STUDIES IN EXPERIMENTAL EOSINOPHILIA

III. THE INDUCTION OF PERITONEAL EOSINOPHILIA BY THE PASSIVE TRANSFER OF SERUM ANTIBODY

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Experimental eosinophilia is readily induced by repeated injections of foreign protein; a single injection results in little, if any, response (1–6). Although it seems evident that some intermediate changes must occur in the host which prepare it to develop substantial eosinophilia in response to subsequent injections of foreign protein, no details are known regarding either the sequence of reactions or the reactants involved in this response. Previous studies (7) have shown that peritoneal eosinophilia may be induced by the transfer of tissues, tissue extracts or serum. Such transfers were most often successful when both the donor and recipient had each been prepared by a series of injections with a different non-cross-reacting protein, and when the transferred material was accompanied by the protein which had been used to prepare the donor. These experiments suggested that antibody might mediate eosinophilia. This paper presents evidence that the active material which can be passively transferred does have the properties of antibody and that the active material in vivo is an immune complex.

MATERIALS AND METHODS

Assay for eosinophilotactic activity. To test whether a particular material could attract eosinophils, the material was introduced into the peritoneal cavity of suitably prepared guinea pigs and the resultant exudate was examined 24 hr later. The method of preparing recipient guinea pigs by repeated injections of foreign protein and the method of quantitating peritoneal eosinophilia by peritoneal lavage have been described previously (8). Since not all guinea pigs receiving foreign protein develop eosinophilia, the negative or low responders were discarded. Only guinea pigs which had demonstrated the capacity to mobilize eosinophils rapidly were used: suitable responders were those which accumulated at least 15 million eosinophils in the peritoneal cavity within 24 hr after an injection of the protein with which they had been prepared. The test materials were injected at least 1 week after the last preparatory injection, at a time when less than 5 million eosinophils were entering the peritoneal cavity during a 24 hr period.

Antigens. Bovine serum albumin (BSA), crystallized, was obtained from Pentex Inc., Kanakee, Illinois. Toxoids were obtained from the Commonwealth of Massachusetts Department of Public Health Antitoxin and Vaccine Laboratory, Boston, Massachusetts. The diphtheria toxoid (Lot PT-110) contained 362Lf/ml and 2080Lf/mg N. The tetanus toxoid (Lot LP-194) contained 1250Lf/ml and 1600Lf/mg N. The egg albumin was obtained from Nutritional Biochemicals Corp., Cleveland, Ohio. The stock hemocyanin solution, prepared as described previously (8), contained 11.4mg N and 112μg Cu/ml. All solutions were made in 0.85% NaCl.

Guinea pigs which were prepared by toxoid injections were injected weekly with 1Lf of either diphtheria or tetanus toxoid. The eosinophil response to toxoid was similar to that described previously for hemocyanin, horse serum and human serum albumin (Table I). Egg albumin resulted in a high incidence of anaphylaxis (after 5 months, only 10 of 48 guinea pigs survived),
TABLE I

<table>
<thead>
<tr>
<th>Protein Injected</th>
<th>Number of Months of Weekly Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1Lf diphtheria toxoid</td>
<td>10</td>
</tr>
<tr>
<td>1Lf tetanus toxoid</td>
<td>10</td>
</tr>
<tr>
<td>1 cc 1% egg albumin</td>
<td>18</td>
</tr>
</tbody>
</table>

* Average total number of peritoneal eosinophils in millions 24 hr after the last preparatory injection.

and a low degree of eosinophilia; it, therefore, was not useful for this study.

**Antiserum.** Anti-BSA rabbit serum was obtained through the kindness of Dr. Sidney Leskowitz, who had injected rabbits by three routes with a BSA solution containing 7.5 mg/ml in complete Freund's adjuvant. They were given 0.1 ml in each toe pad, 0.2 ml intramuscularly in each hind quarter, and 0.4 ml intraperitoneally. Serum was collected 4 months afterwards.

