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on

THE EOSINOPHILE LEUCOCYTE:
Its OCCURRENCE and SIGNIFICANCE with SPECIAL
REFERENCE to ASTHMA.

by

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C O N T E N T S.

INTRODUCTION. A. MORPHOLOGY and PHYSIOLOGY.
 B. THE EOSINOPHILE LEUCOCYTES
 IN NORMAL BLOOD.

I. THE OCCURRENCE OF EOSINOPHILIA.

- A. THE INFECTIOUS DISEASES.
- B. MISCELLANEOUS CONDITIONS.
- C. TOXIC CONDITIONS.
- D. PARASITIC DISEASES.
- E. SKIN DISEASES.
- F. ASTHMA and ALLIED CONDITIONS.

II. THE EXPERIMENTAL PRODUCTION OF EOSINOPHILIA.

III. THE SIGNIFICANCE OF EOSINOPHILIA.

IV. CONCLUSIONS.

THE EOSINOPHILE LEUCOCYTE:
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INTRODUCTION.

A. MORPHOLOGY and PHYSIOLOGY.

The eosinophile leucocyte is a member of the granular series of white blood cells, and is very readily distinguished by the presence within its cytoplasm of large, coarse, highly refractile granules. Its nucleus is less complex as a rule than that of the polymorphonuclear neutrophile leucocyte, and very often consists of only two lobes. Occasionally there may be three or even four lobes. The cytoplasm is filled with large, closely packed granules, which have a marked affinity for acid dyes - the α granules of EHRLICH. In preparations stained with these dyes the eosinophile leucocytes may be easily recognised by the presence within them of these large, brightly staining granules.

The nature of the eosinophilic substance has been a matter of dispute. Some authors (WEIDENREICH, quoted by CLERC⁽¹⁵⁾) regard them as fragments/

fragments of red corpuscles which have been absorbed
and subsequently transformed. ⁽⁷⁵⁾ PETRY and
⁽⁷⁶⁾ MARCEL PRENANT have endeavoured to analyse the
granules obtained from the leucocytes of the horse,
and they conclude that the α granules are formed by
a nucleo-proteid, rich in phosphorus, combined with
calcium and probably iron. A close chemical rela-
tionship has also been suggested between the α
granules and the Charcot-Leyden crystals which so
frequently occur in association with eosinophile leu-
cocytes. ⁽⁷⁷⁾ DE JONG and ROMIEU indeed regard these
crystals as the principal product of disintegration
of the α granules.

Certain physiological properties of these
cells have been clearly established. ⁽¹⁾ JOLLY
studying the leucocytes in leukaemic blood was able
to demonstrate that the eosinophile cell is capable
of amoeboid movements. According to him these move-
ments are very clear; sometimes, however, they are
not real progressive movements, but almost "constant-
ly slow and slight deformations with displacement of
the granules". ⁽²⁾ Miss F.R. SABIN studied living
human blood cells by the method of vital staining,
and found that the eosinophile leucocytes show
active amoeboid movements with streaming of the
granules. ⁽³⁾ BONNE has shown that the eosinophile
leucocyte/

leucocyte is also capable of diapedesis. Phagocytic powers have been claimed for these cells, but most authors agree that they have little, if any, of such properties.

The experimental production of eosinophilia by the injection of various substances appears to show that these cells possess certain very definite chemiotactic properties. This, however, is a subject which can be more appropriately discussed in a later section.

(4)
AUDIBERT has laid great stress upon another property - the "swarming" ("l'essaimage") of the eosinophile granules, by which he means "the power this cell has of driving out the granules it contains by centrifugal action". This view is based upon the appearance in stained films of cells in which the eosinophile granules are no longer contained within the cell, but are scattered at varying distances from the nucleus. This appearance is much more frequent in the eosinophile leucocytes than in any others. Indeed it is rare to examine a stained film without finding at least one or two of these disintegrated cells with scattered granules. The appearance is, however, most probably due to rupture of the cell in the preparation of the film, since we have never seen it in films prepared by the method of vital staining.

B. THE EOSINOPHILE LEUCOCYTES IN NORMAL BLOOD.

Numerous estimations have been made of the percentage of eosinophile cells usually found in adults in good health and the following are among the figures which have been obtained:-

ZAPPERT	(5)	1 - 3%
JOLLY	(6)	0.9%
LEREDDE and BEZANÇON	(7)	1 - 2%
AUDIBERT	(8)	2 - 3%
LEFAS	(9)	1 - 3%
EWING	(10)	1 - 4%
LAZARUS and EHRLICH		2 - 4%
HAYEM, SOLLY, da COSTA		0.5 - 5%

On the basis of such figures as these, it is usually assumed that any increase of the eosinophile cells above 4% constitutes a condition of eosinophilia.

I./

I. THE OCCURRENCE OF EOSINOPHILIA.

Broadly speaking there is general agreement that eosinophilia occurs in the following conditions:-

- (i) During convalescence from acute infectious diseases.
- (ii) In many parasitic diseases.
- (iii) In certain dermatological conditions.
- (iv) In asthma and allied conditions.

It has also been reported in a large number of miscellaneous and apparently unrelated conditions, in which no mention has been made as a rule of the presence or absence of any of the above, and especially of parasitic infestation. In many of these, however, an unfortunate prominence has been given to positive cases, and there are very few conditions, in which the frequency of occurrence of an eosinophilia has been worked out. In what follows we shall endeavour to summarise the extensive literature of the subject with the addition of such observations of our own as may be relevant in order that we may arrive at some conclusion as to the possible significance of this condition and its diagnostic and prognostic value.

A. THE INFECTIOUS DISEASES.

There is a general agreement that in most cases the acute infectious diseases are accompanied by a diminution in the numbers of eosinophile leucocytes. BEZANÇON and MOREAU⁽¹³⁾ state that as a general rule the normal eosinophile cells of the blood disappear more or less completely in acute infections during the height of the condition and reappear as it declines. A transient eosinophilia is then produced. They further state that in those diseases where the decline of the fever takes place by crisis, as in pneumonia, the reappearance of the eosinophile cells is sudden and forms part of the phenomena of the crisis. In these cases there is not as a rule any eosinophilia, In those diseases in which the decline is by lysis, as in typhoid fever, the eosinophiles reappear before the end of the disease, sometimes even before the beginning of defervescence, they increase **during** convalescence, often reach a rather high percentage and then return to normal. The eosinophila may in these cases reach as much as 13 per cent.

⁽⁷⁸⁾
 PINEY describes the changes which occur in the composition of the blood picture in an infective malady. "First there is extreme neutrophilia with/

"with great reduction, or even disappearance, of
 "eosinophiles and basophiles, and reduction of
 "lymphocytes.....In chronic cases well marked hyper-
 "plasia and even macroscopic increase in the extent
 "of the marrow can be found at autopsy. This increase
 "in the amount of myeloid tissue has a definite effect
 "upon the composition of the blood picture; the re-
 "lative neutrophilia tends to decrease, and the types
 "of cells, which have been so much reduced or have
 "entirely disappeared, are again found, although in
 "numbers smaller than normal.... During the subsidence
 "of an infection and the period of convalescence the
 "neutrophiles gradually fall to normal numbers, but
 "the lymphocytes increase both relatively and absol-
 "utely to figures well above normal. The eosinophiles
 "and often the monocytes also show an increase during
 "convalescence".

The following cases from the present
 writer's records are illustrative of the changes
 which occur in the composition of the blood picture
 at the time of and immediately following the crisis
 in pneumonia. In each case total white cell counts
 were taken, and also differential counts and ARNETH
 counts, made by COOKE'S method.

NO. I/

NO. 1. The patient was admitted to the ward suffering from asthma. While in the ward he developed an attack of pneumonia which resolved by crisis on the fifth day. The blood counts were made on the fourth day (that is the day before the crisis) and on subsequent days as noted in the accompanying TABLE I.

TABLE I.

DAY	IV.	V.	VI.	IX.	XIII.
Temperature	100.8	98.6	98	-	-
Pulse	104	90	86	-	-
Respiration	30	25	25	-	-
W.B.C.	29,200	23,000	16,400	10,000	7,400
Poly-morphs	86%	81%	74.6%	55.3%	51%
Lymphocytes	6	15.3	15	31	39
Monocytes	3	3	6	9	7
Eosinophiles	0	1.7% i.e. 391	3.3% - 541	4.3% - 410	2% - 148 per c.mm.
Basophiles	0	0	1	0	1
Arneth					
I	95%	77	72	54	50
II	5%	23	23	36	36
III	0	0	5	10	13
IV	0	0	0	0	1
V	0	0	0	0	0

This case illustrates very clearly the marked neutrophilia with great "shift to the left" of the ARNETH count and complete disappearance of eosinophiles during the height of the disease. The latter reappeared suddenly at the time of the crisis several days before the total white cell count returned to normal, and while there was still a very pronounced "shift to the left" of the ARNETH count. It is probably, therefore, one of the earliest indications in the blood picture that the crisis has been reached. There was no indication in this case of a post-infective eosinophilia, although there was an increase of eosinophiles, both relative and absolute, for a few days.

NO. 2. Another case of pneumonia in a non-asthmatic patient in which counts were made just before and after the crisis, is shown in TABLE II.

TABLE II/

TABLE II.

DATE	10:3:30	11:3:30	12:3:30
Temp.	100	98.8	98
Pulse	88	84	84
Respiration	25	25	25
W.B.C.	14,700	10,000	6,000
Poly-morphs	82%	64	63
Lymphocytes	15	24	25
Monocytes	8	10	9
Eosinophiles	0	2% i.e. 200 p.c.mm.	3% - 180 p. c.mm

This case also showed the same sudden re-appearance of eosinophiles at the time of the crisis, but the eosinophiles did not increase as in the previous case.

(14)

CARNEGIE DICKSON in his studies of the bone marrow finds that "in very early cases of "pneumonia, that is during the first day or two of the "fever, though none of the cells may be present in the "circulating/

"circulating blood, the increase of eosinophiles in the marrow may be distinct. During the height of the disease they are still absent from the circulation and their behaviour in the marrow is uncertain, being sometimes increased or unchanged, but more usually diminished in their relative proportion to the neutrophile cells, while later there is a critical or post-critical rise in their numbers, both in the marrow and in the blood". He also points out that whenever the bone marrow makes a big effort, it specialises in one or other type of cell, and does not produce two kinds in large numbers at the same time. This suggests that the disappearance of the eosinophiles in a disease like pneumonia is due to the greatly increased production of neutrophile polymorphs and a diminution or cessation in the production of eosinophiles. At the crisis the increased production of polymorphs abruptly ceases, and the output of eosinophiles quickly rises.

