

# THE BRITISH JOURNAL

OF

## TUBERCULOSIS

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Vol. X.

October, 1916.

No. 4.

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### ORIGINAL ARTICLES.

#### A STUDY ON THE LEUCOCYTE COUNT IN PULMONARY TUBERCULOSIS.

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THE gradually increasing and oft conflicting evidence brought forward in connection with the number and morphology of the polymorphonuclear leucocytes in pulmonary tuberculosis led me to make some observations on the blood of patients suffering from this disease, with the remote hope that a further clue to the clinical pathology of the disease might present itself. How far that hope has been realized remains to be seen, but from the results of the blood-examinations detailed below one cannot but conclude that a systemic infection like pulmonary tuberculosis sooner or later makes itself apparent by an alteration in the blood, which up till now has received scant recognition from clinical pathologists and diagnosticians,

It is well known that the number of polymorphonuclear leucocytes is variable in health. According to Gulland and Goodall,<sup>1</sup> digestion leucocytosis is a chronic condition which is ever present with us, the increase reaching its maximum four hours after food has been taken. These observers claim that an increase of 1,000 to 1,500 per cubic millimetre represents the increased leucocyte response to the digestion of food. Reidler gives the average increase in health after

<sup>1</sup> Gulland and Goodall: "The Blood," 2nd ed. Edinburgh: W. Green and Sons, Ltd.

the intake of food at 33 per cent. Although it does not follow that a similar physiological increase occurs in disease, one must constantly bear in mind the effect of food on the leucocytes of those who may be convalescent from a disease, or in those who have but a mild infection.

There are other causes of leucocytosis—*e.g.*, pregnancy, parturition, exercise, massage, heat, etc.—but the digestion leucocytosis serves to illustrate the fact that in health there is a variation in the number of leucocytes in the circulating blood.

In certain diseases there is also a variation in the number of leucocytes, although the literature confirming this statement is not very abundant. It is an interesting fact that, although so much attention has been paid by hæmatologists to the physiological variations in the leucocyte count, comparatively little has been devoted to its daily fluctuation in diseased conditions.

In chronic diseases such as pulmonary tuberculosis, Hodgkin's disease, carcinoma of the stomach, etc., there is some evidence to show that a variation in the daily count takes place. Marlin<sup>1</sup> has made some interesting observations on the consecutive leucocyte counts in pulmonary tuberculosis in forty cases. He found that, as a rule, the number of leucocytes was less at night and in the early morning, and that there was a definite fluctuation in most cases. By the use of tables he shows that consecutive counts on patients with mitral disease, rheumatic fever, and pneumonia (after the crisis), are remarkably uniform as compared with those done on patients suffering from pulmonary tuberculosis.

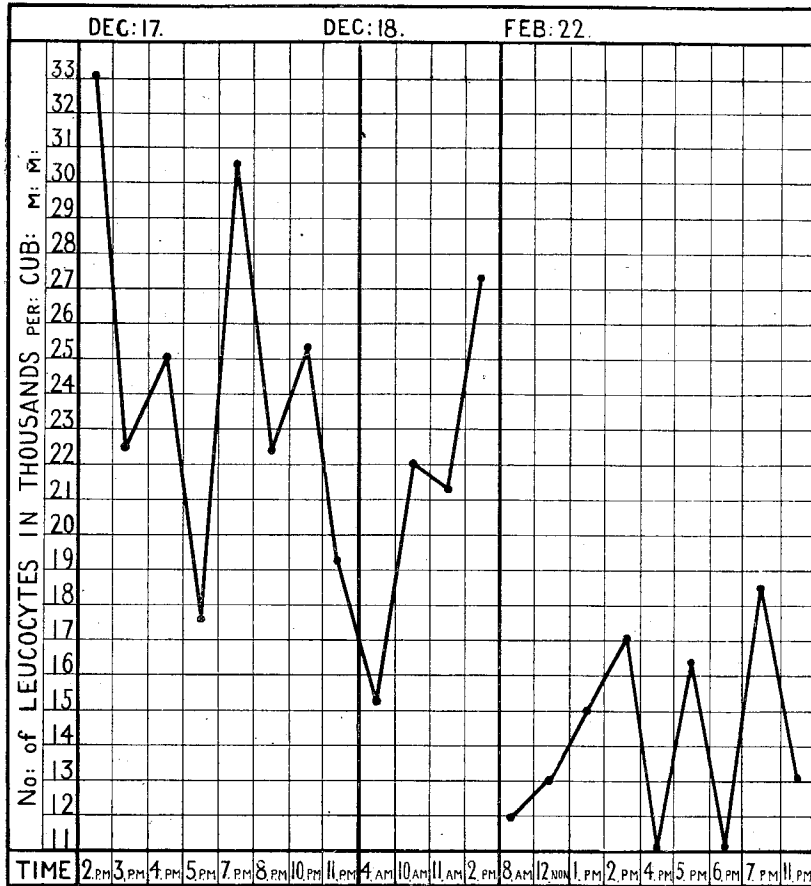
Marlin's work is the fullest account of the phenomenon to be found in the literature of the subject. Beyond the fact that a leucocytosis follows the injection of tuberculin (B.E.), he is at a loss to explain this variation in the number of white cells. Thomson<sup>2</sup> has urged the advisability of a systematic research on what I have termed the "leucocyte swing." In cases of carcinoma of the stomach, myositis ossificans, and Hodgkin's disease, he found a remarkable departure from normal in the number of leucocytes in the blood. He wisely suggests that a series of leucocyte counts made daily over a considerable period of time in various diseases might help to put this remarkable variation on a more firm basis.

My own investigations have been confined to pulmonary tuberculosis in its various stages and clinical manifestations. The instrument used was the Thoma-Zeiss hæmocyto-meter, and the dilution

<sup>1</sup> Marlin: "Consecutive Counts in Pulmonary Tuberculosis," *Journal of Clinical Research*, vol. v., No. 2, 1912.