**Antihemocyanin guinea pig serum.** Guinea pigs were inoculated in the nape of the neck with 10 mg hemocyanin in complete Freund's adjuvant, and were bled 6 to 8 weeks later. When the antiserum diffused against the antigen in agar gel, four precipitin bands were detected. Previous studies (9) have indicated that hemocyanin dissociates at pH 6.8 into four ultracentrifugally distinct components, and it has been suggested (10) that the multiple zones of flocculation observed with antisera may be related to the existence of hemocyanin as a species of multiple molecular sizes. By sequential addition of hemocyanin and removal of the precipitates which formed (after 1 hr at 37°C and overnight at 4°C), an antibody preparation could be obtained which gave only one band in gel diffusion against antigen. This preparation was used in these studies.

**Antihemocyanin rabbit serum.** Rabbits were injected in each toe pad with 2.5 mg hemocyanin in complete Freund's adjuvant, and intravenously with 10 mg hemocyanin for 8 successive weeks thereafter. The rabbits were bled 7 days after the last injection. As with the guinea pig antiserum, four bands were noted in gel diffusion against antigen, and the three minor bands were absorbed before the serum was used.

All sera were pooled from several animals and were stored at 4°C with 1:10,000 Merthiolate as preservative. The sera were used over a period of 2 years.

**Titration of antisera.** Two methods were used. The first was the standard method of analyzing washed precipitates prepared in slight antigen excess. Supernatants were checked by ring test and by diffusion in 1% agar gel (1 cm²-wells, 3.5 mm deep, 6.5 cm apart, incubated for 7 days at 37°C); the latter was the more sensitive method. The second method, used with the antihemocyanin sera, exploited the special properties of hemocyanin (high molecular weight and copper content): it consisted of adding a large excess of hemocyanin, centrifuging in a Spinco Model L ultracentrifuge for 2 hr at 37,000 rpm, and analyzing the pellet. Copper was determined spectrophotometrically as the cupric bis cyclohexanoneoxalylidihydrazone (11) (copper was released from the pellet by 3N HCl). From the copper value and the Cu/N ratio (1:100) of hemocyanin, the nitrogen in the pellet which was attributable to hemocyanin was calculated and subtracted from the total Kjeldahl nitrogen, which was determined by the Markham modification of the micro-Kjeldahl technique (12).

The titer of the rabbit anti-BSA was 700 μg antibody N/ml, of the guinea pig antihemocyanin, 450 μg antibody N/ml, and of the rabbit antihemocyanin, 350 μg antibody N/ml.

**Antigen-antibody mixtures.** Antigen was added to antiserum when mixtures in antibody excess were prepared; the reverse order of addition was used when preparing mixtures in antigen excess or in equivalence. The mixture, in a volume of 1 to 2 ml, was incubated for 30 min at 37°C before injection. In preparing precipitates or in absorbing sera, the mixtures, in addition, were stored at 4°C for 1 week. The precipitates were packed by centrifugation and washed twice with 0.85% NaCl. Completeness of absorption was determined by analyzing the supernatant using the gel diffusion method described above.

**RESULTS**

In previous experiments (7), eosinophilic activity was detected in the serum of guinea pigs when the serum was transferred from one guinea pig into the peritoneal cavity of another. In the
TABLE II

Peritoneal eosinophilia induced in guinea pigs by BSA-anti-BSA complexes

<table>
<thead>
<tr>
<th>Type of Complex</th>
<th>BSA-N (µg)</th>
<th>Anti-BSA RS (µg Ab N)</th>
<th>Millions of Peritoneal Eosinophils in Recipients 24 hr after Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive responses</td>
</tr>
<tr>
<td>8X Ag excess</td>
<td>240</td>
<td>150</td>
<td>8</td>
</tr>
<tr>
<td>4X Ag excess</td>
<td>240</td>
<td>300</td>
<td>11</td>
</tr>
<tr>
<td>2X Ag excess</td>
<td>40</td>
<td>100</td>
<td>15, 14, 12, 10, 10, 8, 8, 7, 7</td>
</tr>
<tr>
<td>2X Ag excess</td>
<td>120</td>
<td>300</td>
<td>14, 9, 8</td>
</tr>
<tr>
<td>Equivalence</td>
<td>60</td>
<td>300</td>
<td>15</td>
</tr>
<tr>
<td>Equivalence</td>
<td>245</td>
<td>1220</td>
<td>15</td>
</tr>
<tr>
<td>2X Ab excess</td>
<td>30</td>
<td>300</td>
<td>127, 47, 42, 40, 38, 29, 18, 17, 12, 11</td>
</tr>
<tr>
<td>4X Ab excess</td>
<td>15</td>
<td>300</td>
<td>19, 18, 17, 17, 16, 8</td>
</tr>
<tr>
<td>8X Ab excess</td>
<td>7.5</td>
<td>300</td>
<td>25, 11, 11</td>
</tr>
<tr>
<td>Reverse passive transfer</td>
<td>30</td>
<td>300</td>
<td>18, 9</td>
</tr>
<tr>
<td>Washed precipitates: 2X Ab excess</td>
<td>30</td>
<td>300</td>
<td>38, 30, 27, 19, 14, 11, 10, 10, 9, 8</td>
</tr>
<tr>
<td>Absorbed antiserum: 2X Ab excess</td>
<td>30</td>
<td>(300)</td>
<td>10</td>
</tr>
</tbody>
</table>

