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SOME ASPECTS ON THE PROBLEM OF EOSINOPHILIA¹

*Errors of Method, Diurnal Rhythm and
Eosinophilia in Allergy*

By

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Introduction.

The eosinophile cell was first described in 1846 by Jones. In 1878 Ehrlich named it and characterized it as a morphological entity. Where the eosinophils are formed was long debated. Nowadays it must be considered established that the eosinophils have differentiated from the premyelocytes in the bone marrow. All forms of eosinophilia, be it in blood or tissues, are preceded by eosinophilia in the bone marrow.

During the century or so since the discovery of the eosinophile granulocyte, it has been the subject of considerable attention which is documented in a vast literature. Thus, as long ago as 1914, Schwarz listed more than 3000 publications about these eosinophile cells.

Various figures are given in the literature for the number of eosinophils per cubic millimetre of normal blood, for example:

	<i>Range</i>	<i>Average</i>
Kämmerer (1956)	100-200	—
Heilmeyer (1951)	40-600	175
Fisher (1951)	10-400	200
Samter (1949)	30-250	—

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Today it is generally considered that up to some 400 eosinophile cells per cubic millimetre of blood must be accepted as normal.

Much speculation has been devoted to the function of the eosinophile cells, but as yet the question seems inconclusively answered. To these cells, and especially to the eosinophile granules, *Schlecht* (1912) attributed a defensive function against toxins liberated by decomposing foreign proteins. *Kämmerer* (1956) postulated that the granules are bearers of special enzymes for aiding the destruction of foreign proteins. Many authors, notably *Vercauteren* (1953), have studied the chemical composition of the granules and particularly of their enzymes.

Esselier & coworkers (1954), and *Stobbe* (1956) endowed the eosinophile cells with a phagocytic function. The latter has been associated with the transporting activity of these cells reported by *Esselier* (1954), who stated that the eosinophils transport foreign proteins to the reticuloendothelial system. In addition he took up the problem whether this system is capable of regulating the production of eosinophils.

Whereas *Parrot & Gabe* (1947) maintained that the eosinophils are particularly rich in histamine, *Code & McDonald* (1937) expressed the view that their main function is to bring about an enzymatic decomposition of histamine.

In *Vaughn's* (1953) opinion the essential function of the eosinophils is to take up and inactivate the histamine liberated by the antigen-antibody reaction. He assumed that the eosinophile cells serve as transporters of histamine, as he found that the eosinophilia resulting from administration of an antigen fails to develop when an antihistamine is given. *Samter* (1949) obtained the opposite result.

Randolph & Rackeman (1941) and *Rose* (1941) were unable to discover any correlation between the histamine content of and the number of eosinophils in the blood. *Dalton* (1949) regarded the eosinophile cells as the source of the histamine liberated in an allergic reaction. The increased vascular permeability induced by the histamine thus made available would

therefore enable more neutralizing antibodies to reach the shock organ.

All experimental evidence and hypotheses notwithstanding, the fact remains that the problem of the role of the eosinophile leukocytes in the metabolism of histamine is yet unsolved. Nevertheless it is generally believed that one of the functions of the eosinophils is to protect the organism against allergens entering therein. One reason for this view is that administration of an allergen is capable of stimulating the bone marrow to accelerated eosinophilopoiesis.

Eosinophilia of greater or lesser degree occurs in a variety of diseases. These may be classified as follows (cf. *Kämmerer*, 1956):

1. Conditions due to allergy. This group includes bronchial asthma, various forms of rhinitis and conjunctivitis, urticaria, Quincke's edema, gastrointestinal allergies, and certain skin disorders.

2. Conditions where allergy or anaphylaxis may be involved. This group comprises eosinophilous helminthiasis and post-infective states attended by eosinophilia. Other possibilities are eosinophilous neoplasms, some types of collagenosis, Löffler's syndrome, and, perhaps, Basedow's disease (exophthalmic goitre).