<sup>2</sup> Thomson: "Remarkable Variations in the Leucocytes in Certain Diseases," *British Medical Journal*, May 30, 1914.

employed 1 in 20; for if the dilution be 1 in 10, one has sometimes a difficulty in making an accurate observation when the cells are numerous. All my examinations were made after treating the cells with a solution composed of glacial acetic acid 1 c.c., distilled water

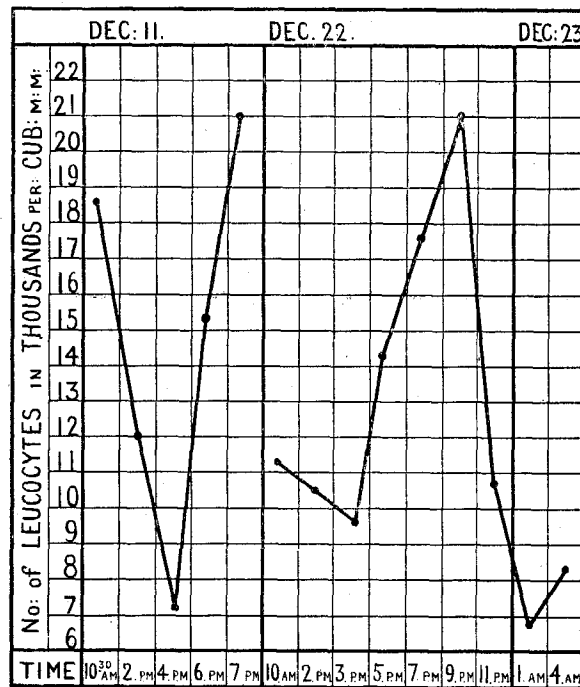


CASE I.: MALE, ÆT. 22.

*Physical Signs.*—On Percussion: Impairment of resonance over right upper lobe. On Auscultation: R. M. increased in intensity over right upper lobe; also posteriorly on right side at the level of seventh dorsal vertebra. Crepitations abundant over right upper lobe.

*Remarks.*—On admission patient was pale and very much emaciated. At first the temperature was very unsteady, running between 98 and 100° F. The pulse-rate did not come below 90, despite the fact that the evening temperature on January 24 was normal. Several examinations of the sputum were made, and on each occasion tubercle bacilli were found. On every slide pus cells were numerous. The patient's general condition improved; on February 24—i.e., two days after the last series of counts was made—there was a great improvement in the local condition in the chest also. On February 29 there was a dramatic close to the case. Hæmoptysis set in, and was so profuse that the patient died in five minutes after the onset of the bleeding.

100 c.c., and methyl green q.s., and one could, with a little care, make a differential count at the same time, for the nuclei are plainly visible in size and contour. This method of making a differential count, however, I did not employ. The entire 400 squares were examined and the total number of white cells enumerated. The counting chamber was now cleaned, and a second drop placed on the slide; a comparison of the second estimation was then made with the first. If these results differed by more than 300, a third examina-

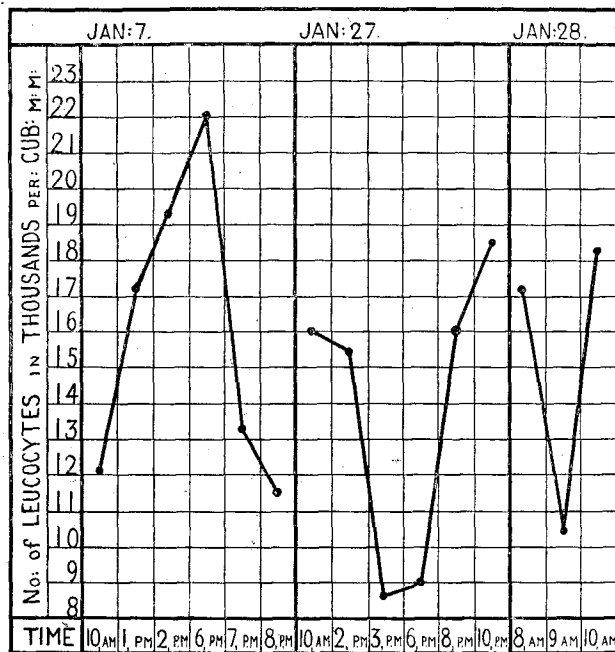
CASE II.: MALE, *ÆT.* 24.

*Physical Signs.*—On Percussion: Right upper lobe dull anteriorly and posteriorly. On Auscultation: Breath sounds very harsh over both upper lobes, especially the left. Numerous crepitations were heard over both upper lobes anteriorly, and over the left upper lobe posteriorly. There was friction at the apex of the lower lobe on the left side.

*Remarks.*—The temperature swung between 97.8 and 99.4° F. with regularity. Tubercle bacilli were found in the sputum repeatedly; pus cells were very numerous. Small and larger diplococci were innumerable at the second, third, and fourth examinations, and small chains of cocci—presumably streptococci—were observed, as well as many clumps of staphylococci. On patient's discharge the lesion in the chest was noted to be progressive. Died April, 1916.

tion was made of the third drop of diluted blood. The average of the three was then taken. Provided one takes care to get the cells uniformly distributed in the counting chamber, a third examination

is rarely necessary. In the charts which are reproduced, one point is definitely established—viz., that a distinct “leucocyte swing” is a characteristic feature of certain cases of pulmonary tuberculosis, and that the swing bears a certain relation to the morbid processes going on in the system.



CASE III.: MALE,  $\text{ÆT. 25}$ .

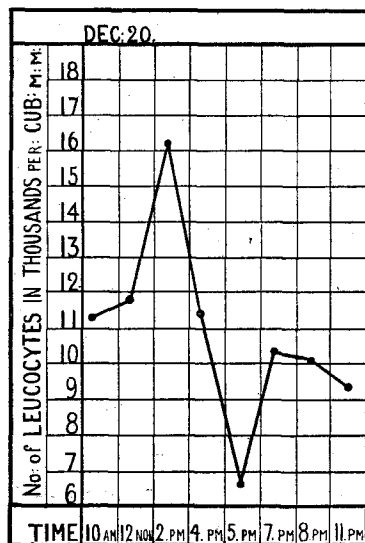
*Physical Signs.*—On Percussion: Both apices lacking in normal resonance, anteriorly and posteriorly. On Auscultation: R.M. intense at both apices. Numerous moist sounds were present at the right apex, and at the left a few scattered crepitations were heard.

*Remarks.*—Patient had a disturbing cough and a fair amount of expectoration. The temperature rose occasionally to  $99^{\circ}$  F. in the evenings, but no very definite symptoms displayed themselves. On January 2 the patient was allowed up and was given some light exercise. On January 20 he complained of cough and expectoration being more frequent than formerly. The sputum was tinged with blood. Examination on February 3 showed that the disease had made startling progress. The left apex was now infiltrated, and the pulse-rate was 100 to 110 per minute. Sputum examination showed tubercle bacilli in fair numbers, elastic fibres, and abundant pus cells. Staphylococci and small diplococci were found at all examinations. Patient was discharged “worse” on February 15.