* BSA = bovine serum albumin; RS = rabbit serum; Ag = antigen; Ab = antibody. Recipients were prepared by 4 months of weekly injections of hemocyanin.

experiments reported in this paper, pooled sera with known antibody titer were used, and samples, variously treated and combined, were injected into the recipients. Various mixtures of antigen with antiserum did not elicit eosinophilia when given to normal animals, but were effective when given to animals which had been prepared by repeated injections of a non-cross-reacting foreign protein.

Activity of BSA-anti BSA Complexes. Neither BSA nor anti-BSA elicited eosinophilia. However, various combinations of BSA and anti-BSA rabbit serum were effective (Table II). In the region of antigen excess, as little as 100 µg antibody N (the lowest amount tried) was effective, and the ratio of antibody N to antigen N could be varied between 2- and 8-fold antigen excess without apparent effect on activity. The magnitude of the responses was fairly uniform with the different doses used, whereas the frequency with which eosinophilia was induced was high: 14 out of 19 trials. Two equivalence mixtures also resulted in eosinophilia.

Similar results were obtained when mixtures prepared in antibody excess were used. However the magnitude of the responses were, in general, substantially higher than those obtained in the zones of equivalence and of antigen excess.

It was possible to effect a reverse passive transfer, the antigen being administered 24 hr before the antibody. In spite of the fact that the peritoneal cavity was washed out just prior to the injection of antibody, enough antigen had apparently remained from the previous day's injection to react with the antibody.

When the antibody was precipitated out of the serum by specific antigen, the activity was found in the washed precipitates, the absorbed antiserum having virtually no activity.

Activity of hemocyanin-guinea pig anti-hemocyanin complexes. Hemocyanin complexed with guinea pig antibody induced eosinophilia in 24 of 26 recipients (Table III). Activity was detected with as little as 225 µg, but not with 135 µg antibody N; however, too few animals were used to establish the minimum effective dose of antibody. In this system, too, the activity was associated with washed precipitates and was
TABLE III

Peritoneal eosinophilia induced in guinea pigs by Hcy–guinea pig anti-Hcy complexes

<table>
<thead>
<tr>
<th>Type of Complex</th>
<th>Hcy-N (µg)</th>
<th>Anti-Hcy GpS (µg Ab N)</th>
<th>Millions of Peritoneal Eosinophils in Recipients 24 hr after Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>3X Ag excess</td>
<td>900</td>
<td>450</td>
<td>34, 26, 24, 23, 20, 19, 18, 16, 16, 15, 14, 14, 13, 13, 11, 11, 10, 10, 10, 10, 10, 8, 7, 6, 5</td>
</tr>
<tr>
<td>2X Ag excess</td>
<td>600</td>
<td>450</td>
<td>36, 12, 11, 10, 8, 7</td>
</tr>
<tr>
<td>2X Ag excess</td>
<td>450</td>
<td>340</td>
<td>6, 5, 4</td>
</tr>
<tr>
<td>2X Ag excess</td>
<td>300</td>
<td>225</td>
<td>5, 2</td>
</tr>
<tr>
<td>2X Ag excess</td>
<td>180</td>
<td>135</td>
<td>5, 3, 1</td>
</tr>
<tr>
<td>2X Ag excess</td>
<td>60</td>
<td>45</td>
<td>4, 3, 2, 2</td>
</tr>
<tr>
<td>Ag given 1 day after Ab: 3X Ag excess</td>
<td>900</td>
<td>450</td>
<td>17, 12, 11, 10, 8, 7</td>
</tr>
<tr>
<td>Washed precipitates: equivalence</td>
<td>1200</td>
<td>1800</td>
<td>27, 21, 16, 12</td>
</tr>
<tr>
<td>Washed precipitates: 1.3X Ab excess</td>
<td>556</td>
<td>1100</td>
<td>3</td>
</tr>
<tr>
<td>Absorbed antiserum: 3X Ag excess</td>
<td>900 (450)</td>
<td>15, 10</td>
<td>6, 6, 5, 5, 5, 5, 4, 4, 3, 3, 2, 2, 2, 2, 1, 1, 1, 0</td>
</tr>
</tbody>
</table>

