood, bone marrow, spleen and trachea in unsensitized gp of the 4 strains and the difference between them in developing eosinophilia following immunization with ovalbumin (oa) $\pm$ adjuvants.

Material and methods

Experimental animals

The study was performed with 4 strains of gp selectively bred (brother $\times$ sister for about 30 genera-

tions) for either high (IMM/S 209 and 740) or low (IMM/R 201-16 and 203) responsiveness to inhalation of aerosolized aqueous ovalbumin as measured by the respiratory anaphylaxis induced (21). Animals of both sexes were used.

The gp were bred and held in conventional animal rooms, the strains 740 and 203 together in one room and 209 and 201-16 each in separate rooms. The colonies of the 4 gp-strains were always isolated from other experimental animals, and they were fed the same commercial pellets free of poultry products.

Leukocyte counts

Direct method: Counts of total leukocytes and eos were performed in the morning to avoid diurnal variations in blood levels (3, 4). 20 μ l blood samples were collected from a bleeding ear vein with heparinized micropipettes (Vitrex 20 NK) and were diluted 1:15 in Türk's solution and eosin solution, respectively. The eosin solution consisted of eosin 0.1%, sodium citrate 0.3%, acetone 15% in deionized water. After 15 min the cells were counted in a Bürker-Türk hemocytometer.

Indirect method: Blood smears for differential counts were fixed and stained with May-Grünvald and Giemsa stains, and a minimum of 200 cells were counted. The levels of eos were expressed as percentages of all leukocytes counted. In the gp, the total leukocyte count is usually $8-10 \times 10^9/l$ blood.

From the differential count and the total leukocyte count an estimation of the number of eos/l blood was calculated.

For convenience, strains and individual gp with blood eos levels $<0.5 \times 10^9/l$ will be designated in the following as normal eos, $\geq 0.5 \times 10^9/l$ as high-eos, and $\geq 1.5 \times 10^9/l$ as hyper-eos.

Tissue analysis

Gp were killed and immediately thereafter were bled by a throat cut and dissected. Smears were prepared from the bifurcation of the trachea, from a cross-section of the upper half of the spleen and from aspirated marrow of the right femur. All smears were immediately fixed and stained with May-Grünvald and Giemsa stains. For each tissue preparation 800–1000 nucleated cells were counted and the percentages of eos estimated. In the bone marrow and in the spleen both mature and immature eos were counted.

Immunization

The gp were immunized by intraperitoneal injections on day 0 and day 7 of 10 μ g oa either 1) in 1 ml phosphate-buffered saline (PBS), or 2) adsorbed on

1 mg $Al(OH)_3$ (alhydrogel, Superfos, DK) in 1 ml PBS, or 3) in 0.5 ml PBS incorporated in 0.5 ml Freund's complete adjuvant (FCA), containing 0.5 mg/ml *Mycobacterium tuberculosis* (Statens Seruminstitut, Copenhagen).

Statistics

Since eos counts of the animals were not distributed normally, differences were analysed by the non-parametric Wilcoxon matched-pairs test or the Mann-Whitney U-test, according to the material.

The number of normal and high eosinophilic animals in different groups was compared by the chi-square test (χ^2 -test). Pearson's correlation coefficient and the parameter of regression line were calculated.

Results

The occurrence of eosinophilia was compared in different age groups of 4 strains of gp, 2 high-asthma (IMM/S 209 and 740) and 2 low-asthma (IMM/R 201-16 and 203) strains.

Determination of eos in peripheral blood

In 181 cases we compared the results of blood eos counts obtained with the direct and indirect methods (see "Material and methods"). Fig. 1 shows excellent agreement between the two kinds of measurements. This is consistent with results presented by other investigators (19).