#### The Significance of the Leucocyte Count in Pulmonary Tuberculosis.

It has been said that a leucocyte count *per se* is of very little practical value unless it has also been determined which cells participate in bringing the count up to the given value. Such a dictum may be very sound in theory, but one must recognize that once it

has been established that a certain cell is the predominating one in any particular disease, then a total white cell count must be relied upon to give some clue to the content of that cell in the blood. Take, for instance, the ordinary septic infections. From clinical experience we know that the polymorphonuclear leucocytes are the cells which are present in largest numbers, and which constitute, in effect, the leucocytosis. Similarly, in lymphocythæmia, the lymphocytes constitute the cells upon which the high counts of that disease depend.



CASE IV.: MALE, ÆT. 24.

*Physical Signs.*—On Percussion: Both sides of the chest, back, and front, dull to percussion. On Auscultation: R.M. very harsh over entire chest, especially on left side, where whispering pectoriloquy could be heard. There were other definite signs of cavity formation over the upper lobe on the left side. Numerous moist sounds accompanied both inspiration and expiration in both upper lobes.

*Remarks.*—Patient was extremely emaciated. The temperature was, on an average, between 99.4 and 100.4° F. The sputum contained tubercle bacilli in large numbers, the average being fifty or sixty to the field. No secondary organisms could be found either intra- or extra-cellularly. Pus cells were comparatively scarce.

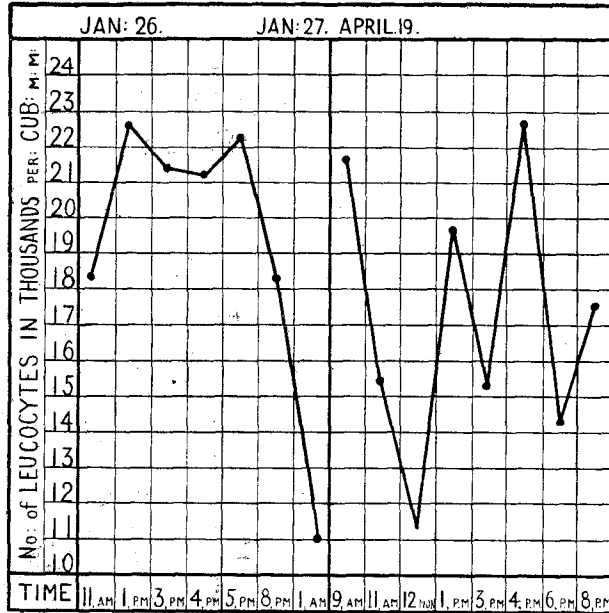
It is far from me to minimize the importance of a differential blood-count. On the contrary, the differential count is of extreme importance as an aid to diagnosis; but from some observations I have made I agree with those who say that, in cases commonly known as cases of "mixed infection," the predominating cell is the polymorphonuclear leucocyte. Klebs,<sup>1</sup> Holmes,<sup>2</sup> Da Costa,<sup>3</sup> Bandelier and

<sup>1</sup> Klebs: "Tuberculosis." London: Appleton and Co., 1909.

<sup>2</sup> Holmes: *Journ. Amer. Med. Assoc.*, vol. xxix., 1897.

<sup>3</sup> Da Costa: "Clinical Hæmatology." Philadelphia: Blakiston's Sons and Co., 1907.

Roepke,<sup>1</sup> Einhorn,<sup>2</sup> and Neubert,<sup>3</sup> are of this opinion, while Gulland and Goodall<sup>4</sup> state that the polymorphonuclear leucocytes in advanced cases of tuberculosis are the result of the septic rather than the tuberculous infection. I have found the polymorph to amount to as much a 90 per cent. of the total leucocyte count in certain cases of pulmonary tuberculosis. In early cases of phthisis showing a leucocyte count within normal limits, the polymorph does not have the same numerical



CASE V.: MALE, ÆT. 38.

*Physical Signs.*—On Percussion: Right side of chest dull to percussion all over; left upper lobe also dull. On Auscultation: Numerous moist sounds were heard over both upper lobes, back and front. Signs of cavity formation were noticed at right apex.

*Remarks.*—Patient's temperature was seldom below 99.6° F. in the evenings. The pulse-rate was about 90 per minute. Sputum examination revealed the presence of tubercle bacilli at every examination; staphylococci, streptococci, and small diplococci, were repeatedly found, and pus cells and elastic tissue fibres were never absent. Patient was in bed most of the time he was a patient in the sanatorium.

value. In fact, in early cases the neutrophile leucocytes are frequently decreased in number at the cost of an increase in the number of lymphocytes.

A careful study of the cases in which consecutive leucocyte counts

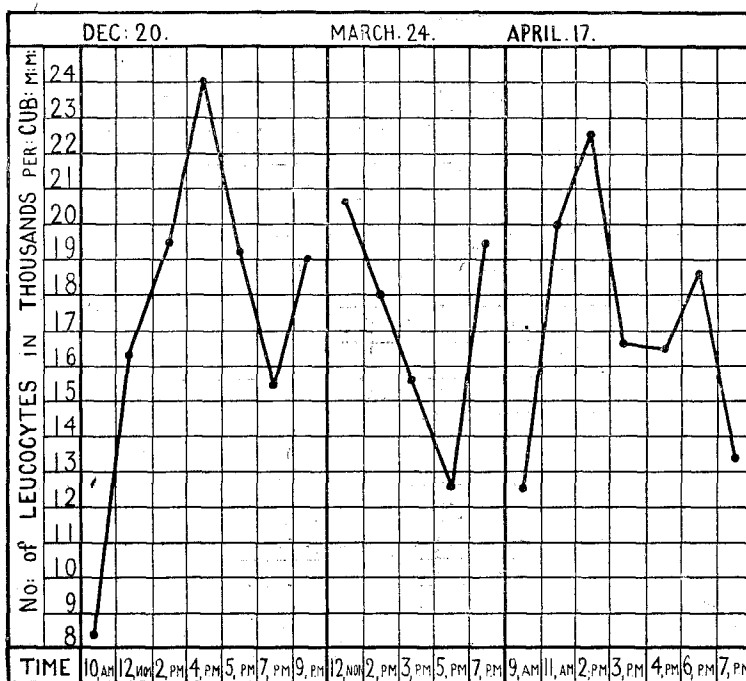
<sup>1</sup> Bandelier and Roepke: "A. Clinical System of Tuberculosis." London: Bale, Sons and Danielsson, 1913.