* Hcy = hemocyanin; GpS = guinea pig serum; Ag = antigen; Ab = antibody. Recipients were prepared by 4 months of weekly injections of horse serum.

TABLE IV

Peritoneal eosinophilia induced in guinea pigs by Hcy–rabbit anti-Hcy complexes

<table>
<thead>
<tr>
<th>Type of Complex</th>
<th>Hcy-N (µg)</th>
<th>Anti-Hcy RS (µg Ab N)</th>
<th>Millions of Peritoneal Eosinophils in Recipients 24 hr after Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>3X Ag excess</td>
<td>325</td>
<td>350</td>
<td>28, 12, 10, 9, 8, 7</td>
</tr>
<tr>
<td>Absorbed antiserum: 3X Ag excess</td>
<td>325</td>
<td>350</td>
<td>4</td>
</tr>
</tbody>
</table>

* Hcy = hemocyanin; RS = rabbit serum; Ag = antigen; Ab = antibody. Recipients were prepared by 4 months of weekly injections of either tetanus or diphtheria toxoid.

virtually absent when the antibody was removed by absorption with specific antigen. Four trials in which the antigen was administered 24 hr after the antibody failed to induce eosinophilia.

A high degree of activity was also detected in a second pool of guinea pig antibody (titer not determined); injection of 1 ml of this antiserum with 285 µg hemocyanin N resulted in 43, 25, 25 and 3 million peritoneal eosinophils, respectively.

Activity of hemocyanin–rabbit anti-hemocyanin complexes. In a third system, hemocyanin and rabbit antibody, eosinophil-inducing activity which was present in whole serum was abolished when the antibody was absorbed (Table IV).

**DISCUSSION**

Eosinophilia was induced passively in guinea pigs by mixtures of antigen and antiserum (Tables II, III and IV). Both heterologous, as well as homologous antiserum proved effective. Successful passive transfer required the presence of antibody: the activity disappeared completely or almost completely upon absorption of the antisera with specific antigen, whereas the specific immune precipitates were active. Al-
though the association of eosinophilia with immune (hypersensitive) events has been known for a long time, and the probable participation of antibody has been surmised, this paper presents the first direct evidence for the participation of antibody, and, moreover, suggests that the biologically active stimulus to eosinophilia is an immune complex.

In active sensitization experiments, the induction of eosinophilia parallels in every respect the appearance of serum antibody. Thus, neither antibody synthesis nor eosinophilia is ordinarily found in normal animals. Both result from exposure to foreign protein, although first exposure results in little, if any, response. A lag of several weeks must occur after the first stimulus. Significant responses occur after the second and subsequent exposures. Repeated stimuli result in increasing response. The response is highly specific, occurring only when the same or very similar protein is used.

Although both eosinophilia and antibody synthesis occur under similar circumstances, it has not been clear hitherto whether the two are causally related. In a series of papers on eosinophilia in mice, Speirs has presented data which he believes supports the theory that the eosinophil is an essential mediator in the process of antibody synthesis. This view rests, for the major part, on the following observations: a) Following antigenic challenge, eosinophils always arrived in the peritoneal cavity before antibody appeared in the circulation (13); b) Doses of cortisone and x-irradiation which prevented the accumulation of eosinophils also inhibited antibody production (14, 15). c) Passively administered antigen-antibody complexes did not induce eosinophilia (16, 17). Speirs concluded, therefore, that the ability of an animal to form antibody is dependent on the number of eosinophils responding to the antigen (13).