In the material presented in this paper we did not notice any marked alterations in the differential

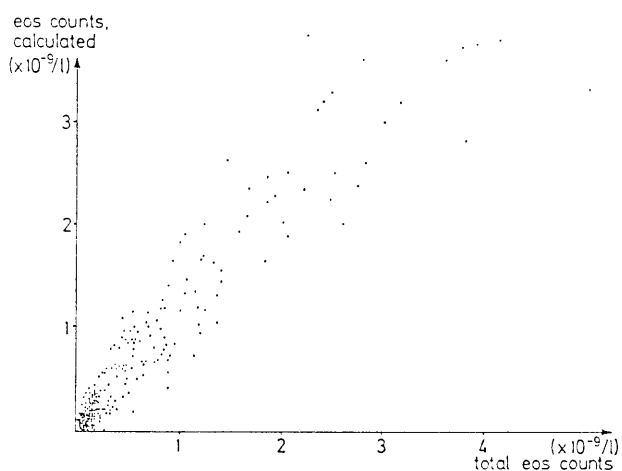


Fig. 1. Eosinophilic granule counts in blood estimated by the direct (abscissa) and the indirect (ordinate) methods (see "Material and methods"). Comparison of counts from 181 guinea pigs. Correlation between the methods was significant ($p = 0.001$), $y = 0.85x + 16$; $r = 0.99$.

counts of other leukocytes linked with the occurrence of high eosinophilia.

In the following, the results are given in absolute eos counts measured directly.

Levels of eos in the blood of unimmunized guinea pigs

Three-month-old guinea pigs. The levels of eos in the blood were estimated for a number of sexually mature (2.5–3.5 months old) gp.

Two of the strains, the high-asthma strain 209 and the low-asthma strain 203, showed a significantly higher proportion of animals with high eos than the 2 other strains, the high-asthma strain 740 and the low-asthma strain 201-16, which had normal low counts of eos in almost all animals (Fig. 2).

The χ^2 -test showed a significant difference in the proportion of animals with eosinophilia between the 2 high-asthma strains ($p < 0.001$) and between the 2 low-asthma strains ($p < 0.01$), while the differences in proportion of eosinophilic animals between strain 209 and strain 203 and between strain 740 and strain 201-16 were not significant.

6–12-month-old guinea pigs. Fig. 2 also shows the levels of eos in the blood of the older (6–12 months old) gp of the same 4 strains. In strains 209 and 203 almost all animals were hyper-eos. In strain 740 a small but significant ($p < 0.001$) increase of the proportion of high-eos gp was found while there was no significant difference in strain 201-16.

The significant differences in the proportion of high eosinophilic animals between the 2 high-asthma

strains ($p < 0.001$) and between the 2 low-asthma strains ($p < 0.001$) are maintained in the older gp. The differences in the proportion of high eosinophilic animals between strains 209 and 203 and between strains 740 and 201-16 were not significant either in the older gp.

Onset of blood eosinophilia in gp strains 209 and 203

We investigated the development of eosinophilia in the 2 high-eos strains 209 and 203 by following the levels of eos in the blood in young gp from each of the strains for a period of 2 months. The absolute eos counts in each of the animals were estimated for the first time when the animals were taken from their mothers at 4 weeks old. The results show normal levels of eos in the blood of all the 4-week-old gp ($< 0.2 \times 10^9/l$).

Cases of a rather sudden rise in the blood eos levels began at the age of 8–10 weeks. However, a pronounced dispersion in the levels of blood eos was found as a characteristic trait in gp of these 2 strains, though the median blood eos count at this age was still $< 0.5 \times 10^9/l$. At the age of 6–12 months 203 and 209 gp mainly are hyper-eos.

Levels of eos in tissue of unimmunized gp

The percentages of eos in the bone marrow, spleen and trachea were investigated in 3-month and 6–12-month-old gp of each of the strains (Fig. 3). In gp of the 2 strains with high eos levels in blood these percentages were significantly increased at the age of 6–12 months. In the 2 low-eos strains there was no such tendency, as can be seen from Fig. 3. It can also be seen that a good correlation exists in all strains, between the level of eos in peripheral blood and the proportion of eos in the spleen. None of the gp of the low-eos strains (740, 201-16) had more than 3% eosinophilic cells in their spleens, whereas the proportion increased steeply in all the gp of the high-eos 209 strain, one even reaching 28%.

The percentage of eos in the bone marrow was about the same in gp of all 4 strains at 3 months of age. However, only gp of the high-eos strains (209, 203) had a considerably higher proportion of eos in their bone marrow with increasing age.