<sup>2</sup> Einhorn: Inaug. Dissert., Berlin, 1884.

<sup>3</sup> Neubert: *St. Petersburg Med. Woch.*, No. 32, 1889.

<sup>4</sup> Gulland and Goodall: "The Blood," 2nd ed., p. 287. Edinburgh: W. Green and Sons, Ltd.

were done brings up several points for consideration, the most important of which is the daily variation in the number of white cells found. By the term "variation" I mean variation in excess of that occurring normally. It requires only a cursory glance through the foregoing charts to show that there is a remarkable tendency for the leucocyte count to vary enormously in certain cases of tuberculosis of the lung. This variation does not, as can be seen, occur in all, but I propose to consider one or two circumstances which, in my opinion, are responsible for such a phenomenon.



CASE VI.: MALE,  $\text{\AA ET. 26.}$

*Physical Signs.*—On Percussion: Right upper lobe impaired in resonance; left apex dull. On Auscultation: Harsh breath sound over both upper lobes; a few scattered râles were heard over right upper lobe.

*Remarks.*—The temperature in this case was normal throughout the course of treatment. The pulse-rate rarely came below 90 beats per minute. Patient's chief complaint was shortness of breath on exertion. The sputum showed tubercle bacilli, staphylococci, streptococci, and large diplococci, at every examination, although none of these organisms were very abundant.

Pulmonary tuberculosis being a disease of chronic tendencies involving the respiratory organs, it is obvious that not only must the diseased tissue be exposed at some time or other to contamination with organisms other than the tubercle bacillus, but its very chronicity renders it possible for such extraneous organisms to postpone their



attack, as it were, to a more favourable time. In some cases—in fact, in all cases at first—the tuberculous lesion is a closed one; and if the process of encapsulation of the bacilli be complete, there may be no symptoms or signs whatever to justify the diagnosis of tubercle. In such cases the tubercle bacillus is the only organism concerned in the pathological process. Sooner or later, however, the lesion becomes “open,” and the clinical manifestations are tubercle bacilli in the sputum, some slight bronchitis localized to one apex, and perhaps a slight elevation of the temperature. The presence of tubercle bacilli in the sputum represents an advancement in the pathology of the disease; but there is another element which strikes me as being of undoubted value when found in any quantity in the sputum. I refer to pus cells. By the ordinary method of counter-staining sputum specimens with methylene blue or malachite green, these pus cells can be found in almost every sputum examined. But I doubt very much whether sufficient importance has been attached to their presence. I know of no method whereby it is possible to count the numbers of pus cells in any given sputum, but their presence in enormous numbers in some cases is paramount evidence that they play an important part in the reaction of the body to invading organisms in the lungs and bronchi. Both Lowenstein<sup>1</sup> and Wolff<sup>2</sup> have in the past directed attention to the significance of pus cells in the sputum, but altogether they have attracted comparatively little notice. The rôle of the pus cell in ordinary pyogenic infection is no longer a subject of contention. We now know that a pus cell represents a dead piece of protoplasm the victim of direct organismal attack, or indirect, by means of toxins. Further, the presence of pus in any quantity signifies the presence of pus-forming organisms; and when the tubercle bacillus is found in association with pus cells in large numbers, one must reflect on the term “non-pyogenic” as applied to the Koch bacillus. From microscopical sections from tuberculous tissues, we have seen that the polymorphonuclear leucocyte plays a very inferior part in the construction of the tubercle in its earliest conception. If, however, the tubercle erodes its way into a bronchus, or even if it comes into communication with the inspired air through the medium of alveolar tissue, the result will be the same—namely, contamination with other organisms. The discharge from even a very small tuberculous lesion will excite a local inflammatory process by virtue of the irritation which it, as foreign matter, produces. Incidentally this will lead to a weakening of the tissue—a bronchiole it may be—and a bronchiolitis is thus

<sup>1</sup> Lowenstein: “Beitrag. z. Histologie d. tuberkulösen Auswurfes,” *Zeitsch. f. Tuberk.*, Leipzig, x. 47.

<sup>2</sup> Wolff, quoted by Klebs in “Tuberculosis.” New York and London: Appleton and Co.

produced, which may manifest itself clinically in slight cough and expectoration, even when no physical signs in the chest are to be observed. One might conclude, *a priori*, that an advancing lesion of this nature, which includes alveolitis, bronchiolitis, and bronchitis, according to the situation of the lesion, would evidence itself in ways other than by physical signs in the chest alone. In those cases where an elevation of temperature complicates the tuberculous process, we have been in the habit of ascribing the former vaguely to "mixed infection," even when it has been impossible to find the organism or organisms other than the tubercle bacillus responsible for the condition. The researches of Inman<sup>1</sup> have proved conclusively that it is impossible, by methods at present at our disposal, to tell whether "mixed infection" is absent. In many cases we can definitely say that it is present, but the mere fact that a normal temperature, and it may be a normal pulse-rate, characterizes a case is not sufficient to exclude a mixed infection. With this view many writers, including Ortner,<sup>2</sup> agree. The latter lays particular stress on the distinction between the tuberculous and the pneumonic processes going on in the pulmonary tissues; they are different histologically as well as etiologically. The pneumonic processes, he says, so common in pulmonary tuberculosis are the result of the activity of the *Micrococcus pneumoniae*, the tubercles of that of the tubercle bacillus. Riviere and Morland define a mixed infection as follows: "For a mixed infection, the two germs must be present, not merely at the same time, but also in the same place, and a mixed infection in phthisis is one in which the tubercular tissue becomes secondarily the settling-ground of other organisms." As these authors themselves say, it is a matter of considerable difficulty to accept this definition, for an organism does not necessarily require to be in the tubercular tissue in order to make its presence felt. The definition is therefore open to argument, and cannot be said to represent the case. Bearing in mind the frequency with which phthisis follows chronic or even acute bronchitis, pneumonia, and influenza, the association of other organisms with the tubercle bacillus is not to be wondered at. Of course, it does not follow that these organisms are always virulent, but my contention is that they *do* make their presence felt much more commonly than is observed. We are familiar with the havoc played by other organisms—the staphylococcus and the streptococcus particularly—in lupus, and in "cold" abscesses which have been opened and left unheeded. What holds true of lupus, *mutatis mutandis*, is true of every tuberculous affection to which microbes can gain access (A. E. Wright).<sup>3</sup>

<sup>1</sup> Inman: *Lancet*, vol. clxxxii., p. 876.

