OLIGOLEUCOCYTHAEMIA (Leucopenia)

T H E S I S

presented for

the Degree of M.D. of Edinburgh University

by

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"OLIGOLEUCOCYTHAEMIA," "LEUCOPENIA," "LEUCOCYTOLYSIS," "LEUCOCYTOPENIA," "OLIGOLEUKAEMIA," "SPLENIC ALEU-KAEMIA," "HYPOLEUCOCYTOSIS" or "ALEUCOCYTOSIS" are all names indicating poverty of leucocytes.

While leucocytosis has occupied much of the attention and time of many observers, on the other hand very little attention, and, that only lately, has been directed to the opposite condition viz. diminution in the number of white blood corpuscles.

My attention to this peculiar and interesting blood condition was first drawn by Sir Thomas (then Professor) Grainger Stewart while a clerk in his wards in the Edinburgh Royal Infirmary. The case which he demonstrated to his clinique as a unique one is noted in my clinical[1] notes of his lectures, but, as it was afterwards fully reported by Dr Murray Leslie in the Edinburgh Hospital Reports[2], I cannot do better than give a few extracts from that source.

"The patient whose history is here recorded was "admitted to Ward 22, Royal Infirmary, in April 1893, "having brought with him a note of recommendation to "Professor Grainger Stewart from Dr. Niven of Newburgh.

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[1] Grainger Stewart - Lectures on Clinical Medicine.
[2] Murray Leslie - Edinburgh Hospital Reports, Vol. II., p. 258.

"Newburgh. The case was a very puzzling one and pre-
"sented many points of difficulty in diagnosis. Clini-
"cal interest centred in the great enlargement of the
"spleen.

"After careful consideration of all the clinical
"features presented by this patient, Professor Grain-
"ger Stewart was of opinion that the condition of the
"spleen was not referable to any of the usual diseas-
"es which bring about an enlargement of that organ.

"Leucocythaemia was negatived by the condition
"of the blood, an examination of which revealed a
"decided decrease instead of an increase in the number
"of white blood corpuscles.

"..... There was nothing either in the
"past history of the patient, who had never been out
"of Scotland, or in the condition of the blood to
"suggest malaria. ..... Accordingly Pro-
"fessor Grainger Stewart came to the conclusion that
"the disease from which the patient suffered, if not
"an unknown condition, was at all events a very rare
"and unusual one. He knew of no recorded case pre-
"senting precisely similar features.

"The blood was examined the day after admission -
"the red corpuscles numbered 4,000,000 per cubic
"millimetre /

"millimetre (Thoma-Zeiss haemocytometer), the haemo-
"globin about 75% (Gowers' haemoglobinometer), while
"the leucocytes were much diminished in number, 1,500
"per cubic millimetre.

"Nature of the Disease :- As to the exact nature of
"the malady, it is difficult to express an opinion.
"It no doubt presents many analogies to leucocythaemia
"and lymphadenoma but it appears to be quite distinct
"from either of these. As to whether the essential
"lesion is to be found in the spleen or whether the
"changes in the spleen, liver and blood, are simply
"manifestations of a more general underlying morbid
"process, it is also difficult to say. More probably
"the latter view is the correct one. It is just pos-
"sible that the exposure to foul air, to which the
"patient so definitely attributed his illness, may have
"had some influence in determining the onset of the
"malady and I have heard of other cases of allied
"disease with a similar history. The condition of the
"spleen is not unlike that found in leucocythaemia,
"though in many features both clinical & pathological
"the two conditions stand out in marked contra-distinc-
"tion. The most striking of these is of course the
"leucocytosis/ /

"leucocytosis in leukaemia and the diminished number of "leucocytes in the present case. This feature alone, "considering its rarity, apart from general anaemia, "would almost suggest the term "Oligo-leucocythaemia", "or the less correct but more euphonious name "Oligo-"leukaemia" as applicable to the disease; "Splenic "Aleukaemia" has also been suggested as a suitable "descriptive term.

"Clinically the condition resembles some recorded "cases of Hodgkin's disease, tho' it is questionable "if the spleen ever attains such dimensions in "lymphadenoma. This was, to some extent, the view "entertained by Professor Grainger Stewart, who point-"ed out the distinctions between it and leucocythaemia "on the one hand and between it and typical Hodgkin's "disease on the other, and remarked that it must either "turn out to be a malady not yet described or be an "unusual form of lymphadenoma. The present case "would doubtless be considered by Continental authors "as an aberrant example of pseudo-leukaemia, an un-"fortunate term which has probably done not a little "to obscure our knowledge of the diseases of the "haemopoietic system and which tho' supposed to be "synonymous /

"synonymous with Hodgkin's disease probably includes "a number of separate maladies with no special re- "lation either to leukaemia or lymphadenoma."

In an addendum to his paper on the above case, Dr Murray Leslie says that he has seen two other cases in the Royal Infirmary with similar enlargement of the spleen, accompanied by a diminution in the number of white blood corpuscles. One of these cases showed almost precisely similar features to the above case:- "Much enlarged spleen, extending 3 inches below the "umbilicus, leucocytes 2,900 per cubic millimetre, "attacks of diarrhoea ..... no history or sign "of enlargement of lymphatic glands."

I have quoted largely as above, as it was the first case of leucopenia I had seen, and it seemed to correspond so closely with a case which was under my care last year; but now, having investigated the subject, I can distinguish the difference. I shall however give the record of my own case and in doing so must express my indebtedness to Dr Haig Ferguson whose patient he was, and who very kindly handed over the care of the patient to me.

W.J.F., aet. 25, single, went out to Assam in the beginning of 1896 as scientific adviser to a large tea company /

company. Before doing so he had to pass a severe medical scrutiny by a medical man chosen by the Company and who had been many years in Calcutta - which he did successfully.

He arrived in Calcutta in the end of February, 1896, going up country in the beginning of the following month when he had his first "touch" of malaria. Up till July of the following year (1897) he had frequent attacks of fever, which, however, rarely kept him in his bungalow more than a day at a time. These attacks became less frequent as he seemed to get acclimatised. Ague on several occasions accompanied the fever and once he was laid up for a fortnight with malarial fever and boils which he says were the result of the malaria, and he had to be sent off for a week's change. On the 5th July he rode home at mid-day feeling seedy and remained indoors for two days when Dr Lavertine saw him; then he became worse, showed symptoms of jaundice and his medical advisers began to suspect haemoglobinuria, which supervened in a few days. On the 9th ague and high fever set in. 10th :- No abatement - he suffered severe abdominal pain and in the evening Dr Lavertine injected quinine into the veins of both arms.

11th /

11th :- In the afternoon the case was considered hopeless, but toward night the fever began to abate. He had had 160 grains of quinine in the previous 24 hours. The temperature did not exceed 105° F.

14th :- Feeling better.

16th :- Able to get up and lie on a chair in the verandah.

One night he developed severe intercostal neuralgia necessitating opium. He was ordered home and arrived in England in the end of September, 1897, much the better of the voyage.

On 9th December, while visiting friends in Suffolk, fever commenced, and by the 17th he was utterly played out and then entered Guy's Hospital having been sent in by Dr Baird, who had spent many years in India, and who said he was suffering from typho-malaria. In Guy's Hospital he was under Dr Washbourn who at first thought he was suffering from typhoid, but his blood did not give the serum reaction and malarial parasites were carefully sought for, but never found. He was dismissed from Guy's on 2nd February feeling better and went to stay at Kelso, where he called in a medical man who also at first thought he had typhoid and then treated him for slight pneumonia. A fortnight /

fortnight afterwards he turned suddenly worse and the Dr, after consultation with another medical man, pronounced him to be suffering from hopeless tuberculosis. (The Dr has since told me that at that time moist râles could be heard extensively over both lungs) He improved somewhat up till July when he came to Edinburgh. During May and the first half of June he had a discharge from his left ear, and during June he says his gums were very spongy and used to bleed on the slightest provocation.

Such is his history so far as one can get it before he came under my notice in August 1898, and I shall now give a few notes regarding his condition when he first came under my observation:-

Family History good. Father and mother both alive and well. One brother and sister died in infancy from children's diseases, the rest of the family healthy. No constitutional disease in family.

Previous Illnesses :- Had typhoid fever when 5 years old, pneumonia when 14 - No other illnesses. No history of syphilis.

Surroundings :- While in this country had always been good.

Complains of :- "General weakness, feverishness and swelling of abdomen."

The /

The patient is 5 ft. 6 in. high and weighs 9 st. 4 lbs. He is a man who had always enjoyed the best of health before going to India, indulging in all kinds of athletic exercises, and, altho' temperate, had never indulged in any alcoholic excess.

His skin is somewhat pale and here and there are seen a few petechiæ, such as one frequently sees in leucocythaemia.

ALIMENTARY SYSTEM : Lips dry, teeth good, gums spongy and tend to bleed, faeces paler than normal. Abdomen - circumference 33½ inches at umbilicus. On inspection the abdomen is seen to be distended more especially on the left side and on palpation a hard resisting tumour with a flat regular surface can be felt on the left side. The lower margin of the liver can also be palpated.

On percussion the absolute liver dullness is found to be 7 inches and the mass on the left side is absolutely dull on percussion.

HAEMOPOIETIC SYSTEM : No enlarged glands can be felt in the groin, axilla or anywhere. The spleen is enlarged and can be palpated between the two hands. The absolute dullness extends for 10 inches downwards and inwards towards the umbilicus. A notch can also be felt on its inner margin.

Blood :- /

Blood :- On August 3rd I examined his blood with the following results :

Hb.	70%
R.B.C.	4,800,000 per cub. mil.
W.B.C.	1,500 " " "

Using Gowers' haemoglobinometer and the Thoma-Zeiss haemocytometer.

CIRCULATORY SYSTEM : No subjective Phenomena or obvious disease.

RESPIRATORY SYSTEM : Normal except for a number of moist râles at both bases anteriorly and posteriorly, apparently due to œdema of lungs.

INTEGUMENTARY SYSTEM : Skin acting freely, petechiæ here and there.

URINARY SYSTEM : No subjective phenomena. Urine Amber, acid, no abnormal constituents, S.G. 1021, mucus deposit.

REPRODUCTIVE SYSTEM : Shows nothing abnormal.

NERVOUS SYSTEM : Sight good, fundus pale in colour.

Such is the history of the case when I first examined him on August 3rd 1898. I was so much struck with the extraordinary diminution of the leucocytes that I asked Dr George Gibson to make the calculation which he did on August 8th with these results :

Hb. /

Hb.. 75%

R.B.C. 5,400.000

W.B.C. 1,500

On August 17th Dr Lovell Gulland also saw the patient with me and examined his blood with this result :

Hb.. 80%

R.B.C. 4,800,000

W.B.C. 1,800

There can be therefore no doubt as to the number of the white blood corpuscles. At this time he complained of feeling sick, his temperature was always above normal but never above 100° F. except on August 2nd, 4th, 5th, 6th, (103.4), 7th, 24th, (103.5), 25th and 26th.

He was treated with Arsenic and quinine, but this had to be stopped on August 25th owing to a sharp attack of diarrhoea. His appetite on the whole was good. He never had any ague and never prespired to any extent. He gradually recovered from the fever. I examined his blood again in October and found the

Hb.. 75%

R.B.C. 4,800,000

W.B.C. 2,500

I examined it again in December :

Hb.. /

Hb..	80%
R.B.C.	4,500,000
W.B.C.	4,500

At none of the examinations were any malarial parasites observed and the differential count of the corpuscles showed that the different varieties of leucocytes were all proportionately diminished.

By the end of October the patient was feeling very well and was walking about and taking exercise. His abdominal circumference was then 29½ inches (33½ inches before), liver dullness 4¾ inches (7 inches before) and his splenic dullness 6 inches (10 inches before).

He shortly afterwards went to England and the last letter I had from him stated that he was taking a large amount of exercise and indulging in horse exercise for the greater part of the day and feeling in the best of health.

It seemed to me at that time most remarkable that this patient should get quite well, the liver and spleen diminish in size, and the white blood corpuscles become restored to their normal number.

The facts of the case having been thus submitted the question arose "Was this patient suffering simply from /

from malaria with a concomitant diminished re- - lative proportion of white blood corpuscles to red blood corpuscles or was he suffering from some other disease the outstanding feature of which was the diminished number of leucocytes" ?

I wrote to Dr Washbourn of Guy's Hospital under whose care the patient was in London and received the following answer :-

6 Cavendish Place,
Cavendish Square, W.
Sept. 14th.

My dear Sir,

I was away on my holiday when your letter arrived, and I was detained longer than I expected through illness.

I have looked up the notes of W. F. and I remember his case quite well. He came into Guy's with a history of malaria. The spleen was enlarged and could be definitely felt below the costal margin. His temperature kept near 103° F. for about three weeks and then subsided. At first he was considered to have an attack of malaria, but afterwards the symptoms pointed more to typhoid. Malaria parasites were not found in the blood and the serum on three occasions /

occasions at various intervals gave a negative reaction to the typhoid test. There was no definite symptom of typhoid or malaria and I am not sure what was the nature of the attack. Hoping that these details will even at this late period be of interest to you,

I remain,

Yours sincerely,

J.W.WASHBOURN.

Since studying the condition more carefully I have come to the conclusion that my patient merely suffered from an attack of sub-acute malaria with diminution in the number of white blood corpuscles,a condition which has recently been found to be the usual accompaniment of malaria.

A study of this case has led me to investigate those conditions, besides malaria, in which leucopenia is found and I shall now endeavour to submit a synopsis of the work which has been done on the subject.

Terms Employed to indicate the condition :- First of all as regards the names which have been applied to this condition : they are numerous and include such terms as "Oligoleucocythaemia", "Leucocytolysis", "Leucocytopenia", "Oligo-leukaemia", "Splenic /

"Splenic Aleukaemia", "Leucopenia", "Hypoleucocytosis", and "Aleucocytosis".

Probably, on the whole, the term "Leucopenia" is the best one, as it is etymologically correct, which cannot be said of all the others. I have used the term "Oligoleucocythaemia" for this Thesis as it was the name under which I first became acquainted with the condition.

Normal /

NORMAL NUMBER of WHITE CORPUSCLES in a HEALTHY PERSON :

Before further entering upon the discussion of a subject which involves a deviation from the normal number of corpuscles, it is essential to define what is accepted as the average normal number of white corpuscles found in a healthy person. According to Von Jaksch[1] the white corpuscles are found in the blood, one or two hours after the principal meal, to be in the proportion of 1 : 150 or even 1 : 100 of red corpuscles, diminishing soon after to 1 : 350 or 600, or according to Gräber[2] between 1 : 521 and 821. A large number of observations conducted in V. Jacksch's clinic gave the proportion of leucocytes to red corpuscles as 1 : 500 - 800 in healthy adults.