3. Conditions probably or definitely of non-allergic nature. To this group belong eosinophilous leukemias and possibly also the so-called familial or constitutional type of eosinophilia.

The allergic disorders are the largest group of diseases in which the organism responds by a reaction in the eosinophile cellular system.

Ehrlich (1879) already demonstrated that in anaphylactic states the blood and tissues frequently contain an excess of eosinophile cells. In the period 1910–1912, *Schlecht* published a series of experimental papers on eosinophilia and anaphylaxis. Having found that anaphylactic shock regularly gave rise to a markedly elevated blood eosinophil count in guinea pigs, he designated these cells as "Zellen der Allergie und Anaphylaxie".

Schlecht (1942) maintained, furthermore, that every form of eosinophilia should be interpreted as a sign of an allergic constitution. A failure to find allergy in many patients with eosinophilia might merely be due to our having imperfect diagnostic tools. Rather than a sign of an allergic constitution, *Feinberg* (1946) considered eosinophilia an active allergic reaction.

Own investigations.

The experiments to be described were mainly designed to shed light on three problems:

A. What *errors of method* affect estimations of eosinophil leukocytes derived from, respectively, differential counts and direct determinations in a counting chamber? Is there any difference between determinations made simultaneously on the same sample with both methods?

B. What is the *diurnal rhythm* of the eosinophile leukocytes?

C. What is the *incidence* of eosinophilia in various allergic disorders?

Dahlberg's (1948) methods and nomenclature have been adopted for the statistical analysis, and all the calculations and estimations except those under A₅ were done by the same person.

A. ERRORS OF METHOD

Introduction.

Eosinophile cells do not readily lend themselves to counting. The techniques commonly adopted are either differential counting of white blood corpuscles after May-Grünwald-Giemsa staining or counting-chamber determination after selective staining. Differential counting is the method usually adopted. For a normal eosinophil count thus obtained the standard error given by *Brandt* (1926) is 16.4 per cent while *Björn-Hansen's* is as high as 44 per cent. *Barnett* (1933) characterized differential counting as one of the most unreliable quantitative procedures in all medical science and maintained that the unavoidable errors would be very considerable even

when at least 400 cells are counted. *Rud* (1947) expressed the opinion that to be relatively reliable a differential count must involve not less than 1000 cells.

Many consider determinations made in a counting chamber more reliable. The preferred staining techniques seem to be *Dunger's* (1942) eosine method and *Randolph's* (1949) phloxine method. In Scandinavia the procedure of choice is that described by *Rud* (1947), where counting is done in a Fuchs-Rosenthal counting-chamber after staining with Magdala red.

The margins of error for these methods of estimating eosinophilia may be rather wide dependent on the principles applied. Hence the data given in the literature also vary within wide limits.

Experimental.

With the object of assessing the error of method for various modes of estimating eosinophilia the following experiments were made:

1. Capillary blood was drawn simultaneously from two fingertips of the same person. The blood was stained with Magdala red according to *Rud* (1947) and the number of eosinophils was determined by counting particles in a Fuchs-Rosenthal chamber having a capacity of 6.4 mm^3 . For each 100's of eosinophils, 64 particles were counted in the chamber.
2. Capillary blood from one subject was smeared on a slide and stained according to May-Grünwald-Giemsa. 1600 white blood corpuscles in the smear were counted and classified differentially, separate percentages being recorded for consecutive 100's counted.
3. Capillary blood was drawn simultaneously from two fingertips of the same person. The white blood corpuscles were estimated by *Boström's* (1954) method, the number of particles being counted in a Bürker chamber. For each 100's of white corpuscles, one particle was counted in the chamber.
4. Capillary blood samples from 16 subjects were smeared on slides and stained according to May-Grünwald-Giemsa.

800 white blood corpuscles in each smear were counted and classified differentially, separate percentages being recorded for consecutive 100's counted.