<sup>2</sup> Ortner, quoted by Inman: *Lancet*, 1912, vol. i., p. 975.

<sup>3</sup> Wright (A. E.): "Principles of Vaccine-Therapy," *Journal American Medical Association*, Chicago, xlix. 567.

Besides, it does not follow that an organism like the *Micrococcus catarrhalis*, for example, remains only moderately pathogenic when in symbiosis with other organisms. Prudden's<sup>1</sup> experiments show conclusively that the concurrent action of two distinct pathogenic organisms may result in a considerable modification of the lesion which either could produce alone. Von Korczynski<sup>2</sup> has gone farther, and proved that the poison of the tubercle bacillus increases the virulence of some organisms—*e.g.*, *B. coli*, streptococcus, and staphylococcus.

If, now, in the case of pulmonary tuberculosis, we start with the assumption that the tubercle bacillus is not a pus-producing organism in the proper sense of the term "pyogenic," we must find another explanation for the presence of pus cells in such large numbers in so many cases of the phthisical sputa examined. It has been shown that many organisms may be present in conjunction with, or in association with, the tubercle bacillus. Their relative frequency is, however, for the purposes of our argument, of little value, but Hastings,<sup>3</sup> Ortnier,<sup>4</sup> Petroff,<sup>5</sup> Ravenel and Irwin,<sup>6</sup> amongst others, agree that the *Streptococcus pyogenes*, staphylococcus, pneumococcus, *Micrococcus tetragenus*, and the *Micrococcus catarrhalis*, are the most frequent organisms found in association with the tubercle bacillus. The power of some of these organisms to produce pus is undisputed, and it is a very significant fact that most of them belong to the class of true pyogenic organisms. Remembering for a moment that with a case of advanced phthisis with cavity formation, and an open lesion discharging tubercle bacilli, elastic fibres, and connective-tissue fibres, and running a typical hectic fever, we are in possession of a typical case of mixed infection, we must inquire into the blood-picture to see if any help can be obtained therefrom, or if any parallel can be drawn between the nature of the case in question and the leucocyte count.

Reference to Cases I., II. and III. will show that the amount of leucocyte swing is considerable, reaching as much as 22,000, and falling as low as 8,600 in Case III. On the other hand, in Case IV., where there was cavity formation, and a temperature of 100.4° F.

<sup>1</sup> Prudden: "Concurrent Infection and the Formation of Cavities in Acute Pulmonary Tuberculosis," *New York Med. Journ.*, lx. 7.

<sup>2</sup> Von Korczynski: "Ueber f. Einfluss d. Tuberkelbazillengifte auf Wachstum u. Giftigkeit anderer Bakterien speciell des *Bact. Coli Comm.*," *Wien. Klin. Wochenschr.*, xviii. 29-34.

<sup>3</sup> Hastings: Unpublished thesis quoted by Gerald Webb in Klebs' "Tuberculosis."

<sup>4</sup> Ortnier: *Lancet*, vol. clxxxii., p. 876 (quoted by Inman).

<sup>5</sup> Petroff: "L'Infection mixte dans la tuberculose Chirurgicale," *Annales de l'Inst. Pasteur*, 1904, xviii. 502.

<sup>6</sup> Ravenel and Irwin: "Studies in Mixed Infection in Tuberculosis," *Trans. Nat. Assoc. for Study and Prevent. of Tuber.* Lancaster, Pa., U.S.A.: New Era Printing Company, 1905.

on the day of examination, the highest leucocyte count obtained was only 16,200; all the other counts were well within normal limits. In this case also, although tubercle bacilli were found repeatedly, no other organisms were ever noted, which of course does not signify that they were absent; and I have noted particularly that pus cells were comparatively scarce. From my experience of cases like this one, I can endorse the views of those who dissent from Stein and Erbmann,<sup>1</sup> who have maintained that the absence of leucocytosis excludes cases with cavity formation. Undoubtedly, the beginning of cavity formation is the beginning of a pneumonic process, with ultimate expectoration of the necrotic tissue. The leucocytosis in some cases is certainly associated with the presence of other organisms. Once the cavity is established, however, repair may be complete and very few secondary organisms found, provided the case shows any signs of arrest. It is in such cases that a leucocytosis need not necessarily accompany cavity formation. This theory is in keeping, I have noted, with that set forth by Kjer-Petersen<sup>2</sup> in 1906.

In Case I., on the other hand, which is in many ways the most interesting in the series, it is to be noted—

1. The temperature was not hectic; it never reached more than 98·8° F.
2. The patient's general condition was, to all appearances, improving.
3. There was also an improvement in the physical signs in the chest.
4. There was no cavity formation.

The only points which suggested themselves to me that this patient was not altogether free from danger were—

1. The accelerated pulse-rate.
2. The presence in the sputum of pus cells in large numbers, and tubercle bacilli.
3. The leucocytosis, never below 10,000 per cubic millimetre.

Here, then, are cases which vary widely in respect of physical signs in the chest, and which present features of more than usual interest. Is it possible to reconcile the blood-findings with the physical signs? Briefly put, it appears as if the leucocyte count bears a definite relationship to the acuteness of the process, and the acuteness of the process, in turn, has a more or less intimate connection with the presence of organisms other than the tubercle bacillus. The consensus of opinion is in favour of this view. Thus, Grawitz<sup>3</sup>

<sup>1</sup> Stein and Erbmann: "Zurfrage d. Leukocytose bei Tub. Processen," *Deutsches Arch. f. Klin. Med.*, Leipzig, lvi. 323.

<sup>2</sup> Kjer-Petersen: "Die numerischen Verhältnisse der Leukocyten bei Lungentuberkulose beitr. z. Klinik d. Tuberk.," Würzburg, 1906.

<sup>3</sup> Grawitz: "Ueber die Einwirkung des Höhenklimas auf die Zusammensetzung des Blutes," *Klin. Wochens.*, xxxii. 713.

maintains that in Stage 1 the number of leucocytes is unaltered; in Stage 2 they are moderately increased, and in Stage 3, with fever, the leucocytes are much increased. Ullom and Craig<sup>1</sup> found them to average 10,285 in the first stage, 12,772 in the second stage, and 14,041 in the third stage.