[3]Reinecke's figures are 1 : 720.

Stengel /

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[1]V. Jacksch and Cagney - Clinical Diagnosis.
[2]Gräber, E. :- Zur Klinischen Diagnostik der Blutkrankheiten - Haematologische Studien, p.64. Leipzig, 1888.
[3]Reinecke :- Fortschritte der Medicin, IX., 1891. Virchow's Archiv CXVIII., 148, 1889.

Stengel[1] says we may fix upon the number 6000 as indicating the number which shall represent the lowest limit that may be considered normal, and that, roughly speaking, when the number per cubic millimetre exceeds 10,000, the condition is one of leucocytosis.

Cabot[2] remarks that the figure usually given for adults is 7,500, per cubic millimetre. Hayem[3] gives their number as 6,000 per c.mm. Von Limbeck[4] as 8-9000, allowing an increase or decrease of a thousand and the proportion of white to red corpuscles as about 1 to 5 or 600. Afanassiew[5] states the proportion as 1 to 600.

Muir /

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[1]Stengel - - Twentieth Century Practice of Medicine, Vol. VJJ., p. 306.
[2]Cabot - - Clinical Examination of the Blood p.46
[3]Hayem - - Du Sang p. 166.
[4]V.Limbeck - Grundriss einer Klinischen Pathologie des Blutes, Jena, 1896.
[5]Afanassiew M. Ueber den dritten Formbestandtheil des Blutes im normalen und pathol. Zustande und über die Beziehung desselben zur Regeneration des Blutes. Deutsch Archiv f. klin. Med, XXXV., 1884, S. 217.

[1]Muir considers that the proportion of 1 to 500 is rarely exceeded without some pathological condition being present.

NORMAL BLOOD at BIRTH.

The white corpuscles are more numerous at birth than in adults or in young children.

[2]Schiff found the highest counts, in the first twenty-four hours following the first feeding, to be from 26,000 to 36,000 per cubic millimetre. He called attention to the daily variation in consequence of digestion, which is of the utmost importance to bear in mind when examining pathological blood. He estimated that from the twelfth to the eighteenth day the average figures are from 12,000 to 13,000, and for older children 10,000.

Hayem /

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[1]Muir - Contribution to the Physiology of the Blood. - Jour. of Anat. and Phys. Vols 25, 26, 27, 1891.

[2]Schiff - Ueber des quantitative Verhalten der Blutkorperchen und des Hämoglobins bei neugeborenen Kinder - Zeitschrift für Heilkunde Bd XI., 1890.

[1]Hayem found that in the first few days of life there were three or four times more leucocytes than in adult blood and his estimated average was 18,000 until the physiological loss of weight was ended when it was rapidly reduced from 14,000 to 12,000. At the time when the infant begins to gain weight the count rises to from 19,000 to 23,000 and then remains constant for a few days. The daily variations in the early days of life are more marked than in adults. Hayem[2] gives the following table to illustrate these points :-

I. Enfant à terme, sexe masculine, né le 30 décembre 1878, à 1h. du matin :-

Dates	Poids	Nombre des blancs
	K	
30 décembre à 10h. ½	3,865	19,500
" " 1h. ½	"	18,000
31 " 10h. ½	3,520	14,000
1 janv. 1879 à " "	3,715	20,000
2 " " " "	3,965	20,000
3 " " " "	4,125	12,000
4 " " " "	4,055	10,000
6 " " " "	4,017	15,000
8 " " " "	3,965	10,000
12 " " " "	4,075	5,000
19 /		

[1]Hayem - Du Sang p. 180.
[2]Hayem - Du Sang p. 182.

Dates	Poids	Nombre des blancs
19 janv.1879 à 10h. ½	4,250	12,500
1 février " "	4,530	12,000

Les deux observations suivantes sont empruntées à M. Cadet.[1] Les poids ne sont pas notés.

II. Garçon à terme, né cette nuit, 5 janvier 1881 tous les examens ont été faits le matin à 9 heures.

Dates	Nombre des blancs
5 janvier	17,000
6 "	15,000
7 "	10,000
8 "	6,700
9 "	7,300
10 "	7,000
11 "	5,400

III. Fille à terme née le 2 janvier 1881. Numérations faites tous les matins à 9 heures et demie.

Dates	Nombre des blancs
2 janvier	25,700
3 "	23,200
4 "	14,700
5 "	10,000
6 /	

[1] Cadet - Etude Physiologique des eléments figurés du sang - Dissert. Paris, 1881.

Dates	Nombre des blancs
6 janvier	7,000
7 "	6,000
8 "	15,000
9 "	7,000

[1]Gundobin, in an examination of infants from 10 days to a year old, found an average of 12,900, the variations being from 10,000 to 14,000. The adult variation he estimates to be from 7,000 to 10,000.

[2]Bouchut and Dubrisay found the average of a number of counts in children, from two to fifteen years of age, to be 6,700. Denis[3] examined the blood of artificially fed and breast-fed infants. He found the diminution of the leucocytes occurring on the fourth day and that it took place more rapidly in the breast-fed than in the artificially fed. He observed that the counts in infants were higher than in adults and that an increase of the white corpuscles occurred in poorly /

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[1]Gundobin - Ueber die Morphologie und Pothologie des Blutes bei Kindern. - Jahrb f. Kinderheilk Bd. XXXV. 1893.
[2]Bouchut et Dubrisay - Gazette Médicale de Paris, 1878.
[3]Denis - Recherches expérimentales sur le Sang. Paris 1880.

poorly nourished infants. He refers to the influence of food on the counts and states that soon after feeding an increase in the leucocytes was observed.

[1]Anna Bayer estimates the leucocytes of new born infants and young children as between 16,000 and 23,000. In later childhood, up to the sixth year, she placed them at from 9,000 to 10,000.

[2]Cabot says all the signs by which sickness is shown in the blood of adults are exaggerated in children and he gives the following table as being compiled from the best authorities on the subject (Schiff, Gundobin, Bayer, Hayem, and others).

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[1]Bayer - Ueber die Zahlenverhältnisse der rothen und weissen Zellen im Blute von Neugeborenen und Säuglingen. - - Dissert, Bern, 1881.

[2]Cabot - Clin. Exam. of the Blood p. 86.

AGE	Red Cells	Leucocytes.
At Birth.	5,900,000	17,000 to 21,000 (26,000 to 36,000 after first feeding)
End of first day.	7,000,000 to 8,800,000	24,000
" second "	generally increased	30,000
" fourth "	6,000,000	20,000
" seventh "	5,000,000	15,000.
Tenth day.		10,000 to 14,000
Twelfth to eighteenth day		12,000
Sixth month.		12,000
Sixth year and upward.		7,500

We may therefore accept Cabot's table as indicating a fair average proportion of the number of leucocytes normally found in the blood of children and judge a case as being one of leucopenia according as the number of white blood corpuscles falls short of that standard.

A comparison of the number of leucocytes found normally in the child and in the adult shows how necessary it is to have a separate standard for each, because, if this were not taken into account, a case of leucopenia in a child might be a case of leucocytosis in an adult and vice versa, if we adopted "6,000" as the normal number of leucocytes irrespective of age.

DEFINITION : Cabot[1] in his 'Guide to the Clinical Examination of the Blood' defines the condition as "A diminution in the number of white cells in the peripheral circulation as compared with the number normal for the given individual.

[2]Stengel says "In clinical studies it is somewhat difficult /

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[1]Cabot - Clin. Exam. of the Blood for Diagnostic purposes p. 87.

[2]Stengel - "Twentieth Century Practice of Medicine" Vol. VII., p. 306

"difficult to establish a number which shall represent "the lowest limit that may be considered normal. "Arbitrarily, however, we may fix upon the number six "thousand."

According to Stengel the term leucopenia was introduced by Löwitt[1] to indicate poverty of leucocytes and that the diminished number of leucocytes results from increased destruction.

Schulz[2], Goldscheider and Jakob[3] as quoted by Stengel found that, if they injected various toxic substances, the capillaries of the internal organs, especially the lungs, were overloaded with leucocytes while the peripheral circulation showed a decrease of leucocytes.

(As a contrast I shall here interpolate Cabot's[4] definition of leucocytosis. He says, "There are many "difficulties in defining leucocytosis. To my mind "the term is best used to mean 'An increase in the "'number /

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[1]Löwitt - Studien zur Physiol und Pathol des Blutes u. der Lymphe.

[2]Schulz Georg - D. Archiv f. Klin Med.Bd.51,1893, S. 234.

[3]Goldscheider & Jacob - Ueber die Variationen der Leukocytose - Zeitschr f. Klin Med.Bd.25, Hft. 5,6.

[4]Cabot - Clin. Exam. of the Blood p. 82.

"'number of leucocytes in the peripheral blood over
"'the number normal in the individual case, this in-
"'crease never involving a diminution in the polymor-
"'phonuclear varieties, but generally a marked absolute
"'and relative gain over the number previously present.
"I say in the peripheral blood, because the majority
"of observers now hold that leucocytosis is not a real
"increase in the total number of leucocytes in the
"blood, but only an affair of distribution, the cells
"being drawn or attracted to the periphery and out of
"the internal organs)."

In discussing this question one must of course remember that the relative number of leucocytes is influenced by various conditions and what would be considered pathological in one person would not be thought so in another. For the sake of comparison I shall give Cabot's[1] Classification of leucocytosis

I. Physiological : /

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[1] Cabot - Clin. Exam. of the Blood p. 83.

I. Physiological :

1. Leucocytosis of the New-born
2. Leucocytosis of digestion
3. Leucocytosis of pregnancy
4. Leucocytosis of post-partum
5. Leucocytosis after violent exercise, massage and cold baths
6. Leucocytosis of the moribund state.

II. Pathological :

1. Post haemorrhagic leucocytosis
2. Inflammatory leucocytosis
3. Toxic leucocytosis
4. Leucocytosis in malignant disease
5. Leucocytosis due to therapeutic and experimental influences

Causes /

CAUSES of LEUCOPENIA.

The conditions producing leucopenia are by no means so numerous or so well investigated as those producing leucocytosis.

Leucocytes react very rapidly to any untoward influence.

[1]Löwitt has shown that gradual tying down of an animal (rabbit) will cause a marked decrease in the number of white corpuscles, which decrease he ascribes to arrested development of the leucocytes in the blood forming tissues, the uninuclear elements being those which diminish most. On the other hand if the animal be tied down rapidly, or if shock be produced by vigorously shaking it or striking it on the head, the result is a rapid diminution in the number of leucocytes, of the uninuclear as much as of the other elements. According to Kanthack[2] the number of the leucocytes /

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[1]Löwitt :- Studien zur Physiol und Pathol. des Blutes u. der Lymphe.

[2]Kanthack :- The Histological Changes of Blood in Diseased Conditions - Manchester Medical Chronicle Vol. I. 1894, p.333.

leucocytes in the blood-forming organs remains unaltered in such cases, so that there is an actual leucolysis, the decrease being due not to an arrest of development but to an actual destruction of the blood.

Starvation certainly tends to lower the leucocyte count as in the case of the professional faster Succi (quoted by Cabot)[1], where in the first week the number sank to 861 per cubic millimetre. At the end of the first week it rose to 1,530 and remained so during the thirty days of his fasting (Lanciani)[2]. Such a condition of affairs would seem to be of no practical importance, but in one case an observer was able to diagnose stenosis of the gullet by the lowness of the leucocyte count (2,700) in a patient, who could only talk Russian. This diagnosis was afterwards confirmed by the probang. One could also form some idea of the amount of food taken by a patient, living at a distance by this means.

Any /

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[1] Cabot - Clin. Exam. of Blood p. 84.

[2] Lanciani - "Des Hungern" German translation, by O. Frankel, Hamburg, 1890.

Any condition leading to starvation e.g., cancer of the gullet produces a similar leucopenia. Short hot baths or prolonged cold baths have been found by Winternitz[1] to produce leucopenia while prolonged hot baths or short cold ones produced leucocytosis.

In cases of leucocytosis due to therapeutic and experimental influences Goldscheider and Jakob[2] found always a temporary diminution of white corpuscles to precede the subsequent leucocytosis, just as Löwitt[3] found a similar state of matters after injecting hemi albumose, peptone, pepsin nucleinic acid, nuclein extract of blood leech, pyocyanin, tuberculin, curare uric acid, urate of sodium, or urea.

With regard to the injection of Bacteria and their toxines it is found that, if the dose injected be large, the leucocytes are diminished and the animal dies, whereas, if not sufficient to kill the animal, leucocytosis is preceded by a passing leucopenia.

There /

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[1]Winternitz :- Imperio Royal Medical Society, Hamburg, 1890

[2]Goldscheider & Jakob :- Arch. f. Exp. Path. u. Pharm. Vol. V. p. 122.

[3]Löwitt:- Studien zur Physiol. u. Pathol. des Blutes u. der Lymphe.

There are some ~~of the~~ pathological conditions which cause leucopenia e.g. grippe, malaria, typhoid especially in the later weeks, miliary tuberculosis etc., in fact most of the infective diseases not accompanied by leucocytosis, and in this connection it is interesting to note that the diagnosis of some of these conditions may be made from the leucocyte count because in many diseases, whose clinical symptoms resemble those of the above, there is leucocytosis. More especially has the diagnostic value of the leucocyte count been found in differentiating between tuberculous and simple inflammatory infections where, as is well known, there is always leucocytosis.

Nearly all the prolonged pyrexias which are not accompanied by inflammation are characterised by leucopenia and in this connection it is interesting to note Hayem's remarks on this subject. He says "Toutes les pyrexies de longue durée, non compliquées "de /

Hayem :- " Du Sang" p. 380.

"de lésions inflammatoires, c'est-à-dire d'états path-
"ologiques qui par eux-mêmes sont une cause de multipli-
"cation des globules blancs, tendent à faire baisser
"le chiffre de ces éléments. Le type de ces pyrexies
"est la fièvre typhöide dans ces formes complexes et
"traînantes. On peut alors voir progressivement le
"nombre des leucocytes tomber jusqu'à 2,000. Le même
"fait peut se rencontrer dans les anémies extrêmes.
"Dans ces dernières circonstances on pourrait se de-
"mander, vu le dégoût des malades pour les aliments et
"l'état de souffrance très prolongé du tube digestif,
"si cette diminution dans la production des leucocytes
"n'est pas la conséquence de l'abstinence".

As stated above by Hayem different forms of anaemia, especially pernicious anaemia, are associated with a great diminution in the number of leucocytes. Rickets and syphilis also often produce the same condition. Having given this short introduction to the subject of leucopenia it is now my intention to discuss more in detail the different diseases in which this condition is found. Having come across the condition first in a case of malaria I shall begin with that disease.