With regard to the eos levels of trachea, it is evident from Fig. 3 that in many cases there is no correlation with the blood eos counts. The percentages of eos in trachea smears in 3-month-old gp of the strains 740 and 201-16 with low-eos in the blood, were very high compared with percentages of eos in the blood and significantly higher than the corresponding values found in the 2 strains 209 and 203 with high-eos in the blood. We have no explanation for that. The number of eos could possibly be influenced by che-

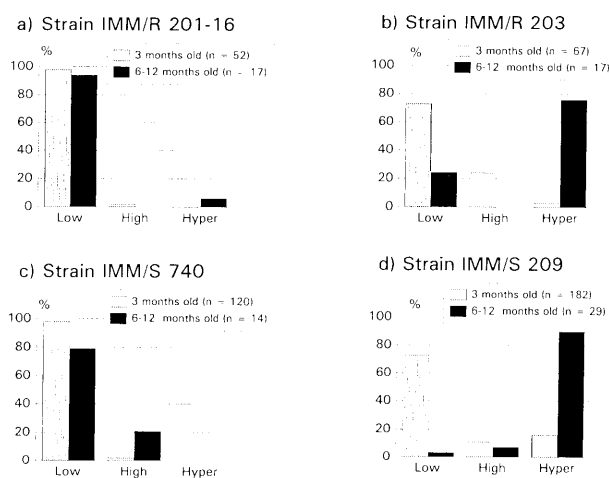


Fig. 2. The distribution of low- ($< 0.5 \times 10^9/l$), high- ($\geq 0.5 \times 10^9/l$) and hyper-eos ($\geq 1.5 \times 10^9/l$) in peripheral blood in 3 and 6–12-month-old guinea pigs of a) strain IMM/R 201-16, b) strain IMM/R 203, c) strain IMM/S 740 and d) strain IMM/S 209.

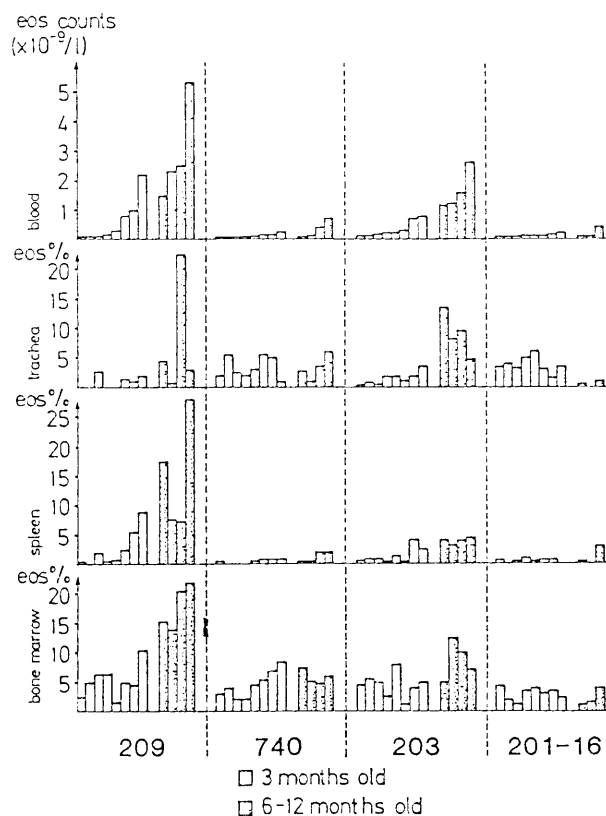


Fig. 3. Blood and tissue eosinophilic granulocytes in 3 and 6–12-month-old guinea pigs of the strains IMM/S 209, 740 and IMM/R 201-16, 203. Eosinophilic granulocytes were counted in blood (total count), and trachea, spleen and bone marrow (% of all cells). Columns with the same abscissa show results from the same guinea pig.

motaxis caused by accidental inflammatory processes.

Levels of eos in the blood of gp following different immunizations

The levels of blood eos in gp of the 4 strains were investigated immediately before the first and the second injection of 10 μ g oa in $\text{Al}(\text{OH})_3$ and again 1, 2 and 3 weeks later. As seen from Fig. 4 the levels of eos were unchanged during this period in gp of the strains 201-16, 203 and 740, while a significant increase was noted in gp of strain 209. Due to these results we restricted the measurements of blood eos to days 0 and 28 of immunization.

As controls, we treated some of the gp with PBS, $\text{Al}(\text{OH})_3$ or FCA without addition of oa (Figs. 5, 6, 7).

Immunization with oa dissolved in PBS. Eos levels of the immunized gp of strains 209 and 740 were not significantly different from those of unimmunized gp (Wilcoxon's test) (Fig. 5).