However, an alternative deduction seems equally tenable, namely, that the ability of an animal to mobilize eosinophils is dependent on its ability to synthesize the necessary antibody. a) Although the data of Speirs (13, 17) show that peritoneal eosinophils appear 1 to 2 days before newly-formed, precipitable, circulating antibody, the eosinophils actually may have appeared after antibody, since the precipitin test is not the most sensitive detector of antibody. Using the accelerated elimination of I18Z-labeled antigen from the blood as an early manifestation of the immune response, other workers have shown (18, 19) that antibody appears several days before it is detectable by the precipitin method. b) Although x-irradiation and cortisone do inhibit both eosinophilia and antibody synthesis in parallel fashion, the data do not show whether either of the two events mediates the other, and, if so, which is primary and which secondary. If antibody were required for eosinophilia to occur, any agent which inhibited antibody synthesis would thereby inhibit eosinophilia. c) Although eosinophilia did not occur when mice were given immune complexes passively, both blood (20) and tissue (7) eosinophilia can be passively induced.

The reasons for the failure to induce eosinophilia in mice by passive transfer are not evident. However, the experiments differed in several respects from ours. In mice, the response was measured mainly on the 4th day, at which time the concentration of eosinophils reaches peak value (16, 17). In guinea pigs, challenge of actively sensitized animals leads to substantial, if not peak, eosinophilia within 24 hr. In our experiments with transfer of whole tissue or of immune complexes, a response was likewise detected within 24 hr. This time was used to minimize the possible complication of new antibody synthesis or other time-consuming processes. Perhaps more important is the fact that in the experiments of Speirs and of Samter et al. (20), the recipients were normal animals, whereas in our experiments the animals were hyperimmune to a non-cross-reacting protein. Although passive transfer succeeds in normal recipients (7, 20), greater success attends the use of sensitized recipients. In summary, there does not appear to be any convincing evidence that eosinophilia antecedes antibody production.

The evidence, rather, appears to support the view that eosinophilia occurs as a consequence of the union of antigen with antibody. When antigen is injected into a hyperimmune animal, the antigen combines with previously-formed antibody, and the resulting immune complexes circulate in the blood during the period immediately preceding the appearance of newly-formed antibody (21, 22). It is in this period that eosinophilia commences in both guinea pigs and mice. In the guinea pig, eosinophilia develops within 24 hr of the challenging injection. In mice,
if the challenging injection is given at a time when there is a significant level of antibody in the serum, the antibody titer falls substantially during the ensuing 2 days (presumably largely as a result of complexing with antigen), while, coincidentally, eosinophils begin to accumulate at the site of challenge (17). The demonstration that passively acquired immune complexes also provoke eosinophilia within 24 hr strongly suggests that they are the mediator in the actively sensitized animal. However, it seems likely that factors other than antibody are also important, since great variation of response persists despite the administration of measured uniform doses of complex. One requirement may be a bone marrow which is primed to produce large numbers of eosinophils at an accelerated rate. Since no information is available to suggest whether the complex itself is eosinophilotactic or whether it triggers a more complex event, it is conceivable that another limiting factor may be some intermediate which is generated by antigen-antibody union. That such an intermediate may exist is suggested by the finding that various kinds of antigen-antibody mixtures can attract eosinophils.