(15)

CLERC also finds that the eosinophiles disappear during acute infections, and re-appear during convalescence when they may increase up to 6 and even 12 per cent.

(17)

LAMS quotes WIEDEMAN as having found 8 to 9 per cent of eosinophiles in the blood at the end/

end of typhoid fever. He states that during convalescence from acute rheumatic fever the eosinophile may vary between 5 and 10 per cent. and mentions that HORDER has found 20 per cent. LEFAS⁽⁹⁾ gives figures ranging from 1 to 15 per cent for the same condition.

SCARLET FEVER is apparently the only one of the acute infectious diseases in which a marked eosinophilia occurs along with a neutrophile leucocytosis. The following are instances of the figures which have been recorded:-

(5)
ZAPPERT examined three cases and found an average eosinophile count of 7.7 per cent.

(16)
TÜRCK found in one case 13.33 per cent and in another 14.33 per cent. KOTSCHERKOFF, quoted by

(17)
LAMS gives figures ranging from 8 per cent to 15 per cent, and BERG finds from 1.3 to 11 per cent.

(18)
RECKZEH examined twenty patients and found the eosinophile count varied from 0 to 23 per cent.

(19)
SACQUÉPÉE finds that in scarlet fever after the fourth or fifth day the eosinophiles in the blood rise abruptly to as much as 13 per cent. This rise is maintained during the second and third weeks, and then their number falls progressively during the third and fourth weeks, though still keeping above the normal. Finally at the termination of the disease the curve rises again markedly and/

and rapidly. At this point desquamation is sometimes accompanied by an eosinophilia of 15 per cent. This lasts a long time, and may be encountered three months after the beginning of the condition. Often it is only in the sixth month that the eosinophiles reach their normal level.

(79)
BOWIE has studied the changes in the white cells in scarlet fever very fully. He finds that practically all cases show leucocytosis, which reaches its maximum at or shortly after the height of severity of the disease and then gradually sinks to normal. Eosinophiles are diminished at the onset of the fever. They increase rapidly in simple favourable cases till the height of the disease is past. They may number 11 per cent. on the third day. The more severe the case the longer are the eosinophiles subnormal before they rise again. In fatal cases they never rise, and generally disappear from the circulation.

(80)
CRAMB found that eosinophiles are diminished till the fourth day, and then increase till the ninth day at least.

These observations are of importance since they show that under certain conditions at least the bone marrow is capable of producing more than one kind of cell in greatly increased numbers. They/

They also have a diagnostic value, since as GULLAND and GOODALL⁽⁸¹⁾ point out no conditions likely to be confused with scarlatina except diphtheria with a serum rash and gonorrhoea with a drug rash show similar blood changes.

CARRIÈRE⁽²⁰⁾ has investigated whooping cough in children, and finds that during convalescence the eosinophiles may reach as much as twelve to fifteen per cent, a figure he considers slightly raised since the child normally has seven per cent.

Eosinophilia is also said to occur during convalescence from chronic infectious diseases. BEZANÇON and MOREAU⁽¹³⁾ state that in pulmonary tuberculosis the eosinophiles disappear or are considerably diminished in the pneumonic forms with grave or fatal development, while in the more slowly developing forms they follow the same general rules as in the acute fevers. Greatly diminished, if not altogether absent, at the height of the condition, they re-appear as the fever diminishes, and the general condition improves. A slight eosinophilia marks the approach of convalescence. While in the acute diseases eosinophilia is always of short duration, in tuberculosis the "eosinophilic crisis" continues for weeks and even months, and one often observes/

observes it in tuberculous patients at the end of attacks and in the intervals between them.

(21)
APFELBAUM, however, has found a notable increase of eosinophiles at the beginning of tuberculosis.

Of the other chronic infectious diseases leprosy appears to be most often associated with eosinophilia. (22)
BETTMANN gives figures ranging (23 & 24) from 7 to 18 per cent and JOLLY reports a (17) case with 23 per cent. LAMS quotes the following figures:-

SICARD and GUILLAIN	8.48 per cent
GAUCHER and BENSANDE	8 - 28 " "
HORDER	30 - 42 " "
DARIER	61 " "
MITSUDA	64 " "

(13)
BEZANÇON and MOREAU point out that in leprosy the facts are complex, since in addition to the infectious cause there is the cutaneous reaction, which may be sufficient in itself to account for the eosinophilia. They state that eosinophilia is chiefly found in the tubercular form of leprosy and is rare or absent in the nervous forms. They also suggest that in leprosy the true cause of the eosinophilia may be a concomitant parasitic infection.

B. MISCELLANEOUS CONDITIONS.

A variety of conditions, in which cases of eosinophilia have occasionally been reported, may be conveniently summarised at this point. In many instances it seems probable that positive cases have attracted undue attention, and that more extensive observations would show that eosinophilia is a comparatively infrequent occurrence in these conditions. The possibility must also be kept in mind of the occasional presence in any series of cases of a particular disease of certain individuals with a condition which, while giving rise to no obvious symptoms, may cause an eosinophilia, particularly any form of parasitic infestation.

(25)

LAIGNEL-LAVASTINE finds that in patients suffering from old grumbling appendicitis ("appendicites torpides") eosinophilia may be present and amount to 8 per cent. This is probably simply another instance of the subsidence of an acute infection being accompanied by a slight eosinophilia.

(26)

SABRAZES has found eosinophilia in patients suffering from adenoids.

(5)

(27)

ZAPPERT and von NOORDEN both record eosinophilia/

eosinophilia as occurring in nephritis. After the cure of nephritis LEFAS⁽²⁸⁾ and PIERACINI⁽²⁹⁾ find 7.13, 12.6 and 13.19 per cent of eosinophiles in the blood. In the light of the preceding section on the acute infectious diseases, one may suspect that these were probably post-scarlatinal cases.

In chorea ZAPPERT⁽⁵⁾ has found 8.71 and 19.54 per cent.

In the blood diseases eosinophilia is commonly found in leukaemia. JOLLY⁽³⁰⁾ has recorded cases with 1, 3 and 6 per cent. RECKZEH⁽¹⁸⁾ gives figures ranging from 1 to 14.6 per cent. Other published figures are those of LOEPER⁽³¹⁾ - 16 per cent, CANON⁽³²⁾ - 20 per cent, LOEWIT⁽³³⁾ - 80 per cent.

In pernicious anaemia RECKZEH⁽¹⁸⁾ has found from 1 to 8 per cent. More recently PINEY⁽⁸²⁾ states that eosinophiles are much reduced in number, but a few can always be found. During a remission, occurring spontaneously or as the result of liver treatment, eosinophiles often rise to numbers well above normal.

Eosinophilia has also been recorded in connection with some neoplasms. LAMS⁽¹⁷⁾ states that "DONATI has found 3, 4 and 6 per cent in cases of epithelioma of the skin; at the commencement of carcinoma/

"carcinoma of the breast and of the oesophagus 5 - 9 per cent; in cases of sarcoma REINBACH has found (34) 7 or 8 per cent up to 48 per cent". PINEY

states that eosinophilia is found occasionally with growths of the cervix or stomach, and may rise to 20 per cent. The present writer has observed one case of a patient who was found at autopsy to have a small, primary scirrhous carcinoma in the splenic flexure of the large intestine and large secondary deposits in the liver. On three occasions during the time that he was under observation, the eosinophile count was found to be 15, 16 and 7 per cent.

The connection of eosinophilia with disorders of the internal secretions has also received attention. (17) LAMS states that an eosinophilia of 3.72 to 8.7 per cent has been found in cases of Addison's disease and from 5 to 7 per cent in cases of myxoedema. (13) BEZANÇON and MOREAU state that in women a transitory eosinophilia occurs as a physiological condition in the premenstrual period corresponding to the development of the corpus luteum. They also state that it has been noted in Addison's disease and in acromegaly, but that it does not occur in exophthalmic goitre or in myxoedema. In 20 cases of myxoedema VAQUEZ found a slight eosinophilia in only one case. In a patient who had been subject to thyroidectomy ten years previously/

previously they found 12 per cent of eosinophiles in the blood. GULLAND and GOODALL⁽⁸¹⁾ find that percentages of 6 and 8 of eosinophiles are not uncommon in Addison's disease, and have met with a case showing 10 per cent.

A certain number of investigators have also found a connection between eosinophilia and gonococcal infections. Thus EUGENIO⁽³⁵⁾ observed that the eosinophiles increase in number during the second week in acute anterior urethritis; sometimes the increase is very marked in the first week, but then there is a diminution the following week. The eosinophiles increase remarkably when the process extends to the posterior portion of the urethra, especially in cases of epididymitis, funiculitis and blenorrhagic rheumatism. BETTMANN⁽²²⁾ found an evident increase of eosinophiles in the pus in the third week after infection and an increase also in the blood. He also states that the appearance of a posterior urethritis, and especially of an epididymitis, most often causes their number to reach a maximum in the blood, and cites the case of a patient in whom an epididymitis caused the percentage of eosinophiles to rise to 32.5 per cent.⁽¹⁷⁾ LAMS, however, states that besides these records, there are many negative findings, and that certain authors/

authors find only neutrophiles in the pus and a normal leucocytic formula.

C. TOXIC EOSINOPHILIA.

Eosinophilia has been noted in cases of alcoholism, jaundice, absorption of phosphorus, of nuclein, of salicylate of sodium and after injections of anti-toxic sera - LAMS (17) .

Tuberculin injections have been said to produce a considerable eosinophilia, late according to some, immediate according to others. Thus BOTKIN (36) has recorded a case with 50 per cent of eosinophiles, while GRAWITZ, TSCHITOWITCH and ZAPPERT (37) once noted 91.11 per cent. ACHARD and CLERC (38) and ACHARD and LOEPER (39) have recorded a case of picric acid poisoning accompanied by a rather considerable cutaneous eruption, in which there was a high degree of eosinophilia. LEREDDE (40) has recorded a case of potassium iodide poisoning in which a vesicular eruption appeared on the face and limbs accompanied by anaemia and/

and 14 per cent of eosinophiles in the blood.