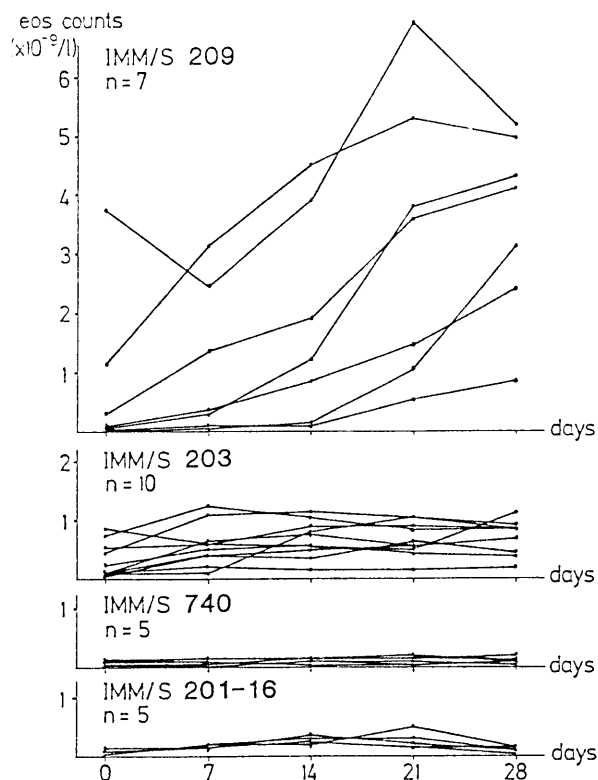


Fig. 4. Influence of immunization on blood eos counts. 3-month-old guinea pigs of the strains IMM/S 209, 740 and IMM/R 201-16, 203 were injected intraperitoneally with 10 μ g oa + $\text{Al}(\text{OH})_3$ on days 0 and 7, eos counts were measured on days 0, 7, 14, 21 and 28. n = numbers of guinea pigs.

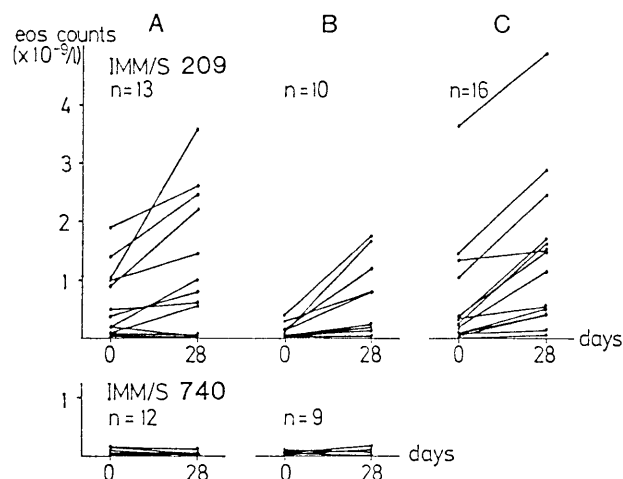


Fig. 5. Influence of immunization on blood eos counts. 3-month-old guinea pigs of the strains IMM/S 209 and 740 were injected intraperitoneally on days 0 and 7 with 10 μ g oa in PBS (A), with PBS alone (B), or remained untreated (C). Eos counts were measured on days 0 and 28. n = numbers of guinea pigs.

Immunization with oa adsorbed on $\text{Al}(\text{OH})_3$. Compared with the findings in control animals, the immunization caused a significant increase in blood eos counts