At the same time white blood corpuscles were counted after staining by *Boström's* method. The value recorded for each patient was the mean of two duplicate determinations.

By so doing the degree of eosinophilia could readily be evaluated.

Simultaneously the eosinophil count was determined by Rud's technique (see 1. above). The value recorded for each patient was the mean of two duplicate determinations.

With the aid of this analysis the degree of eosinophilia could also be simply determined and consequently it became possible to compare the results of differential counting with those based on counting-chamber determinations.

5. The proportion of eosinophils in blood samples from 524 persons was determined both by the differential counting method (i.e. by counting the number of white blood corpuscles and calculating the percentage of eosinophils in smears) and by the counting chamber technique.

Results.

1. The difference between duplicate eosinophil determinations is presented in Table 1. It will be seen that no correlation appeared between the number of particles counted and the magnitude of the difference.

TABLE 1¹

Difference between duplicate eosinophil determinations by Rud's method¹.

n	M	$\epsilon(M)$
21	10	± 1.7

2. In this experiment the percentages of the various types of white blood corpuscles varied as set out in Table 2.

¹ In this and following Tables, n = number of observations; M = mean; $\epsilon(M)$ = standard error of the mean. (cf. Dahlberg, 1948).

TABLE 2

Differential blood count after May-Grünewald-Giemsa staining.

Type of white blood corpuscles	n	M	$\varepsilon(M)$
Band forms	16	1	—
Segmental forms	16	52	± 1.0
Eosinophils	16	14	± 0.4
Basophils	16	0	—
Lymphocytes	16	29	± 0.3
Monocytes	16	4	± 0.4

3. The difference between two duplicate determinations of white blood corpuscles appears in Table 3. It will be seen that no correlation existed between the number of particles counted and the magnitude of the difference.

TABLE 3

Difference between duplicate white blood corpuscle counts by Boström's method.

n	M	$\varepsilon(M)$
21	333	± 22.5

4. The results of this experiment will be found in Table 4.

The table discloses that eosinophil determinations based on differential counting yielded varying results depending on the total number of cells counted. Clearly, however, the difference in most cases became rather insignificant when 400 cells were counted, and counting of more than 400 cells was of no value.

Differential analyses and counting-chamber determinations gave rise to dissimilar eosinophil counts. In cases 1, 2, 7, 9, 12 and 16 the deviation was negative (i.e. the number of eosinophils determined by the differential counting technique was lower than that obtained by the counting-chamber method). These negative deviations are not particularly large and might well be due to unavoidable laboratory errors. In all the remaining cases the deviation was positive and occasionally quite appreciable. The order of magnitude of these deviations indicates that laboratory errors had definitely not been responsible. Accordingly the two methods would seem to lead to eosinophil

counts which systematically deviate from one another. We were able to verify this observation by examining a larger series of test subjects, as revealed by experiment 5 below.

TABLE 4

Number of eosinophils calculated on the basis of white blood corpuscle determinations and differential counts and number of eosinophils according to the counting-chamber technique.

To facilitate comparisons the results of the former method are given after 100, 200, 300, 400, 500, 600, 700, and 800 consecutive cells were counted.

No. of patient	Differential counting								Counting chamber method
	100	200	300	400	500	600	700	800	
1	200	260	252	272	264	252	260	264	295
2	426	479	568	568	582	575	596	589	703
3	410	387	378	400	376	355	369	364	285
4	315	315	315	284	252	284	268	252	163
5	1160	1269	1305	1269	1247	1218	1211	1240	1085
6	1481	1551	1502	1551	1568	1586	1551	1523	1288
7	104	104	88	104	125	130	114	114	180
8	80	56	64	80	64	48	56	38	40
9	360	330	318	330	324	330	348	360	363
10	560	494	679	700	742	742	728	714	508
11	1240	1318	1318	1380	1386	1442	1504	1550	903
12	88	88	88	114	123	132	106	106	148
13	1122	1122	1122	1122	1183	1132	1122	1132	653
14	413	413	454	454	466	481	509	495	280
15	473	216	260	260	260	260	242	268	333
16	20	15	18	15	16	17	16	15	50

5. The results of eosinophil determinations in 524 subjects by differential counting and the counting-chamber method are given in Table 5.