BEZANÇON and MOREAU⁽¹³⁾, however, report two cases of potassium iodide poisoning in which they found only 1.5 per cent of eosinophiles. They quote NEILSON and MARCHILDON as finding 10 to 20 per cent.

In two cases of acute mercurial poisoning ACHARD and LOEPER⁽³⁹⁾ found 8 to 12 per cent of eosinophiles. BEZANÇON and LABBÉ⁽⁴¹⁾ reported a case of calomel poisoning in an infant accompanied by a generalised erythema. They found 6 per cent of eosinophiles at the acute period, and 14 per cent when the eruption passed off. In two cases of mercurial dermatitis HOFFMANN⁽⁴²⁾ records 49 per cent of eosinophiles, while RECKZEH⁽¹⁸⁾ in 10 cases found from 0 to 31.5 per cent.

In a case of camphor poisoning von NOORDEN⁽⁴³⁾ found 20 per cent of eosinophiles.

LAMS⁽¹⁷⁾ quotes a case of accidental swallowing of benzene, followed by the appearance of a polymorphous erythema, in which SIMONIN found 25 per cent of eosinophiles which disappeared as the toxic signs did.

It will be noted that in most of these cases the poisoning was accompanied by skin eruptions, and it is difficult to say whether the eosinophilia/

eosinophilia was due to the poison itself or to the skin reaction. The present writer has examined two cases of lead poisoning, in which there were no skin manifestations, and found only 1 and 1.5 per cent of eosinophiles.

Injections of sera have been stated to produce eosinophilia. The present writer has had the opportunity of examining a patient who was given several subcutaneous injections of horse serum. Two cubic centimetres were given every other day and after three such injections a marked serum rash appeared at the site of the injections. Previous to these injections the eosinophile percentage had been determined on three different occasions, and found to be 2.5, 3.3, and 3.3 per cent. The day after the first injection the percentage was 4.6. Subsequently it varied from 1.6 to 4.6 per cent, and did not rise above this figure even when the rash appeared.

D. EOSINOPHILIA and PARASITIC DISEASES.

Eosinophilia is seen most markedly in the parasitic diseases in which very high figures have frequently been recorded. BEZANÇON and MOREAU⁽¹³⁾ state that in these diseases it occurs not only in the blood but also locally, and that one characteristically/

characteristically finds large numbers of eosinophiles surrounding the wall of an hydatid cyst or round a filaria-loa or trichina which has penetrated the tissues. Typical figures for the percentage of eosinophiles in the blood in the different varieties of parasitic infestation are given below.

(1) TREMATODES.

BILHARZIA HAEMATOBIA. Eosinophilia is very frequent and is often of a high grade. (44)
 A.C. COLES (45) has recorded 20 per cent and (46)
 A.E. RUSSELL 23.8 to 33.6 per cent. BALFOUR (47)
 has found 16.8 per cent. A.E. BOYCOTT examined 5 cases and found more than 20 per cent in each of them at some period. In one case a count of 47 per cent fell to 5 per cent when the patient ceased to pass any ova or blood. (48)
 KAUTSKY-BEY gives figures ranging from 3 to 15 per cent in children and records the following results in adults:-

5 cases	5 - 10 per cent
12 cases	10 - 20 " "
2 cases	20 - 30 " "
1 case	39 " "
1 case	40 " "
1 case	53 " "

No clear case of active disease with normal eosinophiles seems to have been recorded.

(2) NEMATODES.

ASCARIS LUMBRICOIDES. High counts are sometimes found. SOLLEY⁽¹⁰⁾ for instance records⁽⁴⁷⁾ one with 33 per cent of eosinophiles. BOYCOTT mentions two cases in which the faeces showed the presence of Trichocephalus and Ascaris and in which the eosinophile count was 23.8 and 25.6 per cent. Since Trichocephalus is according to him only exceptionally associated with eosinophilia, he regards these figures as being probably due to the Ascaris infection. Completely negative cases have, however, been recorded by BUCKLERS⁽⁴⁹⁾, BOYCOTT⁽⁵⁰⁾ and LIMASSET⁽⁵¹⁾.

OXYURIS VERMICULARIS. BUCKLERS⁽⁴⁹⁾ has recorded a count of 16 per cent in an adult. LIMASSET⁽⁵¹⁾ had four negative cases. MEYER⁽⁶⁸⁾ records four cases with 5.5, 6.5, 9.71, and 13.7 per cent. BOYCOTT⁽⁵²⁾ examined a series of 18 infected children; these showed two with more than 10 per cent (12.8 and 13.7), six between 5 and 10 per cent, and ten with less than 5 per cent. He concludes that while low grades of eosinophilia are not infrequent, it is rare to find a high eosinophilia, and quite common to find none.

TRICHINA/

TRICHINA SPIRALIS. The original discovery of the blood changes in this disease was made by T.R. BROWN (53) in 1898, and since then many cases have been recorded which show most extreme grades of eosinophilia. Most of them show a real eosinophile leucocytosis. PATEK (54) has recorded a case with 30 per cent and STAUBLI (55) finds from 22 to 26 per cent. CABOT (56) collected 21 cases which on first examination averaged 16,000 (8,000 to 28,000) leucocytes with 32 per cent (10 to 67) eosinophiles. A single negative case has been recorded by DA COSTA (57) though a local eosinophilia was found in the affected muscles, and a probably negative case by HOWARD (58).

FILARIA. The eosinophiles vary from 4 per cent, as recorded by BLOCH (59) up to 70 per cent, recorded by REMBINGER (60). Numerous cases have been noted by A.C. COLES (62), G.L. GULLAND (61), VAQUEZ (63), J.A. SICARD (64) and CALVERT in which the eosinophiles vary from 7 to 20 per cent. GULLAND (61) found that the number of eosinophiles appears to correspond with the number of embryos in the circulating blood, and, as these are usually most numerous at night (in the case of *Filaria Bancrofti*), eosinophiles are then in greatest abundance. He made the following observations on the number of eosinophiles per cubic millimetre in one case:-/

case:-

11.10 a.m.	276	10.20p.m.	808
3.0 p.m.	283	11.10p.m.	1500
4.0 p.m.	476	11.20p.m.	1224
10.10 p.m.	742		

The present writer has had the opportunity (through the courtesy of Lt. Col. Greig) of examining a European, who returned from West Africa, and from whose eye a dead filaria (*Filaria loa*) was removed. On the day the worm was removed he was found to have 19 per cent of eosinophiles and a week later 16.5 per cent. No series of cases seems to have been published from which the frequency and grade of eosinophilia can be properly ascertained, but apparently most cases are about 7 to 12 per cent.

TRICHOCEPHALUS DISPAR. No clear case of any marked degree of eosinophilia has been recorded. P.K. BROWN (65) finds eosinophilia a "strikingly constant symptom" in every case of worm infection, and says that "in no less than ten or twelve cases where the *Trichocephalus hominis* alone appeared, the percentage of eosinophiles rarely fell below 5." BOYCOTT (47) examined 25 samples of faeces/

faeces from Cornish miners and found *Trichocephalus* in 24 (96 per cent). Blood films were taken from 41 men, and of these only five showed 5 per cent or more eosinophiles. Only two of these were above 10 per cent and these were found to be infected with *Ascaris* also. In the remaining three cases (5.0, 6.4 and 8.4 per cent) the blood condition may have been due to *Trichocephalus*. On the other hand in 42 films from men in another mine comparable counts were obtained (5.2, 6.0, 6.8, 7.2 per cent), though no evidence of the presence of any worms could be found. BOYCOTT therefore concludes that "it is only very exceptionally, if ever, that the presence of this worm gives rise to any eosinophilia".

ANGUILLULA STERCORALIS. Only four blood examinations seem to have been recorded. BUCKLERS (49) found 13.5 per cent, P.K. BROWN (65) 6.3 per cent, PAPPENHEIM (66) 0.8 per cent and R.P. STRONG (67) 0.1 to 0.3 per cent.

ANKYLOSTOMA DUODENALE and A. AMERICANUM.

Eosinophilia is very marked in association with ankylostomiasis. The following are among the figures recorded:-

MULLER/

MULLER and RIEDER (9)	(69)	8.2 - 9.7 per cent	
LEFAS		7 - 12	" "
KAUTSKY BEY (59)	(48)	5 - 13	" "
BLOCH		33.1 & 40.1	" "
STOCKMANN	(70)	12 - 43	" "
LEICHTENSTERN	(71)	62 and 72	" "

(49)
BUCKLERS records twelve cases in which the count varied from 10 to 56.6 per cent. Ten of these were between 10 and 25 per cent, one was 42 per cent and another 56.6 per cent.

(72)
BRUNS, LIEFMANN and MACKEL examined five hundred subjects affected with ankylostomiasis and found between 8.15 and 20 per cent of eosinophiles.

(73)
ASHFORD and KING have recorded 86 differential counts in sixty-two cases of infection with *A. americanum*, all of whom were severely anaemic when first seen. Their results may be grouped as follows in TABLE III.

TABLE III.

PERCENTAGE EOSINOPHILES	NO. of CASES	PERCENTAGE of TOTAL CASES
Less than 5 per cent	17	21
5 - 8	15	18
More than 8	50	61
More than 20	11	13

ASHFORD regards a low eosinophile count as indicative of a failure on the part of the individual to react to the infection and as a sign of unfavourable prognosis.

(47)
A.E. BOYCOTT has published an interesting survey of 148 cases of Cornish miners infected with *A. duodenale*. Grouping his cases as above the following figures are obtained:-

TABLE IV.

PERCENTAGE EOSINOPHILES	NO. of CASES	PERCENTAGE of TOTAL CASES
Less than 5	5	3.4
5 - 8	3	2.7
More than 8	91	93.9
More than 20	49	33.1

BOYCOTT points out that this series shows a frequency and intensity of eosinophilia considerably higher than that found by ASHFORD and KING, and thinks that this may be due to differences in the degree of anaemia in the two series. All ASHFORD'S cases were extremely anaemic, having a haemoglobin percentage of less than 50, whereas some 20 only of the/

the Cornish miners had less than 50 per cent haemoglobin. He concludes that "the eosinophile reaction is most constant and best marked in those who are not suffering from a definite anaemia, that is in just those persons who show nothing to suggest that they are harbouring the worm".