MALARIA. /

M A L A R I A.

Very little attention has been paid to the leucocytes in malaria and the literature on the subject is scanty. The work that has been done has chiefly related to the pigmented leucocytes which occur in malarial fever and which do not concern us here.

[1]Rieder in his work on the leucocytoses refers to the fact that Kelsch[2], Von Limbeck[3], Fahrmann[4] and others have found no leucocytosis in malarial fever - one or two of them state that the number of leucocytes falls below normal.

[2]Kelsch found the leucocytes diminished from one third to a half in malarial fever and remarks that at the beginning of the paroxysm there is a slight transient increase in the number of leucocytes in the blood.

He /

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[1]Rieder - "Beiträge zur Kentniss der Leukocytosis."
[2]Kelsch - Arch. de Physiol 1875 p. 690.
[3]V. Limbeck - Klinisches und Experimentelles über die entzündl. Leukocytose Zeitschr. f. Heilk, Bd. X, 1890, s. 392.
[4]Fahrmann - Deutsche militärärtzliche Zeitschr., 1874 No. 12.

He found that the minimum number of the leucocytes corresponded to the maximum enlargement of the spleen and that when the size of the spleen was diminished by means of an electrical current, there was a transient increase in the number of the leucocytes.

[1]Hayem has observed the diminution in the white corpuscles.

[2]Kalindero noted a marked diminution in the number of the white corpuscles especially in the more acute cases, and that during the paroxysm there was a tendency toward an increase in the number.

[3]Dionisi observed that the white corpuscles suffer the same variations as the red, except that, in some long continued anaemiae, the white corpuscles remain subnormal in number for a long time.

The /

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[1]Hayem - - Du Sang, p. 923.
[2]Kalindero - Les globules sanguins dans l'impaludisme. Jour. de Med. et de Pharm. de l'Algiers, 1889, XIV. 123 (June).
[3]Dionisi - Variazoni dei globuli rossi e dei globuli bianchi &c Lavori del III° congresso della societa italiana di medicina interne Milan, Oct. 1890, 169.

The most exhaustive article on the subject is Bastianelli's[1]. He quotes Golgi who holds that phagocytosis occurs regularly as a function of the leucocytes, obtaining at definite phases of development of the organism. Golgi[2] also believes that phagocytosis may account for the spontaneous recovery observed in so many cases, and that it plays an important part in the prevention of all malarialfevers from becoming pernicious.

[3]Bastianelli finds :-

1. The number of leucocyte is always diminished in malarial fever.
2. The number of pigmented leucocytes increases markedly at the time of sporulation of the organism in the tertian cases; i.e. at the beginning of the febrile paroxysm.
3. In cases of spontaneous recovery no increase is to be observed in the number of pigmented leucocytes. This phenomenon of phagocytosis may occur /

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1 & 3 Bastianelli - Bull d. Real Accad. Med. d. Roma, Ann. XVIII. Fasic. V. p. 487.

2 Golgi - - Sur l'infection malarique Arch. italiennes di biologie, 1887, t. 8.

occur at all stages of the cycle of evolution of the organism in the aestivo-autumnal cases.

4. The phagocytic leucocytes rapidly become necrotic and disappear from the blood. This probably accounts for the diminution in number of the leucocytes which takes place in malarial fever.

5. The phagocytosis is accomplished chiefly by the large mononuclear forms. He made a series of differential blood counts and showed that, in those cases with leucopenia, while the proportion of small mononuclear elements remained normal, the large mononuclear leucocytes were greatly increased and the polymorphonuclear neutrophiles diminished to a certain degree. Eosinophiles he found to be scanty.

[1]John S. Billings, Jr. gives the results of his investigations on the leucocytes in malarial fever. He says :-

"Malaria is very prevalent in the immediate neighbour-
"hood of Baltimore, and three types of fever are seen
"as /

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[1]Billings J.S. - Johns Hopkin's Hospital Bulletin, Vol. V. p. 89.

"as follows :-

1: The spring or tertian type. This is most common in the spring and early summer, tho' cases are often seen in the autumn. The paroxysms occur every other day, if the case be one of single tertian, and daily, if it be one of double tertian; i.e. with two sets of organisms in the blood, maturing on alternate days. This latter form is the commonest type seen in Baltimore.

2. The quartan type. This is rarely seen, there being only five cases on record in the hospital. The paroxysms are rarely as severe as those in the previously mentioned type of the disease. They may occur every third day, two out of every three days or every day according as there may be one, two, or three sets of organisms in the blood.

3. The fall type. This is the aestivo-autumnal type of the Italian observers, and occurs in the late summer and fall. The course of the fever is irregular. There may be definite paroxysms, as in the tertian type of the disease, or the temperature may be continuously elevated for days /

days. The paroxysms may occur daily or there may be no regular periodicity.

The counts were made with the Thoma-Zeiss haemocytometer and care was taken that the counts should not be made within two hours after meals. Four whole fields were counted in each case. The nomenclature used is according to Thayer[1] which is a modification of those used by Ehrlich[2] and Uskow.[3] The lymphocytes and small mononuclear forms of Ehrlich are given together under the head of small mononuclears, while the large mononuclear and transitional forms are classified together as large mononuclears. It is difficult to draw any hard and fast line between these two groups.

In looking over the table of tertian cases it is striking to note the uniform diminution in the number of leucocytes during the febrile paroxysm (leucocytolysis). It is also to be noted that the maximum number of leucocytes is to be found as a rule two or three hours after the chill. From that time on there is /

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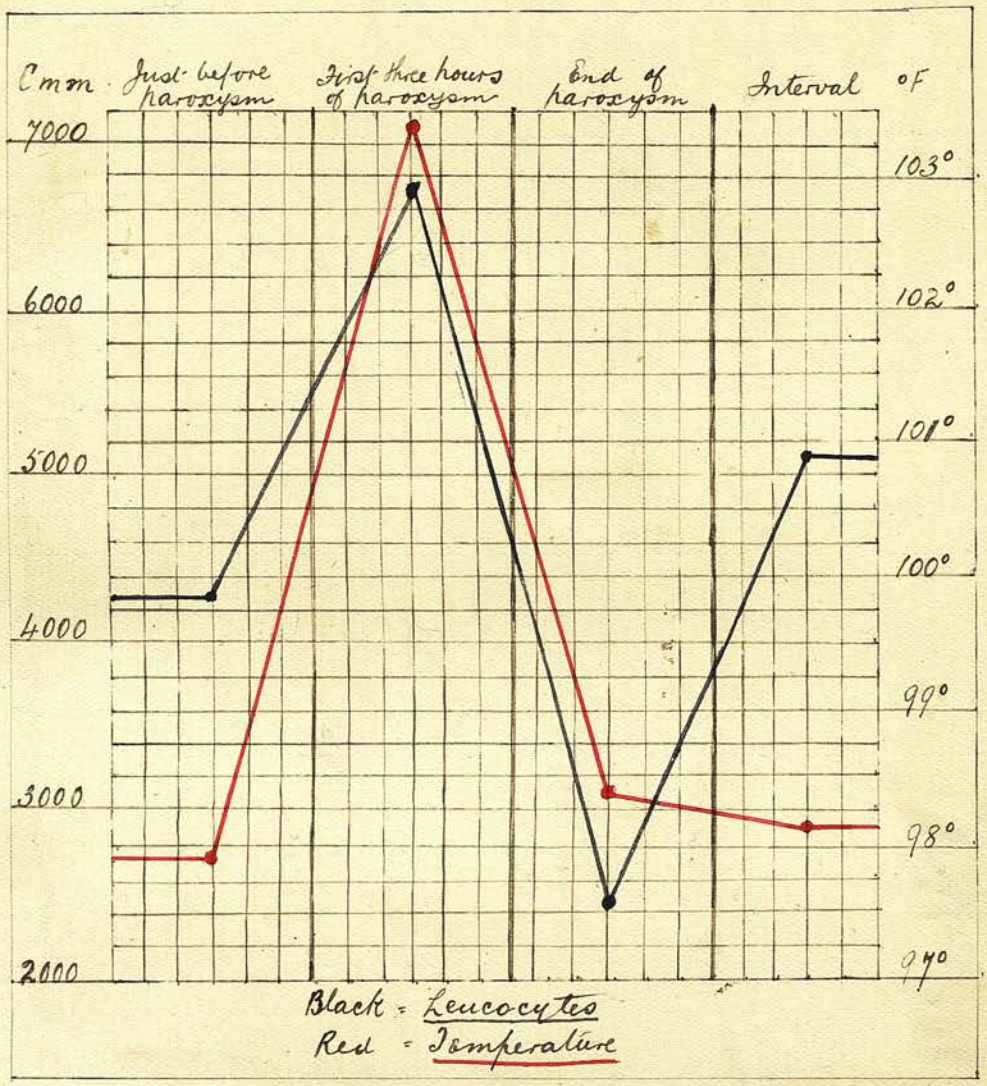
[1] Thayer - The Malarial Fevers of Baltimore etc. Baltimore 1895.

[2] Ehrlich - Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes - Berlin 1891. I. Theil.

[3] Uskow - Centralbl. f. d. Med. Wiss., 1878, s. 499.

is a progressive diminution until the minimum number of leucocytes is reached at the end of the paroxysm, when the temperature is subnormal, which is usually for some hours. The number of leucocytes then rises somewhat and during the interval occupies a position about mid-way between the maximum and minimum above mentioned. The increase at the beginning of the paroxysm does not take place until after the chill, as the average number of leucocytes just before the chill is very slightly higher than the average number during the interval. These points are well shown if the average number of leucocytes at the different stages of the paroxysm be represented graphically together with the average temperature at these times (see chart)


Cmm
Just before paroxysm
First three hours of paroxysm
End of paroxysm
Interval
°F
7000
6000
5000
4000
3000
2000
103°
102°
101°
100°
99°
98°
97°
Black = Leucocytes
Red = Temperature

Billings points out that the strong objection to the occurrence of this apparently regular oscillation of the number of leucocytes is the fact that the differences involved are so extremely small as to almost come within the limit of error of the haemocytometer. This may be placed at 2,000 at the outside if sufficient care be taken. Billings goes on to say that while we may be in doubt as to the occurrence of an increase in the number of leucocytes in the blood at the beginning of the malarial paroxysm, there can be little doubt that there is a definite diminution in the number of leucocytes toward the end of the paroxysm. The difference between the average maximum and the average minimum number of leucocytes is 4,271, which is well outside the limit of error. The average number of leucocytes three hours after the beginning of the paroxysm is only 2,300 more than the average number just before the beginning of the paroxysm. Yet, this increase, slight as it may be, occurs in seven of his ten cases.

Billings' Chart of Sixteen Cases. /

Billings' Chart of Sixteen Cases.

No.	Patient	Date admitted Previous duration	Type of organism	Date	Hour	Temperature.	Leucocytes p.cmm	Remarks	% polynuclears	% small mononuclears	% large mononuclears	% Eosinophiles.
1	K.Male 26 White.	August 16,1893 Illness began Aug.16 '93. Daily paroxysms	Tertian (double)	Aug,18	1 p.m.	104.2o	3,250	Beginning of chill	68.2	15.1	15.6	1.1
					4 p.m.	103.6o	6,000	---------	73.2	11.9	14.1	.8
					6 p.m.	101.6o	4,100	---------	62.4	15.2	20.3	2.1
					12 mid.	97.8o	2,000	---------	54.7	20.5	23.8	1.
2	M.Male 33 White.	August 16,1893 Illness began Aug.11 '93.Daily paroxysms.	Tertian (double)	Aug.19	1.45 p.m.	101o	5,500	Beginning of chill	71.3	17.4	11.1	.2
				" 20	10 a.m.	97.2o	4,500	---------	68	7.3	24.2	.5
				------	10 p.m.	103o	2,666	Chill be-	52.7	12.8	33.2	1.3
				Aug.21	9 a.m.	97o	2,500	gan at 2. p.m.	49.8	18.6	30.9	.7
3	S.Male 17 White.	August 21,1893 Illness began Aug.14 '94. Paroxysms every other day.	Tertian (single)	Aug.23	9 a.m.	100.2o	6,000	Beginning of chill	82.1	12.1	5.1	.7
					10 a.m.	103.6o	7,750	---------	----	----	----	---
					11 a.m.	103.2o	7,500	---------	75.8	7.1	16.	1.1
					12 m.	102.6o	4,750	Sweating	----	----	----	---
					1 p.m.	100.1o	5,000	---------	----	----	----	---
					4 p.m.	99o	3,500	---------	66.	22.4	10.6	1.
				Aug.24	12 m.	98o	3,750	---------	65.1	23.7	9.2	2.
4	Same case	----------	--------	Aug.25	8 a.m.	102o	7,250	Beginning of chill	78.1	12.4	7.4	2.1
					10 a.m.	104.8o	9,750	---------	79.2	8.1	12.4	.3
					12 m.	102o	6,250	Sweating	70.8	15.1	13.7	.4
					2 p.m.	100o	6,000	---------	64.	13.5	21.5	1.
					4 p.m.	98.6o	5,250	---------	----	----	----	---
					8 p.m.	98,6o	5,000	---------	63.2	22	8.8	6.
5	S.Male 20 White	August 24, 1893 Illness began Aug.10 '93. Daily paroxysms	Tertian (double)	Aug.24	8 p.m.	98.6o	3,000	---------	63.1	21.8	14	1.1
					11 p.m.	105o	2,250	Beginning of chill	75.2	14	10.2	.6
					12 p.m.	105o	3,000	---------	----	-----	----	---
				Aug.25	1 a.m.	104.9o	4,200	---------	----	----	----	---
					2 a.m.	104.7o	6,750	Sweating	74.6	7.5	17.4	.5
					3 a.m.	103.9o	4.500	---------	----	----	----	---
					4 a.m.	103.2o	3,250	---------	----	----	----	---
					5 a.m.	102.4o	3,500	---------	66.8	17.	16.	.2
					6 a.m.	101.1o	3,000	---------	----	----	----	---
6/					8 a.m.	98.4o	2,600	---------	70.2	20.6	7	.2

