

THE LEUCOCYTES IN APPENDICITIS.

BY RAYMOND CUSTER TURCK, M.D.

Extra-Mural Professor of Surgery, Chicago, Post Graduate Medical School, Jacksonville, Florida.

The art of diagnosis in appendiceal disorders is as yet far from perfection. Every operator in the major abdominal field can recall numerous instances in which the operation findings failed to confirm the initial diagnosis, and this is true in an astonishingly large percentage of cases when a post-operative histo-pathological and bacteriological examination is made.

Reflection upon this fact determined the writer to a study and analysis of the factors entering into the problem of a definite and positive diagnosis and prognosis of the various forms of appendicitis. It is with the factor of leucocytosis that this paper deals. In an effort to focus information regarding the behavior of the white cells in appendiceal inflammations and infections one cannot but be amazed at the chaotic and contradictory character of the literature, and in view of this fact it is not surprising that the majority of surgeons, and physicians as well, are inclined to take a prefatory view of the subject, and to place but little, if any, reliance upon the blood examination; the blood count if taken at all being largely a matter of form, and being considered of no more importance than the temperature, both, according to Deaver,¹ being of about equal value, and both subject to wide fluctuation.

That hematological reactions to infective and inflammatory processes vary according to the reactive and resistive powers of the individual must be conceded by all who have given a thought to the subject of immunity, or to the behavior of the blood in disease. It

seems absurd to presume that white cells of a feeble and anemic child of ten will show exactly the same reaction in infections of equal scope and virulence as the cells of a strongly robust man of forty, yet the literature is teeming with definite standards of white cell counts as applicable to definite conditions. The failure of these standard counts to invariably coincide with existing conditions as revealed at operation or in the laboratory is due in part to a failure to take into consideration the individual equation of reaction and resistance.

Certain fundamental hematologic reactions have, however, been demonstrated as occurring in practically all cases of like infections and inflammations, variation being a matter of degree only. It is through a consideration of these fundamentals, throwing aside uncertainties, probabilities, and average standardizations, that an examination of the blood offers the greatest aid to a determination of the variety and scope of appendiceal, as well as other, infective or inflammatory processes.

The term leucocytosis is generally used and understood as indicative of an increase, above normal, in the total number of white cells in cubic millimeter of blood. Strictly, however, *leucocytosis should be defined as an increase or decrease in the total number of white cells normal to the individual, or a variation in the percentage of the different kinds of leucocytes normal to the individual.*

According to Simon,² leucocytosis should be considered as hyper-leucocytosis, an increase in the total number of leucocytes, or hypo-leucocytosis, a decrease in the total num-

ber of leucocytes. Simon further divides the general subject of leucocytosis according to the increase or decrease in the relative proportion of the different forms of cells.

It seems advisable at this point to further recall that leucocytosis (more properly hyper-leucocytosis) may be *physiological*, that is, and increase in the total number of leucocytes due to *physiologic* reaction, not due to disease; or, *pathological*, that is, dependent upon and the result of definite *pathologic* processes. It is interesting to note in this connection that, as Cabot³ states, the studies of Ehrlich and others have shown that in physiological leucocytosis no new cell formation occurs, the leucocytes being drawn from the internal organs and deep vessels into the peripheral circulation by chemotaxis or thermotaxis. In a pathological leucocytosis, particularly in long standing suppurations, "there is no doubt that leucocytes are formed and turned into the circulation more rapidly than under normal conditions."

In a strictly physiologic leucocytosis the increase in the total number of leucocytes takes place at the expense of no one kind of cell, the normal relative proportion of the white cells being undisturbed.