He has also investigated the relation of eosinophilia to treatment. He states that the effect of efficient treatment is inconstant and uncertain. The eosinophiles never seem to diminish quickly. In one case the eosinophile percentage was still 13.4 per cent more than a year after commencing treatment, although no eggs had been found in the stools in three successive examinations.

(3) CESTODES.

TAENIA SOLIUM and T. MEDIOCANELLATA.

Positive examples have been recorded by several investigators, some of which are noted here.

(49)
BUCKLERS has recorded six cases, of which only one was over 10 per cent. ACHARD and LOEPER (74) give figures of 10 to 11 per cent. LEFAS (9) records figures ranging from 1.8 to 13 per cent.

(51)
H. LIMASSET counted sixteen cases; five showed at some period more than 5 per cent, but of these only two reached more than 10 per cent (10.8 and 26.1 per cent). (68)
MEYER records six cases. Of these/

these three were under 10 per cent, and three over 10 per cent (11, 21.4 and 32). LEICHTENSTERN (71) has recorded the highest figure, 34 per cent. (47) BOYCOTT examined eight cases: four were less than 5 per cent, three were between 5 and 10 per cent and one over 10 per cent (13.0 per cent). The present writer has examined two cases and found in one 3 per cent and in the other 2.3 per cent. It would seem, therefore, that eosinophilia is not common, and, if present, is usually of a low grade.

ECHINOCOCCUS CYSTS. A high degree of eosinophilia may occur, but there are numerous reported cases where the reaction apparently does not occur. The following are among the published figures:-

	Per cent.
LIMASSET (51)	3 - 4 per cent
BEZANÇON and LABBÉ (41)	4 " "
TUFFIER (83)	5 " "
MEYER (68)	2.7, 4, 5.8 "
LAUBRY (84)	10
AUDIBERT (8)	5, 6, 7, 12
DARGEIU and TRIBOUDEAU (85)	12
BLOCH (86)	14.7
SABRAZÈS (26)	4.4, 5.88, 11.81, 17
LEFAS (9)	6 - 20
MEMNI in 12 cases (87)	7 - 20
ACHARD and CLERC (88)	40
SELIGMANN and DUDGEON (89)	57

It is interesting to note that if suppuration occurs in a cyst, the eosinophilia gives way to neutrophilia.

CYSTICERCUS CYSTS. H. LIMASSET (51) records 10 per cent. ACHARD and LOEPER (74) 11 per cent. BOYCOTT (47) mentions a case of generalised infection of two years' duration which showed 8 per cent. MARIE (90) and others have recorded negative cases.

BOTHRIOCEPHALUS LATUS. Very little information is available as to the behaviour of the leucocytes in infections with this parasite, and all the records apply to anaemic cases. The anaemia, which is so often associated with its presence, may obscure the true leucocytic reaction, but as far as our information goes, the presence of this worm does not cause an eosinophilia.

(4) MISCELLANEOUS PARASITES.

ENTAMOEBIA COLI. Eosinophilia has been recorded in cases of amoebic dysentery (GULLAND (81) and GOODALL), but is apparently inconstant and not of high degree. The present writer has examined two cases of amoebic abscess of the liver, and in one case the eosinophiles varied from 0 to 1.6 per cent; in the other they were from 2 to 3 per cent.

BALANTIDIUM COLI/

(91)

BALANTIDIUM COLI. EHRNROOTH found
no eosinophilia in a case of chronic enteritis due
to this parasite.

(92)

PULEX PENETRANS. BUSHNELL found 8.2
to 19.3 per cent of eosinophiles in a case of malaria;
this was apparently due to the presence of a "jigger"
in the foot.

(93)

SARCOPTES SCABIEI. HAYMAN and FAY
examined fifty-five cases and found eosinophilia
ranging from 1 to 15 per cent with an average of
5.5 per cent. The higher percentages were obtained
in the most extensive cases. The present writer has
examined two cases and found in one 2 per cent, and
in the other 8 per cent.

The pediculi, the malarial parasites and
trypanosomes do not appear to give rise to any in-
crease of eosinophiles in the blood.

E. SKIN DISEASES.

Eosinophilia occurs in a large number of
skin diseases, more particularly in those of a
bullous type. In pemphigus⁽⁵⁾ and dermatitis
herpetiformis⁽⁴⁰⁾ some degree of eosinophilia
(generally 10 - 20 per cent) is very frequent, but
not/

(15)

not constant. In the latter LEREDDE and PERRIN state that it may reach as high as 33 per cent, and they regard this as a means of differentiating "Duhring's disease" from other bullous dermatoses. A high degree of eosinophilia may, however, be found in other skin diseases such as pemphigus, herpes gestationis, Unna's disease and many chronic skin affections. The present writer has seen one case of very extensive pemphigus in which the eosinophile percentage was at first 32 per cent, and fell to 18 per cent as the condition improved.

It would appear that almost any skin affection may be accompanied by eosinophilia, but that its intensity is very variable, and it is exceptional to find an eosinophilia among any ordinary body of patients suffering from skin diseases. This is clearly shewn by the records of FRENCH (94) :- Of 90 cases, including most of the ordinary conditions, 13 shewed more than 5 per cent, and only 4 more than 10 per cent.

F. ASTHMA and ALLIED CONDITIONS.

HISTORICAL REVIEW.

(95)

FINK in 1890 and

(96)

GABRITSCHIEWSKY in 1891 were the first to determine the percentage of eosinophiles in the blood of the ir/

their patients suffering from asthma. The former found 5 to 6 per cent in the absence of a paroxysm, the latter 3 per cent in the absence of a paroxysm, and during the paroxysm, 10, 8 to 22, 4 to 9, 2 to 16, and 7 per cent. Following upon this LEYDEN in 1891, GOLLASCH, ZAPPERT, CANON, von NOORDEN and SCHWERSCHIEWSKI in 1895, established that eosinophilia appears only at the time of the paroxysm, and that in the intervals the percentage remains normal. In 1897 BILLINGS reported a case of asthma in a syphilitic patient, in whom he found 53.6 per cent of eosinophiles during the paroxysm. In 1900 WOLFF in the course of an attack of asthma found 10 per cent of eosinophiles. In 1911 HERRICK noted 72 per cent during a paroxysm of asthma. KLINKERT found 15 per cent and noted that the family of an asthmatic is often eosinophilic. In 1914 BEZANÇON and MOREAU state that "eosinophilia is constantly present in the blood during the paroxysms, reaching 8 and 10 per cent, sometimes 22 per cent and even 53 per cent, and that it often persists in the interval between the paroxysms at about 6 to 7 per cent". In 1919 NAEGELI drew attention to the existence of eosinophilia during asthmatic paroxysms.

CLAUDE/

(104)

CLAUDE determined the percentage of eosinophiles every ten minutes during an experimentally produced attack of asthma and found 8.3, 6.4 and 5 per cent. The same patient before the attack had 5 to 6 eosinophiles per cent. According to BEZANÇON and

(105)

de JONG "all the researches establish that there "exists during the asthmatic paroxysm a marked blood "eosinophilia of 6 to 12 per cent or sometimes more, "and that between the attacks the count is most often normal or sometimes slightly raised."

(97)

PASTEUR VALLERY RADOT and his fellow workers have published a survey of 84 cases, in which they include only adults, since children may frequently have a slight eosinophilia. They regard a count of more than 4 per cent as indicative of eosinophilia. Of 51 cases observed during the paroxysm, 39 had 4 per cent or more, and of these 6 reached or exceeded 10 per cent. They conclude that 76 per cent of asthmatics observed at the height of the attack show eosinophilia. Thirteen of the above cases were examined between the attacks and only one had a figure above normal, viz. 4.5 per cent. Thirty-three other cases were studied between the attacks and nine had 4 per cent or more. Therefore of 46 patients taken between attacks 10 only (22 per cent) show eosinophilia and that only very slight.

More/

(106)

More recently DR. MARJORIE GILLESPIE has stated that of the cases she had studied in six months (total number not stated), "only two had an eosinophile count of less than 4 per cent, while "the normal count was usually 2 per cent. The average count in these patients was somewhere between 7 "and 10 per cent, but a good many were over 10 and a "few over 20 per cent. The eosinophilia varied "according to the state of the patient. During an "attack, in the majority of cases there was a fall to perhaps half the former percentage". It will be noted that all previous investigators report a rise in the percentage during an attack.

(106)

BRAY finds in his cases an average eosinophile count of 7 per cent with variations from 3 to 23 per cent.

It is well known that eosinophile cells occur in the sputum of asthmatics, as well as in the blood. According to BABONNEIX (107) this was first noticed by COLLASCH, and since then by numerous authors. TEICHMULLER endeavoured to show that this was not characteristic of asthma, but was found in many respiratory conditions.

(108)

BEZANÇON and de JONG, however, claim that eosinophils are never seen in the sputum in the absence/

absence of true asthma. According to them the sputum of asthmatics contains -

- (i) hyaline mucus in thick sheets,
and
(ii) numerous eosinophile cells.

There are a few cases on record of patients dying in the course of an asthmatic attack and coming to autopsy. In one such case FRAENKEL⁽¹⁰⁹⁾ found the bronchi filled with greyish mucous masses. At the periphery of these mucous plugs eosinophiles were seen. In the walls of the small bronchi the author noted masses of leucocytes, mostly eosinophiles. There were also eosinophiles in the lumen of the bronchi. LEMIERRE, KINDBERG and LÉVESQUE⁽¹¹⁰⁾ also describe a case of fatal asthma. At autopsy mucous casts were found obstructing the bronchi. These were literally crammed with eosinophiles and Charcot-Leyden crystals. At the histological examination the mucosa and muscle coat appeared to be infiltrated with leucocytes evidently eosinophiles. Outside the mucosa and the peripheral coat of the bronchi there was intense hyperaemia, a very marked cellular infiltration with an almost absolute predominance of eosinophiles. Round the bronchial glands there was a similar infiltration of cells, chiefly eosinophiles. WALTHER-DEHNER⁽¹¹¹⁾ has also described two cases with a similar abundance of eosinophiles/

eosinophiles round the bronchi. BEZANÇON and
 (109)
 BERNARD regard these anatomico-pathological findings as proof that the eosinophilic reaction is specially characteristic of the local lesion in asthma. These authors indeed regard eosinophilia of the blood and of the sputum in asthmatics as being of such importance and of so general a character as to make it possible in a certain number of cases to suggest the diagnosis of asthma, although the clinical signs are uncertain or point to a different diagnosis. Further they maintain that a very close analytical study should be made of every case where eosinophilia is absent, since no other clinical or biological criterion is so constant as to enable us to arrive with certainty at the diagnosis of asthma. They conclude that eosinophilia of the blood and of the sputum is essential for the diagnosis of asthma. "It is the humoral signature, most constant, most faithful, and most easily obtained as evidence".