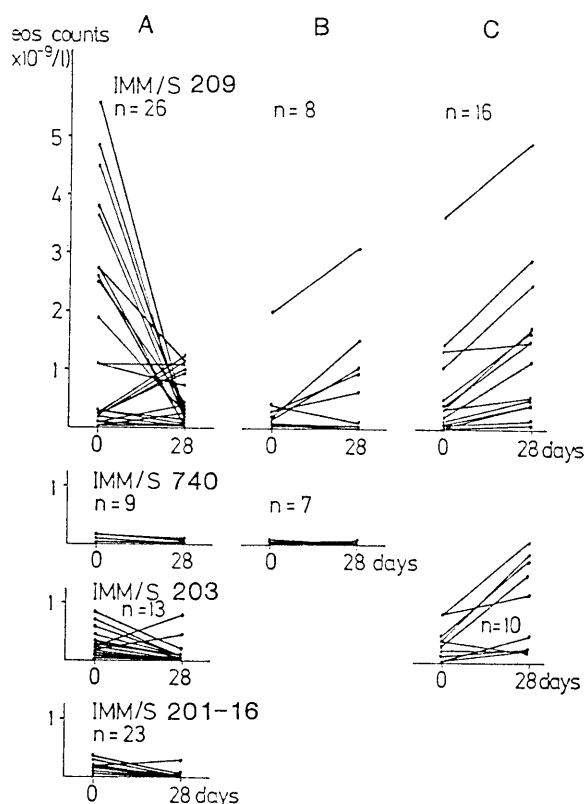


Fig. 6. Influence of immunization on blood eos counts. 3-month-old guinea pigs of the strains IMM/S 209, 740 and IMM/R 201-16, 203 were injected intraperitoneally on days 0 and 7 with $10 \mu\text{g}$ oa + $\text{Al}(\text{OH})_3$ (A), with $\text{Al}(\text{OH})_3$ alone (B), or remained untreated (C). Eos counts were measured on days 0 and 28. n = numbers of guinea pigs.

only in gp of the high-eos and high-asthma strain 209 (Mann-Whitney U-test) (Fig. 6).

Immunization with oa incorporated in FCA. The levels of blood eos decreased significantly in all gp following the immunizations with oa in FCA ($p < 0.005$) for all 4 strains, (Wilcoxon's matched-pairs test), though the alterations for strain 209 were particularly striking.

Immunization with FCA alone was carried out in gp of strains 209 and 740. Gp of strain 209 responded with a slight increase in the levels of blood eos (Fig. 7).

Discussion

A possible correlation between susceptibility to respiratory anaphylaxis and development of eosinophilia was studied in 4 strains of guinea pigs, with high (IMM/S 209, 740) and low (IMM/R 201-16, 203) susceptibility to respiratory anaphylaxis, respectively (21).

The experience from humans (17, 24) and mice (28) concerning background levels of eos in the blood

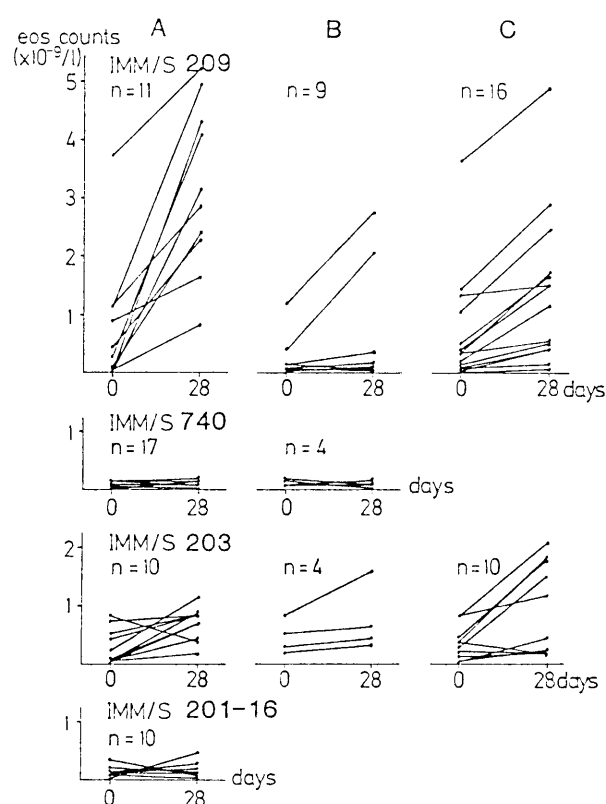


Fig. 7. Influence of immunization on blood eos counts. 3-month-old guinea pigs of the strains IMM/S 209, 740 and IMM/R 201-16, 203 were injected intraperitoneally on days 0 and 7 with $10 \mu\text{g}$ oa + FCA (A), with FCA alone (B), or remained untreated (C). Eos counts were measured on days 0 and 28. n = numbers of guinea pigs.

is fairly comparable with our previous, limited observations on randomly bred gp, which showed that all animals of the 3-month age group had blood eos levels $< 0.4 \times 10^9/\text{l}$ (unpublished). On this basis we decided to consider counts of $< 0.5 \times 10^9/\text{l}$ as "normal" and counts of $\geq 0.5 \times 10^9/\text{l}$ as high-eos in gp. Counts of $\geq 1.5 \times 10^9/\text{l}$ may be considered as hypereosinophilia, as accepted for humans.