Pathologic leucocytosis is defined by West⁴ as "an increase in one kind of leucocyte at the expense of the others." We may, therefore, have a pathological leucocytosis with or without an increase in the total number of cells, indeed, we may have a pathological leucocytosis, in which there is a decrease in the total number of leucocytes (leucopenia). Since a pathologic leucocytosis depends primarily upon a variation in the percentages of the kinds of leucocytes, the total increase or decrease in white cells must be a matter of secondary consideration and importance, so far as the determination of pathologic processes by blood findings is concerned. The mere fact of finding in any case an increase in leucocytes shows nothing definite. It is impossible to determine by simple white cell

counts up to 20,000 to 25,000 per cmm. whether the increase is physiological or pathological, whether it is due to pus producing organisms, or animal parasites, or whether or not it is a form of beginning leukemia. Even in the higher counts, unless the clinical symptoms are so positive as to admit of no possible error, the absolute cell count may give no definite information. While it is true that very high counts are usually a form of lymphocytosis, yet, according to Holt,² polymorpho nuclear hyper-leucocytosis in children may run as high as 100,000 per cmm. In these cases it certainly is necessary to know whether the increase is in the poly-nuclear or in the mono-nuclear forms. Cabot³ states that "given a count of 80,000 per cmm. we cannot tell, without knowing the variety of cells present, whether the case is a genuine leukemia or merely a leucocytosis symptomatic of pneumonia, suppuration, malignant disease, or other condition."

In the inflammations and infections of the vermiform appendix, as in other infectious, inflammatory or suppurative processes, and in all infectious diseases except five (i.e., typhoid fever, tuberculosis, measles, malaria and influenza), a hyper-leucocytosis, if present, is always due to an increase in the poly-morpho nuclear neutrophiles.

The great majority of observers in studying the reaction of the leucocytes in cases of appendicitis take for granted that if the white cells are increased, the increase must be in the neutrophiles. No increase being found, it is assumed that the relative proportion of the cells is normal and that no pathological leucocytosis exists.

The severity, and in many instances the form of the infection, inflammation or suppuration has, until recently, been judged solely by the absolute count of leucocytes. Thus the elimination of the essential and vital feature of the blood reaction in disease has resulted in a confusion of statistics, and it is

not surprising that the deductions and conclusions are varied and contradictory.

It is unfortunate that in studying reported series of counts we have in a majority of instances, no definite assurance that the reported hyper-leucocytoses were not oftentimes physiological, eosinophilic or lymphocytic, nor that in cases showing no increase, or an absolute decrease, there was not a pathological leucocytosis present, as evidenced by a relative increase or decrease in the poly-nuclear forms. In this connection, the following quotation from West⁴ is pertinent:

"It is through oversight of the fact that it is the percentages which show a leucocytosis to be pathological or not, that much odium has been cast upon leucocytic readings. This censure has come from those who have judged a leucocytosis by the number to the cmm. and given no heed to the percentages * * * we should know that it is possible to have a pathological leucocytosis in the sense of the above definition, without an increase in the total number of white cells. 95 per cent. neutrophilia has been noted when the total number of leucocytes to the cmm. was only 6,000. * * *

A careful review of the literature of appendical leucocytosis (Simon,² Cabot,³ West,⁴ Holt,⁵ Sahli,⁶ Da Costa,⁹ Boston,¹⁰ Emerson,¹¹ Arneill,¹² Deaver,¹³ Kelly,¹⁴ Bloodgood,¹⁵ cannot but lead one to agree with Deaver that for purposes of diagnosis in cases where time allows of but one, or possibly two counts, practically nothing is to be gained from the knowledge of the absolute number of leucocytes.

With the possibility of a normal total count in simple catarrhal appendicitis, fulminant appendicitis and fatal peritonitis, and in view of the fact that chronic cases, and cases with abscess range from 6,000 to 60,000 white cells per cmm., the positive diagnostic value of a single count in itself is nil. Indeed considering the single absolute count from a diagnostic standpoint, we have no assurance that a hyper-

leucocytosis, if present, is neutrophilic and not physiologic or lymphocytic.

Assuming, however, from positive clinical symptoms, that a hyper-leucocytosis, if present, is due to an increase in polymorpho nuclears, that it is without doubt dependent upon an infective process, we are warranted in stating upon authority that the infective process increasing in virulence or extent (if in an individual of normal reactive powers) will produce an increase in leucocytes in direct ratio to the increase in the infection.

On the other hand, an infective process decreasing in virulence or extent, will produce in the blood a correspondingly gradual decrease in the total number of leucocytes (in this we must include abscesses, from which, by reason of progressive walling off, absorption of proteins or toxins, is gradually lessening).

These two facts are unquestionably fundamentally correct, but in their practical surgical application, in dealing with the absolute count alone, we must work to a certain extent upon assumptions and not entirely upon facts.