In several of my cases there was no reason to suppose that the patients had any active disease as judged by the physical signs in the chest, the pulse-rate, and the temperature; and in these same cases one can hardly doubt that phthisis existed. The diagnosis in these cases was that of chronic phthisis, or early phthisis in the process of arrest. In these cases one can conclude justly that, although the tuberculous process was still present, the pulse-rate, temperature, and physical signs, pointed to quiescence of the disease. The leucocyte count in these cases was well within normal limit. The sputum examination was either negative for tubercle bacilli, or else it showed very few pus cells or other organisms with tubercle bacilli. We may state, therefore, that in those cases—cases of uncomplicated tuberculous infection—the leucocyte count is normal.

When, however, we come to examine many of the cases, we find that not only is there a leucocytosis, but that the leucocytosis is not constant in the sense that the leucocytosis of pneumonia, or of a moderately severe septic infection, is constant. It is in those cases that there is what I have termed a "leucocyte swing," which is a distinct departure from normal.

In the extreme cases of mixed infection, there is an infection not only by the tubercle bacillus, but also by other organisms. All the organisms present in the diseased focus are in a vascular area, so to speak. Now, the usual explanation given for an abrupt rise in temperature occurring in a tuberculous individual running a hitherto normal temperature is that it is caused by an auto-inoculation. The physiology of an auto-inoculation is, briefly, a carrying away from the tuberculous area of the patient's own tuberculin by means of the blood-stream. If, however, there are products of other organisms to be carried into the blood-stream as well, it follows that the auto-inoculation must be a compound one, composed of the toxins of the organisms present in the diseased tissue. The advanced phthisical case, then, with the lung tissue swarming with streptococci, staphylococci, tubercle bacilli, etc., is merely containing in his chest an incubator for these organisms. No doubt part of the defence of the body in this state is by means of the leucocytes, acting as phagocytic agents or as carriers of complement. But what is the

<sup>1</sup> Ullom and Craig: "Examination of the Blood in Pulmonary Tuberculosis, with Special Reference to Prognosis," Transactions Nat. Assoc. for Study and Prevent. of Tuberculosis, New York, i. 166.

explanation of the extreme variation in the count which occurs? One can do no more than suggest some possible explanation. The function of the polymorphonuclear leucocyte, despite what is known of its structure and life-history, is far from clear. If we regard it as being a weapon of defence, then we must specify whether it defends by direct or by indirect methods. There are, in other words, two main views as to the function of the cell—firstly, that it is phagocytic; secondly, that it is an important element in the process of immunity. The first view is the one which was held previous to the formation of the hypothesis of immunity elaborated by Ehrlich. In order to fit in with Ehrlich's theory, it was necessary to ascribe to the leucocyte a rôle in the production of immunity and, according to Metchnikoff, the complement of Ehrlich is represented by the alexins, certain chemical substances of the nature of an unstable nucleo-proteid. So far as the phagocytic function is concerned, there is no doubt that the polymorphonuclear leucocyte possesses this power in a marked degree—to some organisms more than to others. It is in relation to the immunizing properties of the polymorphonuclear leucocyte that special interest arises. So intimately, however, is the question of immunity bound up with that of phagocytosis that it is convenient to give several possible causes for the remarkable intermissions in the daily leucocyte counts which interpolate themselves with such regularity in certain cases of tuberculosis of the lungs.

1. *That they are due to REST.* This obviously is not the case; for although the counts tend to be lower during the usual resting hours, in keeping with the diminution in physiological activity, yet one can find a very low count during the daytime, when patients are up and going about. It is the very existence of this low count in the daytime that gives the successive counts their characteristic "swing" when recorded in series. Absolute rest does, however, tend to reduce the total number of cells by reducing the working of all the body processes, of which the heart's action is the most important, to a minimum.

2. *That they are due to BONE-MARROW EXHAUSTION.* If this were the case, one would expect that one low count would be followed by another. So far as the total number of cells is concerned, this is not the case. At present we are considering the quantitative rather than the qualitative change in the cells, and from the observations I have recorded we are not entitled to say that a temporary diminution in the total white cell count is indicative of marrow exhaustion. But an interesting point presents itself here. Suppose, for example, we reconsider Case I. The counts taken on December 17 represent acute processes which are being responded to by leucocytosis. The counts taken on February 22, on the other hand, may represent one of two

things—either that the lung disease was becoming less acute, and that a smaller leucocyte response was necessary; or that the bone marrow was becoming exhausted. One is hardly in a position to say that a leucocyte count of 18,500 denotes marrow exhaustion from a quantitative point of view. It is not at all uncommon to find a very poor qualitative picture with a leucocyte count of 12,000 to 20,000 cells per cubic millimetre. By the term “qualitative” picture I mean a differential leucocyte count, not only of the white cells *en masse*, but of the polymorphonuclear cells in particular, as has been estimated by the methods of Arneth<sup>1</sup> and Schilling.<sup>2</sup> By making use of these combined methods of estimating the value of the polymorphs, one is enabled to say definitely whether a given leucocyte count represents a healthy reaction on the part of the bone marrow to infection, or whether the apparently satisfactory quantitative reaction is in reality a bad qualitative one, indicating, therefore, a failure on the part of the bone marrow to satisfy the demands of the body. It has been proved definitely by Andrewes<sup>3</sup> and Cadbury<sup>4</sup> that, in cases of wasting diseases—*e.g.*, tuberculosis—the bone marrow itself was in a condition of mucoid transformation, even when the leucocyte count was as high as 100,000 per cubic millimetre.

The outcome of this argument, then, is that the comparatively low counts which present themselves daily in some cases do not *per se* represent an exhaustion of the resources of the bone marrow, unless it can be also demonstrated that the cells are qualitatively deficient. In all my investigations on the leucocyte counts in patients suffering from pulmonary tuberculosis, I have not had a case showing constant leucopænia. In some respects I have been surprised at this, for in many cases the daily output of white cells is five times greater than that occurring normally, and this output has been kept up for weeks at a time. It is not fair to assume that the hæmopoietic tissues can keep up the necessary quality as well as the requisite quantity.

3. *That they are due to periodical intermissions of substances acting on them by a process of NEGATIVE CHEMIOTAXIS.* It is only by supposing that some such substances exist that the periodical remissions of the leucocytes can be explained with any degree of satisfaction. In the light of our present knowledge, we can state two facts with certainty: firstly, pyogenic organisms have the power of producing

<sup>1</sup> Arneth: “Die Neutrophilen Leukozyten b. Infektionskrankheiten,” *Deut. Med. Woch.*, 1904. xxk. 54; and other papers.

