Survey of some of the conditions causing eosinophilia with notes on the significance of the eosinophile cell

John R. Darrah
University of Nebraska Medical Center

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A SURVEY OF SOME OF THE CONDITIONS CAUSING EOSINOPHILIA WITH NOTES ON THE SIGNIFICANCE OF THE EOSINOPHILE CELL

by

John Russell Darrah, A.B., B.Sc.,

Presented to the Faculty of the College of Medicine of the University of Nebraska in Partial Fulfillment of the Requirements of the Degree of Doctor of Medicine

Omaha, Nebraska

1935
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"The blood, this soul of the flesh, (Moses), this treasure of life (Ambroise Pare), this liquid flesh (Bordeu), this fluid, the source of all other fluids in the body, unceasingly moving in the process of circulation, unceasingly reanimated by the act of respiration, unceasingly changing, and unceasingly renewed by the act of nutrition, has always attracted the attention of observers, and most medical writers of different ages have assigned to it an important place in pathology. In our days, when exactness of methods derived from mechanics and chemistry enables us to study with minuteness the chief alterations in the blood, we find numerous investigations with regard to this fluid, both in its healthy and morbid conditions. A summary of these investigations, as concise and thorough as possible, will form the basis of this dissertation."

HISTORICAL

Although Jan Swammerdam was the first man to see the red corpuscles of the blood, and Malpighi was the second, it was van Leeuwenhoek who initiated the study of the blood when he read his report to the Royal Society in 1674. The observations of Swammerdam in 1658 were not published until after his death, in 1738. Malpighii mistook the red corpuscles for fat droplets (1665) and just missed adding another sensational discovery to his already long list of anatomical achievements.

Following the report of van Leeuwenhoek, there was little real advance in knowledge of the cellular components of the blood until the time of Hewson (1770) and Wm. Hunter (1794). Various experimenters observed the reactions of the erythrocytes to the usual chemical solutions then in popular use as reagents, but the discovery of the white blood cells by Hewson initiated a long series of experiments on the blood. Nevertheless, the knowledge was slow in accumulating for another century. As late as 1854, for example, there was a distinction made between the cells found in inflammatory exudates, and the white corpuscles of the blood, which were supposed to be without a nucleus, although Jones and Sieveking (1854) reported that under the influence of acetic acid there was the appearance of "one, two, or three granules similar to those seen in pus cells."

At this time there was no method for making blood counts, although changes in the blood were recognized as being important
and were the subject of much controversy in the literature of the time. The quantity of red blood cells was estimated by the height of a column of cells that settled out of a drawn specimen of blood. There was supposed to be a relative "plethora" in the acute infectious diseases, and in fever, estimated by the increase in parts per thousand of the cell column over the amount of fluid drawn. The function of the erythrocyte had not been proven, although considerable work at this time was based upon the correct hypothesis, as we see it, and shortly thereafter the initial significant work in metabolism was done.

Lehmann* had claimed an increase in the white blood cells in the condition of "pyemia", and Vogel had already introduced the term "granule cell" from his studies of inflammatory exudates. In 1846 Wharton Jones described two types of granular cells in the circulating blood, one form which had fine granules, and the other with coarse granules. This observation was apparently slow in getting into the general literature, since it is not mentioned in contemporary works on pathology and physiology, but was of significance to Max Schultze (1865) who observed the ameboid movements of the finely granular cells in the blood on a warm stage, and differentiated these cells from coarsely granular cells and lymphocytes.

Work at this time was slow and tedious, and it was necessary to examine the blood with whatever reagents were available almost as soon as it was drawn because, "Studying the blood after it has been abstracted from the body, is really but making an

*Quoted by Jones and Sieveking, no reference cited.
autopsy of it, if we may be allowed, so to speak, and the longer its examination is postponed after its abstraction, the less favorable will be the conditions for ascertaining its real nature, as entering into the composition of the living body. Many microscopical observations, and even chemical analyses have been erroneous from the necessity of studying these fluids after they have lost the characteristics of life.footnote

When Ehrlich introduced stained preparations in 1879 and the simpler processes of fixation of tissues, the necessity for this haste disappeared, and soon afterward Ehrlich brought out the first complete classification and description of the cells found in the circulating blood, showing that the coarse granules of Max Schultze and Wharton Jones had a strong affinity for eosin. He named these leucocytes "eosinophiles", and that designation has since persisted in the literature.

Although it took almost another generation to clear up Ehrlich's few misconceptions, especially those regarding the "transitional cells", the general classification of Ehrlich still stands. Soon after this, with the impetus given by Ehrlich and Koch, the knowledge of staining and microtomic technic advanced rapidly and hematology began to take on new importance in scientific medicine, adding new concepts of disease and immunity. Every new fact discovered or proven opens new channels for research, yet there are still some cells of the blood about which very little is known.

*Gilbert, 1843.
With the advent of stained microscopic sections, the bone marrow was almost immediately discovered to be the seat of granulopoiesis and erythropoiesis, and the spleen and lymph nodes were shown to be the site of formation for the lymphocytic elements of the blood. It was generally considered by all the early investigators, and by some of the present day workers, that these two sources separately supplied their individual constituents to the blood, and that neither overlapped upon the function of the other. As newer methods developed, cytological knowledge advanced, and in the study of inflammation in receding stages it was discovered that a number of interesting changes took place in the cells themselves in these areas, and that the individual cells could no longer be regarded as separate and distinct individual entities, but that the lymphocytic series at least possessed multiple potentialities for differentiation into other forms. Hematologists were slower, as a rule, in accepting the view of multiple potentialities than the investigators who spent their time on more general pathological studies, but early in the twentieth century Pappenheim and Maximow had gathered such evidence that most of the scientific world was prepared to admit that all cells of the blood, both red and white, came from one basic ancestral form or primitive cell which resembled the large lymphocyte. In spite of the fact that this viewpoint explained all the points concerning which there had originally been discrepancies, some workers still adhere to the dualist theory of blood origin, maintaining that the lymphocytes and granulocytes are two distinctly
separate races, and that their paths never cross. Functionally, this may be true, but morphologically it is not, since the more primitive lymphocytic forms are known to be able to differentiate into blood cells of a more specialized nature, and also that they are able to form some of the connective tissue elements.

The studies of the granular leucocytes of the blood have been both gratifying and disappointing. That these cells are "end cells", highly specialized for their particular function is well recognized. Even this point presents its difficulties, since studies of these cells must take place under the special circumstances under which they are the most active, whereas the less specialized cells may be investigated under a variety of circumstances.

The first studies of leucocytic reactions were directed at the responses of all the white cells of the blood, and since it was found that the finely granular or heterophilic cell was the most active participant in inflammatory reactions, work was soon centered on this type of cell at the expense of investigations of the other types. The cells with more obscure function were investigated only spasmodically as their secrets continued to resist solution, and in many cases it was summarily concluded that all were steps in the formation of the heterophilic leucocyte, and had no function at all until they had passed over into that form. Indeed, many early workers concluded that the eosinophile was an aged and degenerate heterophile, no longer active, and some shaped their investigations to this end.
Later, more exact workers have turned their attention to the eosinophiles, and have contributed to the knowledge of this, and other cell types, but the real function of the eosinophile is still unknown.

Nearly all the pathological conditions and diseases affecting the eosinophile content of the blood and tissues are known, and tabulated after a fashion, but the story is not complete. The role of these cells in these conditions is also unknown for want of the application of some key or significant feature of their physiology. In most cases, even the etiological factors concerning those diseases, and their pathological physiology, are also unknown.

The brightness of the eosinophile in the stained smear, and its peculiar behavior in little understood pathological conditions at once made it the center of numerous early investigations, the very brilliance of its appearance attracting attention to it. After Ehrlich had classified the cells of the blood, he turned considerable attention to the eosinophilic cells hoping to use them to demonstrate the function of all leucocytic granules. In studies of the diseases of the blood, he first demonstrated the presence of increased numbers of eosinophilias in myeloid leucemias, but considerable time elapsed before their presence was ascertained in the other diseases. It was 1889 before H. F. Müller directed the work of Gollasch to the study of asthmatic sputums, and about the same time Müller and Rieder showed that infants and children commonly showed a higher eosinophilia than adults. At the
same time they reported that they had observed a nearly constant eosinophilia in chronic tumors of the spleen. Neusser (1892) showed an eosinophilia in pemphigus, and by implication in the "xanthin diatheses" in the diseases which he classified as being due to a disturbed uric acid metabolism. Canon (1892) added to the knowledge of eosinophilia in diseases of the skin, as did Strümpel, who added mucous colitis to the list of the diseases already known to cause an increase in the eosinophiles of the blood.

Zappert's monograph (1893) summarized and collected all the extensive work done in eosinophilia, and was probably the most significant single piece of work since the discovery of the cells by Ehrlich. Zappert not only gathered previous work, but gathered series of blood counts on practically every disease and physiological condition available to him at the time. T. R. Brown at the time he was a medical student at Johns Hopkins (1897) made the observation that there was a pronounced eosinophilia in patients suffering from the parasitic infestation, trichinosis, and suggested a possible diagnostic value of this observation. The observation was also reported by Thayer prior to the complete report by Brown the following year.

Opie (1904) likewise devoted considerable thought to the eosinophile and selected the same infestation for his studies, which lead him to first rule out the effect of nutrition, and then to study the effect in certain bacterial diseases.
A DESCRIPTION OF THE EOSINOPHILIC GRANULOCYTE

I. Terminology.

The normal leucocytes of the blood usually present distinct differences which make them easily recognized by one with even limited experience. There are, however, intermediate stages in the lymphooytic series which offer some difficulty in classification. In pathological bloods there are immature forms of granulocytes which may offer even greater difficulties. For the purposes of a study of this sort, only the mature cells can be considered, except in those cases where the younger but easily recognized cell types are of a significance worthy of mention.

The term leucocyte is loosely applied in the literature, and may apply to any of the white blood cells, and for this reason the term granulocyte has been adapted when it is desired to refer specifically to the granular leucocytes of the blood. Following the practice of Maximow, the name neutrophile has been largely discontinued by hematologists, since it is not true that the specific granules of these cells take neutral stains in contradistinction to the acidophilic (eosinophilic) and basophilic granulocytes, but a mixture of the stains employed. This is especially true in some of the more specialized blood stains and in the study of aberrant cell forms appearing in the leucemias. It is also true in acute inflammatory processes where there are apt to be many young forms in the blood stream. The term 'neutrophile' also does not apply to rabbits and guinea pigs, useful laboratory animals, since the granules in these animals are distinctly acidophilic in character. For these reasons, the term heterophile is more accurate and has been
adapted by most hematologists, especially where the discussions are apt to involve the descriptions of leucoocytes of several species."

II. The Eosinophilic Granulocyte.

The normal, mature eosinophilic granulocyte, also called the acidophilic or oxyphylic granulocyte or leucoocyte of the peripheral blood is slightly larger than the heterophilic leucoocyte. In size, it averages between 12 and 15 microns in diameter in the stained smear (human blood), where it is considerably flattened. In fresh preparations, and in sections, where the cell maintains its normal spherical shape, it is about 10 microns in diameter. All forms appearing in the blood and in most cases in the tissues represent approximately the same stage in development. There is little variation in size, granules, or in nuclear configuration outside the blood-forming centers, or in the absence of pathology.

Immature forms are rarely seen in the peripheral blood except in the blood dyscrasias, where they may appear in great numbers. Normally the eosinophiles constitute only 2 to 4% of the total white blood count, or about 100 to 400 eosinophile cells per cubic millimeter of blood. The eosinophile content of the peripheral blood is strangely uniform in all mammals under normal conditions. The same percentages and absolute eosinophile content of the blood cited from human blood will include the normal limits for practically all the common laboratory animals, and for other
mammals upon which investigations have been made. Birds may show a somewhat higher count, since two types of eosinophilic cells may be present in their blood, one form with round or oval granules, and one with spindle-shaped granules. The latter type is considered to be a pseudo-eosinophiles by some authors.

**Motion.**

The eosinophile is actively motile, although the motion is generally considered to be less marked than in the heterophiles. The pseudopodia of the eosinophile are usually shorter than those of the heterophile, and usually sent out at a slower rate. Sabin has noted that the eosinophile may move as fast as the heterophile, but the more rapid motion is usually restricted, and ordinarily does not last as long as the motion of the heterophilic granulocytes. Observed on the warm stage, this rapid motion usually ceases in less than thirty minutes. Ladvowsky also considered the movements of the eosinophile the most rapid of all the cells.

**Nucleus.**

The nucleus of the human eosinophile is usually bilobed, and the two portions are connected by a thin filament of nuclear substance. Cells with more numerous lobulations are occasionally seen, and those with three lobes are not uncommon. Nuclei with four lobes are rare, but the lobulations may be increased to five or six in severe diseases of the blood, especially in pernicious anemia, where the nuclear lobulations of the heterophilic leucocytes are also greatly increased.
There is considerable variation in the configuration of the nucleus in various animals, and in some of the disease conditions. In general, the nucleus of the eosinophile is less complex than the nucleus of the heterophile in the same species. In the rat, the eosinophile nucleus is usually in the form of a thick, irregularly nodular ring. The eosinophile nucleus stains considerably more weakly than the nuclei of the other leucocytes, but it is nevertheless well marked, especially with the more complex blood stains. It shows less variation from the nuclei of other body cells than does the nucleus of the heterophile, but this by no means indicates a less specialized function. It is less dense than the heterophile nucleus, and the chromatin granules are more easily seen. A nucleolus is reported by Bunting and others, but its presence is denied by Maximow.