In observing the fluctuations of counts of from 15,000 to 40,000 we have a fair assurance of obtaining a reasonably exact knowledge of the progress of the infection. We are further justified in stating that counts below 15,000, or the fluctuation of counts below 15,000, have practically no diagnostic or prognostic significance whatever. To this the writer would add, *unless at the same time we closely observe the relative proportions of the different forms of leucocytes.*

A realization of the inadequacy and unreliability of the absolute cell count taken alone, as well as the conclusion, so concisely stated by Sondern,¹⁶ that "the increase in the relative number of polynuclear cells is an indication of the severity of the toxic absorption, and the degree of leucocytosis is an evidence of the body resistance toward the infection," has of late directed attention to the differential percentages.

Simon,¹⁷ in his recent work on Clinical Diagnosis, emphasizes the value of the differential count, and in this connection says: "Until quite recently the general tendency in clinical laboratories has been to lay special stress upon the absolute leukocyte count and to leave the relative values of the different forms out of sight. This should not be, and I cannot insist too strongly upon the importance of the relative count, which in many respects is far greater than a knowledge of the total number."

Simon comments upon the fact that because of the many variations and exceptions, surgeons not unnaturally decline to be guided in their operative work by the results of the absolute blood count. He further states that he values the absolute count in the study of the progress of appendicitis—only so far as a progressive increase is concerned.

The basis of the study of the differential must be a determination of the relative cell percentages in an individual of average strength, nutrition and reactive power.

Cabot,¹⁸ places the normal percentages in a healthy adult as follows:

Small lymphocytes20% to 30%
Large lymphocytes4% to 8%
Neutrophiles62% to 70%
Eosinophiles½% to 4%

Simon¹⁹ states that before the age of five, the percentage of small lymphocytes may be as high as 40 per cent., but that after the fifth year adult values are the rule. During the first year the polynuclears range from 20 to 40 per cent., gradually rising until the twelfth year, after which adult values are obtained. Simon places the percentages in the normal adult as follows:

Small lymphocytes20% to 30%
Large lymphocytes and transitionals1% to 6%
Neutrophiles60% to 70%
Eosinophiles1% to 4%

Zeit²⁰ gives the following normal adult percentages:

Small lymphocytes20% to 30%
Large lymphocytes25% to 70%
Neutrophiles60% to 70%
Eosinophiles1% to 3%

It seems safe to accept 60 to 70 per cent. for polynuclears as a normal standard for the healthy adult, but the possibility of individual variation should always be borne in mind, and in patients not obviously robust an allowance be made of perhaps 5 per cent. each way.

Gibson²¹ in his paper upon the application of the differential in conjunction with the total count, in the diagnosis of appendicitis, takes 75 per cent. neutrophiles and 10,000 total leucocytes as his basis standards.

We are indebted to Gibson for his work in this field. The greatest value of his paper, however, lies not in his standard chart as given, but in his directing attention to and awakening interest in the differential itself.

Gibson believes that the relative proportion or disproportion between the increase in neutrophiles and the increase in total cells is the important diagnostic factor. His standard chart, while perhaps correct in a majority of instances, is so open to error that it is of uncertain value in practical diagnosis.

Noethen,²² in reporting the blood findings in seventy-two cases of acute appendicitis in services of Doctors Kammerer, Kiliani and Willy Meyer states that, according to Gibson's chart, six out of fourteen of his cases of diffuse or spreading peritonitis would be adjudged "mild and safe."

Noehren advocates the employment of the differential alone, without regarding the total count, and concludes that *a percentage of 90 per cent. or more neutrophiles indicates a very severe process, that needs immediate operation. A percentage below 78 per cent. indicates a mild or safe process in which immediate operation is not necessarily indicated.* A percentage between the two extremes speaks for

the one condition or the other, according as it approaches the one extreme or the other.

Noehren's findings are additional proof that practically without exception every case of acute appendicitis showing a neutrophile or over 80 per cent. is serious, and this without regard to the total number of leucocytes present. However, if the patient is resisting, when we find a high neutrophile, we expect a high degree of leucocytosis, the total leucocytosis being the index of resistance, the neutrophilia being the index of virulency.