<sup>2</sup> Schilling: “Fol. Hæmat.,” vi. 322 (1908).

<sup>3</sup> Andrewes: “The Behaviour of the Leucocytes in Infection and Immunity,” Croonian Lecture. *Lancet*, vol. ii., 1910.

<sup>4</sup> Cadbury: “Marrow Studies in Tuberculosis,” Fifth Annual Report of the Henry Phipps Institute. *Lancet*, p. 87, vol. ii., 1810.

a leucocytosis when present in the body in requisite number, or when sufficiently virulent; secondly, tubercle bacilli do not possess this property. Muir<sup>1</sup> was among the first to show that a leucocytosis of inflammatory origin was synonymous with a leucoblastic reaction in the bone marrow. Andrewes,<sup>2</sup> on the other hand, failed to get any leucoblastic response after infection with the tubercle bacillus, the bone marrow appearing normal in all respects.

In the extreme case of miliary tuberculosis, where the body tissues are inundated with tubercle bacilli or their toxins, the existing condition in the blood is one of leucopænia, a point of special significance in virtue of the fact that in such a case we are dealing with an overwhelming dose of tubercle bacilli and toxins. Now, in those cases of miliary tuberculosis one cannot say that the bone marrow is exhausted, in the sense that it has produced so many polymorphs that it cannot produce more. We must, as in the case of typhoid infection, suppose that there exists in the circulation a substance inhibiting the production of leucocytes. The tuberculo-toxin is, then, an aggressin, but what the exact nature of the aggressin is we do not know. Bail regarded his aggressins as non-toxic substances, but it is only fair to state that others—*e.g.*, Sauerbeck<sup>3</sup>—dissent from this view, and regard negative chemiotaxis as a minor manifestation of toxicity. Andrewes<sup>4</sup> supports my contention in the following: "I do not find it illogical to conceive that certain inherent products of the natural bacterial body may have become positively chemiotactic to the leucocytes—thus explaining the facts of spontaneous phagocytosis—while believing that the more highly specialized parasites have secondarily acquired the power of producing another chemical substance which may keep phagocytosis in abeyance. "In the advanced cases of phthisis—typically cases of mixed infection—the tuberculo-toxin, or aggressin, is also present, but only in conjunction with the toxins of streptococci, staphylococci, pneumococci, etc., which are essentially stimulators of leucocyte production. The balance between the various toxins is never equal, or one other predominates at various times, and in this way the leucocyte swing is maintained, being high when the bone marrow is suitably stimulated and being low when the tuberculo-toxin is acting. From such an hypothesis it is easy to explain why the extent of the lesion may be of negligible value in giving a prognosis in a given case. It may be

<sup>1</sup> Muir: *B.M.J.*, 1898, vol. ii., p. 604; also *Trans. Path. Soc. Lond.*, 1902, vol. liii., p. 379.

<sup>2</sup> Andrewes: "The Behaviour of the Leucocytes in Infection and Immunity," Croonian Lecture. *Lancet*, vol. ii., 1910.

<sup>3</sup> Sauerbeck, quoted by Hiss and Zinsser.

<sup>4</sup> Andrewes: "The Behaviour of the Leucocytes in Infection and Immunity," Croonian Lecture. *Lancet*, vol. ii., 1910.



pertinently asked at this juncture: "What happens to the surplus of leucocytes when low counts interpolate themselves between high ones?"

Experiments done by Ellerman and Erlandsen of Copenhagen<sup>1</sup> show that, in health, the assumption of the erect posture, or the sudden change to the recumbent position from the erect posture, may be associated with an equally sudden change in the number of leucocytes—that is, there is a static leucocyte reaction. The explanation which they offer for the occurrence of this phenomenon is that the increased rapidity of the heart's action, and the greater velocity of the blood-stream produced in consequence, forces the leucocytes from the deeper vessels into the superficial capillaries. In phthisis and more particularly in advanced phthisis the heart's action is extremely uncertain as regards rate. The intoxication of the system by the offending organisms and their toxins is the cause of the accelerated pulse-rate, and the same toxins are carried throughout the body at an increased velocity to act on the leucopoietic organs. The stimulation of leucocyte production has been proved definitely to be a result of pyogenic organisms, but whether the inhibition of leucocyte production is worked from the bone marrow as a centre is extremely problematical. The researches of Goldscheider and Jacob,<sup>2</sup> and of Bruce,<sup>3</sup> and of Andrewes,<sup>4</sup> go to show that, in cases of rapid decrease in the leucocyte content of the blood, the cells are "held up in the lung, screened off, as it were, by the pulmonary capillaries." Why the leucocytes should go to the pulmonary capillaries is, again, a matter for speculation. To me there appear to be two explanations: firstly, for oxygenation, the view supported by Andrewes; and, secondly, for the combined purpose of phagocytosis and distribution of complement. In connection with the second theory, I beg to submit that so long as the leucocyte count remains normal in every respect—and by that I mean quantitatively as well as qualitatively—the leucocytes are carrying sufficient complement for the reaction between antigen and antibody to take place. The disease may progress in the lung and yet the balance between antibody and antigen may be quite good, the only difference being a qualitative change in the leucocytes, as can be estimated by Arneth's method. With, however, the onset of any complication, such as pneumonia, secondary infection, or bronchitis, there is a demand for complement of two, or it may be more, kinds, according to the nature of the infection.

<sup>1</sup> Ellerman and Erlandsen: *Archiv für Experimentelle Pathologie und Pharmakologie*, December, 1910.

<sup>2</sup> Goldscheider and Jacob: quoted by Klebs (*loc. cit.*).

<sup>3</sup> Bruce: *Proceedings of the Royal Society*, vol. lv., 1894.

<sup>4</sup> Andrewes: "The Behaviour of the Leucocytes in Infection and Immunity," Croonian Lecture, *Lancet*, vol. ii., 1910.

In such cases the bone marrow may or may not be able to supply the demand thus made upon it, and degeneration sets in—a degeneration which affects the polymorphs morphologically in most cases. If, in spite of the intensity of the infection, the leucocytes respond, the patient will overcome his infection simply because his immunity has been sufficient in virtue of his successful qualitative polymorph response—qualitative because increased leucocytosis *per se* is not necessarily associated with increase of complement. In some cases a successful outcome will result from a leucocytosis of 14,000, and in others it may require 30,000. The ebb of the leucocyte swing means, therefore, that the leucocytes are required on another front—namely, the lung—in order to carry out the two processes upon which life depends: viz., immunity and phagocytosis.