Cytoplasm.

The cytoplasm of the eosinophile consists of an inner granular zone, and an outer hyalin portion, or ectoplasm. The ectoplasm is most apparent in fresh preparations, and when the cell is in ameboid motion. There are no vacuoles or "segregation apparatus" in the eosinophile, although these have sometimes been described in the heterophile by the use of vital dyes. The granular cytoplasm rarely stains in any species except in those regions where there are few, if any, granules. In man, the cytoplasm is typically a uniform grayish color with all the common stains. In rats, there is often a portion of the cytoplasm which is relatively free from granules and which
Description

takes a pale blue stain with Wright's stain, or Wright-Giemsa. These areas are paler by comparison than the cytoplasm of the large lymphocyte of the same smear. Under high magnifications and with careful technic, the cytoplasm may be found to stain very faintly with the basic stains in a thin network between the specific granules, giving the appearance of thin partitions separating larger spaces in which lie the eosin-staining granules. Maximow (1930) describes a cytocentrum and diplosome in a clear area in the center of the cell, but this structure is not easily found, and is ignored in most descriptions of the eosinophilic leucocyte.

Cowdry (1914) succeeded in staining a few rod-like mitochondria in some eosinophiles by the use of Janus-green. Most eosinophiles, however, seemed to be free from mitochondria. Simpson, (1921) found them to be much more infrequent than in heterophiles. Sabin, Austrian, Cunningham and Doan (1924) found fewer mitochondria in adult than young eosinophiles and heterophiles, and there was the definite indication that the mitochondria decreased as the formation of specific granules increased, so that by the time the cells were mature, the number of mitochondria were negligible. The technic of demonstration of these organoids may become simple enough in practice to use in the study of leucemic bloods, but at present it is scarcely feasible as a routine laboratory procedure.

There is rarely any phagocytyzed foreign body seen in the cytoplasm of the eosinophilic leucocyte, even in the
conditions in which it is most active. However, it is capable of phagocytosis, and occasionally this function may be demonstrated. Weinberg and Séquin showed phagocytosis in the eosinophiles of the guinea pig (1915), and Josey and Lawrence observed it in man (1932).

Granules.

Seen in tissues, the eosinophile is immediately recognized by the intensely brilliant stain of the large granules, which usually stand out as a bright red (eosin counterstain) in a field of tissue which is largely basophilic. The granules often appear more closely packed and more numerous than in the stained smear, because of the more spherical shape of the cell in section. The nuclear configuration can also be brought out more distinctly by the use of more selective staining in sections. In intensely inflamed areas, or where the pathological changes are marked, the details of the eosinophiles are not easily seen and the cells themselves are often not recognized, but the same holds true of most of the other cells in the same areas. In some cases where the accumulation of eosinophiles is marked, the field will be littered by groups of acidophilic dots, probably extruded granules from dead cells.

The coarse, intensely acidophilic specific granulations of the cytoplasm are the most striking thing about the eosinophilic granulocyte, and give the cell its name. The granules are large, practically uniform in size for each species, and when seen in the fresh state, are very highly refractive. This phenomenon lead many early workers to consider them as fat droplets, although
they were insoluble in most of the ordinary fat-solvent reagents. In all species, the eosinophilic granules which typify the cell are larger and fewer in number than the granules of the heterophilic cells, and in all cases there is the distinct and characteristic affinity for the acid stains.

The shape of the specific granules is usually round, but some species have elongate, oval, barrel, or rod-shaped granules. The spindle-shaped granules are common among birds. Maximow (1930) describes the granules of the rat and guinea pig as short rods, but this shape is not usually apparent with the type of microscope in general use.

Tissue Eosinophiles.

Some tissues of the body commonly show a greater concentration of eosinophilic granulocytes than others under normal conditions. Maximow describes eosinophiles constantly in all the connective tissues of most animals commonly used in laboratory work, and in man. Bunting reports them in embryological blood-forming organs as early or earlier than the heterophiles (1922). Maximow believes that the tissue eosinophiles, except those in the intestinal mucosa where special conditions prevail, are in all respects identical with those of the circulating blood, and that both are derived from the bone-marrow, escaping into the connective tissues in small numbers where their function, if any, is unknown. Eosinophiles appear in greater numbers, however, at sites where some immunological process has gone on persisting for some time at the site of injection of an antigenic
Description, in tissues.

substance (Arthus), being especially prevalent in tissues where there is a local sensitization, and a breakdown of tissues with local necrosis from the antigen injection (Arthus phenomenon). 46

Nonides (1920) reports the presence of considerable eosinophilia in the gonads of the fowl, and describes low grade hematopoiesis of the embryos and even to some extent in the mature birds. Other workers note a relatively constant presence of eosinophiles in noteworthy numbers in the interstitial tissues of the testicle, ovary, uterine submuosa, and in the prostate. Gruner 49 mentions that the interstitial tissues of the kidney normally contain more eosinophiles than most parenchymatous organs.

The hemopoietic system naturally contains a great number of eosinophilic cells, and at some points their concentration is far in excess to the indications of their presence by the percentages found in the blood and in other organs. The bone marrow is characteristically high in eosinophilic cells in all stages of development, and they are likewise numerous in the hemolymph nodes. Latta (1924) showed that there is a slow, but steady production of eosinophiles in lymphatic nodes of normal individuals. 44 The spleen normally contains a considerable number of eosinophiles, and is capable of producing them in great numbers under the stress of acute disease, hemorrhage, anemia, and in other conditions where the hemopoietic function of the body is altered, or where there is great demand upon the body defenses generally. At the same time there may or may not be evidences of other forms of hematopoiesis in this organ.

Lymphoid organs like the tonsils, thymus (Badertscher 1916) 47 and
interstitial tissues of the thyroid commonly contain many eosinophiles, as is true of lymphatic structures generally, although their presence is not at once obvious on casual examination. Gruner (1913)\(^4\) considers that the secretion of the thymus attracts the eosinophilic leucocytes, while Badertscher believes they form there, at least in the fetus.

The submucosa and walls of the gastrointestinal tract commonly contain considerable numbers of eosinophiles.\(^7\) They are especially numerous in the small and large intestine, where they are found in greatest concentration around the bases of the intestinal glands and crypts. They are usually less numerous, or scanty in the villi, and sometimes are less frequent in the neighborhood of Peyer's patches (Gruner), although they are usually numerous even in these areas.\(^7\) The lymphoid areas of the normal appendix contain a number of eosinophiles, and the number is increased in the catarrhal, or lower forms of appendicitis.\(^8\) There is a local decrease of eosinophiles in the intestine after prolonged fasting in guinea pigs (Opie 1904).\(^9\) They are rarely present in the intestine of newborn puppies (Schlecht and Schwenker 1912) but were uniformly present in the adult dogs, and were more plentiful when the nutrition was good.\(^9\)

Eosinophiles are numerous in the interstitial tissues of the lactating breast (Berka, Michaelis) especially if the secretion is interrupted by removal of the young. Other glands and glandular tissues may likewise show an interstitial eosinophilia during the active or secretory phase,
or in cases of congestion and low grade inflammation.

The bronchial mucosa normally contains eosinophiles, which become greatly increased in number in any inflammatory process, and especially in asthmatic and other allergic conditions. When the numbers of eosinophiles are greatly increased, there is the appearance of Charcot-Leyden crystals in the sputum, an apparently related phenomenon. In a like manner, the excessive increase in eosinophiles in the intestinal mucosa in the presence of a heavy parasitic infestations and in some inflammatory conditions is commonly associated with the appearance of these crystals in the feces. In both instances, there is an unusually high number of mononuclear and other young forms of cells present in the affected tissues and exudates.
THE ORIGIN AND DEVELOPMENT OF THE EOSINOPHILIC GRANULOCYTE

I. Granulopoiesis.

The eosinophile cells commonly arise from similar cell types of the bone marrow, and may be derived from these cells by both mitotic and amitotic division. These early eosinophiles are the eosinophilic myelocytes, and are seen in the blood during severe myeloid leukemias. There is also in the bone marrow, a direct series of changes from the primitive hemocytoblast, or primitive blood cell to the eosinophilic myelocyte. The stage of development at which the younger forms of eosinophiles are no longer capable of multiplication is not definitely known, nor has the rate at which they develop been ascertained.

The eosinophilic cells can also arise directly from lymphoid cells which resemble or are identical with the hemocytoblast. In this process the cell cytoplasm gradually loses its basophilic quality, becomes faintly acid, and the specific granules begin to appear. It is not necessary for the entire cell cytoplasm to change at the same time, but the changes may go on in one area at a time, as described by Latta (1924) in the normal human lymph nodes. In some animals, such as the guinea pig, there may be a prodromal basophilic granulation which later changes its nature, but such changes have not been uniformly demonstrated in human tissues. The nuclear configuration need not change simultaneously with the cytoplasm, but may precede or follow it. Both types of changes must be differentiated from the phagocytosis of acidophilic cellular debris by monocytic cells, which may have the appearance of eosinophile formation.
The direct process is the one usually seen in small local aggregations of eosinophiles in parenchymal body tissues, especially the lymphoid structures. Maximow considers the eosinophiles of the loose connective tissues to be identical with the eosinophiles of the blood, and derived from the bone marrow.

II. Sources of the Eosinophiles.

Even in the presence of extramedullary granulopoiesis in small and limited areas, there is no evidence that the eosinophilic granulocyte of the blood stream arises from any other source but the bone marrow. In pathological conditions where there are immense accumulations of these cells in certain areas of the body, and strong evidence that at least part of the cells present may have formed in that location, the possibility is not remote that at least a small portion of the circulating cells may have come from this source.

When the local accumulation of eosinophiles in inflammatory exudates are considered, the source of these cells may be open to considerable argument. There are two possibilities. First, that all the cells present migrated there from the blood stream, having been produced and released from the bone marrow subject to some strong chemotactic influence, such as is in evidence in the operation of the heterophilic granulocyte in the usual type of inflammatory change. The second possibility is that all the cells present have been formed in situ by the tissue changes subsequent to the inflammation. The second hypothesis largely removes from consideration any possible function of the eosino-
philes of the blood, inasmuch as it would not permit them to react in these instances where it is obvious that they must have some function, and in the states where there is also a noticeable increase in blood eosinophilia, such a possibility is extremely unlikely. On the other hand, in large aggregations of eosinophiles in inflammatory exudates, there is a high percentage of mononucleated and other young forms including the spindle forms of Pappenheim. Using the substances that seem to specifically stimulate eosinophile production, notably the parasitic extracts, various workers have been able to bring about changes in tissues that specifically indicate that there is a strong likelihood that these cells do form locally.

In favor of the hematogenous origin of the eosinophiles is the fact that in most cases without abnormally severe response, such as the usual case of asthma, the blood increase is sufficient to account for the local accumulation by a process of filtration. In addition, when the total number of eosinophiles in all the blood in the body is considered, there is quite enough in even normal blood to account for a local emigration. Diapedesis of eosinophilic cells has also been observed and is not uncommon in some tissue studies. Heinecke and Deutschmann also report a marked eosinopenia of the blood following an asthmatic attack.

In favor of a histiogenic source of these cells in exudates or in local conditions is the discrepancies which often appear between a prevalent local accumulation in natural and experimental conditions and the level of the blood eosinophilia, or the
state of the bone marrow. Amitosis has been observed locally, although emphatically denied by other investigators, and the mononuclear forms are usually present. In pemphigus and in lymphoid leucoemias, the exudate of another specific type of lesion contains cells typical of that type of lesion, and not of the type prevalent in the blood, or present in the other lesions and exudates.

To satisfy all objections, there is a third possibility, that some of the cells form locally at the site of maximum specific stimulation, and that the others are brought in from reserve supplies in the blood and bone marrow, being formed there in sufficient numbers to meet the specific stimulation brought to the hemopoietic centers by the blood stream from the original inflammatory site. There is no reason why the two types of change, local and distant, should not be produced by the same type of stimulation, and there is no reason why the more primitive cell types might not just as well form eosinophiles as histiocytes, providing that the stimulus was specific in that direction rather than in some other, since the formation of a specific cell form entails the regular sequence of metabolic changes resulting from a given stimulation under conditions which that cell type are best adapted to meet.
CONDITIONS PRODUCING LOCALIZED OR GENERALIZED EOSINOPHILIA

I. General Considerations.

The eosinophilic granulocytes under certain conditions are increased in the blood or in the tissues. When the number of eosinophiles in the blood increases beyond 300 to 400 of these cells per cubic millimeter of blood, an absolute eosinophilia is then said to be present. A relative eosinophilia occurs when the eosinophilic granulocytes exceed four per cent. of the leucocytes counted on the differential white blood count. These values constitute the upper limits of normal, although varying standards set by different authorities do not agree exactly as to the normal percentages of these cells in the blood of healthy, normal individuals. An eosinophilia of five per cent. occurring in a blood count otherwise normal is probably without significance if done by an experienced technician, and is very likely within the limits of error in an ordinary blood count. If, however, the same percentage appears in a patient with some other variation in the blood picture, such as a total white blood count of 15,000, it is of significance, since the absolute content in such a case is almost double the normal. A similar relative eosinophilia reported by an inexperienced technician may or may not be of significance, since the eosinophile is usually ignored or missed entirely by such workers, unless present in sufficient numbers as to demand especial attention. Another factor of importance in determining an eosinophilia is the taking of proper smears, and accurate technic in counting. The slide smears in general use are usually inadequate for accurate determination of the percentage...
of the less frequent elements of the blood, since all granulocytes have a tendency to accumulate at the edges of such a smear, and the distribution of leucocytes is uneven, and does not represent a true picture of their distribution in the blood. The eosinophile is particularly prone to adhere at the outside limits of such a smear, and usually is missed entirely in a routine count. If such smears are used routinely, the drop should be small, and the streak narrow enough so that both sides are included in a side to side path. The cover glass smears are much more accurate, and should be done in every case where the accurate determination of less frequent cell types is important. This applies not only to eosinophilias, but to blood studies in anemia, leucemias, and every other type of examination where accuracy is an important factor.