TABLE 5

Estimations of eosinophil leukocytes by differential counting and by the counting-chamber technique.

Method	n	M	$\epsilon(M)$
Differential counting	524	424	± 18.3
Counting-chamber	524	315	± 15.2

The table discloses that a systematic difference exists between eosinophil determinations based on differential counting and the counting-chamber method respectively. This difference showed no correlation with the total number of particles counted (regression constant $r = -0.10 \pm 0.001$).

Discussion.

Determinations of eosinophils according to counting-chamber analysis, of white blood corpuscles and the method of differential counting in smears all suffer from errors of method which are not particularly serious. We venture to suggest that, provided due care is taken and technical errors as far as possible are eliminated, trained staff should be quite capable of performing these determinations without incurring errors of the magnitude reported by previous authors.

Why there should be a systematic difference between the results of the counting-chamber method and the differential count technique is obscure. Considering that technical and personal systematic errors were eliminated, the remaining possibility would seem to be that May-Grünwald-Giemsa staining and Rud's Magdala red staining affect the blood corpuscles in different ways. Accordingly the eosinophile blood cells may be chemically heterogeneous which in turn causes them to show dissimilar staining properties. As a matter of fact direct microscopical examination already reveals that all eosinophils are not morphologically identical in appearance, some of them for example being vacuolated.

In deciding upon the method to be used for determining the eosinophil count one must therefore keep in mind the possibility that partly not the same particles may be counted by the two methods. Essentially, therefore, the same procedure should be adopted for serial determinations of blood eosinophilia on different occasions.

Direct comparisons between estimations based on different methods will lead to misleading results.

We have come to the conclusion that it would be most ra-

tional to use the counting-chamber procedure in the remainder of the present investigation. As it requires fewer technical operations and more particles are counted, the sources of error will be reduced in number.

B. DIURNAL RHYTHM

Introduction.

Just as other leukocytes, the eosinophile cells exhibit marked diurnal variations, and according to *Rud* (1947) their number undergoes rapid and abrupt fluctuations.

Appel's (1939) findings demonstrated that the eosinophil rhythm follows a curve which has a minimum in the forenoon, rises during the course of the day and culminates in the evening. *Appel* stated that the eosinophils are controlled by a 24-hour rhythm that is affected neither by diet, nor by age or sex, nor by various diseases. In his view this diurnal rhythm is regulated by the autonomic nervous system as well as by hormonal factors.

The eosinophil rhythm has also been analyzed by *Rud* (1947) who, taking the noon level as the reference point, established that a minimum about 20 per cent below the reference point, established that a minimum about 20 per cent below the reference level occurs at about 10 o'clock in the morning. After passing the reference level at 12 noon the value then rises steadily by some 30 per cent during the afternoon and evening hours, and after midnight it again begins to decline (see Fig. 1). Unlike sleeping or waking, prolonged fasting seems capable of influencing the configuration of the curve. *Rud* concluded from his findings that the 24-hour variation of the eosinophile cells conforms to an autonomous rhythm whose ultimate causes are unknown.

Having studied the variations of the eosinophile cells under physiological conditions, *Best & Samter* (1951) came to approximately the same conclusions as *Rud* (see Fig. 2).

Nevertheless it seems to us that the data given in the literature are incomplete. Thus *Appel* made only 5 determinations

Experimental.

With the object of ascertaining the diurnal eosinophil rhythm in human beings, we made counting-chamber determinations of the eosinophile cells every second hour during daytime and every third hour at night in 16 normal subjects and in 22 patients with asthma.