(112)

Quite recently GARROD has attempted to distinguish between cases of asthma with and without eosinophilia, and has stated that the sputa in these two types of the disease differ bacteriologically. In the non-eosinophilic type there is almost invariably clear evidence of infection, the organism being usually *B. pfeiffer* or a pneumococcus. In the eosinophilic sputum films are devoid of organisms/

organisms, and cultures, if made from clean material, are almost sterile.

PERSONAL OBSERVATIONS.

The present writer has examined every case of asthma occurring amongst both in-patients and out-patients in Wards 22 and 24 of the Royal Infirmary, Edinburgh, during a period of six months. Investigations into other aspects of asthma were being prosecuted in these wards at the same time, so that the writer had special opportunities of examining patients in whom the diagnosis of asthma had been fully established. The out-patients naturally attended during intervals between attacks, while in most cases the attacks seemed to cease entirely once the patients were admitted to the wards. The figures obtained, therefore, refer principally to the condition between the attacks. In the accompanying table the figures obtained in the differential blood count in each of 23 cases are set out:-

TABLE V./

TABLE V.

NO.	NAME	DATE	P.	L.	E.	B.	REMARKS
1.	Mrs McL		74	20	0.3	0	
2.	M.F.		56	45	1.0	0	
3.	J.G.		84.3	19.2	1.6	0.6	Patient later had pneumonia. See above
4.	Mrs McC		60.3	36.3	2.0	1.0	
5.	Mrs K.	27:11:29	62.3	36	2.0	0	During an attack.
			51	36	2.5	0	After the attack
6.	A.L.		60.5	39	2.5	0.5	
7.	P.I.	14:11:29	75.5	25	2.5	0	Patient was given injections of sera at a later date. See above
		15:11:29	68	29	3.3	0	
		17: 1:30	71.6	24.5	3.3	0.6	
8.	Mrs Mo.		53.6	41.9	3.6	1.6	
9.	H.W.	22:11:29	57.4	38	5	0	
		26:11:29	52.5	43	5	0	
10.	Mrs Be		77.5	17.5	5.0	0	
11.	N.G.		68	26.3	5.6	0	
12.	Mrs Bo.	11:12:29	56.3	37.9	5.3	0	Between attacks.
		10:12:29	46	47.3	7.3	0	Attack just commencing.
			39	54	7.3	0	Attack at its worst.
			40	55	5.0	0	Attack passing after mx adrenalin.

TABLE V. contd.

NO.	NAME	DATE	P.	L.	E.	B.	REMARKS.
13	M.K.	23:12:29	56	37	7.0	0	Course of vaccines 15:1:30 to 4:3:30. Had 5 bad attacks in that time, the last on 9:3:30.
		12:3:30	52	43	5.0	0	
14	M.G.		45	48	7.0	0.3	
15	Mrs Mi	2:2:30	51	40	7.6	1.3	Three doses of vaccine (0.6c.c. in all) given between these two dates.
		11:3:30	54	37	8.0	1.0	
16	A.H.		52.3	39.2	7.3	0	Chronic asthma and eczema.
17	Mrs J.	6:12:29	73	19	8	0	Asthma and eczema
		11:12:29 11 a.m.	69	21	10	0	11.15a.m. Given a streptococcal vaccine subcutaneously.
		4.30p.m.	65	27	7.3	0	
		24:12:29	53.6	30.9	15.3	0	
18	A.K.	7:11:30	64	31.3	4.0	0	Asthma, eczema and albuminuria
		10:1:30	59	33	8	0	
		15:1:30	51.3	40.2	8	0	
		21:1:30	62.3	28.6	7.6	1.3	
19 (see No 5 also)	Mrs K.	27:1:30	37.3	53.2	8.6	0.6	On admission after numerous bad attacks.
		28:1:30	54	40.5	5.0	0.3	Slight attack at 4.30 a.m. Breathless all day.
		30:1:30	47	48.2	4.3	0.3	No attacks
		3:2:30	49.6	44.2	5.6	0.3	Rather breathless since 4 a.m.

TABLE V. contd.

NO.	NAME	DATE	P.	L.	E.	B.	REMARKS.
20	R.M.		56.6	34.0	8.6	0	
21	M.T.		40	50	10	0	Chronic asthma and eczema
22	J.M.	13:12:29	43.3	48.3	10	0	See later.
23	J.D.	11:12:29	41.5	42.9	15	0	Complete course of vaccine treat- ment from 5:1:30 to 10:2:30. No attacks since the former date.
		12: 3:30	50	44	6	0	

In/

In this series we have, therefore, 38 determinations made in the intervals between attacks of asthma. The average eosinophile percentage for these is 6.1, the lowest percentage being 0.3 and the highest 15.3.

It is of interest in the first place to compare these results with those of other investigators. So far as the writer is aware the only extensive series of observations which have been published are those of VALLERY-RADOT⁽⁹⁷⁾ which we have already summarised. For the sake of comparison we may take the same criterion as his that anything over 4 per cent constitutes eosinophilia. Of our 23 cases then 8 had less than 4 per cent, and 15 more than 4 per cent. Of the latter only 2 had 10 per cent, and one had 15 per cent. In TABLE VI these figures and VALLERY-RADOT'S are both given.

TABLE VI.

	EOSINOPHILES LESS THAN 4%		MORE THAN 4%	
	Cases	Percent of Total	Cases	Percent of Total
Our series	8	34.8	15	65.25
VALLERY-RADOT	36	78	10	22

It/

It will at once be seen that our figures indicate a considerably greater frequency of eosinophilia between attacks of asthma than do VALLERY-RADOT'S.

On the other hand our figures are distinctly less than those recently published by DR. GILLESPIE (106). She does not give her total number of cases, but states that only two were less than 4 per cent, a good many were over 10 per cent, and a few over 20 per cent. Her average was between 7 and 10 per cent, whereas ours is only 6 per cent. With regard to our eight cases in which the eosinophilia is less than 4 per cent, we could find no evidence that these were any less truly allergic patients than those with a higher percentage.

Our figures may be still further analysed to determine the frequency with which different degrees of eosinophilia occur. In TABLE VII we give the number of cases classified according to the percentage of eosinophilia present. From this it will be seen that approximately 60 per cent of the counts are between 4 and 10 per cent.

TABLE/

TABLE VII.

EOSIN- OPHILES	LESS THAN 2%	2-4%	4-6%	6-8%	8-10%	10-12%	12-14%	14-16%
No. of counts	3	8	10	9	6	3	0	2
Percent of to- tal	7.3	19.6	24.5	22	14.7	7.3	0	4.9
			61.2%					

On the basis of these figures we would suggest that approximately fifty per cent of asthmatic patients show a low grade eosinophilia, which rarely exceeds 10 per cent, in the intervals between their attacks.

It is of interest also to determine in what way the increase of eosinophiles affects the general composition of the blood picture. It does not result in a total leucocytosis for even in a case in which the eosinophile percentage was 15 per cent, the total white count was only 6,800 cells per cubic millimetre. Comparing the cases in which the eosinophile percentage is less than 4 per cent with those in which it is greater, one is struck by the fact that in the former the percentage of neutrophile polymorphonuclears is distinctly greater than in/

in the latter. This impression is confirmed on further analysis. If we take those cases, in which the percentage of eosinophiles is less than 4 per cent, we find that the average percentage of polymorphs is 65.2 per cent, while in those cases, in which the eosinophiles are more than 4 per cent, the average polymorph count is 53.7 per cent. Further, of the eleven counts, in which the eosinophile percentage is less than 4, only three (that is 27 per cent) have a polymorph percentage less than 60 per cent, while of the thirty one counts, in which the eosinophile percentage is over 4, twenty-four (that is 76.8 per cent) have a polymorph percentage below 60.

As far as the lymphocytes are concerned the differences are less striking. In the cases, in which the eosinophile percentage is less than 4, the lymphocytes average 32 per cent; in the remaining cases they average 38.7 per cent. In the earlier cases all the lymphocytes were counted together, but later the true lymphocytes and monocytes were counted separately. When these cases are considered there is a more pronounced difference in the lymphocyte count. In five cases, in which the eosinophile count was less than 4, the average lymphocyte/

lymphocyte percentage was 25.3, and the average monocyte percentage 6.2. In 19 cases in which the eosinophile count was above 4 per cent, the average lymphocyte percentage was 32.8, and the average monocyte percentage 6.0. It would, therefore, appear that in these cases we are not dealing with a simple increase of eosinophiles at the expense of all other types of leucocytes, but that both eosinophiles and lymphocytes are increased mainly at the expense of the neutrophiles.

One or two further points of interest may be noted. In a few cases several determinations were made on different occasions, and some of these show considerable variation in the eosinophile percentage. For example, in TABLE I No. 5 and 19 are from the same patient with an interval of two months between them, and the eosinophile count varies from 2 to 8.6 per cent; in No. 17 the count varies from 7.3 to 15.3; in No. 18 from 4.0 to 8.0; and in No. 23 from 6 to 15. Some of these cases show very clearly that an increase of eosinophiles is associated with an increase of lymphocytes and a decrease of neutrophiles. Examples are given in TABLE VIII.

TABLE/

TABLE VIII.

CASE	NO. IN TABLE I	P.	L.	E	
Mrs K.	5	51	36	2.5	
	19	27:1:30	37.3	53.2	8.6
Mrs J.	17	6:12:29	73	19	8
		24:12:29	53.6	30.9	15.3
A.K.	18	7:1:30	64	31.3	4.0
		15:1:30	51.3	40.2	8.0

Four of the cases in TABLE I had a chronic form of eczema associated with the asthma. In all of these the eosinophile count was high. They are No. 16 with 7.3 per cent, No. 17 with 7.3, 8, 10 and 15.3 per cent, No. 18 with 4, 7.6 and 8 per cent, and No. 21 with 10 per cent. In view of the association already described between skin diseases and eosinophilia, it seems probable that every case of asthma and eczema will show similar figures, and it is, of course, difficult to know to which of these conditions the eosinophilia is really due.