There are also other considerations in the blood examination. The normal fluctuations of leucocytes must be taken into consideration since they are not constant in the body at any time, but are known to vary throughout the day. The nutritional state and age of the patient are also factors. Another factor often overlooked is the variation between peripheral or capillary blood usually taken, and the blood in larger vessels. Blood taken from a vein for other determinations will not show the same white cell count or index as a capillary specimen taken at the same time. Factors in blood pressure, diapedesis, fluid exchange and inflammation will produce wide variations in content and concentration of the cells in the blood. Unger and Wisotski (1921) have shown that there are more leucocytes in the vessels leading
to an inflammatory zone than in the capillaries and veins draining that zone. Stahl (1922) also proved that the skin vessels contained blood with a higher concentration of leucocytes than the larger vessels. Since most normals are arrived at from researches on capillary blood, a count done from venous blood should be so indicated. Medication must also be taken into consideration, and even morphine is capable of producing a transitory rise in the white blood count.

For special purposes of study in a given case of eosinophilia, or for research problems, the blood eosinophilia can be rapidly and accurately estimated at the same time the total white blood count is determined by utilizing the method of Dunger, or one of its more recent modifications.

In tissue examinations, the determination of an eosinophilia is much more difficult, but if there are sufficient eosinophiles present to make their presence easily noted in tissues where they are usually absent or scanty, it is probable that a local eosinophilia exists.

II. Localized eosinophilias.

The local eosinophilias are commonly seen in the normal body tissues already mentioned where a physiological eosinophilia seems to exist under normal conditions. There is also a local eosinophilia of mild degree which becomes manifest in all inflammatory conditions fairly early in the healing stages almost as soon as the recovery phase sets in. This does not usually include the degenerative and fibrotic conditions of reoeding inflammation where the local reaction is tending to
Local eosinophilia

become chronic, although a mild local eosinophilia is sometimes seen in such areas also. Certain inflammatory areas and tissues commonly show eosinophilia, and some specific infections and inflammations commonly produce it locally. In this category are most inflammatory changes in the skin, except the pyogenic types, the lesions of the nasal and oral surfaces, and those of the genital organs, rectum and anus. Inflammatory lesions of the intestine commonly show a local eosinophilia in excess of the normal presence of these cells in that area. Gonorrhea commonly produces a local eosinophilia, and the eosinophiles are very numerous in the gonorrheal discharge, especially when few organisms are present. In a study of 30 cases, Joseph and Polano found this ratio to hold true in 27, and attempted to arrive at some sort of prognostic formula for their presence or absence.

Local eosinophilia is common in other forms of inflammation of the genito-urinary apparatus, salpingitis (gonorrheal), and prostatitis commonly show this phenomenon. Malignancy of the cervix of the uterus, or the corpus may also show a local eosinophilia. Schock (1925) claimed that in his cases of carcinoma of the cervix uteri, those which showed a local eosinophilia were much more amendable to cure by radiation. He cited a series of 40 cases studied by biopsy in which about 10% showed local eosinophilia. Of these, there was a 46% cure, compared to only 13.2% of cures in the entire series. His interpretation was that the eosinophilia was an index of the degree of malignancy and local resistance of the tissues to the invasion.
Local eosinophilia

All areas subject to allergic and immunological reactions exhibit a marked local eosinophilia during the course of such a reaction, and for considerable time thereafter. Such areas are seen at the site of immunizing and sensitizing injections beneath the skin, in Arthus' phenomenon, in urticarial wheals, in the nasal mucosa during hay fever, in the bronchial mucosa during asthma, and in any other site where there is an allergic or strong immunological response without the presence of complicating secondary invasion.

The pleura may be the site of an extremely high localization of eosinophiles in certain types of inflammation. The etiological factors do not seem to enter into the eosinophilia so much as the complicating causes of the empyema. Hemorrhagic exudates from the pleura more commonly are associated with eosinophilia than those with thick pus of the strictly staphylococcic type. In most cases of the type described, the eosinophiles may reach as high as 90% of the cells of the exudate, and percentages of 70% are not uncommon. Bayne-Jones added his case to 68 such cases collected from the literature in 1916. The presence of the eosinophiles, or their absence in no way seems to affect the prognosis of the case, or its course. Most cases reported do not show a blood eosinophilia in spite of the surprising prevalence of these cells in the pleural exudate. In Bayne-Jones case, not a single eosinophile was encountered in counting 250 cells. Other investigators report similar experiences. No estimate of the probability of encountering such a case can be given, since blood stains are infrequently used in the examinations of exudates in general, the routine bacterial
Local eosinophilia

stains being more commonly employed. From a survey of the reports of such cases, autopsy findings are very infrequent, and the marrow changes are never reported. It is consequently possible that a more complete study may reveal that the finding of a high percentage of eosinophiles in a pleural exudate may have a favorable prognosis, as in the case of post-febrile eosinophilias.

Local eosinophilia is commonly seen in lesions of the gastro-intestinal tract below the stomach, where it is apparently quite rare. All types of gastro-intestinal tract parasites commonly produce immense local increases in eosinophiles as well as causing an appreciable increase in the blood eosinophilia. In the case of hookworm (ankylostomiasis) the eosinophiles are also found in abundance in the lumen of the intestine, and are associated with the presence of Charcot-Leyden crystals in the feces. Other infestations are usually less severe in their manifestations, but the roundworm Ascaris may also produce a marked local response. Amebiasis may also produce a local eosinophilia in the colonic submucosa, the change being more marked near the ulcerations. Chronic appendicitis is also commonly associated with an increased local eosinophilia, the various patterns of which are considered diagnostic for each grade of change by Kühnel (1922). Unfortunately, the changes in the local picture in the gastro-intestinal tract are usually not available for clinical study where they would be of value as diagnostic aids until the post-mortem examination is made. Polyps, tumors and other pathological processes of the sigmoid and rectum may show eosinophilia as a
Local eosinophilia

part of the general pathological picture, but such a finding is rarely of any diagnostic importance.

Many malignant tumors of the skin and mucous surfaces commonly show local eosinophilia, notably epitheliomata, rodent ulcer, and the carcinomata of the cervix uteri already noted. Benign tumors commonly show eosinophilia where their structure is such that there is a disturbance in the circulation, such as pedunculated mucoid polyps. This is particularly true where factors of trauma, exposure or lowgrade infection and irritation may enter in, as in the case of nasal polyps. Lymphoid tumors also show local eosinophilia, especially when they are malignant, or have some of the attributes of malignancy. Such conditions are commonly seen in lymphogranulomata, lymphosarcomata, and in Hodgkin's disease, where their presence is almost diagnostic.

Gruner's theory, which is also that of many other investigators, is that the breakdown of tissue cells, and especially of epithelial cells produces some substance which stimulates the accumulation and formation of eosinophilial cells, since a marked accumulation occurs in most cases where these conditions are met. Such conditions are seen in many skin diseases, some chronic tuberulous lesions without secondary infection, and in the growing edge of neoplasms. It is also seen in tissues undergoing repair, where there may be analogous changes.

In diseases of the skin, practically any except the acute pyogenic infections may show an eosinophilic change. This is especially true of pemphigus, and the eosinophilic cells in the exudate is characteristic of that disease. Local eosino-
Local eosinophilia

Eosinophilia has also been described in the lesions of scarlet fever, in psoriasis, herpes, urticaria and some forms of eczema. Some erythemas and prurigos may also show a local eosinophilia. All these conditions may also show a generalized (blood) eosinophilia at some stage or other, and the state in the localized lesions is not always indicative of the count to be discovered upon examination of the blood stream, and vice versa.93

Not only are mucous surfaces in general prone to produce or accumulate eosinophiles as a part of their response to inflammation, but the conjunctiva seems particularly active in this respect. Many forms of conjunctivitis, blephoritis, and other afflictions of the eyelids are commonly associated with an exudate or discharge which is high in eosinophilic content. It is seemingly common even in trachoma.

The subject of local eosinophilia is a problem of interest chiefly to the laboratory specialists, and will constitute the basis of a separate thesis. Only some of the more common conditions and more general considerations have been included in this discussion. For a complete knowledge of the reactions, capabilities and physiology of this type of cell, as well as any type of leucocyte, its action in a locally inflamed area must be studied, since it is in these areas that function and activity of the cell becomes manifest, its appearance in the blood being merely a signal that such a process is under way at some point in the body, the location of which may be remote.
III. Blood Eosinophilia

1. Classification.

The conditions causing an increase of the eosinophiles circulating in the peripheral blood may be separated roughly under the headings of physiological causes, and pathological causes of a blood eosinophilia. Between these two groups is a common form of eosinophilia variously termed "postfebrile", "reactive", or "convalescent". This phase is an eosinophilia which occurs following any acute infectious disease or severe disease condition during the convalescent state. This type of reaction is pathological in the sense that pathology has been, or still is, present. It is physiological in the sense that the body is returning to normal rapidly, and is building up resistance to that particular type of infection. In addition to this general division, there is a further classification of miscellaneous eosinophilias due entirely to the activity of, or pathology in the hemopoietic system. This includes the so-called constitutional or familial eosinophilias, in which some pathology may be present, although not proven, and the definitely pathological eosinophilias of blood dyscrasias and those occurring with certain types of pathology of the spleen. The "constitutional" eosinophilias may also be considered under the physiological eosinophilias, granting that no undiscovered pathology exists, and that such a blood picture is normal in that individual, or appears with consistency in his blood relations.

There is also a fourth general group, usually seen only under experimental conditions, and includes eosinophilias due to the
oral administration of some drug which is not one of the biological preparations. Drugs capable of producing an eosinophilia are usually of a type which directly stimulates the parasympathetic nervous system, as pilocarpin. Of little importance clinically, such a condition must be kept in mind, and may account for a bizarre blood count which may appear suddenly in some patient under such a treatment. This group will also include cases of eosinophilia from poisoning by drugs, especially those in the heavy metal series, such as arsenic. In some of these cases the presence of an eosinophilia is a valuable diagnostic aid.

Biological drugs must also be considered under this heading, especially the effect of adrenalin and thyroxin which usually decrease the eosinophile count when administered therapeutically. In most cases, the anaphylactoid effect of a biological preparation cannot be ruled out, and therefore such drugs must be considered along with other anaphylactoid reactions. Raw liver is a single exception, since it is known to contain a substance which specifically stimulates the bone marrow, but even in this instance, with the prepared product which obviously contains the same element, there is discrepancy in action. Most protein-free biological extracts, like adrenalin, thyroxin, or spleen extract have the power of reducing the eosinophile content of the blood.

The diseases increasing the number of eosinophiles in a given tissue, or freely circulating in the blood stream are sufficiently manifold as to require the listing of practically
Eosinophilia, classification

every known disease condition. There are, however, several disease entities which regularly and constantly produce or cause an increase in the acidophilic elements either locally or generally. Practically all parasitic infestations cause an increase in the eosinophiles, which is generally manifest by a blood eosinophilia. Some forms of bacterial disease likewise cause a relative increase in these cells. The single condition in which the eosinophiles are most markedly and constantly increased is the "allergic state", the manifestations of which are manifold, and which require careful study and subdivision until they require the attention of a separate specialty in the medical sciences.

The classification of an eosinophilia, then, may be grouped according to this scheme:

A. Physiological eosinophilias.
   1. Infancy and childhood.
   2. Nutritional state.
   3. Possible effects of a sexual cycle.
   4. Senility.
B. Reactive or convalescent eosinophilia.
C. Pathological increases.
   1. Allergic or immunological responses.
   2. Metabolic and deficiency diseases.
   3. Parasitic diseases.
   5. Inflammatory changes and communicable diseases.
D. Drug eosinophilias.
2. Physiological Increases.