Times for meals and other external factors were the same for the two groups. The asthmatics were given no medical treatment 2-3 days before or during the period of observation.

Results.

Mean eosinophil counts, expressed in per cent of the 24-hour mean, at different times during day and night in normal subjects and asthmatic patients will be found in Table 6.

A graphical delineation of the results appears in Fig. 3.

TABLE 6

Mean eosinophil counts, in per cent of the 24-hour mean, at different times of the day and night for 16 normal and 22 asthmatic subjects.

Time of day	Normals		Asthmatics	
	M Per cent	$\pm(M)$ Per cent	M Per cent	$\pm(M)$ Per cent
07	93	± 6.0	114	± 4.6
09	83	± 4.7	121	± 4.3
11	83	± 4.1	118	± 4.5
13	91	± 5.7	119	± 2.9
15	98	± 3.8	114	± 2.8
17	99	± 3.8	109	± 3.5
19	94	± 5.1	79	± 4.5
21	98	± 4.5	77	± 4.3
24	126	± 4.1	73	± 4.2
03	130	± 5.5	74	± 4.0
06	111	± 4.3	109	± 4.3

Discussion.

From Table 6 and Fig. 3 it is evident that normal and asthmatic subjects have completely different diurnal eosinophil

Eosinophils in per cent of the 24-hour mean

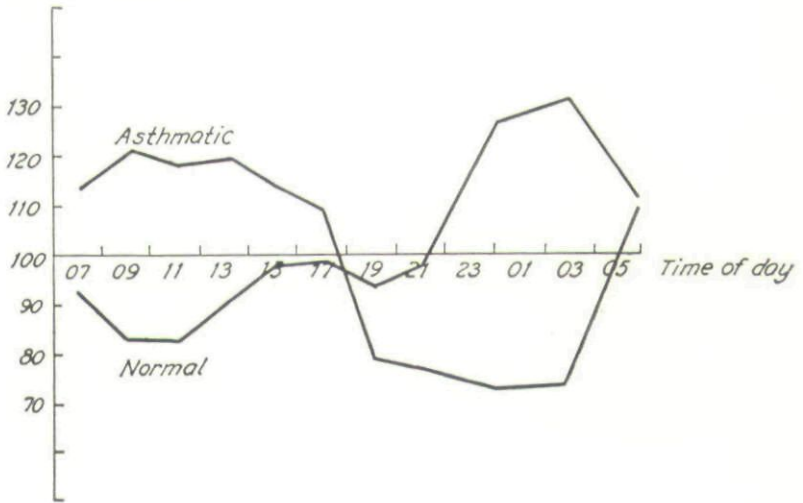


Fig. 3.

Diurnal eosinophil rhythm for normal and asthmatic subjects.

rhythms. So far as we can find from the literature this has not been observed previously.

The reason for this rhythm difference is obscure.

The result of this experiment is of practical importance for evaluation of the Thorn test. The outcome of this test will naturally be misleading unless it is kept in mind that during the morning hours the eosinophil count drops in healthy persons and rises in asthmatics. Another peculiar thing is that the eosinophil count is lowest at precisely those times when asthma tends to be most troublesome, that is during the night and in the morning.

C. EOSINOPHILIA AND ALLERGY

Introduction.

The literature is extremely contradictory about the incidence of eosinophilia in allergic disorders. *Stafford* (1955) could find no correlation between allergic activity and the degree of

eosinophilia. In the blood of almost all allergic patients *Storm van Leewen & Niekerk* (1928) recorded an eosinophilia which exhibited no parallels with the severity of the clinical signs and symptoms. *Peipers* (1930) noted that 55 per cent of all asthmatics had eosinophilia which was most severe on days after an asthma attack. *Gänsler* (1921) demonstrated that eosinophilia was present in about 20 per cent of his patients with Quincke's edema. *Bruun & Dragsted* (1950) found eosinophilia only in Quincke-patients who were suffering from other allergic disorders as well. *Hansen* (1957) remarked that whereas almost all hay-fever patients have eosinophilia during the acute phase their eosinophil counts are normal during inactive periods. In baker's coryza *Baagøe* (1935) demonstrated the presence of eosinophilia in 10 per cent of the cases. *Orban* (1949) estimated that eosinophilia will have an incidence of about 78 per cent in any large series of patients with various allergic conditions.