No.	Patient	Date admitted Previous duration	Type of organism	Date	Hour	Temperature	Leucocytes p.c.mm	Remarks	Per cent polynuclears	% small mononuclears	% large mononuclears	% Eosinophiles.
6	B.Male 20 White.	August 25,1893 Illness began Aug.20 '93. Daily paroxysms	Tertian (double)		8 a.m.	98o	6,000	Just before chill	66.9	22.1	10.2	.8
				Aug.26	2 p.m.	105o	8,250	---------	71	13.8	14.1	1.1
					6 p.m.	99o	4,100	Sweating	61.3	15.7	22.6	.4
				Aug.27	8 a.m.	98.6o	2,000	---------	50.4	20.4	29.2	.0
7	P.Male 19 White.	August 28,1893 Illness began Aug.25 '93. Daily paroxysms	Tertian (double)		10 p.m.	97.8o	5,000	Just before chill	70.6	14.5	13.8	1.1
				Aug.29	12 p.m.	104.2o	6,666	---------	81.6	6.4	11.1	.9
				Aug.30	12 m.	97o	2,100	---------	61.4	17.4	19.2	2.
8	W.Male 27 White	March 6,1894 Illness began March 4th 1894.	Tertian (double)	Mch 6	1.15 p.m.	103o	5,000	Beginning of chill	73.2	8.	18.8	.0
					4.15 p.m.	105o	6,250	---------	80.2	6.9	12.6	.3
				Mch 7	8.30 a.m.	97.9o	1,500	---------	43.2	26	30.4	.4
				Mch 8	9 a.m.	98o	3,100	---------	48.8	27.2	13	2.
				Mch 9	11 a.m.	98.6o	5,750	---------	60.8	30.1	8.9	.2
				Mch 10	11.30 a.m.	98.6o	5,200	---------	74.1	20.9	4.2	.8
9	G.Male 22 White.	August 14,1894 Illness began Aug. 9 '94. Daily paroxysms	Tertiam (double)	Aug.15	3.30 p.m.	100o	3,500	Beginning of chill	73.8	13	12.1	1.1
					10 p.m.	101o	1,500	---------	64.1	14.1	21	.8
				Aug.16	8 a.m.	98o	5,000	---------	55.2	21.3	23.3	.2
					2.30 p.m.	98o	3,000	Just before chill	51.6	25.2	19.1	4.1
10	J.Male 48 Black	August 14, 1894 Illness began Aug. 6 '94. Daily paroxysms	Tertian (double)	Aug.16	12 m.	98.6o	5,100	---------	50.2	28.7	20.	1.1
				Aug.17	2 p.m.	101o	7,000	Beginning of chill	81.5	8.	10.	..5
					5.30 p.m.	100.6o	5,750	Sweating	72.8	9.1	17.1	1.
					10 p.m.	98o	2,000	---------	58	13.5	28	.5
11	B.female 13, white	August 24, 1893 Illness began Aug.14 '93. Irregular fever since that date.	Aestivo-autumnal	Aug.27	8 p.m.	103.2o	4,500	Temperate not normal since admission.	62.8	27.6	9.6	.0
				Aug.28	8 p.m.	101.7o	2,200		69.9	20.4	9.5	.2
				Aug.30	8 p.m.	98.2o	3,500	First normal temperature	63.1	7.1	29.6	.2
12/												

No.	Patient.	Date admitted Previous duration	Type of organism	Date	Hour	Temperature	Leucocytes p.c.mm	Remarks	Per cent polynuclears	% small mononuclears	% large mononuclears	% Eosinophiles.
12	T,Male 8, White.	Sept. 2, 1893 Illness began Aug.12 '93. Irreg. fever since that date	Aestivo-autumnal	Sep. 3	10 a.m.	99.8o	6,100	Irregular fever, temperature not touching normal for 3 dys, i.e., until the 5th.	54.1	22.	22.1	.1
					6 p.m.	102o	4,200		69.2	18.	11.3	1.5
				Sep. 4	4 p.m.	104.6o	5,200		48.1	20.2	31.3	.4
				Sep. 5	8 a.m.	99.2o	6,500		65.5	19.9	13.6	1.
13	C.Male 30 Black.	Sept. 11, 1893 Illness began Sep. 6 '93. Irreg.fever with night sweats	Aestivo-autumnal	Sep.11	4.p.m.	105o	6,400	Height of febrile paroxysm lasting 24 hours.	72.1	16.7	11.2	.0
				Sep.12	8 a.m.	98.8o	3,500		70.6	12.4	13.9	3.1
					6 p.m.	98.6o	4,000		68.7	12.7	18.1	.5
14	C.Male 27 White.	Sept. 16, 1893 Illness began Aug.7, '93. Irreg. febrile paroxysms with sweating.	Aestivo-autumnal	Sep.17	8 a.m.	98.6o	2,100	Height of paroxysm lasting 20 hours.	65.3	12.7	20.6	1.4
					8 p.m.	101.4o	2,500		68.7	18.6	12.1	.6
				Sep.18	12 m.	98.6o	3,400		59.	24.7	16.1	.2
15	M.Male 26 White.	Aug.16,1894 Illness began Aug.12 '94. Irreg. febrile paroxysms with chills and sweating.	Aestivo-autumnal	Aug.16	3.30 p.m.	101o	5,150	Temp.falling.	69.6	13.1	16.2	1.1
				Aug.17	10 a.m.	99o	6,750	Temp.began to rise at 2 p.m.	52.5	23.5	23	1.
					5 p.m.	100.7o	4,200		45.1	23.7	30.	1.2
16	K.Male 12 White.	July 19,1894 Previous history not obtainable.	Quartan	July 21	8 a.m.	98.4o	5,500	Height of slight paroxysm.	59.1	24.9	15.7	.3
					8 p.m.	100.5o	5,100		61.3	17.8	18.3	2.6
				July 22	8 a.m.	98.6o	5,200		66	17.2	16.1	.7

QUALITATIVE EXAMINATION.

Billings gives the results of his qualitative examinations of the cases under his care.

Ehrlich[1] gives the relative normal numerical proportion of the various forms of leucocytes as follows :-

Polynuclears	-	70 to 75 per cent.
Lymphocytes	-	15 to 25 per cent.
Mononuclear and transitional forms		6 per cent
Eosinophiles	-	1 to 5 per cent.

Billings uses Uskow's[2] standard, which is :-

Lymphocytes and small mononuclears	18 per cent
Transparent and transitional forms	6 per cent
Polynuclears and Eosinophiles -	76 per cent

He then discusses the proportions in his 6 cases.

1. Polynuclear leucocytes. They are much diminished relatively and absolutely, as low as 43.2 per cent in one case (Case No.8), the greatest reduction being as a rule at the end of /

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[1]Ehrlich. Farbenanalytische Untersuchungen sur Histologie und Klinik des Blutes. Berlin 1891, I. Thiel.

[2]Uskow. Centralbl f.d.med. Wiss, 1878, S.499.

of a paroxysm.

In six cases there is an increase during the first three hours of the paroxysm, corresponding to the increase in the number of leucocytes as a whole.

2. The small mononuclear elements vary widely from 30.1 per cent in Case 8 to 6.4 per cent in Case 7, but nothing definite is to be made out concerning the variations in their percentage.

3. Large mononuclear elements. These are greatly increased relatively and absolutely. The highest count is 33.2 per cent in Case 2; the lowest 4.2 per cent in Case 8. They are above normal in all but two cases and seem to reach their maximum towards the end of the paroxysm, thus counterbalancing the polynuclear forms, which reach their minimum at that time.

4. Eosinophiles. Their percentage is rather below normal but nothing worthyof note is to be made out concerning them.

Taking /

Taking 7,000 per c.mm as the average normal number of leucocytes in human blood, there is, in malarial fever, a diminution on an average of about 38 per cent.

The average numerical proportions of the various forms of leucocytes in the 16 cases were as follows :-

Polynuclears	-	65.04 per cent.
Small mononuclears		16.9 per cent.
Large mononuclears		16.9 per cent.
Eosinophiles	-	0.96 per cent.

Cabot' says that lymphocytosis is the rule in malaria whenever the number of leucocytes is below normal, the larger forms of young cells being especially numerous while the adult cells and eosinophiles are scanty. He also refers to the fact that Grawitz and others have noticed an increase of eosinophiles in post-malarial anaemia.

Pernicious Anaemia.

Leucopenia is constantly observed in Idiopathic or Progressive Pernicious Anaemia. Out of 46 cases examined by Cabot[2], 30 were under 5,000, while the average was 4,200 , the following Table showing his results.

CABOT'S TABLE./

Cabot' Clin. Exam. of Blood, p.326.
Cabot[2] Clin. Exam, of blood, p.121

CABOT'S TABLE.

W H I T E C E L L S.

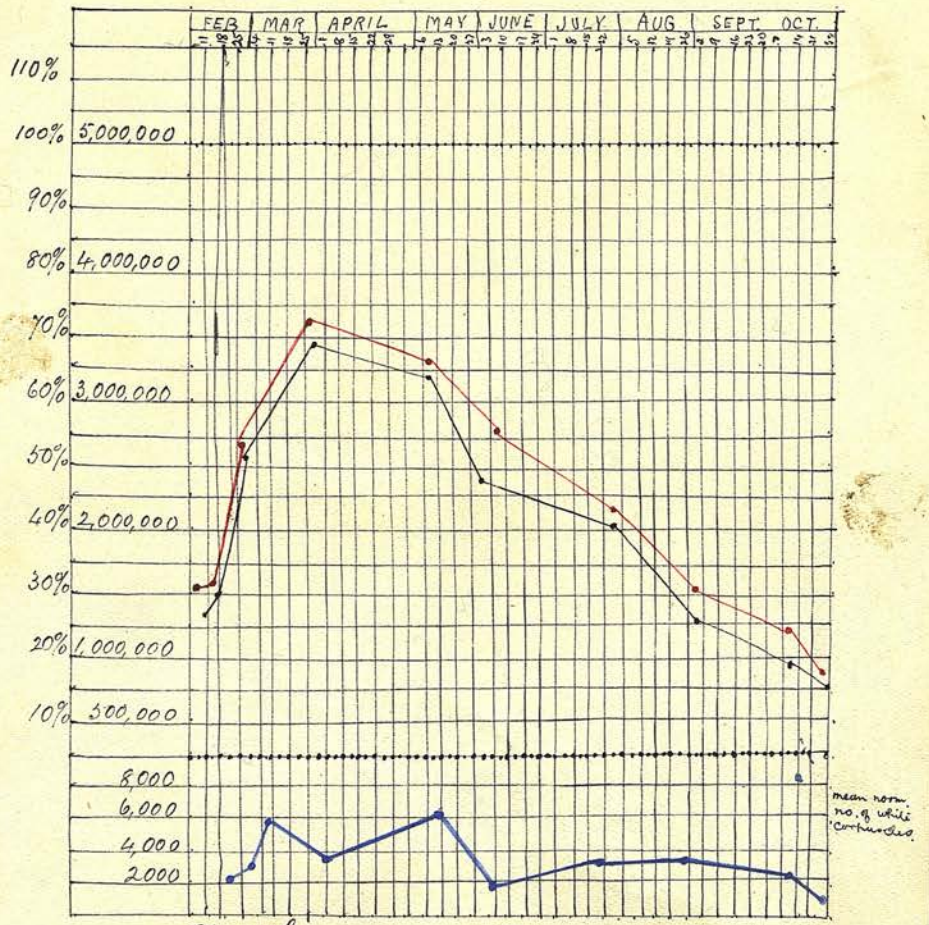
First Examination.

No.	White Cells	No.	White Cells	No.	White Cells
1	400	17	3,200	33	5,600
2	500	18	3,200	34	6,000
3	800	19	3,500	35	6,000
4	1,000	20	3,600	36	6,000
5	1,000	21	3,704	37	6,400
6	1,000	22	4,000	38	6,500
7	1,500	23	4,000	39	7,000
8	1,600	24	4,000	40	7,200
9	1,800	25	4,000	41	7,500
10	2,000	26	4,200	42	7,600
11	2,000	27	4,500	43	9,000
12	2,000	28	4,720	44	9,600
13	2,000	29	4,828	45	10,000
14	2,800	30	4,900	46	10,100
15	2,800	31	5,200		
16	3,000	32	5,300	Average 4,200	

"I have excluded from this series counts made immedi-
"ately after haemorrhages and counts in infants. The
"latter are very apt to show a leucocytosis in connec-
"tion with <u>any</u> form of anaemia." (Cabot loc. cit.)

Osler' also gives an interesting chart which shows vividly the leucopenia present in pernicious anaemia.

'Osler. Theory & Prac.of Med. (Pepper) Vol.II,p.204.



Blood Chart of case of Pernicious Anaemia (Osler)

Black - red corpuscles.
Red - Haemoglobin.
Blue - colourless corpuscles.

Hayem[1] in discussing the same subject says :- "Le chiffre absolu des globules blancs, loin d'être "augmenté, est le plus souvent un peu diminué. Il "parait donc y avoir également un ralentissement dans "la formation de ces éléments.

"Enfin j'attirerai l'attention sur une observation "faite par Litten[2], chez deux jeunes femmes il a vu "survenir une leucocytose intense, mais passagère, dans "le cours de l'anémie pernicieuse progressive."

To illustrate his point Hayem[3] gives records of the blood counts in all his cases, one of which we may give as an example.

He[4] says "Presque toujours, sous l'influence "probable de l'affaiblissement des fonctions hema- "topoiétiques, le nombre de ces éléments diminue, il "peut tomber à 2 ou 3,000."

TABLEAU /

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[1]Hayem. Du sang p.796.

[2]Litten.Zur Pathologie des Bluten. Berlin, Klin. Wochenschr No.27, S.465, 1883.

[3]Hayem. Du sang p.782.

[4]~~Cabot~~. ~~Du sang p.418~~.

TABLEAU des RÉSULTATS NUMÉRIQUES.

DATES	Globules rouges N.	Hémato-blasts H.	Globules blancs B.	Valeur globulaire G.	Richesse globulaire R.
2 novembre 1883			6,200		
3 " "			6,200		
7 " "			6,200		
10 " "			3,906		
13 " "			3,255		
14 " "			3,580		
15 " "			6,510		
16 " "			7,380		
17 " "			5,205		
18 matin			5,530		
18 transfusion					
18 soir			6,835		
19 novembre 1883			5,000		
20 " "			2,600		
21 " "			4,030		
22 matin			2,925		
22 transfusion					
22 soir			3,580		
23 /					

TABLEAU des RÉSULTATS NUMÉRIQUES (contd.)

DATES	Globules rouges N.	Hémato-blasts H.	Globules blancs B.	Valeur globulaire G.	Richesse globulaire R.
23 novembre 1883			6,580		
24 "			2,275		
25 "			2,600		
26 "			3,580		
27 "			5,530		
28 "			3,100		
29 "			3,905		
30 "			7,665		
1st décembre			4,780		
2 "			2,610		
3 "			5,850		
4 "			5,205		
5 "			5,850		
6 "			4,880		
7 "			3,505		
8 "			2,275		
10 "			4,230		
12 "			3,255		
13 "			2,600		
16 "			6,510		
18 "			3,580		
20 "			4,500		
22 "			8,135		
24 "			9,935		
4 janvier 1884			12,084		
16 "			10,720		
19 "			1,937		
23 "			2,480		
2 février			2,100		
7 "			1,947		
25 "			7,402		

It has been observed that as the disease progresses leucocytes fall even more rapidly than the red cells and Cabot[1] says that counts as low as 500 white cells per cubic millemetre are not uncommon.