The eosinophile count varies in the same individual from time to time depending upon the physiological state of that individual. Occasionally quite high eosinophilias are observed under varying physiological conditions. The same variations may be shown by other leucocytes, and the high or low counts should be considered in relation to the possibility of being increased or masked by one of these diurnal tides. Sabin, Cunningham, Doan and Kindwall (1925) conducted extensive investigations into these variations, disclosing a remarkably constant rise in leucocytes during the afternoon in normal individuals. C. Smith (1932) conducted a similar series on students at Mt. Holyoke College for the purpose of ascertaining the presence or absence of a digestive leucocytosis, and partially confirmed the more extensive earlier investigations of Sabin and her coworkers. Similar series have been reported by other workers with confirmatory reports.

Many clinical and standardization discrepancies between blood counts and physical findings are also probably due in part to these same factors, since the onset of an acute inflammatory process during an ebb period is apt to show a less marked blood reaction, and the onset of an identical process when the general tendency was toward a rise might be stimulated to show a greater response than normal. At least, such a consideration is logical, and in neither case would there be any reason why the local reaction at the site of inflammation should vary with the outside blood picture.
Physiological increases

The same generalities apply to eosinophilic findings, since in some cases these cells vary with the physiological state in a manner independent of the other components of the blood, when their own particular stimulus is a variable factor. In general, however, the eosinophiles vary with the lymphocytic elements of the blood, and inversely with the heterophilic granulocytes in those cases where the normal tides are concerned, or where the variation is within rather narrow limits. This does not mean that the lymphocytes and the eosinophiles have identical, or even related functions, but is a mathematical relation only, since the conditions increasing the ordinary heterophile count usually add more of these cells to the blood so that there is only a relative decrease of the lymphocytes and eosinophiles, the absolute numbers remaining about the same. This point of mathematical ratio does not absolutely deny the existence of a relationship between the eosinophiles and the lymphocytes, but that a certain part of their apparent relation to each other may be explained by the more obvious activity of the other cell type. There is indeed some evidence that a relationship in function exists between lymphocytes and eosinophiles, at least in certain phases of their activity. (Opie, Josey and Lawrence.)

The eosinophiles themselves are known to vary with the age of the individual, being more numerous in children and infants than in adults. During puberty, the eosinophilic values are quite variable, as is also true of metabolic factors, defense reactions, and all other physiological factors in older children. Zappert's findings indicate that there is also apt to be an in-
Physiological increases

Increased eosinophilia in senility, but this is by no means a constant finding. Many of the obscure eosinophilias of unknown origin are in aged individuals, and the afflictions for which they present themselves for treatment are in no apparent way associated with the marked eosinophilias sometimes recorded. The case reported by Amberg (1913) had an eosinophilia of 10% and the only complaints were slight dizziness and an occasional running ear. The tests and examinations revealed only slight actual pathology. Beifeld and Barnes (1916) reported a case of a severe anemia with an eosinophilia which reached 53%. This patient was a decrepit individual who presented some complicating findings, inasmuch as he presented himself not for treatment of an almost incapacitating anemia (hemoglobin 40%, RBC 1,600,000), but for shelter and relief from body vermin. In any person of considerable years, past experiences and progressive pathology might create a situation causing a lasting eosinophilia, so the findings in such cases may be expected to be somewhat aberrant.

In the absence of pathology, there is little if any significant change in the blood picture as far as eosinophiles are concerned during the sexual cycles of the female, nor does the sex of the individual influence the eosinophile count. Menstruation, pregnancy, and the adjustments of the puerperium do not seem to affect these cells, although a few isolated studies are reported which indicate rare eosinophilias in all three phases. Most of the extensive studies of the leucocytes in these conditions, although not specifically directed at the eosinophiles, do not indicate
Physiological increases

that they are affected. There is, however, a physiological shift in eosinophilia, and in all the leucocytes, during lactation which depends upon the physiological changes of that function (q.v.)\(^5\). Klinkert reports a mild eosinophilia at the onset of menstruation, but the separation of his cases from those in which he made other studies (migraine) is not absolute. There is supposed to be a moderate eosinophilia after coitus, the statement being carried through the literature from the single suggestion of Zappert, and after the menopausal changes begin to occur.

The nutritional state usually has a direct bearing on the eosinophile content of the blood. Fasting produces an initial rise in eosinophiles, after which the level in the blood varies directly with the body weight. There may, or may not be a digestive leucocytosis, and a digestive eosinophilia. There is equally dependable evidence that there is a digestive leucopenia and eosinopenia. All recent work in this field is conflicting, and the basic factor of interpretation is as yet undiscovered.\(^7\)
The eosinophilia of infancy and childhood.

The eosinophilia of infancy and childhood is a topic which deserves special mention, since it presents some features not seen in adults. In general, the blood counts of infants and children differ from those of adults. High leucooytic counts are not uncommon in normal children, and there is usually a preponderance of lymphocytes in the differential studies. The eosinophilic counts vary irrespectively of the other cells in most cases in infancy and childhood, and abnormally high heterophilic responses to infection are also the general rule. Eosinophilias of 6% are considered normal findings by most investigators, and Misasi has shown that the percentage is often higher (10%) in infants during the first fifteen days of life. Baagøe (1928) found 3% to be the most common finding in children, but higher counts were not uncommon. The eosinophiles were quite variable in children from 3 to 14 years old, and the age and sex offered no clue to the variation. Berger's findings indicate that the eosinophilia may vary from 0 to 10%.

The factors producing this variation in children are quite problematical. In the first place, the general blood picture of infants and children differs from that of adults. Lymphoid elements predominate, and in the bodies of children there are lymphatic structures generally that tend to shrink with growth and age. The type of response in children generally tends to differ from the responses of adults under similar conditions. An infant is also born with little immunity except that of a more or less passive sort derived from the blood stream of the mother. From the moment of birth the child is constantly ex-

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posed to the action of new and different toxic and alien elements to which it must react. However carefully the surroundings are prepared, bacteria cannot be eliminated, and the infant must react to each new type as it is taken into the body from the air, from food, or contact with surrounding objects. The occasional pathogen which is overcome doubtless accounts for many of the immunities which are acquired as the child grows. The adjustments to food and the products of digestion also must require certain changes of accommodation in the body. Berger's experiments, while incomplete, indicate that changes in infant diet may produce a subsequent rise in the eosinophile content of the body for short periods. This reaction is also slow, and somewhat delayed, and only reaches its height about ten days after the introduction of the new article of diet. It can also occur after single feedings of a different nature from that to which the infant has been accustomed.¹⁹

In the older child, the acquiring and building up of the so-called 'vital reserves' and the tremendous expenditures of energy of which children are capable doubtless include wide extremes of metabolic exchange and accommodation which give rise to, or are derived from functions of the body not understood at the present time. The thymus, for instance, is said to be associated with a growth stimulus, but such relationships have never been adequately worked out.

There is adequate experimental evidence that the eosinophile cell is somehow associated with immunological responses. The part played in digestion and accommodation to new foods is
evident, but the exact nature of the reactions and function is a highly controversial subject. The metabolic role is purely conjecture, but a factor which cannot be overlooked in a complete consideration. Since eosinophilias are also common findings in diseases of the bones, DaCosta suggested that the increase so often seen in children was a direct result of the growth factor, because the bones were most affected by a growth stimulus, and the marrow reactions near the epiphyses might carry on at a higher rate than in adults.

From all these sources, bacterial, nutritive, metabolic and growth, there are possible factors for explanation of an increased eosinophilia in children. Probably no two explanations are sufficient in any given case.

Variations with the nutrition and digestive state.

There is supposed by many investigators to be a digestive or absorptive rise in leucocytes in the peripheral blood as a result of the digestion and absorption of food. The peak of this rise occurs at or shortly after the absorptive peak in various experimental animals. A failure of this leucocytic response was the basis of Widal's hemooelastic test for liver function. The eosinophilic granulocytes may or may not follow the trend of the other leucocytes in such reactions. Gruner and others consider that an eosinopenia is the rule after meals, since it has been shown that the eosinophilic cells tend to accumulate in the intestinal mucosa during digestion. At the same time, other writers mention the eosinophilia which
Nutritional states

often occurs during the absorptive, or post-absorptive phase of digestion. Where the eosinophiles follow the general leucoooytic response to digestion, an absolute increase or decrease in these cells is apt to pass unnoticed. A stationary eosinophile content is likewise apt to pass for an increase or a decrease on the relative basis in the differential count, as the other cells increase or decrease.

Arquin (1928) attempted to demonstrate the function of the splanchnic-peripheral balance in cases of so-called digestive leucoooytosis. It is logical to assume that if the great vessels contain less leucocytes per unit volume of blood than the peripheral capillaries under normal circumstances, that an increase in splanchnic circulation might increase the phenomenon. The action of the vegetative nervous system may also play an important part in this function. There is also another mechanical factor which has not been considered in such determinations, and that is the fluid exchange during digestion. Considerable fluid must be taken from the blood, and indirectly from the rest of the body to render the intestinal contents fluid enough, and dilute enough for absorption. This fluid is later reabsorbed, along with that taken with the meal, and although difficult to estimate, should account for some of the apparent blood changes on a simple basis of concentration.

Shifts in a differential count, however, must be argued on a physiological basis. The theory of release of digestive ferments by leucolysins is denied by many workers who base their observations on the same facts that form the basis for the assumption of the theory, namely, the normal digestive leucopenia in infants.
a phenomenon usually ignored by the proponents of the digestive leucocytosis. Schippers and de Lange, and others note this decrease which may amount to 5000 to 16,000 leucocytes, calling attention to it as a point of failure of Widal's functional test of the liver in infants.

The ferments of the leucocytes may very well play an important part in digestive processes, since they contain high concentrations of many active enzymes. These ferments seem in some way to be associated, but not identical, with the specific granules, and are especially potent in the eosinophile cells. Weinberg and Séguin have also shown that these cells are capable of fixing or rendering innocuous the toxic substance of parasitic extracts, and suggest that they might just as well act in the same manner with the alien products of digestion.

Christianna Smith (1932) not only denies the existence of a digestive leucocytosis, but found that variation of the time of meals (considerably restricted), fasting, and variation in activity did not affect the rise which might be considered the normal diurnal tide in these subjects.

These considerations indicate that there is considerable variation in the findings of leucocytic action in general in the physiology of digestion. Consequently, it is not surprising that there is little actual evidence to support the few brief remarks regarding the role of the eosinophile in this process. Practically all descriptions of the cell refer to changes which might be expected during digestion, but the
actual supporting investigations are inadequate to properly demonstrate the changes. The observations of Opie and others have already been mentioned under the local eosinophilias found under normal circumstances.

Since the eosinophiles are known to be active during the defense reactions of the body and in anaphylactoid reactions generally, and the bulk of evidence points to a protein origin of such reactions, it is not illogical to assume that at least a parallel reaction exists in the digestion and metabolism of proteins in the body.

The processes of digestion alone are not sufficient to account for any of the digestive leucocyte changes. The other factors to be considered are the nutritional state of the body, the "biological protein balance", the type of food, the age, weight, and type of individual. Opie's experiments indicate that a higher individual reaction is to be expected after fasting when there is a positive protein balance, and the body is returning to normal. Until late in starvation, there is a similar increase where the body is utilizing its own substance to meet the basic metabolic requirements. If the theories regarding a relation of the eosinophile cell to protein metabolism are correct, a higher value should be found when a diet high in protein is given. Children are definitely more apt to show a high eosinophilia under such circumstances than adults. The weight of the individual, and changes of weight should be considered in connection with the general state of nutrition. "Nervous" types are also
more apt to show eosinophilia than phlegmatic types. This is especially true of "neurotic" types.

**Climate**

Stockton states that the eosinophiles have a ten per cent. higher normal value in people in the tropics. Gruner likewise mentions that 15% of the healthy natives of southern China show high eosinophilias. Neither statement is supported by citation, or by observation. Ruling out the prevalence of hematological changes from the practically universal infestation by helminths in some portions of the tropics, there is definite evidence that different climates do affect the blood picture. The figures cited are high, but people living in the tropics, both natives and foreigners do show higher eosinophile values than inhabitants of the temperate and northern zones.
3. Reactive, or convalescent eosinophilia.

An absolute and a relative eosinophilia occurs during the recovery phase of almost every acute disease condition, especially where there has been fever and a nutritional deficit. A post-infectious reaction occurs following the subsiding of nearly every acute infectious process. The appearance of an eosinophilia during the course of a disease in which there has been a previous eosinopenia is usually a favorable prognostic sign. In diseases where there is an eosinophilia during the acute process, there is usually an increase during the recovery stage.

Ehrlich, Mueller and Rieder, Rieder, and Canon were among the early workers (1891-1892) to observe the decrease in the eosinophiles during the acute infectious processes. Zappert (1893) believed that there was at all times an absolute diminution in the number of eosinophiles during any febrile manifestation, and concluded that this was a part of the febrile manifestation, observing that there was usually an increase of these cells above the normal levels after the disappearance of the fever during the recovery stages of the disease. Later experimental work by Opie (1904) and Lawrence and Josey (1932) and other workers support these early findings, that the rise in eosinophiles following the onset of an infectious process is an important portion of the immunological and reactive response of the individual. Clinically this reaction is separate and distinct from the anaphylactoid reaction which may occur
when a serum or antitoxin is used therapeutically, as in the case of diphtheria which shows a late eosinophilia in the majority of cases.