Most of the cases investigated were undergoing a course of vaccine treatment, and in some of these an attempt was made to determine whether this had any effect upon the eosinophilia. Most of the patients, however, live at considerable distances from Edinburgh/

Edinburgh, and it was not possible to get them to attend for repeated determinations. Four cases in which there was a definite degree of eosinophilia were followed up.

1. The first patient (M.K.) reported on the 23rd December 1929, when her eosinophile count was 7 per cent. She began a course of vaccines on the 1st January 1930, and completed it on the 4th March. During this time she had four bad attacks of asthma, and another on the 9th March. She reported again on the 12th March when her eosinophile count was 5 per cent.

2. The second patient (J.D.) reported on the 11th December 1929, when his eosinophile count was 15 per cent. He began his course of treatment on the 11th January 1930, and completed it on the 10th February. He reported again on the 12th March, having had no asthma since the beginning of the year. His eosinophile count was then 6 per cent.

3./

3. The third patient (Mrs M.) reported on the 2nd February 1930 when her eosinophile count was 8 per cent. She began treatment on the 3rd March and reported again on the 11th March, after three doses of vaccine. She had had a bad attack that morning and her count was still 8 per cent.
4. The fourth patient (J.M.) was able to report more frequently. He first came to us on the 13th December 1929, having had an attack of asthma between 4 and 5 a.m. that morning. He then had 10 per cent eosinophiles. His treatment began on the 4th January, 1930, and he reported again on the 14th January, having had no attacks for ten days. His count was then 8 per cent. Treatment was continued, and he reported again on the 21st January, having had a bad attack on the 17th January. His count was 9.3 per cent. On the 6th February he was very much better, having had only one very slight attack since the 17th January. His count was 6.6 per cent. On the 23rd February he had a very bad attack, the worst since the treatment began/



began. The course was completed on the 26th February and next day his eosinophile count was 9.6 per cent.

These cases are admittedly too few in number to permit any definite conclusions to be drawn. They do, however, suggest that the chief factor in maintaining an increased eosinophile percentage is the asthmatic attack itself. The second patient for instance, had no attacks for over two months, and his count fell from 15 per cent to 6 per cent. The fourth patient had one very slight attack in a period of three weeks, and his count fell from 9.3 per cent to 6.6 per cent. A bad attack a week later was followed by a return of the count to 9.6 per cent. The other two patients who had attacks during treatment show in one case a fall of 2 per cent and in the other no change. Probably the eosinophile count is raised during an attack, and then only slowly falls to normal figures, thus accounting for the raised level of eosinophilia in the intervals between attacks. This suggestion is in line with BOYCOTT'S findings in the cases of ankylostomiasis, that once eosinophilia is established it diminishes very slowly.

HAY/

HAY FEVER.

The composition of the blood picture has been much less studied in this condition than in
 (102)
 asthma. KLINKERT described a case in which the patient had digestive troubles and showed dermographism, and had previously had hay fever. His eosinophile percentage was 8.6 He belonged to a family of which nearly all the members had eosino-
 (113)
 philia. In 1914 EMRYS ROBERTS found in the course of hay fever 7 or 8 and sometimes 13 per cent of eosinophiles, and in the intervals between the
 (13)
 attacks 3 or 4 per cent. BEZANÇON and MOREAU
 (114)
 in one case found 7 per cent. FISCHER in 1915 examining patients during attacks of hay fever, found an increased percentage of eosinophiles of 20 to 30, and even in certain cases 58 per cent. The eosinophilia was specially marked at the beginning of the period of hay fever, then steadily fell and returned to normal about the third week. The most extensive observations are again due to PASTEUR VALLERY
 (97)
 RADOT and his colleagues . They examined 50 cases during attacks. Thirty seven of these had 4 per cent of eosinophiles or more, nine reaching 10 per cent or over. Therefore 74 per cent of the cases showed eosinophilia. Fifty two cases were examined between the attacks and of these eleven only (that is 21 per cent) showed eosinophilia.

URTICARIA/

URTICARIA.

More attention has been paid to this condition than to hay fever. CANON⁽³²⁾ in 1890 found 2 per cent of eosinophiles in this condition. LAZARUS (quoted in 13 and 97) found in one case 60 per cent, but this appears to be the only case which has been reported with eosinophilia of such a degree. LEREDDE⁽¹¹⁵⁾ reported ten cases. In two of these eosinophiles were absent; in one there was at first 0.3 per cent and later 20 per cent; in four the count was less than 4 per cent; in two cases it was 6 and 8 per cent respectively; in one case of chronic urticaria it was 8.8 per cent. SOUMAIRE⁽¹¹⁶⁾ found 2 per cent and 3.2 per cent in the two cases he examined. AUDIBERT⁽⁸⁾ in one case found 1 per cent and 3 per cent. LAMS⁽¹⁷⁾ is of the opinion that eosinophilia is not constant in urticaria. BEZANÇON and MOREAU⁽¹³⁾ examined twenty patients and did not find more than 3 per cent in any of them. VALLERY RADOT⁽⁹⁷⁾ examined thirty cases and found eight (that is 26 per cent) with an eosinophile count equal to or greater than 4 per cent, but the figures are very nearly normal. BOYCOTT⁽⁴⁷⁾ examined a series of eleven cases of acute wide-spread urticaria: in no case did the eosinophiles reach 4 per cent. The present writer has repeatedly examined/

examined a case of chronic urticaria without ever finding an eosinophile percentage greater than 4. In a case of a more acute type the count was only 1 per cent.

FAMILIAL EOSINOPHILIA.

(117)
 KLINKERT records observations on a family in which the father, who suffered from hyperchlorhydria had 6 per cent of eosinophiles, the eldest daughter, who had an idiosyncrasy for fish, had 9 per cent, a son with asthma had 8.6 per cent, a dyspeptic daughter 8 per cent, an asthmatic daughter 15 per cent, and the youngest daughter with a slight Basedow's syndrome 11 per cent.

(13)
 GAUGAIN mentions a family in which the mother had 19 per cent and three children 10, 14 and 15 per cent respectively, though he could discover no pathological cause for this. (13)
 GALLIARD adds to this the observation of a patient with Recklinghausen's disease who had 11 per cent of eosinophiles, and whose healthy children also showed a marked eosinophilia.

II. THE EXPERIMENTAL PRODUCTION OF EOSINOPHILIA.

Numerous workers claim to have succeeded in producing eosinophilia in such animals as the rabbit and guinea pig, by a variety of experimental procedures. Apparently the most certain and effective method of producing it is by the introduction into these animals of certain of the parasitic worms, or by the injection into them of extracts of such parasites.

(119)
 OPIE appears to have been one of the earliest to record observations on these lines.

(119)
 He found that complete withdrawal of food from guinea-pigs is followed by a decrease in the proportion and absolute number of eosinophiles in the peripheral circulation. With the administration of food the eosinophiles of the blood gradually increase in numbers. Variations in weight and in the number of eosinophiles in the blood take opposite directions with much regularity, so that a temporary fall in weight is accompanied by a rapid increase of eosinophile leucocytes while a rise in weight tends to re-

(118)
 tard this. OPIE also found that the administration of trichina spiralis in infected pork caused an/

an increase of eosinophiles in the blood of guinea-pigs. There was no constant alteration till the end of the second week after infection when the relative and absolute number rapidly increased, reaching a maximum at the end of the third week. WILLIAMS and BEUTZ (120) had previously found no increase of eosinophile cells in rats and cats infected with trichinae. OPIE also tried the effect of subcutaneous injections of extracts of taenia saginata, but failed to produce any eosinophilia.

Extracts of various parasitic worms have, however, been repeatedly employed and have apparently (13) been successful in most cases. BEZANÇON and MOREAU for instance, mention that PROESCHER produced eosinophilia in rabbits by intravenous and intraperitoneal injections of extracts of taenia solium and taenia saginata, and that MELNIKOFF obtained similar results in rabbits and guinea-pigs, following subcutaneous injections of extract of taenia solium. Before the experiments the animals had 2 to 4 per cent of eosinophiles, and afterwards 34 to 70 per cent. Similarly WEINBERG has been able to produce eosinophilia by the injection of a variety of parasitic extracts. He noticed that repeated injections of the same extract would produce eosinophilia, although a single massive injection failed to do so. The fluid from hydatid cysts has also been frequently used to cause eosinophilia.

Important contributions to this subject have been made by SCHLECHT and his colleagues in Germany, and also by WEINBERT and SÉGUIN in France. In what follows we propose to summarise briefly their experimental findings, leaving the interpretation which they give of these to be discussed later.

(121)

SCHLECHT found that the percentage of eosinophiles in the blood is raised by repeated injections of serum at intervals of several days. He claims that this occurs in man, especially in children, after repeated injections of antidiphtheritic serum. In guinea-pigs intraperitoneal injections of serum gave rise to a high grade eosinophilia, and he showed that this reaction was not due to the diphtheria antitoxin, but to the serum itself. The same reaction was obtained with various sera such as horse and cow serum, but was not produced by the animal's own serum. Further investigation satisfied him that any protein down to the peptones would produce this reaction, but that the lower amino acids were without effect.

(122)

SCHLECHT has also investigated the relationship between eosinophilia and anaphylaxis. By suitable injections he produced an experimental anaphylactic shock in guinea-pigs, and found that there was first a disappearance of eosinophiles, and then as the animal began to recover there was an enormous/

enormous increase of eosinophiles which rose in a few hours or days to great heights. The eosinophilia remained for a few days and then fell rapidly. A further injection caused a renewed eosinophilia without any accompanying anaphylactic symptoms. These observations have been confirmed by HERRICK (124).

(123)
 SCHLECHT and SCHWENKER have shown that the repeated subcutaneous injection of 1 c.c. of inactivated human serum into a guinea-pig every two or three days, produces a considerable infiltration of eosinophile leucocytes into the connective tissues at the site of the injection. The infiltration became more marked after the third, fourth and fifth injection.