Experimental.

In order to provide some data on the incidence of eosinophilia in allergic states, we have studied a series of persons attending the outpatient allergy clinic in Gothenburg.

The series comprised 496 patients with manifest allergic disorders. Their ages ranged from 10 to 75 years, the majority falling in the 30 to 60 years category. The diagnoses were established by the history, clinical signs, skin tests and exposure reactions. Blood samples were consistently taken at the first examination for eosinophil determination by the counting-chamber method, readings over 400 cells per cubic millimetre being considered elevated.

Results.

The results of this study will be found in Table 7.

TABLE 7
Incidence of eosinophilia in different types of allergy.

Type of allergy	No. of cases	No. of cases with eosinophilia	Per cent cases with eosinophilia
Asthma bronchiale (extrinsic type)	44	40	91
Asthma bronchiale (intrinsic type)	200	107	53
Hay fever (during the season)	43	33	77
Hay fever (out of season)	20	0	0
Vasomotor rhinitis	108	40	37
Urticaria & Quincke's edema	72	10	14
Löffler's pneumonia	9	9	100
Total No. of patients	496	239	Mean 48

Discussion.

The table reveals that 48 per cent of the patients had elevated blood eosinophil counts. The highest readings—3000–4000 cells per mm³—were recorded in persons suffering from Löffler's syndrome. A difference also seemed to exist between endogenous and exogenous asthma. Thus practically all patients in the group with exogenous asthma had eosinophilia, while this was present in only 50 per cent of those with endogenous asthma. In addition a difference was found between patients with active and patients with inactive hay-fever. These findings are in good accord with what has been reported previously in the literature.

SUMMARY

Eosinophile blood corpuscles could be distinguished from other leukocytes as long as 100 years ago, and for several decades eosinophilia as a sign of clinical, predominantly allergic disorders has been discussed in a large number of papers. The present publication commences with a brief review of some topical problems associated with the probable functions of eosinophil cells and with what diseases eosinophilia coexists.

The author's investigations are divided into three groups.

A. In this group an analysis was made of two principal methods for eosinophil determination which have received

widespread acceptance, viz. the differential count technique and the counting-chamber procedure. It is shown that both methods are highly accurate in themselves. However, determinations made simultaneously by both methods on the same samples give discrepant results. Usually the number of eosinophils found by differential counting is a bit higher than that obtained by the counting-chamber procedure. As it could be ruled out that systematic errors of method were responsible for this deviation, the authors attribute the discrepancy to varying stainability of the eosinophile leukocytes. The varying stainability is in turn ascribed to differences in the chemical constitution of the stained eosinophils.

B. The diurnal rhythm of the eosinophile cells has been studied in 16 normal and 22 asthmatic subjects. It appeared that the eosinophil count in normals declines during the morning hours and has its lowest value between 9 and 11 o'clock, thereafter it rises gradually until it reaches a maximum between midnight and 3 o'clock in the morning. In asthmatics the diurnal rhythm is reversed, the eosinophil count being maximal between 9 and 11 in the forenoon and minimal between midnight and 3 in the morning.

C. Finally the incidence of eosinophilia was studied in a series of 496 patients with various allergic conditions. The figures were found to be highly variable. It is safe to say that about 50 per cent of all allergics have blood eosinophilia, that eosinophilia is a much more frequent accompaniment of so-called exogenous allergies than of the endogenous varieties, and that eosinophilia occurs oftener during the active than during the inactive phase of an allergic state.

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