Besides the relative eosinophilias which may occur during the course of the disease, Page, Turner and Wilson (1928) state that a reactive type of eosinophilia occurred in every case of bronchopneumonia and lobar pneumonia in their studies. They had previously ruled out reactive increases in the other studies as being too prevalent to merit further discussion. Arneth (1912) and others mention the eosinophilia of lobar pneumonia, and stress its appearance almost coincidentally with the crisis. It may sometimes appear just ahead of the crisis, in which case the finding would have a marked prognostic value.

In scarlet fever, inflammatory rheumatism, chorea, and rheumatic endocarditis and diseases of related etiology, the eosinophilic count is characteristically high during the course of the disease, but an increased count is usually a favorable sign. An eosinophilia throughout the course of scarlet fever is usually a favorable sign throughout.

Klinkert cites the prevalence of a post-infectious eosinophilia in typhoid fever. The eosinophilia of chicken pox described by Hoffman (1923) doubtless is a reaction of this type, since it occurs during the afebrile stage when there are no symptoms other than the drying scales of the lesions.

A different type of reaction which may also be regarded as a favorable sign is the reappearance of eosinophiles in the
peripheral blood after their disappearance in a severe case of anemia. Such a response is another sign of adjusted bone marrow physiology, and may be regarded as favorable. In such a case, however, raw liver therapy must be disregarded, since it is known to increase the eosinophile count directly. It is possible, however, that the raw liver possesses a stimulating fraction which is not present in the prepared products.

The reason that more general knowledge of reactive eosinophilia is wanting is probably that the blood counts cease as soon as the patient begins to show definite improvement. The period at which it begins to assert itself is about that time at which the fever recedes to short fluctuations between 99°F and 100°F., just before the curve becomes 'flat' which is in itself a favorable sign in most infections. At the same time there are other favorable signs. There is relief from whatever pain there may have been before, the patient begins to show interest in surroundings and the appetite returns. However, the value of a prodromal eosinophilia should not be disregarded, and the finding is confirmatory even if unnecessary when all the other signs point to a favorable prognosis. Its absence should incite some curiosity as to the possibility of latent pathology.
4. Pathological increases in eosinophilia.

Practically every known disease has been reported showing an eosinophilia, or an eosinophilia has been recorded among the blood findings without comment. In older references, where the saving of space was not so much a factor in determining the completeness of a report, these findings were relatively common. In some cases it was necessary to alter the diagnosis in a case in the light of newer learning. At the present time, bulk space is so valuable that in spite of endless number of medical and technical journals a case report is just a case report, and most of the findings listed are those which particularly interested the man reporting the case. Complete blood findings usually include only the erythrocyte count, the hemoglobin, the leucocytes, the lymphocytes and the white blood count. Physical findings and symptoms are recorded in the briefest possible order. The result is that it is impossible for any interpretation to be put on the findings other than those made by the person reporting the case. Routine findings are so rare in reports, that unless a given case especially presents findings that deserve mention in the title, that case is forever lost to subsequent investigators in more general fields. The result is a wide gap in the bibliography between the investigators who initiated a study, and between contemporary reports of cases presenting a feature. There is rarely an opportunity to gather and study a series of cases from recent literature and make a study which will give some idea of the incidence of a single finding which may or may not
Pathological increases

be of subsequent diagnostic or prognostic import. There is consequently a long collected list of 'miscellaneous diseases' which are occasionally known to be associated with an eosinophilia, but which the incidence, and consequently the importance of that finding is an unknown factor. These miscellaneous diseases include uremia, (indicated to occur with eosinophilia with considerable constancy by the series of Page, Turner and Wilson), Gastroptosis, sprue, periarteritis nodosa (2 cases), constipation, angioneurotic edema (allergic?), pyelitis (4 cases), nephrolithiasis, purpura, gonorrhea, syphilis, chlorosis, and diabetes.\(^{139}\)

More common causes of eosinophilia are found associated with the allergic state,\(^{667}\) diseases of the gastro-intestinal tract, the chorea-rheumatic fever group, certain skin and nervous diseases, and in infestations with animal parasites. Other conditions which are often associated with an eosinophilia are goiter, diseases of the blood-forming organs, diseases of the bones, and afflictions of the genito-urinary tract, but it is impossible to collect enough statistics on most of these cases until more specific literature collects on these diseases with a sufficient series of studies on blood findings to form the basis for accurate conclusions.
**Allergic conditions, and immunological reactions.**

The allergic conditions regularly show eosinophilia. As a rule, the percentage is not nearly as marked as the popular concept of these conditions would lead one to believe. Counts between 5 and 10% are most commonly found, although much higher counts are often seen. The severity of an attack in asthma is also no index of the degree of eosinophilia to be found, nor is there any constancy in the rise of the eosinophile cells and the time of the attack. The relation of the eosinophile cell to the allergic and immunological responses of a patient, or an experimental animal, are constant enough and sufficiently noteworthy to indicate that there is some close relation between the physiology of these cells and the allergic states, but the results defy interpretation.

Baagøe's studies in children suffering from asthma indicated that the eosinophiles could show startling increases without an asthmatic attack becoming manifest, and that they may likewise remain low during an attack, but never disappeared from the peripheral blood. His ambulant cases showed higher eosinophile percentages than the hospitalized patients, and only 92 of the 124 hospitalized children showed any remarkable eosinophilia. On the other hand, the investigations of von Noorden (1892) showed that the eosinophiles in the peripheral blood may never return to normal levels, even when the patient was free from an attack over relatively long periods of time.

In a given case of asthma, it must also be considered that there may be contributory pathology of another sort which in itself
Asthma

may be capable of inducing an eosinophilia. Emphysema alone may
give rise to an eosinophilia, as is also true of bronchiectasis,
and chronic bronchitis. The series of Page, Turner and Wilson
contained 38 asthmatics showing eosinophilia, but only 17, or
less than half, had uncomplicated cases. The also included 13
cases of acute upper respiratory disease (pharyngitis, tonsillitis,
bronchitis etc.) and 13 cases of chronic respiratory disease, which
showed increased eosinophilia without presenting any allergic man-
ifestations. Eosinophilia was also a finding in five cases of
pulmonary tuberculosis. These findings may indicate that the
eosinophilia may be a phenomenon of pulmonary pathology alone,
and that the allergic manifestations are only contributory.

Certain types of asthma, however, may show no eosinophilia. In
general, these are the "bacterial types" which present the
clinical symptoms of asthma, due perhaps to a local direct
stimulation of the bronchi and adjacent structures by infection
superimposed upon pre-existing pathology of some type. Such
cases can be found with bronchiectasis and chronic bronchitis,
following pneumonic attacks and in like conditions. The
eosinophiles are likewise absent from the diseased tissues,
and from the sputum of such patients. With the inconsistencies
in eosinophilia observed in the allergic forms, it is impossible
to say at the present time whether the absence of eosinophilia
is diagnostic in such cases or not, but it would seem to be of
some importance in indicating the type of pathology, especially
if associated with an eosinophile-free sputum.
In general, the manifestations of hay fever follow those of allergic asthma, being complicated by local pathology in the same manner. Many such cases are aided, if not permanently cured by the clearing up of local pathology in the form of nasal polyps or chronic sinusitis. The majority of cases, however, are of the secretory, paroxysmal or allergic type. The nasal secretions in such cases show high percentages of eosinophiles, just as the sputum in asthma, and it was this phenomenon which first brought attention to the relationship with the eosinophilic cell in both types of disease. Brown (1927) showed that the blood eosinophilia and that of the sputum or nasal discharge was closely parallel (546 cases).

In considering the allergic manifestations of the skin, even greater inconsistency is found. Urticaria is commonly associated with a local eosinophilia, but the general type of reaction is not so commonly found. When found, the eosinophilia is usually low, not over 10 or 12%, but here again, bizarre counts are sometimes reported. Urticaria may also appear associated with one of the other conditions which is capable of producing an eosinophilia, being associated with parasites, asthma, and hayfever. It is also common in certain neuropses, but the evidence connecting the two systems, nervous and immunological, is incomplete.

Anaphylactoid reactions of all types commonly show eosinophilia. In this connection, it is possible to duplicate natural sensitivities under experimental conditions, giving some oppor-
Anaphylaxis, and immunity

Anaphylaxis, and immunity

tunity to study these conditions in various phases of their manifestations. Apparently all anaphylactoid reactions, including the allergies, are aberrant caricatures of the normal immune response. Weinberg and Seguin, Schlecht and Schwenker, and others have shown the local increase of eosinophiles at the site of immunizing and sensitizing injections, as well as the generalized increase in these cells. Hajós (1928) demonstrated that the immune titer reached its peak at the height of the eosinophilia. A passive sensitivity may be transmitted from one animal to another in the same manner that a passive immunity may be transmitted by the injection of immune serum. Barach (1911) showed that the substance capable of inducing the passive sensitivity was specific for the protein to which the person or animal was sensitive when he attempted to show a failure of transmission of anaphylactin, the theory then popular.

A sensitivity may also be transmitted from a pregnant guinea pig to her offspring, in the same manner that the young acquire temporary immunities from the mother, at the same time an immunity to diphtheria toxin is transmitted to the intrauterine young.

Horse serum sensitization is almost universally recognized as being associated with passive immunities, and other phenomena may be seen associated with related eosinophilia from other causes, such as the urticaria with ruptured echinococcus cyst, or asthma with parasitic infestations.
Schlecht and Schwenker (1912) showed that there was a peripheral increase in the eosinophiles in anaphylactoid reactions evident in shock. The local increase was most marked at the point most severely affected by the anaphylactoid response, i.e., in the lungs of the guinea pig, and in the intestine of dogs. Ahl and Schittenhelm (1913) also demonstrated the effect of foreign protein injections in sensitization and the production of an experimental eosinophilia.

Hajos and Nemeth (1926) showed that the typical reactions of the blood were lacking in anaphylactic shock after exposure to x-rays. Such exposure commonly destroys the specificity of the reticulo-endothelial system, and in the case of anaphylaxis the liver undergoes necrosis, since the entire load of detoxifying the blood stream then falls on that organ.

Different animals are also variable in their response to sensitization, and in the ability with which they are sensitized. The greater portion of the response in dogs is in the gastro-intestinal tract, and the response of guinea pigs is chiefly pulmonary. The white rat is resistant to sensitization until practically starved, or otherwise altered. Flashman showed that suprarenalectomy permitted sensitization in rats, and Seegal and Karazo demonstrated that it was possible after the animals had been restricted to a bread and water diet for long periods. Manwaring demonstrated that a muscle-relaxing substance of the liver in dogs produced all the symptoms.

Many workers have been struck with the similarity between anaphylaxis and various types of vagus stimulation. Neusser...
and other early workers also proposed a theory of "xanthin diatheses" or diseases in which there was an alteration in the metabolism and elimination of the purine bases. With pilocarpin injections, the eosinophilia temporarily fell in these cases, and Neusser and others suggested a connection between this type of metabolism and vagotonia. The diseases in which he found an increased uric acid metabolism, Neusser listed as follows: gout, asthma, goiter, epilepsy and migraine. Hay fever was also included, as were some of the hysterias. With the beginnings of protein sensitization as a cause in some of these diseases, as well as a decrease in the incidence of gout these theories largely fell by the wayside. Following the popular use of adrenalin for the relief of asthma and anaphylactic shock, some workers again began to play with the vagus theories. The principal proponents of this viewpoint now are Ladwig (1922) who pointed out that most of the eosinophilias with malignant tumors could probably be explained by metastasis to lymph nodes where there would be pressure or other interference with the vagus and sympathetic nervous systems. Specifically, he cites the cases from literature as well as his own case, where the metastasis, or origin of the tumors in question was obvious in the neck lymphatics. There was also bradycardia in Ladwig's case.

Klinkert believes that convalescent eosinophilias are a manifestation of the immune reaction, and that these are at least partially under control of the vagus nerve, since they are also accompanied by well known vagus phenomena such as bradycardia.
At the same time he observed an increased uric acid in the blood during these recovery phases. More complete studies indicated that this same blood uric acid increase was present in the various allergic stages (during attacks) of asthma, and in migraine.  

Hajós and his coworkers confirmed this work along different lines using anesthetized guinea pigs and continuous stimulation of the vagi by faradic current, demonstrating also that there was an apparent close relation with nervous tone of the vegetative nervous system generally in these cases. Similar experiments showed indication of a liver function relationship which brings the evidence back to connect up with Klinkert's uric acid and vagus findings. Skóczewsky and Wasserberg (1912) carried out similar experiments on guinea pigs, but failed to find the results given by Hajós, but they had employed only short stimulations of the nerve.

The work of Klinkert with migraine as a menstrual neurosis confirms the findings of other workers who had placed many cases of migraine in the allergic class, chiefly on the basis of the eosinophilic findings. Klinkert considers these manifestations as being wholly due to an imbalance in the vegetative nervous system. Justification of his viewpoint is found in the results obtained with ergotamine therapy. Auer and Lewis (1910) found that section of the vagi, or destruction of the spinal cord did not prevent the development of the anaphylactic symptoms in the guinea pig, so it is possible that the reaction is somehow located in the vagus terminations.