If, on the other hand, we find a high neutrophile with a low, normal or subnormal total count, we are certain that we are dealing with a markedly virulent case in which there is no systemic resistance and we may know positively that the prognosis is bad.

West and others have compared the action of an overwhelming infection upon an individual to a blow upon the head, the patient in each case being stunned, in the latter instance by shock to the central nervous system—in the case of the violent infection by the crushing of the organisms reactive power, with consequent failure to produce the antibodies and cells necessary to successful resistance.

In this connection, one other factor should be borne in mind—that is, the transitional leucocyte. Hematologists have stated that transitional leucocytes are but partly formed polymorpho-nuclear neutrophiles, probably a transition form in the evolution of the bone marrow myelocyte or the large mononuclear to the mature neutrophile. The presence of transitionals in the peripheral blood in quantities is an indication that Nature is attempting to produce neutrophiles for some, but reason is unable to form the perfect cell.

A neutrophilic percentage of 40 to 50 per cent., with an increased percentage of transitionals, may show a much graver and more dangerous condition even than the desperate

case in which we find a high neutrophilic percentage with a low total count.

In this connection the findings in a case of perforated appendicitis, with diffuse septic peritonitis, illustrate this point (i. e., absence of resistance and reaction).

Total leucocyte count, 6,000.

Small lymphocytes, 30 per cent.

Large mononuclears and transitionals, 30 per cent.

Neutrophiles, 40 per cent.

Another case of fatal diffuse septic peritonitis, in which was found but 7,000 total leucocytes with 92 per cent. neutrophiles, illustrates the first point (i. e., presence of a high degree of reaction, but with no resistance).

The above findings, if laid out on Gibson's chart, would have no significance whatever, yet the meaning of the counts must be obvious to the thoughtful observer.

A consideration of the total count as an index of the patient's resistance, and as a measure of how much help we may expect from Nature in our operative efforts, if taken in conjunction with a study of the differential as a measure of the existence and virulency of the infection, aids us materially, not only in diagnosis and prognosis, but in the determination of operative requirements, and oftentimes may warn us against plunging into a hopelessly fatal operation.

The writer feels particularly fortunate and highly honored in being able to present for the first time the views and conclusions on the subject of "Leucocytes in Appendicitis" of Prof. F. Robert Zeit of Chicago.

Prof. Zeit during the past ten years has closely observed the blood findings in many hundred appendiceal disorders, and has carried the operation findings through bacteriological and histo-pathological examination, thus checking up the initial diagnosis, and as a result has a crystalized knowledge of the subject.

Prof. Zeit speaks not as a surgeon, but with the accuracy and calm reasoning of the scientific hematologist and pathologist.

It is greatly to be regretted that Dr. Zeit has not before this presented his views and deductions in detail. However, he has given the writer, in a series of personal communications, his major conclusions, as herein inadequately portrayed.

In his study of the subject, and during the course of his work with Dr. Zeit, the writer was able to follow Zeit's reasoning by an examination of case histories and blood counts, together with examination of blood slides, gross pathologic specimens and microscopic sections.

In dealing with the leucocytes in disease, Zeit emphasizes the fact, as stated but not applied by most hematologists and surgical writers, that it is the variety of leucocytosis that assists in the differential diagnosis of disease, and that from the total counts alone no positive information is to be gained.

Zeit refuses to work upon assumptions. He must know definitely, first, whether a leucocytosis, if present is physiological or pathological, and if pathological whether eosinophilic, lymphocytic, neutrophilic, myelocytic, or transitional. Knowing the kind of leucocytosis, he bases his diagnostic and prognostic deductions not only upon the immediate size at the progress of the leucocytosis in question.

He states that, so far as appendicitis is concerned, we are dealing, in a majority of cases, with the pyogenic micro-organisms, and since pus germs and infective processes are chemotactic to polymorphonuclear cells, it is to variations in the neutrophils that we must look for information.

Zeit's views on certain phases of appendiceal leucocytosis may be summarized as follows, i. e., *having clinical symptoms of appendicitis and a pathologic pyogenic leucocytosis, as evidenced by the presence of a neutrophilia.*

(1) An increasing leucocytosis indicates a spreading infection.