Stengel[2] on the other hand maintains that the white corpuscles play no important part in this disease and that while frequently in the earlier stages there may be a decrease in the number of leucocytes there more frequently is a definite leucocytosis. He says that towards the end of the disease the leucocyte count may rise so high as to lead to the suspicion of leukaemia, and that some of the cases which have been recorded as instances of the transformation of pernicious anaemia to leukaemia have been of this nature.

Cabot[3] on the other hand maintains that when leucocytosis is found in an adult with pernicious anaemia, it is nearly always due to some complication like haemorrhage or suppuration.

Although /

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[1]Cabot. Clin. Exam. of Blood. p. 121

[2]Stengel. Twentieth Century Prac.of Med.,Vol.VII p. 376

[3]Cabot. Clin. Exam. of Blood. p. 121

Although leucopenia is seldom found to any extent in children still it exists in some cases of pernicious anaemia in children.

Rotch[1] says there is generally a diminution of leucocytes but at times a distinct leucocytosis and gives the blood examinations of three cases.

Case 1. WHITNEY and WENTWORTH :

Erythrocytes	2,937,500
Haemoglobin	35 per cent
Leucocytes	5500
Small mononuclear	55 per cent
large "	10 " "
polynuclear	35 " "
Eosinophiles	5 " "

Case II. WENTWORTH :

Erythrocytes	1,022,509
Haemoglobin	17 per cent
Leucocytes /	

[1] Rotch. Hygienic and Med.Treat.of Children. Vol.I p.357

Leucocytes	16,000

Case III. DANE :

Erythrocytes	1,571,000
Haemoglobin	22 per cent
Leucocytes	19,000
Small mononuclear	42 per cent
Large "	18 " "
Polynuclear	40 " "
Eosinophiles	0 " "

In a case of pernicious anaemia recorded by Dr George Gibson[1] in the Edinburgh Medical Journal he found no absolute change in the number of the leucocytes.

Qualitative /

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[1] Gibson. Edin.. Med. Journal Oct. 1892.

Qualitative changes in the White Corpuscles in Pernicious Anaemia :-

lymphocytosis is the outstanding feature in the white corpuscles here and to demonstrate this Cabot[1] gives the following table.

PERCENTAGES of LEUCOCYTES in PERNICIOUS ANAEMIA :

Lymphocytes		Eosinophiles		Number of
No.	Per cent	No.	Per cent	Count
1	79	1	9	1
2	71	2	6.2	1
3	61.6	3	4.7	2
4	57.6	4	4.6	2
5	57.2	5	4.5	3
6	53.8	6	4.4	1
7	51.5	7	4.3	1
8	49.5	8	4	5
9	47.9	9	4	1
10	47.9	10	3.7	2
11 /				

[1] Cabot. Clin. Exam. of Blood. p. 127.

Lymphocytes		Eosinophiles		Number of
No.	Per cent	No.	Per cent	Count
11	45.9	11	3.5	1
12	44.7	12	3.4	1
13	43.7	13	3.1	1
14	42.2	14	2.8	2
15	41	15	2.7	2
16	40.8	16	2.6	1
17	40.5	17	2	1
18	38	18	1.5	5
19	38	19	1.5	2
20	37.8	20	1.5	1
21	35.7	21	1.5	1
22	35.6	22	1.4	1
23	35.6	23	1.2	1
24	34	24	1.2	1
25	33.1	25	.8	1
26	33	26	.8	1
27	29.4	27	.8	1
28	27.2	28	.6	1
29 /				

Lymphocytes		Eosinophiles		Number of
No.	Per cent	No.	Per cent	Count
29	26.5	29	.5	1
30	24.2	30	?	1
31	22	31	.0	1
32	21.2	32	.0	1
33	19.8	33	.0	1
34	16	34	.0	1

In 34 cases which he examined, the number of lymphocytes (large and small) averaged 45.9% and, as the fatal termination approached, the percentage of lymphocytes rose. In one case recorded by Cabot[1] the increase during the moribund state, which was long continued, was so great as to simulate lymphatic leukaemia. "The patient had presented the signs and symptoms of "pernicious anaemia and the blood was typical of the "disease in all respects, except for the lack of "nucleated red cells." Two other cases showed respectively 71 and 79 per cent of lymphocytes a few days /

[1] Cabot. Clin. Exam. of Blood p. 90

days before death.

Stengel[1] also finds a large increase in the number of lymphocytes but says he has also seen large numbers of the mononuclear forms. In the latter part of the statement he agrees with Osler[2] who says there is nothing remarkable about the leucocytes except that the large mononuclear elements are relatively somewhat increased.

The Eosinophiles are occasionally increased, the average in 49 examinations made in Cabot's[3] 34 cases being 2.7 per cent. Everyone seems to be agreed that small percentages of <u>myelocytes</u> are the rule.

They were present in 29 out of Cabot's 35 cases :-

No.	Percentages of Myelocytes	No.	Percentages of Myelocytes	No.	Percentages of Myelocytes
1	9.2	13	2	25	.6
2	8.8	14	1.8	26	.6
3	8	15	1.5	27	.5
4	6	16	1.2	28	.4
5 /					

1 Stengel 20th Century Prac.of Med. Vol. VII p.376

2 Osler Theory & Prac.of Medicine Vol.II p. 205

3 Cabot. Clin. Exam. of Blood p. 128

No.	Percentages of Myelocytes	No.	Percentages of Myelocytes	No.	Percentages of Myelocytes
5	4.6	17	1	29	.3
6	4	18	1	30	.2
7	3.6	19	1	31	.0
8	3.4	20	1	32	.0
9	2.7	21	.8	33	.0
10	2.5	22	.8	34	.0
11	2.2	23	.6	35	.0
12	2.2	24	.6	Average= 2 per cent.	

Regarding the myelocytes Cabot[1] remarks :-

"The myelocyte is found in a great variety of af-
"fections, although very sparingly in most, but, so far
"as my observations go, its presence is more constant
"and the percentages run higher in pernicious anaemia
"than in any other disease except leukaemia. I am
"speaking now of percentages. With a leucopenia such
"as is usually present in pernicious anaemia, 2 per cent
"of myelocytes means absolutely a very small number per
"cubic millimetre. Taking 4,200 leucocytes per cubic
"millimetre as the average for pernicious anaemia, 2 per
"cent of myelocytes amounts to only 84 per cubic milli-
"metre. In leukaemia the absolute number of leucocytes
"is /

[1] Cabot. Clin. Exam. of Blood p. 128

"is seldom under 50,000 per cubic millimetre."

Hayem[1] discusses the alterative changes in the leucocytes in these words.

"Dans quelques cas les petits éléments de la prem-
"ière variété sont plus nombreux qu'à l' état normal;
"mais on peut également trouver, au contraire, des
"leucocytes de la seconde variété plus ou moins nette-
"ment hypertrophiés. "On note aussi parfois un certain
"état de mollesse et d'amincissement du disque proto-
"plasmique, qui peut être creusé d'espaces vacuolaires.
"J'ai remarqué encore que, dans certain cas, quelques
"globules blancs renferment une petite proportion d'
"hémoglobine, particularité qui s'observe d'ailleurs
"dans toutes les anémies extrêmes."

Hayem's "la première variété"of leucocytes corresponds to our small lymphocytes & his"la seconde variété" corresponds to our polymorphonuclear neutrophiles because"la seconde variété comprend la grande majorité des globules blancs."[2]

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1 Hayem "Du Sang" p. 796

2 Hayem "Du Sang" p. 104

C H L O R O S I S.

Leucopenia is present as a rule in the worst cases of chlorosis just as in pernicious anaemia. In mild cases of uncomplicated chlorosis there is never leucocytosis and in severe cases as improvement progresses the white corpuscles go up faster than the red corpuscles.

Cabot[1] gives the following table to show the number of white corpuscles in 76 cases examined by him. In this series he says that "the occasional leucocytos-"is may be due to digestive or to a variety of other "influences (uterine trouble, etc.) which could not be "excluded."

LEUCOCYTES in CHLOROSIS (CABOT) :

No.	White Corpuscles	No.	White Corpuscles	No.	White Corpuscles
1	15,000	27	8,000	53	6,100
2	14,400	28	7,949	54	6,000
3	12,800	29	7,900	55	6,000
4	12,000	30	7,600	56	6,000
5	12,000	31	7,600	57	5,600
6	12,000	32	7,600	58	5,600
7	11,600	33	7,600	59	5,600
8	11,200	34	7,600	60	5,200
9	11,100	35	7,440	61	5,200

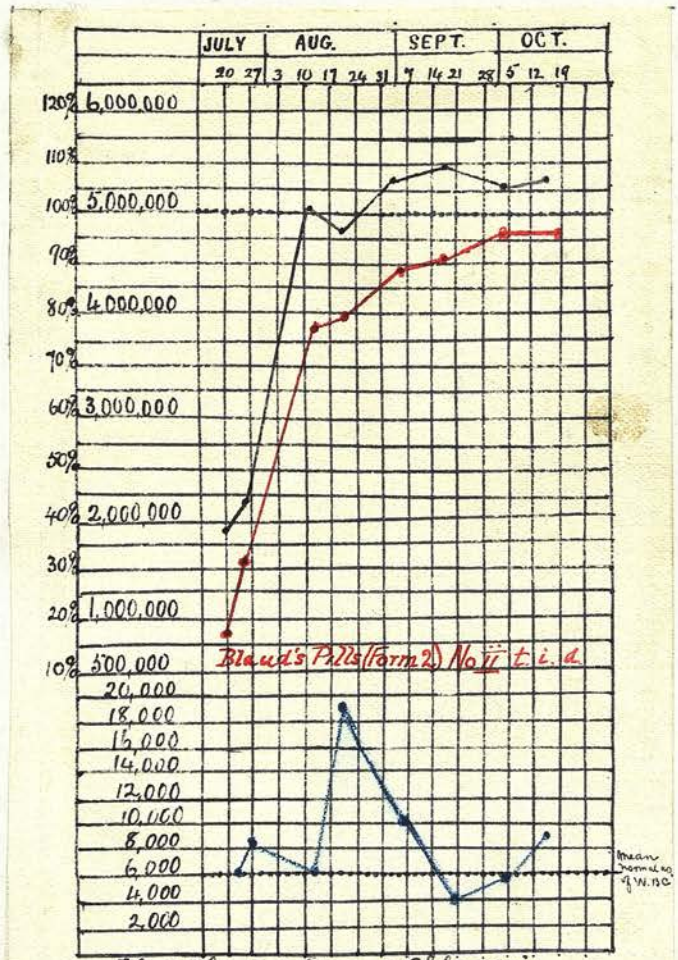
Cabot[1] Clin. Exam. of Blood, p. 137.

No.	White Corpuscles	No.	White Corpuscles	No.	White Corpuscles
10	10,800	36	7,200	62	5,200
11	10,800	37	7,200	63	5,000
12	10,500	38	7,200	64	4,800
13	10,400	39	7,000	65	4,800
14	10,000	40	7,000	66	4,172
15	10,000	41	7,000	67	4,000
16	10,000	42	7,000	68	4,000
17	10,000	43	7,000	69	4,000
18	10,000	44	7,000	70	4,000
19	9,600	45	6,850	71	3,600
20	9,600	46	6,800	72	3,600
21	9,600	47	6,800	73	3,400
22	8,500	48	6,600	74	3,200
23	8,000	49	6,600	75	2,800
24	8,000	50	6,400	76	1,500
25	8,000	51	6,400	Average	7,485
26	8,000	52	6,200		

"The average in Thayer's sixty-three cases was "8,467, in the present series it is 7,485."

'Cabot Clin. Exam. of Blood p.138.

Osler' also quotes Thayer's cases and says that they were studied in his clinique. Osler gives the following chart to illustrate the variation of the leucocytes (also the red corpuscles and haemoglobin) in a case of chlorosis.



Blood Chart of Case of Chlorosis
Black = red corpuscles
Red = haemoglobin
Blue = colourless corpuscles.

Osler-Theory and Prac. of Med. (Pepper)Vol.2 ,p.199.

Stengel[1] says the leucocytes are usually about normal in number and general appearance although according to Sörensen, Leichtenstern, Stifler and Reinert there is occasionally an increase.

Rotch[2] is indefinite on the subject with regard to children and says there is little or no leucocytosis while submitting the following table :-

BLOOD EXAMINATION (Whitney & Wentworth).

Erythrocytes	4,470,000
Haemoglobin	30 per cent
Leucocytes	45 per cent.

Hayem[3] says there are no changes in the number of white corpuscles in chlorosis :-

"Il ne me reste pas, pour achever ce tableau de l'état "du sang dans la chlorose qu'a signaler l'absence très "significative de toute modification du côté des "globules blancs."

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[1] Stengel - 20th Century Prac. of Med.Vol.VII p.341.

[2] Rotch - Hygienic & Med.Treat.of Children Vol.I. p.355.

[3] Hayem - Du Sang p. 623.

QUALITATIVE CHANGES in LEUCOCYTES in CHLOROSIS.

According to Cabot[1] lymphocytosis is usually present as Rieder found in twelve cases an average of 33 % of young cells, the highest percentages being 53.7, 43.5 and 41.7.

Myelocytes seem to be rare but have been found by Hammerschlag[2].

Rotch[3] gives the following numbers in one of his cases :-

Leucocytes	25,000
Small Mononuclear	45 per cent
Large "	21 " "
Polynuclear	30 " "
Eosinophiles	8 " "

LEUKAEMIA /

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[1] Cabot - Clin. Exam. of Blood p. 138

[2] Stengel - Twentieth Century Prac. of Med. Vol.VII. p.341.

[3] Rotch - Hygienic and Med. Treat. of Children Vol. I. p.356.

L E U K A E M I A.