The reactions of asthmatic patients to adrenalin are more
marked than in other people, indicating increased sensitivity to this drug. The responses to pilocarpin are likewise abnormal. Thyroid medication has also been selected as a stimulating factor in patients suffering from asthma, with the theory that a general stimulation of the body would give the sympathetic nervous system a chance to adjust. It has been found especially effective in asthmas of children.

Naegeli indirectly supports the vagus etiology of some hypersensitivity when he describes the tremendous eosinophilias sometimes seen in pathological eosinophilic reactions following directly upon pathology of this nerve, but suggests that it is usually lacking in the so-called purely vagotonic states as such are recognized clinically.
Eosinophilia in Metabolic Diseases.

Eosinophilia is an occasional finding in several of the frankly metabolic diseases, and is most common in this group in thyroid hyperfunction. It is quite probable that the typical blood findings of each group of these diseases, if there is a variation from the normal, is complicated in the presence of an eosinophilia by nutritional, nervous or other factors.

Hyperthyroidism.

References to an eosinophilia in goiter are fairly common in the older literature, but very infrequent in more recent reports. Most textbooks on the blood mention it as a possible condition showing eosinophilia, but do not cite any statistics nor comment on findings within the experience of the authors. It is possible that they also refer back to previous literature on the subject. The series of three hundred patients showing eosinophilia presented by Page, Turner and Wilson contain six cases of goiter showing a relatively high eosinophilia, and a total of 12 cases of hyperthyroidism. In these the eosinophilia varied from 5 to 9%.^138

The last twenty cases of diffuse toxic non-nodular goiter in the University Hospital showed no eosinophilia. In most cases where more than one blood count was run, the eosinophiles seemed to be remarkably low. Only one case showed a high normal, 4% of 6000 white blood cells.
Diabetes.

The finding of an eosinophilia in diabetes is very rare, and occurs only with complicating factors. The senile type most presents this finding, and it is not uncommonly associated with other degenerative pathology, such as arthritis. In the series mentioned, there were three diabetics, all these had some other change. Strangely enough, there have been no references of any importance to the blood changes in diabetes under the different types of treatment, and very few references on the effect of insulin on the blood picture. With the cachexias sometimes seen in diabetes, starvation diets, and other dietary factors carefully controlled, it might seem that these patients present an excellent field for a number of fields of investigation.

The eosinophilia when found is never high, usually not over 6 per cent.

Degenerative diseases.

This group is also very incomplete, and cannot be separated and classified, since each is considered separately in the literature, and only a few cases of each could be considered. The group as a whole represents those conditions commonly found among senile individuals, and includes hypertension, degenerative arthritis, chronic multiple arthritis, chronic nephritis and degenerative lesions generally. Arterosclerosis is a common finding in all these conditions. It is possible that these conditions include some of the cases of Zappert in which the eosinophile increase may have been attributable to some of these causes. The series of cases cited contain 28 in this group, all with other conditions, and is representative of the general findings.
Eosinophilia in Nervous Diseases.

One is at once struck with the prevalence of "hysteria" in the comprehensive list of Zappert on the studies in eosinophilia. Since it is not possible to check the diagnoses on these cases completely, it is necessary accept them as reported, although it is possible that many would have been subdivided into other classifications at the present time. For considerable time, for instance, hay fever was considered to be a neurosis. His series also includes exophthalmic goiter as a nervous disease, as does Gruner, who also includes asthma.

Zappert's conclusions were that diseases of the periperal nervous system commonly showed eosinophilia, but that the psychoses and diseases of the central nervous system usually did not. He showed, however, that the eosinophilia was occasionally increased in epilepsy. Moschoowitz (1911) states that the eosinophiles are increased in individuals with neurotic tendencies, and also in the diseases of these individuals. Gruner mentions increases as high as 22% in puerperal mania, acute mania, melancholia, epilepsy and diseases of the peripheral nervous system. The series of Page, Turner and Wilson include one case of anxiety neurosis (8%), one idiopathic epilepsy (7%), one paralysis agitans (7%), and one case of thromboangitis obliterans (10%). Naegeli records some very high counts in Polyneuritis. The findings in every case are inconstant, since checking other similar cases in available general reports does not show an eosinophilia with any degree of constancy.

The suggested relationship of the vagus nerve has already
been discussed along with its possible etiological influence in allergic conditions. It is possible that similar factors enter in in these cases of other diseases of the nervous system, and that the eosinophilia occasionally noted is a phenomenon directly resulting from associated pathology, or influence on this portion of the nervous system. Naegeli cites a case of vagus neuritis which produced an eosinophilia of 50%, and Falta believed that the eosinophilias seen with drugs, especially pilocarpin and physostigmine were due directly to stimulation of the vagus.

The relation of eosinophilia to tetany may be due to a nervous relationship, or it may be due to the calcium deficiency directly. Most asthmatics also show calcium and phosphorous deficiency also, and the symptoms are relieved by diets high in minerals. The effect of calcium as a "soother" of tissues, especially of nervous tissues is well known. An eosinophilia is likewise shown in rickets.

Leprosy, the only common specific infectious disease of peripheral nerves, is said to be associated with a marked eosinophilia in some stages.
Eosinophilia in Deficiency Diseases.

Although few differential counts are available in the literature, several recent writers mention an eosinophilia which may occur in rickets, pellagra, and beri-beri. Since their statements are not supported by citation or other contributory evidence, they are not cited further. The most complete references available on the deficiency diseases, singly, or as a group, fail to mention the finding of an eosinophile increase in any phase of the disease. Since there is a nutritional factor, however, and in some cases an anemia of a nutritional character, it is not unreasonable to assume that an increase in the eosinophiles might occur during a favorable reaction to therapy.

Unfortunately, all the available cases presented blood findings at too infrequent intervals to verify this possibility in the case of rickets, practically the only common disease of this type in this locality.
Constitutional and Familial Eosinophilias.

Although these conditions are sufficiently rare as to merit special consideration in the literature, they are sufficiently frequent to offer an occasional diagnostic problem.

The case reported by Spiro and Pfanner (1925) suffered from chronic arthritis, and the eosinophilia was considered to be a sign of arthritism in these patients. The brother of one patient presented a similar high eosinophilia. Cirio reports a case of eosinophilia of 66% in an otherwise healthy individual, with higher than normal counts in several members of the same family. Stockton quotes Boekelman who reported 5 cases where there was no diagnosis to account for the increase.

Klinkert (1920) applied to these cases the same principles and theories which he had used in other cases of eosinophilia, namely that they were the result of uric acid-vagus diathesis, and that in adults such individuals were prone to the development of gout, asthma, urticaria and migraine. The familial background could better be explained on the basis of his findings than on the basis of a familial bone marrow activity, and in most cases one or more members of the affected families showed one or more of the diseases which he ascribes to the activity of the autonomic nervous system. A similar condition, he believes, exists in epilepsy, except that the discharge is immediate in epilepsy and gradual in the other diseases. Bolton's results with thyroid medication in epilepsy may be accounted for on the basis of a general stimulation in the same manner that it aids some cases of asthma, and the cure of asthma by an intercurrent disease may be similar in action.
Eosinophilia in Affections of the Gastrointestinal Tract.

The diseases of the gastrointestinal tract are peculiarly prone to show eosinophilias for a number of reasons. There is always an associated disturbance in nutrition of varying degree, and this alone may give rise to an eosinophilia. Where digestion and absorption of food is altered by such diseases, alien by-products may enter the general circulation and there stimulate an eosinophilic response. The nature of the mucosa of the intestine is also eosinophilic, and inflammatory changes in its wall produce a high grade local response which may become manifest either directly or indirectly by a general response of the same nature.

Only rarely does such a response arise from pathology in the stomach, but most of the conditions at or below the pylorus, beginning with duodenal ulcer are known to be associated with an eosinophilia. Constipation has rarely been reported, but proctitis and colitis commonly show it. Stockton (1930) presented six cases of unexplained eosinophilia, and in all of these there was some vague gastrointestinal complaint, usually of the "nervous dyspepsia" type. The intestinal parasites commonly show eosinophilia, but this reaction is probably due more to the specificity of the parasite toxins than to any irritating effect on the intestine.

The height of the eosinophilia in gastrointestinal disorders is as variable as the conditions in which it is met. The cases in the series reported by Page, Turner and Wilson rarely were higher than 10%, and this group included about
Gastrointestinal complaints

3% of the patients showing an eosinophilic response. Stockton's six cases all showed higher counts, from 12 to 42%. All counts returned to normal.

Intestinal polyps may give rise to an eosinophilia, probably by an irritative reaction of some sort. Malignancy of the colon may also show an eosinophilic response.

Among the acute intestinal and colonic infections, Paratyphoid B seems to be the most constant organism which is capable of causing an eosinophilia. Marcovici (1915) considered this eosinophilia to be so constant that it could be counted upon in differential diagnosis. Barnett (1917) presented a case of acute colitis with eosinophilia which reached the surprising height of 47% without an increase in the white blood count (8600). The etiological diagnosis was not made in this case, but the author leaned toward an allergic phenomenon.
The Eosinophilias of Parasitic Infestations.

The occurrence of eosinophilia is so well known that it scarcely merits further consideration. References to eosinophilia with parasitism have practically disappeared from recent literature, although very commonly present up to about 1920. Whether the parasitic infestations are more common in Europe, or whether the European mind is more prone to such investigations is difficult to determine, but the bulk of such reports seem to be in the European literature. Except for the original observation on Trichinella by T.R. Brown (1897) very few of these reports have originated in America.\textsuperscript{24,25}

The eosinophilia of intestinal parasitism is usually low, not over 10%. Ascaris commonly causes a higher rise, which is not uncommon at 20% of the total differential count. Hookworm (Necator, Ancylostoma) may also give rise to a marked eosinophilia as well as a marked anemia.\textsuperscript{24} This parasite in severe infestations is also prone to be associated with the presence of eosinophiles and Charcot-Leyden crystals in the feces.\textsuperscript{27} Oxyuris and Trichiurus (Fimworm and Whipworm) may also show occasional high counts, but in the case of these parasites, the count is usually low except in a severe infestation.

The ordinary tapeworms (Taenia) do not commonly give rise to high eosinophilias. The counts reported in the literature are usually lower than 10%. The broad, or fish tapeworm of man (Diphyllobothrium, or Dibothriocephalus) is more apt to give higher counts than the taenias, and is often associated with
a more or less typical anemia, the reactions of which are capable of producing an eosinophilia, so the eosinophile does not always fall immediately after this worm is driven from the intestine.

The parasite giving the highest eosinophilia is Trichinella spiralis, in which man is both intermediate and final host. The eosinophilia in some infestations of Trichinella have reached as high as 90% of a white count as high as 15,000. Not only is the toxic effect of the parasite a factor in this infestation, but there is also enormous destruction of the host tissues in the lungs, and in the muscles where the parasitic larvae finally encyst.

Amebiasis occasionally is associated with an eosinophilia which may at times get very high. A 62% eosinophilia is reported in one case. Malaria shows a variable eosinophilia which is more common in the tertian form, and when the spleen is involved.

The incidence of parasitic infestation varies in different localities, and in different types of practice, so the finding of an eosinophilia may or may not be of diagnostic aid in determining the presence of parasites. The series of Page, Turner and Wilson should be fairly representative of an average charity, or part charity practice in the temperate zones. In their series of 300 patients with eosinophilia, 31 were attributable to some kind of animal parasite. There were 3 cases of D. latum (broad tapeworm), 2 cases of Ascaris, and the remaining cases were a scattered group. There were no cases of Trichinella, and the eosinophilia presented rarely rose over 20% in any case.
Parasites of the trematode group are uncommon in the United States and northern Europe, and the blood findings in these infestations are exceedingly rare in literature. The other tapeworms of man (Hymenolepis and Dipyllidium) while common infestations in children, are self limiting, and very rarely reported.

Many parasites common in the Orient and in the Tropics are also rarely reported, and the blood findings are given even less frequently. The insect parasites, excluding body vermin, are infrequent in man, and are usually accidental infestations with the larvae of some fly. The blood findings in such cases are not usually reported, but Hadwen describes an eosinophilia in cattle infested with larvae of the warble fly, and it is likely that a parallel can be drawn, since eosinophilia is a common response to parasitism in all mammals. The body vermin do not seem to give rise to an increase in the eosinophilic granulocytes.
Eosinophilia in Inflammatory conditions, and Infectious Diseases.

Generally speaking, the inflammatory conditions and the communicable diseases do not produce an eosinophilia, but rather a leucocytosis that involves chiefly the heterophilic granulocytes. Some diseases are characteristically associated with a leucopenia, and others commonly give rise to lymphoeytosis. In very few instances the blood picture is characteristic for any particular disease. The production of a fever as part of the defense of the body seems in most cases to be a portion of the immune reaction which does not include the eosinophile.

In all cases there is an eosinophilia during the convalescent period of the disease, and the reappearance of eosinophiles after, or during the onset of the fever is usually considered a favorable sign. Later in the course of the disease, an eosinophilia is the rule, indicating that convalescence is under way.

Very few of the specific infections typically give rise to an eosinophilia, but several diseases may show it in some form of their manifestation. Tuberculosis, syphilis, and some of the fungus infections sometimes show eosinophilia. In the more acute class, scarlet fever, smallpox, and acute rheumatic fever show eosinophilia with some constancy. The eosinophilia usually described in chicken pox occurs so late that it is undoubtedly of reactive, or postfebrile nature.