(2) A high stationary count indicates a partly walled-off abscess, or a stationary infection.

(3) A gradually decreasing leucocytosis indicates a gradually decreasing infection.

(4) A sudden fall in total leucocytes from high to low, with neutrophilia, shows an abolishment of systemic resistance and means impending fatality.

It will be noted that Dr. Zeit finds the greatest value of the blood findings, not in a single examination, but in cases where the blood picture may be followed from hour to hour, or from day to day.

Dr. Zeit distinctly makes the following statement: Having the ordinary clinical symptoms of acute appendicitis, with no leucocytosis, and no neutrophilia, no infection is present, and in 75 per cent. of cases, if the removed appendix be taken through histo-pathological examination, it will show true normal tissue, with no sign of pathologic inflammation.

Zeit is convinced that many cases of so-called catarrhal appendicitis are not inflammations at all, but that the clinical symptoms were due to a colic in a histologically normal appendix, the result an excess of contained mucus or fecal matter.

Zeit, however, recognizes a form of true catarrhal appendicitis, and in this true form he has always found a leucocytosis and a moderate neutrophilia.

He classifies true catarrhal appendicitis as an endo-appendicitis, as evidenced by the demonstration microscopically, of congested vessels, edematous mucosa (exudation of serum), interstitial small cell (lymphocytic) infiltration, immense numbers of goblet cells, distended with mucus in the lining epithelium of the mucosa, and at times a moderate number of red blood corpuscles in the interstitial tissue.

This form Zeit believes to be due to a *non-producing micro-organism*.

The writer is convinced, not only from a study of Zeit's data, but from reviews of certain of his own cases, and many of other operators, that, in operating upon cases of acute "catarrhal" appendicitis, surgeons in possibly 50 in each 100 cases, are removing histo-pathologically normal appendices for the relief of symptoms.

It is not beyond the realm of possibility to trace pain, local or referred, to an exaggerated appendiceal peristalsis nor a moderate temperature to colonic disturbance with consequent purin absorption, nor a nausea to a sympathetic nerve reflex.

The removal of a normal "catarrhal" appendix may be justified on prophylactic grounds, but, for the sake of surgical truth, among ourselves at least, we should so designate the procedure.

Dr. Zeit lays stress upon the point that the possibilities for pain and other disturbance in the right iliac fossa are great, and that appendiceal disease is not the only factor to be considered in our dealing with disorders in that locality.

Zeit's views coincide with those of Noehren, in that the higher the neutrophilic percentage the more virulent and extensive is the infection, that a normal neutrophilic percentage shows that there is no active pyogenic process present, and that the severity of the infection may in a measure be gauged by the degree of neutrophilic increase.

He states that the prognosis is always better in pyogenic cases showing a high percentage of total cells (i. e., high resisting powers) than in cases showing pyogenic infection, as evidenced by a neutrophilia, with no or low resistance, as shown by a low total count, and that the prognosis is hopeless in cases showing a low total count, with no reaction, as evidenced by a subnormal neutrophilic percentage with increase of transitionals.

Asked what might be deduced, in a case

presenting clinical symptoms of acute appendicitis, from a total count of 15,000 to 20,000, with a *normal* differential count, Dr. Zeit stated that such a blood picture had no significance whatever, that it argued neither for nor against, and that it would undoubtedly be merely a digestion or physiologic leucocytosis. In such a case it would be perfectly safe to assume that no pyogenic process was present.

As an example of non-inflammatory "appendicitis" clinically typical, Zeit cites a blood picture of 40,000 total leucocytes, with 50 per cent, eosinophilia. The appendix in the case was found histologically normal, but with its cavity packed full of oxyuris vermicularis.

Zeit's records of tubercular appendicitis always show a leucopenia, with no neutrophilia. These cases must be classed as chronic forms, and clinically, unless subjected to a secondary pyogenic infection, do not appear acute, or suppurative.

Sub-acute abscesses usually show a total count of from 20 to 50 thousand, with a neutrophilia of from 80 to 90 per cent. In these cases the abscess, while walled off, contains active living pyogenic bacteria.

In the *chronic forms* of appendicitis, in which there is no active pyogenic or acutely inflammatory process, and in old, well walled-off abscesses, Zeit has found few if any blood changes. Many large, old appendiceal abscesses are sterile, the etiologic bacteria being dead.