4. *That they are due to ANAPHYLACTIC PHENOMENA.* There has been a considerable amount of work done recently on the relation of anaphylaxis to tuberculosis. By some it has been said that the reaction which sometimes follows the injection of tuberculin is an anaphylactic phenomenon. Certain it is that the clinical symptoms of anaphylactic shock in no way resemble the clinical symptoms following tuberculin injection; in the former the temperature is markedly lowered, some dyspnoea results, and the end may be in convulsions; in the latter the temperature is raised, and there is no choking or severe dyspnoea such as is observed in the former. Again, whilst anaphylaxis can be passively transferred from one animal to another, no such phenomenon has ever been known to occur in connection with tubercular sensitiveness (Friedemann,<sup>1</sup> Roepke,<sup>2</sup> etc.). The researches of Rosenau and Anderson, quoted by Hiss and Zinsser,<sup>3</sup> have demonstrated also that anaphylaxis may be inherited, a claim which cannot be extended with certainty to tubercular sensitiveness. On the other hand, it has been found that the condition of anaphylaxis is associated with a disappearance of complement from the serum; and if, as has been taught by Metchnikoff and others, complement is derived from the leucocytes, then one would expect the clinical condition of anaphylaxis to be associated with a diminution in the number of leucocytes. Andrewes has actually observed the initial leucopenia in animals suffering from anaphylaxis, and concludes that "leucopenia is an integral part of the phenomenon of anaphylaxis." Da Costa<sup>4</sup> divides the blood-phenomenon resulting after the injection

<sup>1</sup> Friedemann: "Ueberpassive Ueberempfindlichkeit," *Munch. Med. Woch.*, liv., 1907.

<sup>2</sup> Roepke: "Untersuchungen uber die Diagnose der menschlichen Tuberkulose mittelst Anaphylaxie," *Brauer's Beit. zur Klin. der Tub.*, xiv. 147, 1909.

<sup>3</sup> Hiss and Zinsser: "A Textbook of Bacteriology." New York and London: Appleton and Co., 1912.

<sup>4</sup> Da Costa: "Clinical Hæmatology," p. 239. Philadelphia: Blakiston's Sons and Co., 1907.

of bacteria, toxins, albumins, etc., into animals, into hypoleucocytosis and hyperleucocytosis. The former is the first result of the foreign matter introduced, and is represented by a diminution in the number of leucocytes in the peripheral blood. The latter is manifested by an increase in the number of white cells, and follows the hypoleucocytosis. Both the hypo- and the hyper-leucocytosis are dependent on the intensity of the irritant acting. To quote Da Costa: "If the irritant is slight, the repellent influence is feeble, and the consequent cellular increase is inconspicuous. . . . If the effects of the irritant are severe, both the repellent and the attractive stages are promptly excited and markedly developed, and a general increase in the number of leucocytes through the whole circulatory system promptly results. . . . It sometimes happens that the attractive influence of the chemio-tactic principle predominates over its repellent action, in which case the stage of hyperleucocytosis may develop without the initial stage of hyperleucocytosis. Clinically, the preliminary decrease is practically never observed, perhaps partly for the reason last given, but also in a large measure because the repellent action of the irritant has passed off by the time the disease has developed into a clinical picture." The parallel between this hypo- and hyper-leucocytosis, and the negative and the positive phases of Wright, which follow tuberculinization, is apparent.

Applying what has gone before to the blood-findings in cases of pulmonary tuberculosis, the low counts would represent the stage of hypoleucocytosis, and the high ones the stage of hyperleucocytosis. It is impossible for one to dogmatize further than this. Whether this phenomenon is anaphylactic or not matters very little; the symptoms displayed by patients with low counts do not correspond to the symptoms shown by patients suffering from anaphylaxis. Indeed, so far as I have been able to make out, the patient's condition is absolutely no indication to the leucocyte count. Taking everything into consideration, there appears to be very little in common between the response to inoculation, active or passive, in the tuberculous subject, and anaphylaxis. The fact that one phase in the clinical pathology of the one resembles a similar phase in the clinical pathology of the other is no reason for considering the phenomena identical. As we have seen, there are many points of dissimilarity between the two.

#### **General Conclusions.**

What has gone before does not presume to exhaust the discussion of the rôle of the polymorphonuclear leucocyte in the clinical pathology of pulmonary tuberculosis. The question appears to be one of much greater magnitude. My intentions have been to show that in the

polymorphonuclear leucocytes we have tissue cells which are definitely inimicable to the great majority of the organisms which infect the respiratory passages secondarily, and to which we can attribute much of the damage done in the pulmonary and bronchial substance. Let us make full use of the function of these white cells as a guide to diagnosis, prognosis, and treatment. Evolution works slowly. Who can say but that the same cells or some other cells—*e.g.*, the large mononuclears—may be gradually educating themselves to respond “to the chemical aroma” of the tubercle bacillus, just as they have learned in the past to deal with the lesser complex foes of the human body? As matters are at present I conclude with a quotation from Bushnell: “An objective proof that a toxic absorption is present in a degree which constitutes a tax on the resistance of the afebrile patient is one of the great desiderata in the treatment of pulmonary tuberculosis.”

## THE ECONOMIC ASSISTANCE OF THE TUBERCULOSIS PATIENT.

### A NOTE ON THE TREATMENT OF TUBERCULOUS CASES IN THE COUNTY OF CORNWALL.

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THE symposium of opinions which appeared in a recent issue of this Journal<sup>1</sup> regarding the directions in which those engaged in the anti-tuberculosis campaign should concentrate their efforts under present conditions has attracted widespread interest amongst Tuberculosis Officers. Granted that segregation of infective cases is logically the most desirable of all measures, many circumstances render comprehensive steps in this direction impossible, at any rate at the present time. Most Tuberculosis Officers find themselves working partly developed schemes, to which appropriate extension is denied, owing to depleted staffs and reduced funds.

A short note on the tuberculosis problem, as evidenced in the so-called “Delectable Duchy,” may not be without interest and value. The unenviable position of Cornwall as regards Tuberculosis may be seen by reference to the annual returns of the Registrar-

<sup>1</sup> See BRITISH JOURNAL OF TUBERCULOSIS, January, 1916.