Syphilis

Older writers consider eosinophilia to be a fairly constant finding in congenital syphilis, and C.S. Engel thought that a simultaneous eosinophilia and lymphocytosis in children in-
dicated congenital syphilis. Later findings make this extremely doubtful. Chesney, Kemp and Resnik (1924) describe a type of syphilitic arthritis in which eosinophilia is a finding. Page, Turner and Wilson offer ten cases of eosinophilia in which the primary diagnosis was syphilis, in which the percentage of eosinophiles was between 5 and 17% of the leucocytes. In addition to these, there were twelve cases of eosinophilia occurring with syphilis which was a complication of some other disease. Tabes and paresis, as a rule do not show eosinophilia. All the cases here cited are secondary or tertiary forms of the disease, with a rare primary stage.

Tuberculosis

Tuberculosis may produce an eosinophilia if afebrile and uncomplicated by secondary infection. The infection need not be in the lungs, and tuberculosis of the genito-urinary tract produces it more commonly than any other site. The complicating pathology of emphysema and other compensatory pulmonary changes may aid in the production of an eosinophilia in pulmonary tuberculosis.

Scarlet Fever

Scarlet fever is the one disease which shows eosinophilia with any great degree of constancy. Even in this disease there may be some doubt as to the accuracy of the response, since an eosinophilia does not occur in the severest forms (Naegeli). Most investigators consider the presence of an eosinophilia in
scarlet fever a favorable sign. The occurrence is sufficiently frequent and constant to give rise to the formula 'Desquamation plus eosinophilia equals scarlet fever' of v. Winterfeld and Hahne.\textsuperscript{74}

The eosinophilia of scarlet fever is not high, even in the favorable cases. 10 to 12\% is usually the highest average, with only 1 to 3\% in severer and complicated cases. Fatal cases usually show no eosinophiles.\textsuperscript{75,76}

\textbf{Smallpox.}

The blood findings for \textit{smallpox} are rarely recorded in recent literature, but two quite complete studies have been made. Hoffman (1923) did daily blood counts on 60 cases of smallpox and 40 cases of chicken pox, charting his results.\textsuperscript{77} In the case of smallpox, a mild eosinophilia appeared almost at once, in some cases before the rash, and this was interpreted by the author as being due directly to the action of the virus, and not to the nature of the skin lesions. A similar but milder eosinophilia was reported in many cases by Bunting and Thewlis (1926).\textsuperscript{78}

\textbf{Muscular rheumatism.}

Symwoldt,\textsuperscript{79} Staackert,\textsuperscript{80} and Kaufmann\textsuperscript{81} all report cases of muscular rheumatism, or myositis associated with high eosinophile counts. Kaufmann found eosinophilia fairly frequently in lumbago, but did not consider it to be of much diagnostic importance.
Chorea, rheumatic fever and rheumatic endocarditis.

Chorea, rheumatic fever, and their complication, rheumatic endocarditis typically show an early eosinophilia which is in many cases diagnostic. The eosinophilia does not appear at once with the onset of fever, but does appear soon afterwards. Helmreich (1935) reports that an eosinophilia of 20%, or 2000 eosinophiles (absolute count) is not uncommon, and may persist for many weeks. There is likewise a rise in the eosinophiles under effective therapy, upon which he bases his conclusions for the superior value of gold therapy in treatment of this group of diseases.

In the series of Page, Turner and Wilson, this group constituted 13% of all the patients showing eosinophilia, or 40 of their 300 cases. It is the largest single group in their series, presenting more eosinophilias than either the allergies, or the parasitic infestations, which are usually the two conditions thought of when an eosinophilia is discovered on blood examination.

The eosinophilia of rheumatic heart disease and its associated diseases may vary from time to time even in the same individual, but the eosinophilia is usually a constant finding. As a rule the count is not high, usually below 10% and rarely above 15%.
The Eosinophilia of Malignancy.

Although the presence of even large accumulations of eosinophilic granulocytes is not uncommon in malignant tumors from any part of the body, it is rare that a condition exists which so stimulates the blood forming organs or the local defense reactions of the host that there is a manifestation of the process in a generalized, or blood eosinophilia. In studies of tumors from all parts of the body, Noeske (1900) found eosinophiles present in considerable numbers in the greater percentage of tissues examined. Usually, the accumulation was more marked in the tumor after it had been subject to trauma, or after necrosis or ulceration had set in. Some types of tissue showed eosinophilic infiltration predominantly, and the phenomenon was observed in these types with a fair degree of constancy. Such types of tumors were predominantly from the skin, mucous membranes, and serous surfaces. In malignancies showing necrosis, the eosinophiles also appeared in the necrotic areas in large numbers. Similar observations have since been recorded by several investigators, and are not uncommon in any pathology department or laboratory.

The eosinophiles are less apt to be found in benign tumors, although some types are especially prone to this type of infiltration, the significance of which has never been adequately explained. Tumefactions in the nose, paranasal sinuses, and nasopharynx usually show high grade infiltration by eosinophilic granulocytes.
The eosinophilic infiltration is seen only in the primary sites of malignant tumor growth, where the necrosis and invasion is the greatest. The secondary sites of growth rarely contain many eosinophiles except in lymph nodes very close to the primary site. Sarcomata show eosinophilia much less commonly than carcinomata. Carcinomata of the oral cavity, lips, and gastro-intestinal tract show the most constant and highest grade eosinophilias.

The blood eosinophilia of malignancy is extremely uncommon, and when it does occur, it is usually a low grade eosinophilia, usually under 12% except in those cases such as lymphosarcoma, where the entire blood picture is apt to be bizarre. (Zappert, Neusser, Cabot, DaCosta, Ladwig and others). A superficial survey of the records of the University of Nebraska Hospital revealed few cases which could be used as a basis of comparison, and none of these exhibited any remarkable eosinophilia. A complete survey, however, may disclose a few interesting cases.

Voswinckel (1898) and Baradulin (1910) showed that eosinophiles disappear from the blood, or their numbers decrease in practically every case where the tumor was surgically removed, even in cases where there was no pronounced eosinophilia before the operation. The case of Weiss (1926) confirms these findings, although in this patient the eosinophilia soon returned, and persisted until after discharge of the patient. Cassuto's three cases of malignancy of the prostate follow the same rule.

Zappert (1893) in his monograph on eosinophilia reported the first cases of malignancy with eosinophilia, citing an especially
high eosinophilia in a case of sarcoma. Later the same year, Reinbach (1893) made a more complete survey of the changes in leucocytes in patients suffering from malignancy, citing the blood findings in 40 cases. Four of these patients showed blood eosinophilias varying between 5 and 12%. A fifth case presented the remarkable blood picture of an eosinophilia from 35 to 45% of a total white blood count varying between 50,000 and 120,000 leucocytes. This was a case of lymphosarcoma, with generalized metastasis, affecting the bone marrow, and many other vital organs. It was likewise complicated by chronic pulmonary tuberculosis and mitral stenosis, with less remarkable pathology elsewhere. Voswinckel's series showed many cases of malignancy of the female generative tract which exhibited a mild eosinophilia as a part of the blood picture.

Kappis (1907) case of malignancy of the right lung had a blood eosinophilia which averaged 35% of a total white blood count which varied between 30,000 and 50,000. He considered that the necrotic tumor tissue exerted a specific chemotactic influence on the eosinophiles, calling forth an excessive production of this type of cell, and a secondary invasion of the necrotic tumor mass. Reinbach considered a similar phenomenon in his case of lymphosarcoma, but believed that the eosinophilia represented the manifestation of a lessened resistance of the organism, with a breakdown of the blood forming organs under an unusual demand. Oshima (1907) cited three cases of malignancy involving the kidney, and two of these showed a blood eosino-
philial one reaching 35% of the differential count.

Baradulin reports eosinophilias of 10% in four of his cases of cancer of the lip, 5.6% in a case of cancer of the breast, and 6.5% in two other cases. A few cases of sarcoma showed eosinophilia of 12%. Collins and Kaplan (1911) likewise report a case of malignancy of the pituitary with metastasis to the mediastinum showing a high eosinophilia. Voswinckel (1898) presents many cases of malignancy in his series of 126 gynecological cases, some of which showed a blood eosinophilia. To these must be added the case of carcinoma of the cervix reported by Strisower (1913) which showed a 45% eosinophilia which fell to normal limits before death.

Lymphosarcomata, or malignancies of this type are reported by Zappert, Strisower, Page, Turner and Wilson (1928), and Reinbach. Usually the eosinophilia in these cases was quite high. There were six cases of Lymphosarcoma admitted to the University Hospital between the years of 1925 and 1935, and two more cases in which there was a doubtful diagnosis of lymphosarcoma. Of these eight cases, seven showed no eosinophiles, or only 1% of eosinophiles on the differential blood counts made, and only one (No. 1791) showed any eosinophilia. On one differential count, and eosinophilia of 10% of 6600 leucocytes is recorded.

E. Weiss (1926) reports the second case of carcinoma of the stomach exhibiting an eosinophilia. Dunger (1910) reports, among other cases, a case of carcinoma of the colon with an eosinophilia averaging about 65% of the total white blood count. Csaki's case
Malignancy

(1921) of carcinoma of the colon (with cirrhosis of the liver) presented an eosinophilia of 30% which temporarily obscured the diagnosis, since echinococcus was not uncommon in that neighborhood. Page, Turner, and Wilson (1928) list a case of carcinoma of the rectum with 12% eosinophilia. Donati's case of carcinoma of the breast had a 20% eosinophilia. Schellong (1922) reports a case of abdominal carcinoma with extensive metastasis to the liver in which the eosinophiles represented 11 to 27% of a total leucocyte count of 16,000 to 25,000 cells. Page, Turner and Wilson cite 2 cases of carcinoma of the liver (under their "miscellaneous diseases") showing eosinophilia of 6 to 11%.

In all, there are considerably under fifty cases reported where the primary diagnosis was malignancy, in which a blood eosinophilia was a predominant feature. Some of these have so much complicating pathology, or the nutrition is described as being poor, or other factors enter in so that the toxic effect, chemotaxis, or other factors influencing the eosinophilic leucocytes may be attributable to other causes. In very few cases can the eosinophilia be attributed directly to the presence of malignancy, and the occurrence of the eosinophilia along with malignancy is so rare that it might still be coincidental. In view of the work of Alexis Carrel (1922) on the growth stimulating hormone of leucocytes, this phase of investigation promises to offer some interesting problems. This is especially true of the local infiltrations of eosinophiles in tumor tissue. E. Weiss,
however, showed that extracts of the tumor tissue in his case did
not exhibit specific eosinophile stimulating substances, nor any
substance specifically chemotactic for eosinophiles.

Since eosinophilia is so rare in malignancy, it is probable
that its occurrence is of academic rather than clinical importance.
In only one reported case did its presence serve to confuse the
diagnosis. It is certainly rare enough so that it would never be
of any importance as a diagnostic aid in arriving at a diagnosis
of malignancy in doubtful cases. However, the presence of a
malignant neoplasm is sufficient to account for an eosinophilia,
and eosinophilia occurs in malignancy with sufficient frequency
so that there should be no hesitation in making a diagnosis of
malignancy if it is indicated by all the other symptoms, in spite
of even a high grade blood eosinophilia which at first sight might
indicate that some other condition was present, or superimposed
upon, a malignancy. In differentiating between leucemias, lympho-
sarcoma, and Hodgkin's disease (q.v.), the eosinophilia cannot
be depended upon, since it occurs commonly in all these ap-
parently related conditions.

This group includes the leucemias, pernicious anemia and those diseases characterized by pathology of the lymphatic structures generally, such as Hodgkin's disease. It excludes secondary anemias on an infectious or nutritional basis, although these anemias often show an eosinophilia under treatment, because the reaction in those cases is partially due to the correction of the causative factors, and not to reactions of the hematopoietic organs alone. Secondary anemia from hemorrhage in many cases also shows an eosinophilia during recovery. When at least a portion of the hemorrhage is internal, absorption of a foreign protein is sufficient explanation for most of the eosinophilia, but the occurrence of an eosinophilia after external hemorrhage can be explained only by the manifestation of recovery of the bone marrow.

Pernicious Anemia.

Ehrlich noted the absence of eosinophiles in most cases of anemias very early. Following his early descriptions, other workers noted that in some cases there was a normal eosinophile content in the peripheral blood, and in others still, an actual eosinophilia existed. Before the advent of liver therapy, many hematologists watched for the return of the eosinophile cells, and considered this a favorable sign. In those cases, the bone marrow had undoubtedly gained some of its normal hematopoietic function, and was again reacting normally. With the advent of the reticulocyte count, a closer check of the formation
of the red cells alone was available, and the eosinophile cell was ignored. With the present methods of diagnosing early pernicious anemia, and rapid and effective treatment, the eosinophilia of the remissive stage is rarely seen.