Since an active infectious process is necessary to the production of a neutrophilic reaction, and a stimulation of systematic resistance toward infection, it is useless to expect, or look for, blood changes in chronic inflammations, and sterile abscesses, but this fact, too, should be borne in mind, that, *if the process is not sufficiently active to produce blood changes, there will also be no acute clinical symptoms.*

In the chronic forms of appendiceal inflammation or abscess we are not dealing with time, a difference of days one way or the

other as regards operative procedures is a matter of little importance, and in these cases we may take our time in making a definite diagnosis, and in planning operative or other relief. The value of the blood picture in these cases lies not in what we find, but in what we do not find.

In any case of appendicitis acute, sub-acute, or chronic, if we find a pyogenic, neutrophilic leucocytosis, we may know positively that we are dealing with an acute inflammatory process, a suppuration, a gangrene, a perforation, or a peritonitis.

On the other hand, in any case of appendicitis, acute, sub-acute or chronic, if on repeated counts we find a normal total number of leucocytes and a normal differential percentage, we may know, positively, *that we are not dealing with an active pyogenic process*, that there is no immediate danger to life, that we need not hurry, but that we may make, at our leisure, a differentiation between a colic, a chronic inflammation, a walled-off small abscess, a sterile abscess, or a tubercular appendix, by other means than the blood pictures.

It is indeed fortunate that the blood examination is most valuable to us, in the very class of cases in which we need it most, and it is almost incomprehensible that, because of a failure to find blood changes in certain chronic conditions, many men should throw the whole subject overboard, and thus deprive themselves of a valuable diagnostic and prognostic adjunct in the acute cases, in which definite and positive information is so necessary, and any assistance so acceptable.

CONCLUSIONS.

1. Because of individual variation in resistive and reactive functions, no absolutely invariable single total amounts, or cell percentages can be laid down as significant of definite conditions.

2. The absolute count of leucocytes, if taken alone, has little value as a means of diagnosis.

3. The greatest value of the blood picture in pyogenic processes lies in observation of the neutrophilic percentage, as a measure of the existence and virulency of the infection in conjunction with observation of the total number of leucocytes as an index of the patient's resistive power.

4. The blood picture, utilized with the clinical picture, usually affords much diagnostic and prognostic aid, even in single examination, but its greatest value is shown when it can be followed from hour to hour or from day to day.

5. The progression or retrogression of an acute infection may be determined by observing the progression or retrogression of the neutrophilic percentage and the total cells.

6. In the average adult 7,000 to 9,000 total leucocytes, and 60 per cent. to 70 per cent. neutrophils may be accepted as normal standards.

7. An increase in leucocytes above 12,000 is without doubt in all cases a hyper-leucocytosis, either physiological or pathological, and an increase of neutrophils above 75 per cent. is without doubt a pyogenic neutrophilia in adults.

8. Every case showing a neutrophilia above 80 per cent. has a serious infection, the higher the neutrophilia the more virulent the process, and the higher the total cell count the better is the prognosis.

9. In acute cases showing a virulent infection as indicated by a neutrophilia of 85 to 95 per cent., with no resistance, as evidenced by a low total count, the prognosis is grave.

10. In acute cases showing no reaction, as evidenced by a low neutrophilic percentage, with an increase in transitional leucocytes, and no resistance, as evidenced by a low total count, the prognosis is hopeless.

11. Cases presenting the so-called typical symptoms of acute catarrhal appendicitis, with no hyper-leucocytosis and no neutrophilia, have no infective inflammation, and in a majority of instances are those of mechanical ap-

pendical colic, with possible colonic ptomaine absorption.

12. In any case, acute, sub-acute, or chronic, in which a normal neutrophilic percentage, and no leucocytosis is found, there is no acute infection, there is no immediate danger to life, and there is no necessity for immediate operation.

13. Chronic forms of appendicitis; old, sterile, or *safely* walled-off abscesses produce few if any blood changes.

14. Cases showing a leucocytosis and a neutrophilia require careful watching and immediate attention, and those showing a normal neutrophilic percentage, and no leucocytosis, may be investigated at leisure.

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