Leucocytosis accompanied by lymphocytosis is of course the outstanding feature here, but it is interesting to note the effect of intercurrent affections on the number of leucocytes. Cabot[1] says regarding this point - "There are on record 17 cases in which "leukaemia (acute or chronic) has been complicated "with some intercurrent infection, with marked effect "upon the blood in all but one. This single case "was an acute rheumatic arthritis reported by Richter "in the discussion of Fraenkel's article in the "Deutsche medicinische Wochenschrift for 1895 (Nos.39, "43 and 45) p. 639. Here the blood remained un- "changed. Müller's[2] case of lymphatic leukaemia was "complicated by a septicaemia and the count of white "cells rose from 180,000 to 400,000 per cubic milli- "metre, with a marked increase in the percentage of "polymorphonuclear cells. Here was a genuine "leucocytosis added to a leukaemia with the exception "of these two cases, all those hitherto published have "shown a marked progressive decrease in the total "number /

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[1] Cabot - Clin. Exam. of Blood p. 152.
[2] Müller - Deut. Archiv. fur. Klin. Med. 1892 Vol. 50 p.47

"number of leucocytes without any change in the per-
"centages of the different varieties in twelve, while
"the other five showed, like Müller's, an increased per-
"centage of the polymorphonuclear cells despite the
"decrease in the total leucocyte count. Various
"infections, miliary tuberculosis, pneumonia, grippe,
"erysipelas, abscess of kidney, septic lymph glands,
"alike decreased the leucocyte count."[1]

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[1] "1. Eisenlohr: Virchow's Archiv. Vol. 73 1 case
"2. Henck. " " Vol. 78 1 "
"3. Quincke: Ref. in Münch Med. Woch. No. 1890 1 "
"4. Stintzig: I bidem 1 "
"5. Ortner: Wien. Klin. Woch. 1890. p. 832 1 "
"6. Müller: Deut. Archiv. f. Klin. Med. 1891 Vol. 48, and 1892, Vol 50 2 cases
"7. Kovács: Wien. Klin. Woch. 1893 p. 701 1 case
"8. Fraenkel: Deut. Med. Woch. 1895, p.639. 2 cases
"9. Heubner: I bidem) (1 case
"10. Richter: I bidem) in discussing Fraenkel's cases (3 cases
"11. Freudenstein: Ref. by Fraenkel loc.cit. 1 case
"12. Zeissl: Wien. Klin. Woch. May 14th 1896 1 "
"13. Personal Observation. 1 "

Total 17 cases

"Goldschneider[1] found that by the injection of splenic "extract and other substances he could bring about a "similar diminution in the number of leucocytes, but "that, as in the case of intercurrent affections, this "diminution was not accompanied by an improvement in "the patient's condition and death followed as usual.

"It appears therefore that when an infection com- "plicates leukaemia we may have,

"1. No effect (see case of rheumatic fever as a com- " plication, just mentioned)

"2. A genuine leucocytosis on top, so to speak, of the " leukaemia with an increased percentage of poly- " morphonuclear cells.

"3. A decrease in the leucocyte count with or without " an increase in the polymorphonuclear cells. " This decrease is by for the most common result " and may go far below normal as death approaches."

INFLUENCE /

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[1]Goldschneider. Discussion of Fraenkel's article loc. cit.

INFLUENCE of FEVER on the BLOOD.

Maragliano[1] has shown, and it has since been proved by others, that the effect of fever is to contract the peripheral vessels causing thereby concentration of the blood and a necessary accompanying rise in the number of blood cells per cubic millimetre. When we also remember there is increased loss of water during fever we find in that another element tending to further concentration of the blood and tending to still further increase the blood count. Of course the blood cells also participate in the tissue destruction which accompanies any fever, but this anaemia is concealed by the concentration.

Now when the fever disappears either spontaneously or by the use of antipyretics, it is found that the peripheral vessels dilate resulting in a considerable fall of the blood corpuscles per cubic millimetre, aided also by the febrile destruction of corpuscles which is now apparent.

The /

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[1]Maragliano - Zeit. f. Klin. Med. Vols. 14 and 17.

The suddenness of the fall in the number of corpuscles is found to be proportional to the suddenness in the fall of temperature. As a rule, in enumerating the white blood corpuscle count in fevers, one finds a condition of leucocytosis but there are one or two outstanding exceptions which we shall briefly refer to.

TYPHOID /

TYPHOID FEVER.

Here the absence of any increase of the white cells and leucopenia in the late weeks are the most interesting points. Von Limbeck[1] notes the absence of leucocytosis in typhoid fever.

According to Hayem[2] the leucocyte count often falls below 2000 and, in referring to typhoid fever, he says "Cette diminution dans la production des éléments "du sang ne reste pas limitée aux haematies, elle porte "également sur les globules blancs."

Thayer's[3] figures are as follows :-

First	week	21 counts	6,984
Second	"	50 "	6,468
Third	"	40 "	6,260
Fourth	"	28 "	5,877
Fifth	"	16 "	6,621
Sixth	"	5 "	7,000

In the Massachusetts General Hospital[4] 293 cases were counted with the following results :-

Between /

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[1]Von Limbeck - Klinisches und Experimentelles über die entzündl. Leukocytose. Zeitschr. f. Heilk., Bd.X. 1890, S. 392

[2]Hayem - Du Sang, p.456

[3&4]Cabot - Clin. Exam. of Blood, p. 167

White corpuscles.

Between	1,000	and 2,000	=	7 cases
"	2,000	" 3,000	=	25 "
"	3,000	" 4,000	=	28 "
"	4,000	" 5,000	=	52 "
"	5,000	" 6,000	=	44 "
"	6,000	" 7,000	=	50 "
"	7,000	" 8,000	=	28 "
"	8,000	" 9,000	=	25 "
"	9,000	" 10,000	=	22 "
"	10,000	" 11,000	=	7 "
Over	11,000		=	4 "

292 cases

In an ordinary plain sailing case of typhoid there is no leucocytosis, but leucopenia more or less. If leucocytosis exists there is always some complication to account for it. Sadler[1] points out that leucocytosis indicates a complication with some suppurative disorder. Thus Cabot[2] gives examples of typhoid fever where the leucocytosis present was caused by a definite /

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[1] Sadler - Fortschritte der Medicin, Bd. IX. 1891
[2] Cabot - Clin. Exam. of the Blood, p.169

definite complication :-

		W.B.C
Perforation :-		
Case I.	(a) 5 days before perforation	8,300
	(b) At the time of perforation	24,000
Case II.	" "	18,500
Phlebitis :-		
Case I.	(a) Two days before onset	6,400
	(b) At time of onset	12,900
	(c) One week later	10,100
Case II.	(a) One week before onset	4,800
	(b) At time of onset	16,200
Otitis Media :-		
Case I.	(a) At entrance	5,300
	(b) Mastoid abscess	16,400
Case II.	(a) At entrance	8,400
	(b) Two weeks later after opening drum membrane (seroperulent discharge)	11,200
Case III.	(a) At entrance	7,320
	(b) Otitis	14,000

Rotch[1] gives the blood examination of two cases of /

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[1]Rotch - Hygienic and Med. Treatment of Children, Vol.I.p.371

of typhoid in children :-

Blood Examination - Wentworth.

Erythrocytes	4,602,500
Haemoglobin	60 per cent
Leucocytes	7,000

Blood Examination (Whitney & Wentworth).

Erythrocytes	5,496,250
Haemoglobin	64 per cent
Leucocytes	7,000
small mononuclear	14 per cent
large "	20 " "
polynuclear	66 " "

Osler[1] notes that the leucocytes diminish slightly throughout the course and reach the lowest point when convalescence is well established. He also points out how the absence of leucocytosis may be at times of real diagnostic value in distinguishing typhoid fever from various septic fevers and acute inflammatory processes, and how, when an acute inflammatory process occurs in typhoid fever, the leucocytes show an increase in the polynuclear forms which may be of great diagnostic moment as in perforation.

He /

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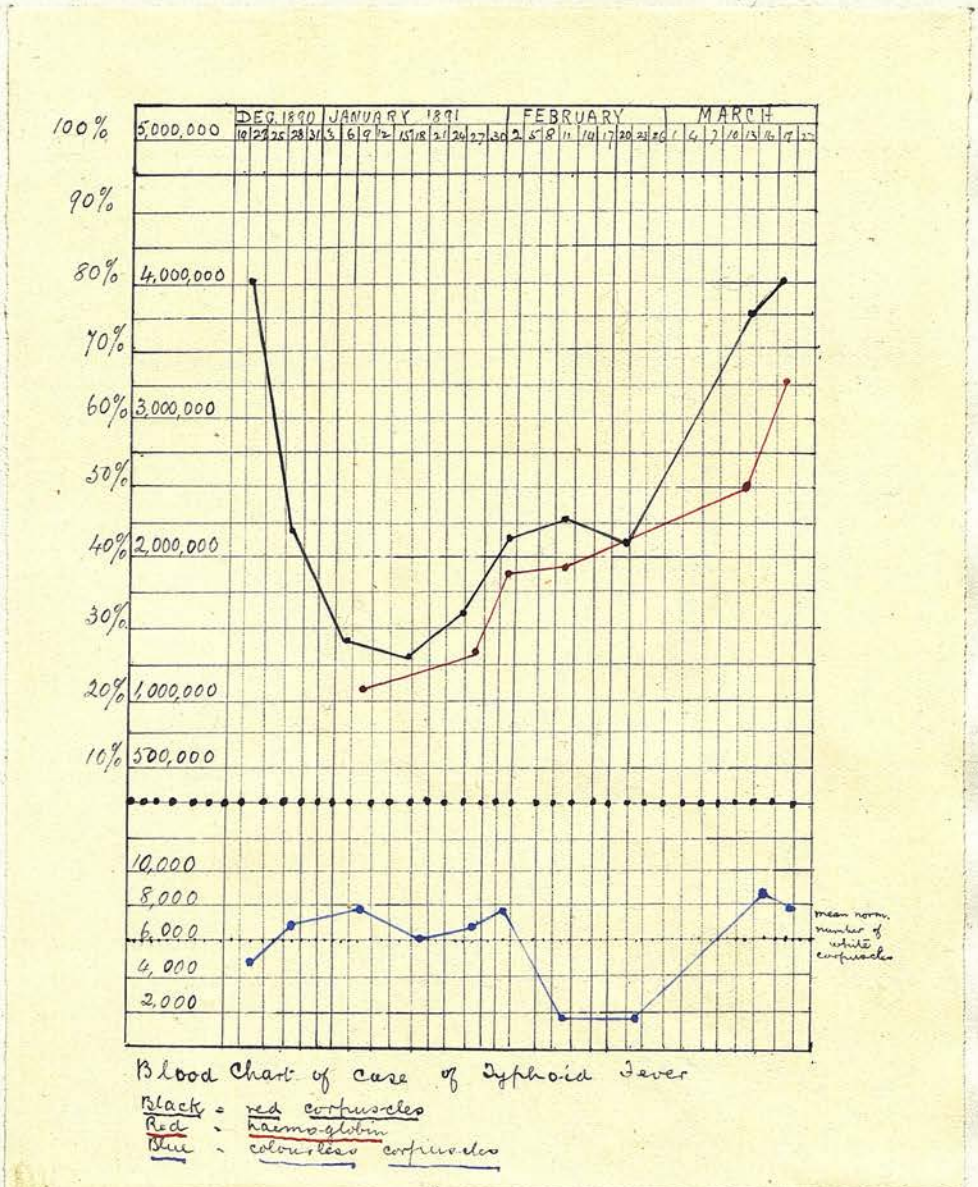
[1] Osler - Principles & Practice of Medicine p. 19.

He says that in typhoid the large mononuclear and transitional forms are increased while the polynuclear neutrophiles are diminished. The accompanying blood chart is taken from Osler to show the changes he refers to.

Blood Chart of Case of Typhoid Fever (Osler).



Qualitative /

QUALITATIVE CHANGES in the WHITE CORPUSCLES in TYPHOID FEVER.

All observers are agreed that the adult cells progressively diminish with a corresponding increase in the young cells, especially towards the end of the fever. The adult cells do not begin again to increase until after the fever has disappeared (from three to ten days after it according to Uskow[1]) and they do not seem to attain their normal percentage until about 10 weeks after. Thayer's[2] differential counts of them is as follows :-

2nd. week	5 counts	71.7 per cent	
3rd "	1 "	66.5 "	"
4th "	3 "	65.3 "	"
5th "	1 "	58.5 "	"
6th "	2 "	53.4 "	"

PNEUMONIA /

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[1]Uskow - Centralbl. f. d. Med. Wiss 1878, S. 499
[2]Thayer - Bulletin of Johns Hopkin's Hospital, Baltimore, Vol. IV, p. 30

P N E U M O N I A.

Leucocytosis is the rule in pneumonia but there are cases where no leucocytosis occurs and it is interesting to note the result of such cases.

Leucocytosis is such a constant condition in pneumonia that it has frequently been the means of establishing the diagnosis of a case where physical signs and symptoms were absent. Thus Cabot[1] records a case of Dr F.C.Shattuck's. "Sick for five days, yet "showing no signs of consolidation of the lung,the pres- "ence of a marked leucocytosis excluded typhoid, the "only other likely diagnosis and led Dr Shattuck to "treat the case as pneumonia, the wisdom of which course "was later demonstrated by the appearance of signs of "consolidation..... In cases of pneumonia occurring "in very old or very young people, in which the fever "and symptoms may be very slight, the presence of leu- "cocytosis may be the first thing to direct our atten- "tion to the lungs, dyspnoea and cough being absent."

The /

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[1] Cabot - Clin. of the Blood p.164.

The absence or presence of leucocytosis in pneumonia is of the utmost importance from the point of view of the prognosis. Where leucocytosis is absent in all except the mildest cases it renders the prognosis extremely grave, but on the other hand the presence of leucocytosis is no guarantee whatever of a favourable issue. To prove the above statement the experiences of the following men are submitted.

Halla[1] was the first to note the increase of leucocytes in pneumonia in a series of 14 cases. In 12 of these there was a leucocytosis, while in the remaining two the leucocytes were not increased and both patients died. He was the first to call attention to the fact that the absence of leucocytosis was of bad omen.

Hayem and Gilbert[2] remarked upon the typhoid character /

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1 Halla :-Prag. Zeitsch. f. Heilk Bd 1V, S. 198, 1883

2 Hayem and Gilbert :- Arch. Gen. d. Med. p. 257, 1884

character of these cases of pneumonia in which there is no leucocytosis.

[1]Kikodse states that leucocytosis is absent only in fatal cases. He believes that the leucocytosis begins before the lung is involved, that it runs parallel with the temperature and that the leucocytes decrease to a number below normal at the crisis in the temperature.

[2]Von Jaksch recognised the bad prognosis in cases of pneumonia without leucocytosis and thought that the fatal termination was due to this absence of leucocytosis. He therefore recommended the use of drugs which would produce an increase in the number of leucocytes such as antipyrin, pilocorpin etc., but such treatment proved ineffectual.

[3]Maragliano, on the other hand, does not think that leucocytosis is any guide to the prognosis in pneumonia. /

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[1]Kikodse :- Path. Anat. d. Blut. b. croup. Lungenentzündung. Inaug. diss. Petersburg 1890

[2]Von Jaksch :- Cb. f. Klin. Med. No. 5, 1892.