Levels of eos in the blood of unimmunized guinea pigs

Two of the gp strains, one high-asthma strain and one low-asthma strain, showed particularly high eos levels with increasing age; nearly all gp of the 2 other strains remained normal low-eos responders.

With increasing age (6–12 months), all the gp of IMM/S 209 and nearly all gp of IMM/R 203 are found to be hyper-eos. Even at the age of 2–3 years, many being hypereosinophilic during months and years, no obvious symptoms of disease have been observed. This is contrary to the situation in the human hypereosinophilic syndrome (2, 10).

The possibility that an exogenous eosinophilia-stimulating factor is responsible for the high levels of

eos was investigated. Thus we examined gp of the 4 strains for parasites of the skin, lungs and intestines. No parasites or gross pathological alterations were found. Likewise, examinations for microbial infections gave negative results. The possibility of a latent virus infection has not been excluded, but viral eosinophilia has never been described.

It should also be emphasized, that the conditions in the animal house were identical and of the same high standard for all 4 strains, so that the differences in the development of eosinophilia can hardly be due to differences in the exposure to external agents (inhaling dust from beddings and food pellets or eating food pellets with antigenic constituents).

Percentages of eos in bone marrow, spleen and trachea of unimmunized gp of the 4 strains

The proportional eos counts in bone marrow, spleen and trachea increased markedly with age only in gp of the 2 strains which develop blood eosinophilia (Fig. 3).

We observed that the percentages of eos in the spleen of the 2 low-eos strains were much lower than those found in the strains with high eos in the blood. In strains of mice with high eos response the spleen was shown, besides the bone marrow, to be an important site of eos production (18).

Finally, we observed, in the 2 high blood eos strains, 209 and 203, a relatively lower eos percentage in the bone marrow and the trachea than in the low blood eos strains, 740 and 201-16. However, several investigators have reported that peripheral blood eos responses do not necessarily reflect events in tissues (12, 27).

This is also in accordance with the findings of Geczy et al. (8) who demonstrated that gp with a genetically determined resistance to a certain parasite had more circulating eos than gp with susceptibility to the same parasite, while the levels of eos in the bone marrow were higher in the susceptible than in the resistant gp.

Eosinophilic response to immunization

Fig. 6 shows that low-eos to high-eos transition could be accelerated by systemic immunization with $\text{oa}/\text{Al}(\text{OH})_3$ in the IMM/S-strain 209 only. The development of eosinophilia in the low asthma strain 203 may explain a disposition in this strain for ocular hypersensitivity following immunization (22). It is surprising that the IMM/S strain 740 with an asthma-response comparable to that of strain 209, has a stringent control of eosinophilia which can not be released by $\text{Al}(\text{OH})_3$ immunization. However, several investigators correlate the high incidence of blood eos with the occurrence of the late asthmatic

reaction (LAR) (1, 6, 14, 25, 32, 34). After allergen exposure, eos in the blood increased in correlation with the bronchial hyperreactivity only in patients with LAR but not in patients with immediate-type asthmatic reactions (IAR) (32).

Accordingly, the results of our investigations indicate a difference between the 2 high-asthma strains related to the high-eos and low-eos response. The high-asthma and high-eos strain 209 is supposed to have a dual anaphylactic response, including both IAR and LAR, while the high-asthma and normal low-eos strain 740 only develops the IAR.

Immunization with $\text{oa} + \text{FCA}$ led to significant decrease in blood eos levels in all 4 strains of gp. This has earlier been demonstrated and explained by the appearance of an eosinophil-directed chemotactic inhibitory factor, spontaneously produced in FCA-treated gp (11, 30). As mentioned above, 209 gp show no spontaneous reversion from high-eos to low-eos, but this can be induced by immunization with $\text{oa} + \text{FCA}$ (Fig. 7). This may be of particular interest for the study of possible therapeutic approaches to the human idiopathic hypereosinophilic syndrome. Although it should be stressed that we do not know whether human and guinea pig hypereosinophilia develop by parallel cytologic mechanisms, it must be of some value to have an animal model that enables studies of the possible mechanism of pathogenesis, therapeutic approaches and the elucidation of a genetic basis. This latter aspect will be the subject of a subsequent paper (35).

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