(125)
 SCHLECHT and SCHWENKER have further observed a pulmonary eosinophilia localised especially round the bronchi and bronchioles in sensitised guinea-pigs, two to twenty-four hours after the production of anaphylactic shock by an intraperitoneal injection of foreign serum. They examined the lungs of a large number of untreated guinea pigs, and never found more than a slight pulmonary eosinophilia even in animals with spontaneous blood eosinophilia. STROBEL (126) also claims to have observed a much more intense local eosinophilia in the lungs/

lungs of guinea-pigs killed twenty four hours after a non-fatal anaphylactic shock than in those of animals dying of acute anaphylaxis, or of untreated guinea-pigs killed as controls.

(127)

WEINBERG and SÉGUIN have repeated many of SCHLECHT'S experiments and have added further observations of their own. In their first series of experiments an extract of *Ascaris megaloccephala* was instilled into the eyes of horses, and the resulting changes in the conjunctiva of the eyelids were noted. They found that this produced an intense local eosinophilia, the intensity being directly proportional to the number of eosinophiles in the blood. Similar effects were produced in guinea pigs by subcutaneous injections of hydatid fluid. They conclude, therefore, that the absorption of verminous toxins results in an intense afflux of eosinophile leucocytes which arrive in the connective tissues in numbers proportional to their abundance in the blood. They also investigated the effects of peritoneal injections after first examining the question of the spontaneous peritoneal eosinophilia, which is frequently found in guinea-pigs. (SZECSI ⁽¹²⁸⁾). One hundred and fifty animals were examined, and only seven found to possess a peritoneal exudate free from eosinophiles. In eighteen the eosinophilia exceeded/

exceeded 30 per cent. SZECSI and EWALD⁽¹²⁹⁾ have published similar figures. As a rule there is a parallelism between the spontaneous peritoneal eosinophilia and the blood eosinophilia. Injection of hydatid fluid into the peritoneal cavity of guinea pigs, after careful estimation of the leucocytic formula of the blood and of the exudate, failed to produce a peritoneal eosinophilia even in animals with a high blood eosinophilia. In the abdominal wall and mesentery, however, there is an eosinophilic infiltration of the tissues, the intensity of which depends upon the extent to which the eosinophile count in the blood is raised. They were, however, able to provoke a peritoneal eosinophilia in animals which received a preliminary series of subcutaneous or intraperitoneal injections at intervals of about a week. They found that this occurred only in animals which showed a definite blood eosinophilia before the final injection. Further even when the first injection failed to provoke eosinophilia in the exudate, the eosinophiles appeared in large numbers and very rapidly after the animals had been prepared by three or four preliminary injections. The authors conclude that "during the immunisation of the animal by an eosinotactic substance, the chemiotactic properties
"of/

"of the eosinophiles increase. The eosinophiles become much more sensitive to the action of the injected substance, to the stimulus of which they respond with greater rapidity and in much greater numbers". They also found that there exists a real specificity of eosinotactic reaction. Guinea-pigs prepared by repeated injections of a given eosinotactic substance react more intensely to that substance than to any other eosinotactic substance.

In a second series of experiments they repeated SCHLECHT and SCHWENKER'S observations on the lungs of guinea-pigs dying of acute anaphylaxis, and of animals which survived an anaphylactic shock produced by the injection of horse serum. They could not find any difference between the intensity of the pulmonary eosinophilia observed in the control guinea-pigs, in those dying of acute anaphylaxis, or in those killed twenty-four hours after a non-fatal anaphylactic shock, and therefore conclude that the pulmonary eosinophilia observed by SCHLECHT and SCHWENKER was not a local eosinophilia provoked by the anaphylactic toxin, but a spontaneous chronic eosinophilia.

WEINBERG and SÉGUIN do, however, confirm SCHLECHT'S observation that the percentage of eosinophiles in the blood is raised in animals which receive repeated/

repeated injections of serum at some days' interval. They find that the increase in the eosinophilia under these conditions has no relation to the gravity of the anaphylactic phenomena produced, and that the eosinophiles increase in numbers in the blood of sensitised guinea-pigs, when the test injection is made subcutaneously without giving rise to the slightest morbid symptom. Further, the anaphylactic crisis, whatever its intensity, is not generally followed by a raising of the eosinophilia when the test injection is given intravenously. They have also produced symptoms of "passive anaphylaxis" by using the serum of guinea-pigs previously sensitised with horse serum, and these were not accompanied by any more than a very slight increase of eosinophiles.

They noted in their experiments that the repeated injection of substances, such as horse serum, produced not only an increase of eosinophiles, but also a notable increase of mast cells in the blood. This fact has also been noted by SCHLECHT and by
(130)
AHL and SCHITTENHELM .

(13)
BEZANÇON and MOREAU could not produce any appreciable rise in eosinophiles in the blood by the injection of human serum into guinea-pigs. In eighteen guinea-pigs only two showed an eosinophilia of 7 to 9 per cent. In the others after five subcutaneous/

subcutaneous injections of serum, the eosinophilia remained at its original figure oscillating between 0.5 and 3 per cent.

A few observations have been made on the composition of the blood picture during the haemoclastic crisis produced by WIDAL'S test ⁽¹³¹⁾ in patients ⁽¹³²⁾ suffering from hepatic insufficiency. SCHIFF claims that this crisis is accompanied by a rise of eosinophiles. ⁽⁹⁷⁾ VALLERY-RADOT examined ten cases and did not once find any modification of the number of eosinophiles. He has also provoked a haemoclastic crisis by intradermal injections of peptone ⁽¹³³⁾ in patients with a respiratory anaphylactic syndrome, and by the application of heat or cold ⁽¹³⁴⁾ to patients with migraine. In none of these was the crisis accompanied by eosinophilia. Nor has he found the eosinophiles increased in the haemoclastic crisis preceding attacks of asthma or urticaria experimentally produced by the inhalation or ingestion of the specific protein.

Injections of such substances as adrenaline, pilocarpine and atropine have also been used. SCHLECHT and SCHWENKER ⁽¹³⁵⁾ were unable to produce eosinophilia with adrenaline and physostigmine and found that these substances did not produce any local pulmonary, glandular or splenic eosinophilia.

III. THE SIGNIFICANCE OF EOSINOPHILIA.

In this section we propose to discuss the significance of the occurrence of eosinophilia -

- (a) from the point of view of diagnosis and prognosis, and
- (b) as regards the probable function of the eosinophile leucocyte.

A. DIAGNOSTIC and PROGNOSTIC SIGNIFICANCE.

Our survey of the literature regarding the conditions in which eosinophiles appear in increased numbers in the blood has led us to conclude that these are principally four in number, viz:-

- (i) During convalescence from infectious fevers, especially scarlet fever.
- (ii) In the course of various skin diseases.
- (iii) In asthmatic patients.
- (iv) In association with parasitic infestations.

It may occasionally be associated with other conditions, such as neoplasms of the cervix or the alimentary canal, or with cases of drug poisoning associated with skin rashes. In any case, in which eosinophilia/

eosinophilia is found, however, attention should first of all be directed to the possibility of one or other of the above four conditions being present. There may, of course, be some other more obvious condition present also, but the eosinophilia should not be associated with this, until the most thorough investigation has eliminated the possible occurrence of a recent infectious fever, of some skin condition, of asthma or of a parasitic infestation.

The eosinophilia which occurs in these conditions is of different degrees of frequency and intensity. We may classify the grades of eosinophilia somewhat arbitrarily as follows:- low grade 4 - 10 per cent; medium grade 10 - 20 per cent; high grade 20 per cent and over. On this basis we should say that generally speaking eosinophilia of low to medium grade is associated with convalescence, with the majority of skin diseases, with asthma and with infestations with such parasites, as *Oxyuris vermicularis*, *Taenia solium* and *mediocanellata*, and *Echinococcus* cysts. This low grade eosinophilia is not constantly present in these conditions.

A high grade eosinophilia is frequently, if not constantly, associated with dermatitis herpetiformis and pemphigus among the skin diseases and with *Bilharzia*, *Trichina*, *Ankylostoma* and *Filaria* among/

among the parasitic infestations. In countries where these diseases are common, examination of the blood may prove of great value in detecting patients likely to harbour parasites and who should be more thoroughly investigated. BOYCOTT⁽⁴⁷⁾ has given an excellent example of this in his work on Ankylostomiasis in Cornish miners. He considers that a blood examination "is a simple and accurate way of investigating a large number of men easily and quickly to see if a suspicion of Ankylostoma infection is thereby raised of sufficient strength to justify the troublesome process of obtaining specimens of stools from a number of men. If specimens of blood from 10 or 20 per cent of the underground men fail to reveal any cases of an increase in the eosinophile cells, it may be assumed that the mine is free from any extensive infection. If, on the other hand, any cases of eosinophilia are met with, the individual source of each blood sample is known; and further examination of each positive case is then made to see whether the abnormality is due to the Ankylostoma or to one of the other causes of eosinophilia. It will be readily seen that the method is most superior to the primary examination of faeces in cases where there is no Ankylostoma infection".

Eosinophilia is probably of very little prognostic significance, though its value in this way might/

might well repay further investigation. The re-appearance of eosinophiles after an infectious fever is a good sign, and their increase may mark the beginning of a remission or of convalescence. Decline of the eosinophilia seems to occur during recovery from such skin diseases as dermatitis herpetiformis or pemphigus. BOYCOTT⁽⁴⁷⁾ finds that the decline is very gradual after recovery from parasitic infestations. We have not been able to discover any relation between eosinophilia and the prognosis in asthma.

B. FUNCTIONAL SIGNIFICANCE OF EOSINOPHILIA.

A great deal of discussion has taken place in regard to this and we propose here merely to summarise the main views which have been expressed, and to indicate the conclusions to which we have come from our own observations and from our study of the literature. One of the most interesting suggestions that has been put forward in recent years principally in Germany is that eosinophilia is to be regarded as the anatomical substratum of certain diatheses. CZERNY, as is well known, has endeavoured to distinguish clinically under the name of the "exudative diathesis"/

diathesis" a morbid grouping common in nurselings and in children characterised by various forms of eczema, prurigo and various erythemata and by asthma and various catarrhs. HISS at the "Congrès de médecine interne de Wiesbaden" in 1911 went further, and proposed in addition to the "exudative diathesis" of CZERNY a real "eosinophilic diathesis", of which asthma and mucomembranous colitis are the principal manifestations. Others have included not only these two conditions, but also hay fever, migraine, eczema, urticaria, angio-neurotic oedema and certain conditions of alimentary idiosyncrasy. Others think it is impossible to draw a clear distinction between the exudative diathesis and the eosinophilic diathesis.