The present experiments offer some insight into the occurrence of eosinophilia in a variety of seemingly unrelated pathologic phenomena. Blood and tissue eosinophilia occur commonly during wheal reactions (23), anaphylaxis (2), asthma (24), hay fever (25), parasitic infections (26), periarteritis nodosa (27), and Hodgkin's disease (28). It has also been reported in rheumatic fever (29), the Arthus phenomenon (30), various chronic skin diseases (6, 31), chronic peptic ulcer (4), neoplastic disease (4, 6, 32), and following many infectious diseases (33-35). The very diversity of these conditions has discouraged suggestions that there might be a common underlying mechanism which leads to eosinophilia. The results of the present experiments suggest the possibility of such a mechanism, namely, that immune complexes may be a common denominator. In almost all of the phenomena cited above, the host has been repeatedly exposed to foreign materials, and the resultant immune responses could have led to the formation of immune complexes. The parts of the organism which most commonly are found to be infiltrated with eosinophils are those most exposed to the outside world: the alimentary tract, the respiratory tract and the skin. When the barriers which normally prevent most foreign material from entering the host are destroyed, eosinophils accumulate at the site of the lesion; e.g., chronic peptic ulcer, chronic skin disease (4), and neoplasms of the gastrointestinal tract. Since even normal intestinal lining allows the passage of small amounts of undigested food (36), the same (immune) mechanism may account for the presence of eosinophils in normal dog intestine (37) and their disappearance from both the intestine and the thoracic duct lymph (38) when dogs are placed on a low protein diet. Similarly, transient blood eosinophilia develops in normal infants when a new protein is introduced into their diet (39). During early convalescence from acute infectious disease, both eosinophils and antibody appear. The demonstrated prognostic usefulness of the eosinophil count (40) may well be related to its reflection of the presence of antibody, which when coupled to antigen, can attract this cell. In diseases of unknown origin, such as Hodgkin's disease, in which eosinophilia is a common occurrence, it may be fruitful to consider that the eosinophil may be the index of an immune event and that such an event may be involved in the pathogenesis of the disease. Although an immune mechanism has not been established for the eosinophilia which is noted in the conditions cited above, and indeed non-immune mechanisms are sometimes involved (7, 41), most eosinophilia occurs under circumstances which predispose to an immune response, and the present experiments establish that eosinophilia can be one of the consequences of a particular phase of the immune response.

Immune complexes have been implicated in the initiation of various hypersensitive states (21, 22, 42-44). The problem concerning the role of antibody in serum sickness (45) has been resolved recently with the recognition that the disease is provoked by immune complexes and that lesions occur during the period when complexes are detectable in the blood (46). During the serum sickness which follows a single dose of

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4 The extent, rather than the type of lesion appears to determine the degree of eosinophilia (31).

5 The greatest incidence of eosinophilia in neoplasms seems to occur in lesions of the gastrointestinal tract, particularly when there is ulceration. Next most frequent are lesions of the lung and skin (4, 6, 32).
foreign serum in humans, eosinophilia is uncommon (49-52). When an eosinophil response is noted, it occurs during early convalescence, at which time both antigen and antibody are detectable in the circulation (53). Large doses of serum are more prone to result in serum sickness than small ones (54), and it is thought that the antigen(s) persists long enough to act, as it were, as the challenging dose. Both serum sickness and eosinophilia result more commonly from repeated, rather than single, doses of foreign serum (49, 50, 52).

Although eosinophilia is a common finding in many diseases of hypersensitivity, its inconsistent occurrence makes its clinical significance problematic. Since the details of man’s exposure to antigens are usually unknown and highly variable, the time when immune complexes appear is correspondingly variable. Therefore, if immune complexes play a role in human eosinophilia, one should not be surprised to discover that eosinophilia is found only during certain stages of a disease. It is common knowledge that repeated eosinophil counts are more likely to reveal eosinophilia than occasional ones. It is also important to look for eosinophils at tissue sites and not, as is the common clinical practice, exclusively in the blood (7). Immune complexes are rapidly cleared from the blood (55); they probably persist longer in tissue sites, where lesions occur and where the eosinophils may be found more regularly and for longer periods (4, 8).

Although this paper offers no direct observations concerning the possible functions of eosinophils, their functions are likely to unfold as the events which follow the formation of immune complexes are studied.

Acknowledgment. The technical assistance of Carolyn Chesebrough is gratefully acknowledged.

SUMMARY

Eosinophilia was induced in the peritoneal cavity of guinea pigs by the passive transfer of antigen-antibody complexes. These results were obtained in three systems: bovine serum albumin and rabbit antibody, hemocyanin and either guinea pig or rabbit antibody. Complexes were effective whether prepared in antigen excess, antibody excess or at equivalence. Activity disappeared from the antisera when the antibody was absorbed by the specific antigen. These experiments identify the active factor in serum as antibody and provide direct evidence that eosinophilia is induced by immune complexes. The conclusion is reached that eosinophilia is one of the consequences of antigen-antibody union and that eosinophils do not mediate the production of antibody. The possibility that a common mechanism underlies the eosinophilia which is noted in diverse pathologic states is discussed.

REFERENCES