[3]Maragliano :- Berl. Klin. Woch. Nos. 36 & 51, 1891.

pneumonia.

[1] Rieder gives the results of his observations in 26 cases. He says a pseudo-crisis in pneumonia may be recognised by the fact that while the temperature may fall to normal there is no diminution in the number of leucocytes.

[2] Tchistovitch inoculated cultures of pneumococcus into rabbits and found leucocytosis present only in those cases which recovered. If he injected stronger culturesso as to kill the rabbit he found (like Rieder) leucocpenia.

[3] Ewing in 101 cases found leucocytosis absent in six and these six died. He concludes that 1:-The greater the amount of lung involved the greater the leucocytosis.

2 :- The amount of leucocytosis corresponds to the 'systemic reaction' the latter being judged by the temperature, pulse, and general condition of the patient i.e. in fatal cases there is no leucocytosis and vice versa /

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1 Rieder :- Beit. z. Kennt.d. Leucocytose, Leipzig, 1892.
2 Tchistovitch :- Ann.d. l'Inst. Pasteur Vol 5 p.7
3 Ewing :- N.Y. Med. Jour. Dec. 16, 1893.

versa.

3 :- A well marked leucocytosis indicates a severe infection, a low leucocytosis is unfavourable, and leucocpenia makes the prognosis very grave.

Billings[1] reports twenty-two cases of pneumonia ten of which died. In six of these cases there was absence of leucocytosis at some period of the disease but the continuous absence was the exception and not the rule in his cases. He therefore concludes that the presence or absence of leucocytosis only shows the virulence of the bacterial poison. It is not a criterion of absolute prognosis. He gives the following interesting chart to show the coincident drop in the fever and in the number of leucocytes.

In /

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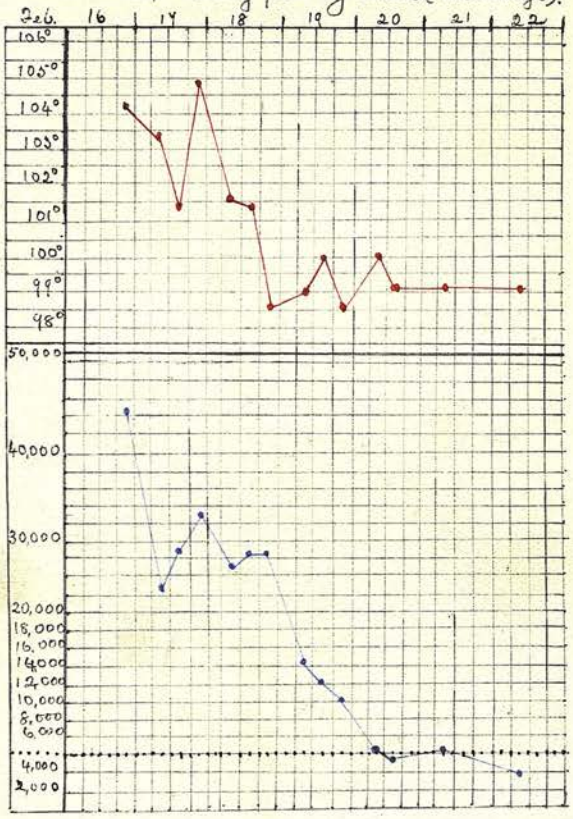
1 Billings :- J.H.H. **Bulletin** Vol V p. 105.

Pneumonia, showing fall by crisis (Billings).



The upper chart shows the course of the temperature, the lower that of the leucocytes (Billings).

In the Massachusetts Hospital[o] 229 cases were studied, 18 of these presented no leucocytosis at any time, and of these 18, 17 died and the other one seemed moribund but finally recovered.

[1]Rotch draws attention to the fact that Von Limbeck's experiments on dogs went to show that Friedlander's bacillus caused a marked leucocytosis whereas Fraenkel's diplococcus caused scarcely any.

[2]Osler also remarks that a point of considerable prognostic importance is that in malignant pneumonia the leucocytosis may be absent and in any case the continuous absence may be regarded as an unfavourable sign.

Tuberculosis /

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[o]Cabot :- Clin. Exam. of the Blood. p. 165.

[1]Rotch :- Hygenic and Med. Treat. of Children Vol.1. p. 372.

[2]Osler :- Principles and Practice of Medicine p. 121.

TUBERCULOSIS.

In tuberculosis the most striking fact is the absence of changes in the white or red corpuscles. So long as the infection remains unmixed the white cells are not increased whether bones, serous membranes or internal organs be affected.

In the lungs and kidneys we frequently find leucocytosis because of the great opportunities for secondary infection and septicaemia in these organs.

Psoas abscesses before being opened often contain only tubercle bacilli and the blood in these cases shows no considerable changes.

Just as there is no leucocytosis in pure tuberculous affections, so there is, as a rule no leucopenia and in consequence they hardly come under the subject we are discussing. I shall therefore merely submit a few tables to show the leucocyte count in the following tubercular affections.

I. PHTHISIS.

When phthisis is incipient the leucocytes are normal /

normal except after haemoptysis when they are increased. This is only what one might expect as it is according to the usual law of post-haemorrhagic leucocytosis.

When cavities are present there is leucocytosis ; in fact this rule is so general that the absence of leucocytosis proves the absence of any cavity of considerable size.

The following table is taken from Cabot' showing cases of phthisis without leucocytosis.

PHTHISIS /

Cabot' Clin. Exam. of Blood page 220.

PHTHISIS without LEUCOCYTOSIS.

No.	Sex	Age	Duration	Red Cells	White Cells	Per cent haemo-globin	Remarks.
1	M.	48	4 years	?	6,200	?	Fibroid phthisis, extensive, died next day; no bacilli.
2	M.	41	3 months	?	6,500	?	Moderate bilateral signs.
3	M.	46	2 months	4,552,000	8,200	105	Dilated stomach also; few râles only at apices
4	M.	35	2 "	5,072,000	5,200	78	May 5th. Signs very slight.
				4,176,000	8,800	60	May 14th. Two days after a haemorrhage of twenty ounces.
				4,224,000	9,200	58	May 21st.
5	M.	22	2 weeks	5,500,000	8,300	86	
6	M.	31	1 year	?	6,700	---	Tubercular enteritis too. Signs slight.
7	F.	35	8 months	---------	5,700	---	Pleurisy. Signs slight.
8	M.	27	3 "	3,600,000	8,500	?	
9	M.	53	1 "	?	9,000	?	
10	M.	33	9 "	4,230,000	7,200	---	Intestinal tuberculosis also.
11	M.	27	few wks	4,964,000	9,000	?	
12	F.	26	8 months	3,088,000	5,200	?	
13	M.	20	2 weeks	5,300,000	9,500	---	During haemorrhage.
14	M.	56	3 months	?	6,400	?	
15	M.	31	5 weeks	4,400,000	6,400		
16	F.	27	4 weeks	---------	9,700	---	Signs extensive unilateral. No fever. Phlebitis (saphenous)
17	F.	26	1 month	3,304,000	6,200	48	Intestinal tuberculosis (?) also. Signs very slight.
18	M.	21	?	---------	5,500	?	
19	M.	51	1 year	4,664,000	4,800	?	With general miliary tuberculosis.
20	F.	?	?	4,284,000	9,750	58	
21	F.	?	6 months	4,400,000	9,500	63	
22	F.	?	?	3,986,000	5,500	68	
23	?	?	?	3,336,000	4,500	55	
24	M.	23	3 weeks	5,380,000	8,250	83	No consolidation. Haemoptysis.
25	M.	37	18 mos.	5,080,000	8,000	60	Signs slight.
26	F.	32	6 months	4,120,000	10,000	48	Signs moderate.
27	M.	56	"years"	?	9,600	?	Fibroid phthisis.
28	M.	50	10 weeks	?	5,400	?	Signs slight.
29	M.	31	4 years	?	6,400	?	Fibroid phthisis.
30	M.	30	8 months	5,864,000	7,200	66	No consolidation.
31	F.	19	12 weeks	?	7,400	?	Signs slight.
32	F.	20	?	2,732,000	3,800	19	

II. BONE TUBERCULOSIS.

Dane[1] has made the most exhaustive study of the blood in this condition.

He examined 41 cases and whenever abscesses appeared cultures were taken when the abscess was opened and again later on, and the coincidence of low counts with absence of pyogenic cocci, and with high counts of secondary pyogenic infection, is most interesting. He tabulates the results of his work as follows:-

1. High leucocyte counts especially in hip disease, point to the probability that there is, or soon will be, abscess formation ; but low counts do not preclude the presence of abscess, especially in long-standing cases.
2. If abscess is present, a low count of white cells indicates the absence of secondary pyogenic infection (proved by cultures).
3. Cases of traumatic origin are generally accompanied by a high leucocyte count .
4. The leucocyte count bears no direct relation to the temperature ; one case with 30,980 leucocytes (five /

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[1] Dane. Boston Med. and Surg. Jour. May 28th 1896.

(five year old girl) showed a temperature of only 99.4° at the time of the count. In another girl of three years, whose temperature ranged between 101° and 104°, the leucocytes were only 7,224 or sub-normal for that age.

5. Cases where at the primary operation the pus proved sterile show an increase in the leucocyte count when the wound becomes infected with pyogenic organisms.

6. The red cells are rarely diminished but the haemoglobin is usually relatively low (mild secondary anaemia in these cases). This absence of a diminution in the red cells in these cases is the more remarkable because they were almost all in young children whose blood is much more sensitive to any deleterious influence than that of adults.

Cabot[1] gives the following cases from the Massachusetts Hospital

Case /

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[1] Cabot Clin. Exam. of the Blood P. 225

Case	Diagnosis	Red Cells	White Cells	Per Cent Haemo-globin
1	Tubercular knee joint	6,472,000	9,400	63
2	" "	2,704,000	8,000	?
3	Metatarsal tuberculosis	4,650,000	6,500	61
4	Tubercular rib	5,016,000	5,800	73

III /

III. ACUTE MILEARY TUBERCULOSIS.

Normal or subnormal counts are the rule in this condition. If leucocytosis should occur, as it occasionally does, we may infer that there is some acute suppurative process super added to raise the leucocyte count. Warthin[1] reports a case in which he made over thirty blood counts and the leucocyte counts were as follows :-

Day	Hour	Leucocytes	Remarks
December 6th	10 a.m.	3,500	
" 12th	8 a.m.	5,000	
" 18th	5 p.m.	3,500	
" 22nd	10 a.m.	5,625	
" 22nd	11-30 a.m.	4,725	
" 22nd	3 p.m.	5,000	
" 22nd	5 p.m.	3,125	
" 24th	8-30 a.m.	3,750	
" 24th	11-30 a.m.	3,750	
" 24th	2 p.m.	2,500	
" 24th	4-30 p.m.	2,500	
" 25th	8 a.m.	1,875	
" 28th	5-30 p.m.	3,750	Red cells 4,125,000
" 29th	10 a.m.	1,250	Haemoglobin 80 %
" 29th	2 p.m.	1,250	
" 29th	5-30 p.m.	3,750	
" 31st	12 m.	1,250	
" 31st	6 p.m.	2,500	
January 2nd	11 a.m.	1,250	
" 2nd	5 p.m.	2,500	
" 3rd	2-30 p.m.	600	Severe chill, count
" 5th	8-30 a.m.	3,750	repeated several
" 5 /			times.

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[1] Warthin - Medical News 1895.

Day		Hour		Leucocytes	Remarks
January	5	11	a.m.	3,137	
"	5	4	p.m.	8,125	moribund.
"	6	9	a.m.	1,000	
"	6	10	a.m.	5,625	
"	6	11	a.m.	2,500	
"	6	12	m.	5,625	
"	6	12-50	p.m.	Death	

In another case he found also a subnormal count.

Cabot[1] illustrates the point by the following cases from the Massachusetts Hospital records.

No. /

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[1] Cabot :- Clin. Exam of the blood p. 227

No.	Age	Sex	Red Cells	White Cells	Per cent haemoglobin.	Remarks.
1	18	M		3,600		Autopsy
2	40	M		3,750		"
3	14	F	3,720,000	4,400	45	"
4	51	M	4,664,000	4,800		" phthisis (chronic) also
5	12	F		6,100		"
6	37	F		7,800 7,200		" May 14th " May 22nd
7	36	M		7,600		" Phthisis (healed) also
8	30	M		9,257 9,457		" April 18th " April 20th
9	Adult	M	5,237,000	10,000		"
10	22	M		12,700		" Phthisis with cavities also
11	36	M		23,000		" Hypertrophic cirrhosis also

IV. TUBERCULOSIS of the SEROUS MEMBRANES.

A. Tubercular Peritonitis.

Leucopenia and leucocytosis are both met with here as shown by Cabot[1] in the following table from the Massachusetts Hospital records :-

No.	Age	Sex	Red Cells	White Cells	Per cent haemoglobin	Remarks.
1	26	F.	3,120,000	2,240	58	
2	24	M.	5,360,000	3,800	---	Jan. 6th 1896.
			5,760,000	5,600	85	April 13th 1896.
3	25	F.	---------	3,900	---	Starting apparently from tubercular tube.
4	Adult	M.	---------	5,000	---	December 18th 1895.
			4,560,000	8,250	76	January 10th 1896.
5	30	F.	---------	5,183	---	Starting apparently from tubercular tube.
6	20	F.	5,936,000	5,400		
7	44	M.	2,974,000	5,530	---	Pleuritic effusion also.
8	16	F.	3,840,000	6,000		
9	33	F.	4,000,000	6,000		
10	50	F.	5,240,000	6,400	---	Glandular tuberculosis also.
11	27	M.	---------	6,700	---	May 22nd 1896.
				7,000	---	May 30th 1896
12	Adult	M.	5,560,000	6,800		
13	44	F.	---------	7,000	73	
14	17	M.	4,904,000	8,000	75	Tapped; one hundred and six ounces serous fluid obtained.
15	32	F.	---------	8,200		
16	20	F.	4,200,000	8,500	58	Starting apparently from tubercular tube.
17	Adult	F.	---------	no increase		
18	50	F.	4,600,000	10,000	50	
19	Adult	M.	5,200,000	10,000		
20	Adult	F.	4,816,000	11,200		
21	21	F.	3,550,000	11,500	65	

[1]Cabot. Clin. Exam. of Blood, p.228.

L E P R O S Y.

Winiarski[1] gives the result of examination of seventeen cases.

There was no increase of the leucocytes in any case and in four they were subnormal. The percentage of young cells is high.

C A N C E R.

The only circumstances under which we find leucopenia in cancer are where there is a tumour of the gullet causing stricture but not extending to other tissues. The leucopenia here is due to the starvation consequent upon the stricture.