EPPINGER and HISS propose another conception of diatheses, which in their view are determined by the disharmony of two regulating systems, the pneumogastric and the sympathetic. According to the predominance of the one or the other of these systems, they believe they can distinguish two great syndromes, vagotonia and sympathicotonia. According to them the vagotonics are subjects who react strongly to pilocarpine; they show a series of small symptoms revealing a latent excitation of the vagus such as dermatographism, enteroptosis, and exaggerated reflexes/

reflexes, and among other pathological manifestations, asthma, urticaria, and mucomembranous colitis. They claim that a considerable eosinophilia is very frequent in such subjects.

We are not here concerned with the legitimacy or otherwise of these conceptions of diatheses, or even with the conditions to be included in them, but simply with the significance of eosinophilia in relation to them. The conditions nearly always grouped under the term "eosinophilic diathesis" or "exudative diathesis" or "vagotonia" are bronchial asthma, hay fever, mucomembranous colitis, urticaria and eczema. Eosinophilia of a low grade undoubtedly occurs in asthma, and according to our observations is present in about half the cases between the attacks. VALLERY RADOT'S figures, already quoted, indicate that eosinophilia is also frequent, during attacks of hay fever, but practically disappears between the attacks. It may also occur in eczema, but it is doubtful whether it does so with any constancy. In any case before it can be regarded as the signature of a constitutional state, it should be shown to persist in the intervals between the eruptions, as otherwise it may be regarded as simply due to the local cutaneous reaction, and of the same significance/

significance as in other skin conditions where it occurs. We have not found any satisfactory evidence of the occurrence of eosinophilia in mucomembranous colitis. BEZANÇON and MOREAU maintain that in this condition there is nothing more than a local eosinophilia such as occurs equally in mucopurulent diarrhoea, in intestinal stenoses, either neoplastic or cicatricial and in a number of chronic affections of the digestive tract. In urticaria the evidence seems to us to be clear that eosinophilia does not occur. We agree, therefore, with BEZANÇON and MOREAU that before we can accept the idea of an eosinophilic diathesis, its constitution needs to be revised. KLINKERT'S observations on familial eosinophilia might lend support to the idea of an eosinophilic diathesis, but they need to be considerably extended. We are of the opinion also, as we shall show later, that eosinophilia, whenever it appears is in response to certain demands or stimuli, and is not to be regarded as the indication of a peculiar constitutional condition.

A second view somewhat allied to the first is that eosinophilia is closely related to anaphylaxis. KLINKERT, for example, suggests that eosinophilia is the haematological expression of anaphylaxis, and from that it would be but a step to regard it/

it as the signature of the anaphylactic state.

SCHLECHT scarcely goes as far as this, but he considers that there is a very close relationship between eosinophilia and anaphylaxis. As a result of his experiments with sera and proteins he concludes that eosinophilia is a defence reaction on the part of the body against the toxicity of foreign proteins, and more particularly against the "anaphylotoxine". He explains the intense local eosinophilia which occurs after injections of sera as being due to the chemiotactic action which the anaphylotoxine, produced locally at the expense of the albumin of the serum, exercises on the eosinophiles of the blood.

BEZANÇON and MOREAU criticise this conception on the ground that eosinophilia appears after the injection of anti-diphtheritic serum, for example, even when there are no accompanying anaphylactic symptoms. The experiments of WEINBERG and SÉGUIN, already mentioned, do not lend support to the views of SCHLECHT and his colleagues. They could not find any relationship between the increase of the eosinophiles and the gravity of the anaphylactic phenomena produced. For example, a serious anaphylactic crisis could occur in animals with weak eosinophilia, and conversely the anaphylactic crisis in animals with/

with considerable eosinophilia is not more intense than in those with slight eosinophilia. They did not find that the anaphylactic crisis was invariably followed by eosinophilia. Further when the final injection was made subcutaneously instead of intraperitoneally the eosinophilia continued to rise as after the preliminary injections although no anaphylactic crisis occurred. They conclude from their experiments that there exists no relation of cause and effect between the increased blood eosinophilia arising in certain conditions after a 'releasing' injection and the production in the organism of anaphylactic toxin. When the eosinophiles in the blood increase after an anaphylactic crisis, it is, in their opinion, a coincidence. The increase of eosinophiles is a phenomenon of immunity, which is explained by the action which the antigen exerts on the haemopoietic centres, and specially the bone marrow, prepared to react after the first injection. It has the same significance as the eosinophilia which is observed following repeated injections at short intervals of any eosinotactic substance whatever..

It will thus be seen that WEINBERG and SÉGUIN regard the production of eosinophilia as a purely/

chemiotactic response to the introduction of certain substances into the organism. This is substantially the view taken by BEZANÇON and MOREAU and the majority of the French school. They regard eosinophilia as truly symptomatic of an intoxication and particularly of intoxication by products of animal origin. The eosinophilia which occurs in asthma they regard as evidence of a latent intoxication and of special sensitiveness to toxic substances. They draw attention to the selective sensitivity of asthmatics to the ingestion of certain foods and especially to serum injections, and suggest that asthma probably develops on a special soil, on which other affections may also develop, having a certain analogy with asthma without eosinophilia being necessarily the connecting link between them. While not admitting the existence of an "eosinophilic" diathesis, they think that certain subjects who show an habitual eosinophilia are more exposed than others to certain affections, which like asthma, betray an intoxication. The eosinophilia is in these cases evidence of a latent intoxication, endogenous or exogenous, which an accidental cause, often quite trivial, suffices to make manifest or exaggerated. They conclude that "eosinophilia is merely a particular reaction to "certain/

"certain intoxications and specially to intoxications
"by albuminous substances. If certain of these in-
"toxications have an analogy with anaphylactic condi-
"tions it does not follow that we can go further and
"consider eosinophilia as the evidence of an anaphy-
"lactic condition."

It seems to the present writer that the above views are based upon too limited a consideration of the conditions under which eosinophilia occurs. He does not accept the view that eosinophilia is an anaphylactic manifestation, since it undoubtedly occurs apart from the occurrence of anaphylaxis and is apparently absent in such conditions as urticaria. As we have seen, there are four main conditions in which some degree of eosinophilia occurs. The first of these - post-infective eosinophilia - is probably quite distinct from the others. During the height of the infection there has been an immense output of neutrophile polymorphonuclear leucocytes and a diminished output of other leucocytes. As the infection declines the haemopoietic centres gradually cease to produce neutrophiles in such abundance and to resume the output of eosinophiles and lymphocytes. The post-infective rise in the numbers of the latter is, therefore, probably of a compensatory character occurring/

occurring before the marrow finally adjusts itself to normal conditions again.

The other three conditions - skin diseases, asthma and parasitic infestations - appear to have this at least in common that in each of them there is some local irritation of the tissues, and in most cases of epithelium, and that this is frequently accompanied by an intense local eosinophilia.

(107)

BABONNEIX has drawn attention to the frequent association of local eosinophilia with many skin diseases, and particularly with the bulbous dermatoses. We have already described the occurrence of intense local pulmonary eosinophilia in asthma, and the association of local eosinophilia of the intestines with parasitic infestations is well known. Further, the experiments of both SCHLECHT and WEINBERG show that injections of verminous products or of sera, produces a marked infiltration of the connective tissues in the neighbourhood of the injection with eosinophiles. SCHLECHT also makes the interesting suggestion, that eosinophilia occurs whenever there is destruction of epithelium, and is caused by toxins liberated by the decomposition of proteins. In view of these facts it seems to us that eosinophilia is probably to be regarded as a response/

response to some form of irritation of certain tissues, notably epithelium. The irritants would seem to be substances of a protein character. The first result of such irritation is to cause a local infiltration of eosinophiles at the affected site, and, if this is maintained, the haemopoietic centres respond by the production, or at least the discharge into the blood, of increased numbers of eosinophiles, which pass to the affected tissues. Obviously this explanation leaves much to be desired, but it does not appear that our present knowledge allows us to be more definite in assessing the true functional significance of eosinophilia.

C. THE RELATIONSHIP OF EOSINOPHILIA TO ASTHMA.

Our own observations on asthmatic patients lead us to conclude that a low grade eosinophilia occurs in about 50 per cent of cases examined during the period of freedom from acute attacks. The increase of eosinophiles is associated with an increase of lymphocytes and a decrease of neutrophiles. The degree of eosinophilia shows considerable variation from/

from time to time in the same patient. In patients who suffer from both asthma and eczema eosinophilia is probably always present, and ranges from 7 to 15 per cent. There is no evidence that vaccine treatment in itself leads to a diminution of the eosinophile count. The main factor in maintaining the raised level of eosinophilia is probably the asthmatic attack itself, and a period of freedom from attacks is followed by a gradual subsidence of the level. On the view we have already expressed the eosinophilia is probably due to some form of irritation of the bronchial epithelium, and its occurrence between acute attacks is due to the persistence in many cases of a mild form of irritation. In those cases in which it disappears between the attacks the irritation may be merely an occasional incident which does not persist.

IV./

IV. CONCLUSIONS.

- I. There are four main groups of conditions in which eosinophilia is of frequent occurrence:-
- (a) Convalescence from infectious fevers, and in the course of scarlet fever.
 - (b) Skin diseases.
 - (c) Asthma.
 - (d) Parasitic infestations.
- II. The eosinophilia is of low grade in convalescence and in most skin diseases, except dermatitis herpetiformis and pemphigus.
- III. A low grade eosinophilia is present in 50 per cent of asthmatic patients.
- IV. High grade eosinophilia is specially associated with infestations of Bilharzia, Filaria, Trichina and Ankylostoma; a low grade eosinophilia may occur with any parasitic infestation.

V. The view is expressed that eosinophilia is associated with certain forms of irritation, probably by protein substances, of the tissues and particularly of epithelium.

In conclusion I should like to express my indebtedness to Professor Murray Lyon, at whose suggestion this work was begun, and who has given me much assistance by his advice and criticism during its execution.

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