Raw liver therapy may bring about enormous increases in the eosinophile count of the blood during pernicious anemia, but whether this is to be looked upon as a favorable sign or not cannot be predicted. It is not seen in liver extract treatment, and the anemias seem to recover just as fast under the extract as under the raw liver. Murchy and Minot observed the reactive eosinophilia early in the course of their investigations, and commented upon it. Muelengracht and Holm observed this rise in other people who ate raw liver. They concluded that it was an accidental and harmless phenomenon of the raw liver diet, and dismissed the subject.

The raw liver reaction appears quite suddenly during the third or fourth week of treatment, and the eosinophilia may rise to 20 to 40% in a very short period, remaining high as long as that treatment is undergone, but dropping gradually.

The Leucemias.

Eosinophilia is a constant finding in myeloid leukemia, so constant that Ehrlich denied the right to make a diagnosis of myeloid leukemia unless an eosinophilia were present. In the face of so many immature cells in the blood, the relative eosinophilia may maintain a low relative level, but the absolute count is very much increased. Adult types of cells may be
rather rare, and the prevalence be of young and immature cells, and myelocytes. Beyond this stage there may be some doubt as to the lineage of the cell in question, although earlier cell types are capable of being differentiated by the trained observer. There is no predictive means for determining the eosinophilia in a case of myeloid leukemia, since it varies with the acuteness or chronicity of the case, and the individual characteristics of each case.

Lymphoid types of leukemia should theoretically show no eosinophilia, and this is usually true. In some cases, where only recognizable cells of the myeloid series are considered, a mild absolute eosinophilia may be found.

Hodgkin's disease.

The blood picture of Hodgkin's disease is apt to vary with the stages of the disease. A marked eosinophilia may be evident in some stages, but these constitute a rather small percentage of the cases. The work of Bunting (1911 and 1914) indicates that about one-fourth of the cases will show a mild or moderate eosinophilia which rarely becomes marked. Most of the significant literature tends to confirm the observations on these earlier series, although the reports of cases with high eosinophilias tend to somewhat distort the picture and give the false impression that a high eosinophilia is the rule rather than the exception.
Eosinophilia with Splenic Disease.

Eosinophilia is a common finding in nearly all cases where there is pathology of the spleen. The nature of the pathology seems to be less important than the location, with few exceptions. Tumors of the spleen commonly give rise to high eosinophilia, yet microscopic examination of many of them reveal that the origin of these cells in the blood must still be the bone marrow, since there is no great increase in eosinophiles in the spleen itself. Ordinarily the spleen does not have any marked granulopoietic function, but maintains the potentialities of a granulopoietic organ, and can function in that direction if necessary. Removal of the spleen is associated with an immediate decrease in the eosinophile cells, followed by a slow progressive rise, the apex of which is reached in six to eight weeks. From that time on, a relative and absolute eosinophilia exists in the splenectomized animal.

The activity of the spleen in this direction must be largely hormonal, since the blood changes and the local changes in this organ are rarely compatible. Failure of the spleen to act may account for some eosinophilias, and the symptoms which accompany these phenomena. A protein-free splenic extract will lower the eosinophilia and stop itching in patients suffering from itching dermatoses."

Trauma to the spleen is a case in point. Unfortunately the reactions here, although identical with a splenectomy as long as the spleen is non-functional do not occur quickly enough to be of any diagnostic value in cases where there is suspected rupture of the spleen. MacQuiddy's case illustrates
the course of such cases rather well*. In this instance there was a history of trauma over the spleen. The eosinophiles gradually rose to 48% in a week and then gradually subsided. At no time were there any severe symptoms, and there was a complete recovery.

A Splenic Disease Entity?

There is in the literature, occurring with increased frequency, numerous descriptions of a syndrome involving a leucocytosis with high eosinophilia, moderate to marked splenic enlargement, and moderate generalized lymphadenopathy. Boekelman (1925)* added the seventh case to the literature, describing this syndrome in a man with a moderate leucocytosis and an eosinophilia varying between 66 and 90%. This case was one reviewed by Stockton in his discussion of unexplained eosinophilias, but did not fall into his classification. Bass (1926) reported a case in a six year old child with high leucocytosis and an eosinophilia of 37 to 64%. Giffin's case was treated by splenectomy and the eosinophiles rose to 90%.* Schmidt-Weyland (1925) reported a case with a leucocyte count of 90,000 and a 67% eosinophilia. In this case there was other pathology, sigmoid ulcers and gastro-intestinal symptoms. In all cases the absence of young forms made the diagnosis of a leucemia extremely unlikely. Harrison (1930) reviewed previous cases, adding one case of his own (with autopsy) and one case of Krumbhaar's with the same picture, and suggested the possibility of a new disease entity.**

*DR. E. L. Macquiddy, personal communication.
Eosinophilies in Miscellaneous Diseases.

Diseases of the Bones.

Some of the diseases of bones and joints which produce an eosinophilia have already been mentioned. Under this heading are the more infrequent findings concerning which only a few erratic statistics are available.

Cabot, DaCosta and Neusser speak of an eosinophilia occurring with osteomalacia. Osgood and Haskins also mention the possibility. Neusser's statements are the only definite evidence that such a finding is apt to occur, and the others are apparently quoting him. The same sources mention tumors in bone as possible causes of eosinophilia. Osgood and Haskins consider it important to consider the possibility of osteomyelitis when there is an eosinophilia associated with an unexplained fever. Page, Turner and Wilson report one case of chronic osteomyelitis with an eosinophilia of 9%. Osteitis fibrosa may cause eosinophilia.

Diseases of the Skin.

There are a good many diseases of the skin which give rise to eosinophilia. Pemphigus is the most striking. In this condition, the eosinophilia may be lacking at the onset, and disappears before the fatal termination of the disease. Psoriasis may show an eosinophilia, eczema usually does not. Herpes, and herpetiform types of lesions commonly show eosinophilia, and erythema bullosum, prurigo, and similar diseases with the same type of pathology may show eosinophilia. Arsenical and luminal reactions commonly show it, but urticarias are inconstant.
Miscellaneous

Urinary diseases.

The first mention of an eosinophilia with diseases of the kidney and urinary tract was by Neusser. Since then few cases have been supported to support his original findings. The series of Page, Turner and Wilson contained 50 cases of eosinophilia in the chronic-nephritis, arterosclerotic class, or 10% of the cases of the series, the same percentage present in the allergic and parasitic groups."
Drug Eosinophilias.

Drug Eruptions.

Very few blood studies have been made on drug eruptions, consequently knowledge regarding blood reactions in this phase of medicine is incomplete. Arsenical dermatitis often shows an eosinophilia, as is also true of mercurial dermatitis. Klieneberger reports marked eosinophilia with luminal eruptions. Since drug eruptions generally depend more or less upon idiosyncracies, or hypersensitiveness to the causative agent, it would be expected that they would commonly be associated with eosinophilia, but reports are too scanty to form the basis for a definite conclusion. Most skin cases of all types are handled in outpatient departments where time elements alone prevent the taking of routine blood counts.

Heavy metals.

Arsenic poisoning is associated with eosinophilia in a large percentage of cases. The most complete series available is that reported where 28 individuals were poisoned at the same dinner. These patients showed variations in the eosinophile percentages between 2 and 40% for the first week, and in those who recovered, the counts gradually returned to normal.

Lead poisoning commonly shows eosinophilia, along with the typical basophilic stippling of the red cells. The degree of eosinophilia is not diagnostic of the degree of poisoning, nor of the nervous changes. Possibly both the nerve damage, and the local effect of lead in the bones play some effect in the production of this eosinophilia. There is probably also
a direct toxic effect.

Mercury poisoning is also reported to produce an eosinophilia in some cases.\textsuperscript{2}

Pilocarpin and related drugs.

The abnormal response of asthmatic patients to pilocarpin has already been mentioned. Aschenheim and Tomono\textsuperscript{5} deny the eosinophilic response to pilocarpin, but it is supported by the experimental evidence of many other investigators. Baráth (1924)\textsuperscript{3} demonstrated a paradoxial action of pilocarpin in patients with an already high eosinophilia, inasmuch as injections lowered the eosinophiles in the blood almost immediately, with a gradual return to the previous level in about two hours. In most cases the immediate reaction is a raised eosinophile level, appearing within fifteen to twenty minutes after injection, with a gradual fall to the previous level (normal) within the two hour period.

Physostigmine is reported to have an action similar to pilocarpin, but the experiments on the action of this drug are much more limited.

The action of adrenalin is worthy of mention in connection with these drugs, although it does not raise the eosinophile count, but rather lowers it. The first reaction of adrenalin, barring the reaction of blood pressure changes, and vessel tonus,\textsuperscript{4} is a transient lymphocytosis, followed by a granulocytosis. Goia (1922)\textsuperscript{6} believed that he demonstrated a typically
different type of response with each of the blood dysorasias, suggesting a possible diagnostic feature to the reactions.

In the same class of drugs is pituitary extract, which has been reported as capable of producing an eosinophilia.

Miscellaneous drugs.

Miscellaneous drugs which have been shown to produce eosinophilias under some experimental conditions are: nuclein, camphor, dinitrobenzol, acetanilid, sodium salicylate, potassium iodide, and toxic phosphorous compounds. Inasmuch as the original citations cannot be traced with any of this list, they are appended here for what they are worth. The pharmacological action of several, and the means by which they could produce eosinophilia is in some cases highly conjectural. The peculiar shock sometimes seen with acetanilid and antipyrine (Neusser) indicates that these may be capable of causing eosinophilia, since their idiosyncracy in some people produces a sort of vasomotor collapse that is dependent upon vegetative nervous system reaction. Nuclein is known to be able to produce extramedullary myelopoiesis (Doan) and an accompanying eosinophilia, while not specifically described, is not unreasonable.
THE SIGNIFICANCE OF EOSINOPHILIA

Occurrence.

The only comparative series of eosinophilia and normal or subnormal eosinophile values is that prepared by Page, Turner and Wilson. In 5500 patients in the Columbia Presbyterian Hospital (Medical Service) between 1923 and 1927, 342 showed eosinophilia at one time or another. Of these, 42 exhibited only a transient phenomenon, and were discarded as being without diagnostic or prognostic import. On this series, the remaining patients constituted about 6 to 7% of the total medical patients. About one patient in 15 then, should show an eosinophilia, and if the finding was of diagnostic or prognostic value in one-half the patients in which it was discovered, periodic routine blood examinations would be justifiable on this basis alone.

The distribution of causes for the eosinophilias found in this series presented some rather surprising results, inasmuch as eosinophilia means parasites or allergy to the average practitioner. About 10% of the cases were diagnosed as parasitic infestations, 13% were among the rheumatic fever-chorea group, and 13% were classified as being due to chronic respiratory disease including emphysema, bronchiectasis, sinusitis, tuberculosis, bronchitis etc. 10% were in the chronic nephritis-general arterosclerotic group. The asthmatic cases were included in the 10% of chronic respiratory disease. In about 40% of the cases, the diagnoses were scattered and in these isolated cases of malignancy, constipation, duodenal ulcer, and other diseases, the occurrence was considered to uncommon to be of diagnostic significance.
Significance

Diagnosis.

From the standpoint of diagnosis, the finding of an eosinophilia is confirmatory rather than indicative. In asthma, it might serve to differentiate between an allergic and a bacterial type, and in some cases of doubtful pulmonary pathology, the eosinophilia might indicate an asthmatic condition in preference to one of the pulmonary conditions presenting a less constant eosinophilia.

In the eruptive diseases, early in the course eosinophilia indicates smallpox rather than chicken pox; and scarlet fever rather than one of the scarletiform erythmatoses. It is diagnostic in joint conditions in some cases, especially in children, where the eosinophilia indicates rheumatic fever. Gruner considers an eosinophilia helpful in differentiating between gout and tuberculosis of a joint, between active malaria and typhoid fever, and between scarlet fever and measles. He also suggests that the degree of eosinophilia should differentiate between acute muscular rheumatism and trichinosis, and states that a sudden decrease in eosinophiles in a case of echinoococcus or amebiasis indicates the beginning of a complicating abscess.

Schmide points out that an eosinophilia in the presence of gastrointestinal symptoms indicates parasites first, and other pathology after these are ruled out. He also considers
eosinophiles important in the diagnosis of blood dyscrasias and in Hodgkin's disease. Marcovich believed the eosinophilia of Paratyphoid B to be of sufficient constancy to serve as a diagnostic aid in differentiating between it and mild cases of typhoid fever. Klieneberger found eosinophilia rather commonly in lobar pneumonia.

Prognosis.

The finding of an eosinophilia after a suppurative process indicates approaching convalescence, and the same holds true for most febrile states. Grace (1934) considered the disappearance of eosinophiles from the blood in pemphigus to indicate a terminal bacteremia. Schook's reports on the favorable outcome of treatment of carcinoma of the cervix in which there was local eosinophilia is of especial significance.

Several attempts have been made to correlate the eosinophilias of tuberculosis with the progress of the disease. The summary of the chief findings to date are that the eosinophiles in the blood decrease in numbers when the sputum is positive. Uncomplicated lesions with a relatively afebrile course show the highest eosinophilia. There are very few if any eosinophiles in cases where there is fever and frank secondary infection of the cavity. Summarily, the findings there are as in any of the infectious processes, but in a modified degree. The presence of an eosinophilia indicates the building up of body resistance, while an absence of eosinophiles indicates the reverse.
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