Hayem[2] and Alexander[3] give some very interesting statistics to show how an operation for cancer has the effect of reducing considerably the number of leucocytes. Leucocytosis is the constant accompaniment of cancer except, as stated above, in cancer causing stricture of the oesophagus :-

1° /

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[1]Winiarski :- Petersburger medicinische Wochenschrift 1892 p. 365.

[2]Hayem :- Du Sang p. 948.

[3]Alexander, G. :- De la leucocytose dans les cancers.

1° Squirrhe du sein

Avant l'opération	21,700
Cinq semaines après l'opération (plaie non complètement cicatrisée)	10,000
Plaie complètement cicatrisée	6,200
Sept mois après l'opération	8,900

The growth recurred some months later and leucocytosis was again present.

2° Squirrhe du sein.

Avant l'opération	(11,500 (11,450
Après l'opération	(8,500 (6,200

3° Squirrhe du sein

Avant l'opération	(11,000 (12,400
Après cicatrisation	8,400

4° /

4° Encéphaloïde du sein

Avant l'opération	10,000
Cicatrisation presque absolument complète	9,000

5° Lymphosarcome de l'aisselle

Avant l'opération	11,700
Après Cicatrisation presque complète	9,000

6° Ostéosarcome du bras

Avant l'opération	11,250
Après Cicatrisation presque complète	5,270

Hayem considers that by watching the leucocyte count we can predict the coming of a recurrence before any physical signs are present. This he did in Case I.

G R I P P E

G R I P P E.

Very little attention has been paid to the condition of the blood in this disease.

Cabot[1] is the only man who has done anything in this direction and gives the results of his work in the following table of 30 cases

G R I P P E /

Cabot - Clinical Examination of the Blood p. 188.

No.	Age	Sex	Red Cells	White Cells	Per cent haemoglobin	Remarks.
1	37	M.	---------	14,200	---	13th. coarse râles in both chests; chlorides diminished
				9,200		15th.
2	Adult	M.	4,840,000	14,400	---	And bronchitis.
3	35	M.	5,111,200	12,800	97	Pharyngitis, cough, considerable sputa, constipated.
4	36	F.	4,771,700	12,100	---	With pharyngitis.
5	Adult	F.	4,644,000	12,000	62	
6	32	F.	3,850,000	11,500	85	
7	27	F.	---------	11,100	---	
8	50	F.	---------	10,900	---	Fine râles and increased voice sounds.
9	19	F.	5,720,000	10,400	---	11th. hysteria (?) temperature 105°.
			5,192,000	7,600	57	27th, 30th. Chill, cyanosis, weak rapid pulse; 82 per cent of adult cells; autopsy.
10	19	M.	---------	10,300		
11	Adult	M.	4,950,000	10,000		
12	35	M.	---------	9,900		
13	40	M.	5,904,000	9,400	---	Sub-acute laryngitis.
14	--	F.	4,860,000	9.200		
15	Adult	F.	4,900,000	9,000		
16	31	M.	5,310,000	9,000		
17	32	F.	4,200,000	8,000	25	
18	23	M.	5,500,000	7,400		
19	25	M.	5,616,000	6,800		
20	Adult	M.	4,240,000	6,800	---	With dry pleurisy.
21	42	M.	5,856,000	6,000		
22	24	M.	4,952,000	6,000		
23	Adult	M.	4,559,000	5,600		
24	30	M.	---------	5,500		
25	Adult	M.	5,600,000	4,600		
26	44	M.	5,685,000	4,550		
27	31	M.	5,424,000	4,000		
28	Adult	M.	5,260,000	3,500		
29	30	F.	5,488,000	3,144		
30	--	-	---------	2,600	---	Temperature 104° ten days after a head operation; question of meningitis.

From the above table it will be seen that the leucocytes are either normal or diminished in three quarters of the cases.

Only seven of the thirty cases showed leucocytosis and in one or more of these some complication was very possibly present, which is of importance in excluding pneumonia and local inflammatory conditions.

LEUCOPENIA /

TOXIC LEUCOPENIA.

Having now discussed the conditions in which one finds leucopenia either constantly or occasionally, it may prove to be not uninteresting if we direct our attention to the artificial reduction of the number of leucocytes by injecting different substances into the circulation.

[1]Ewing has conducted a large number of experiments on rabbits in order to determine the possible changes in the general distribution of leucocytes that may occur after intravenous injection of bacteria, and he examined specimens of blood from the central vessels as well as from the peripheral veins, from which the estimation of leucocytosis is usually made. The organs were then examined microscopically to locate, if possible, the lodging-place of the leucocytes found to disappear from the circulating blood after bacterial injections.

After drawing the specimens of blood, the liver, lungs, heart, kidney, spleen and one femur were removed and hardened for microscopical examination in various agents.

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[1]Ewing, N.Y.Med.Jour., Vol. LXI, p.258.

The order of the experiments was as follows : -

First the normal number of leucocytes in the central vessels was determined in rabbits killed by breaking up the medulla, as no sufficient data on this question could be found. Following this the same vessels were examined at intervals of five minutes to two hours, after injecting into the middle ear vein 0.5 to 1.5 cubic centimetres of a three-weeks-old broth culture of Bacillus pyocyaneus. The injection of this medium was found to reduce the number of leucocytes in the opposite ear vein progressively for at least three hours. Finally, in view of the very great disturbance of the circulation likely to follow destruction of the medulla and immediate failure of respiration, the effect of deep ether narcosis on the blood of the large jugular vein was determined and all these experiments were repeated on rabbits thus anaesthetized. To determine the effect of ether narcosis, the rabbit was rapidly bound to a frame and the internal jugular vein exposed by a few short incisions. The specimen of blood was then drawn from the vein and the animal immediately released. By completing this operation within ten minutes, the effects of cooling and exhaustion were practically avoided. At the end

of /

of a half hour the same animal was deeply etherized and specimens were examined from the same vessel.

Ewing's results were as follows : -

EFFECT of ETHER on LEUCOCYTES in the JUGULAR VEIN :

LEUCOCYTES per Cubic Millimetre:

Number.	Normal.	Fully Etherized.
1 - - - -	6,250 6,500	7,000 7,000
2 - - - -	7,000 7,000	6,000 7,000
3 - - - -	6,000 6,250	6,500 7,000

LEUCOCYTES per CUBIC MILLIMETRE in BLOOD of NORMAL VEINS :

I. Examined after Rupture of Medulla :

Ear	Portal	Hepatic	Small Mesenteric	Splenic	Superior Vena Cava	Inferior Vena Cava
10,000	10,000	7,500	8,500	...	7,500	.....
9,800	...	4,500	9,250	...	...	.....
10,500	...	4,500	12,000	...	6,000	.....
10,000	9,000	9,000	...	9,000	6,500	.....
11,000	13,000	13,500	...	12,000	8,000	.....
12,000	13,000	7,000	...	13,000	6,000	6,800
12,000	...	10,500	9,000	14,000	7,000	.....
11,500	...	...	12,000	13,500	6,000	.....
11,000	...	10,000	10,500	12,500	6,000	5,500
11,250	...	12,500	7,000	12,000	5,000	.....

II. /

II. Examined under Ether :

Ear	Portal	Hepatic	Small Mesenteric	Splenic	Superior Vena Cava	Inferior Vena Cava
8,000	...	...	10,000	11,500	5,500	7,000
7,000	...	...	9,500	...	...	5,000
9,000	...	9,500	10,500	11,000	5,000	...
12,000	...	7,500	...	...	...	...
8,000	...	4,500	...	...	...	...
6,500	...	3,500	...	...	...	...

LEUCOCYTES per CUBIC MILLIMETRE in BLOOD of VEINS after INJECTION of BACILLUS PYOCYANEUS :

I. After Rupture of Medulla :

Ear Vein before Injections	Ear Vein after Injections	Hepatic	Mesenteric	Splenic	Superior vena cava	Inferior vena cava	Puncture of Liver	Time of Examination after injection.
12,000	3,000	3,000	4,000	6,500	2,500	...	...	2 hours.
12,500	2,000	1,500	3,000	5,500	1,750	1,500	...	"
7,500	3,000	5,500	2,500	5,500	2,250	4,000	...	"
10,000	500 500	1,000	1,000	2,000	1,250	2,000	...	"
10,000	15,000	...	2,500	...	2,000	...	...	"

II. /

II. Examined under Ether :

Ear Vein before Injections	Ear Vein after Injections	Hepatic	Mesenteric	Splenic	Superior vena cava	Inferior vena cava	Puncture of Liver	Time of Examination after Injection.
...	...	...	...	...	...	...	2,500	10 mins.
8,000	5,000	...	3,500	2,500	...	3,500	3,000	15 "
10,000	4,500	...	3,000	2,500	...	2,250	3,500	15 to 20 "
8,000	2,500	...	4,000	8,000	...	3,250	10,000	30 mins; liver puncture after death.
10,000	5,250	...	...	4,500	...	...	3,000	30 mins.
7,000	2,000	...	2,000	2,250	1,500	...	2,500	30 "
7,000	2,000	...	2,000	1,000	...	1,000	1,250	30 "
7,000	2,500	...	2,000	1,250	...	2,000	1,000	1 h.30 mins.
7,500	500	...	1,000	...	...	...	...	2 h.20 mins.

LEUCOCYTES per CUBIC MILLIMETRE in BLOOD of NORMAL ARTERIES :

I. After Rupture of Medulla :

Ear Vein	Small Mesenteric	Splenic	Aorta		Renal
			Arch.	Abdominal	
10,000	3,500	...	3,000	5,000	...
7,500	...	...	2,500	2,500	...

II. /

II. Examined under Ether:

Ear Vein	Small Mesenteric	Splenic	Aorta. Arch.	Aorta. Abdominal	Renal
12,000	4,500	7,500	4,500	...	...
8,000	8,500	5,250	4,000	5,000	5,000
8,000	8,000	6,500	3,000	3,500	4,500
6,500	7,000	7,000	...	...	9,000

LEUCOCYTES per CUBIC MILLIMETRE in BLOOD of ARTERIES after INJECTIONS :

I. After Rupture of Medulla :

Ear Vein before Injection	Ear Vein after Injection	Small Mesenteric	Splenic	Aorta Arch	Aorta Abdominal	Large Mesenteric	Renal	Time
8,500	2,500	2,500	1,500	1,500	2,000	...	...	1 Hour
10,000	1,500	1,500	1,750	1,750	1,750	...	...	2 Hours.

II. Examined under Ether :

Ear Vein before Injection	Ear Vein after Injection	Small Mesenteric	Splenic	Aorta Arch	Aorta Abdominal	Large Mesenteric	Renal	Time
8,000	4,500	...	1,250	...	...	1,000	1,500	10 min.
12,500	5,000	2,000	1,500	...	2,000	...	1,500	25 min.
10,000	5,000	...	2,500	...	...	2,000	...	30 min.
7,500	500	2,000	...	2,000	2,000	{500 {250	...	2 h.20 m.

From /

From the above tables we see that during the stage of leucopenia there is a uniform diminution of the leucocytes in all parts of the arterial and venous circulation. Kanthack[1] also states that the immediate effect of injecting physiological or bacterial poisons into the circulation is a marked decrease in the number of leucocytes, which is rapid and sudden, a fact described by many authors besides Löwitt. Among the substances used are pepsine, peptone, leech extract, nucleine, albumose, curare, pyocyanine, tuberculin, and the toxines of many species of bacteria and also snake venom. Kanthack[2] says that it may therefore be stated as an absolute law that the animal body reacts to a vascular intoxication by an initial destruction of leucocytes - a leucolysis, to use Löwitt's term, or a hypoleucocytosis, to borrow from a bad and inadequate French terminology. The most striking effects are those obtained with curare, which may produce all but a total disappearance of leucocytes from the blood.

In connection with these experiments he quotes the names of Löwitt, Rieder, von Limbeck, Römer, Hankin, Hardy, Kanthack, Massart, Bordet, Demoor and Chateney as /

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1 & 2. Kanthack : - The Histological Changes of Blood in Diseased Conditions - Manchester Medical Chronicle, Vo. I, 1894, p.333.

as being by no means an exhaustive list, but sufficient to show a uniformity in results.

Sherrington[1] finds that on producing local inflammation in cats, without the use of bacterial poisons, the immediate effect again is a diminution of the leucocytes in the circulating blood and that previous to recovery from such intoxications an increase in the number of leucocytes always takes place.

Hence we can understand how it is that in such a disease as pneumonia - a process comparable with artificial infection or intoxication - a well-marked leucocytosis always ushers in the crisis or recovery, or, at any rate, is a most favourable sign of great prognostic value. This is of still more interest when we remember that experiments go to show that inoculation of guinea-pigs with pathogenic organisms is followed by a diminution in the number of leucocytes, which gives way to a leucocytosis if the animal recovers and that in immunised animals the initial diminution is absent, leucocytosis making its appearance at once as a result of the inoculation. And so in pneumonia /

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1. Sherrington:- Note on some changes in the Blood of the General Circulation consequent upon certain Inflammations of an acute Local Character - Proc. of the Royal Society, Vol.LV, No.332, 1894.

pneumonia the absence of leucocytosis is a bad sign.

DESTINATION of the LEUCOCYTES in LEUCOPENIA.

The next and final question that one naturally asks is "What is the destination of the leucocytes in leucopenia ?"

Wyssokowitsch[1] found that when he injected bacteria into the circulating blood they rapidly disappeared and were to be found by Gram's stain in the lumen of the capillaries and in the endothelial and fixed connective-tissue cells of the liver, spleen and kidneys. He says, however, that the leucocytes take no part in the process of transfer.

Werigo[2], in 1892, found that in the capillaries of the liver, spleen and kidneys there was a large increase of leucocytes within a few minutes after intravenous injection of bacteria. These leucocytes or phagocytes were apparently in the act of transporting bacteria to the endothelial cells of the hepatic capillaries. In many cases the leucocytes were so abundant as to form minute emboli in the capillaries.

Similar /

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1. Wyssokowitsch:- Zeitschrift für Hygiene Bd I
2. Werigo:- Annal.de l'Institut Pasteur,1892.

Similar appearances, but in a less marked degree, were seen in the spleen and kidney. He also described the normal flat endothelial cells of the hepatic capillaries as much swollen, often partly occluding the lumen of the capillary, sending out protoplasmic processes to entangle the passing leucocytes. One or several leucocytes were sometimes seen completely englobed by the endothelial cells, forming a lenticular giant cell, the nuclei of which were strung along the capillary wall.

Ewing[1] in his experiments hardened imbedded and cut sections of the tissues, examining the organs of normal rabbits as a control. In the normal livers he found the capillaries to present all the appearances described above by Werigo, except thrombi in the vessels and bacteria in the cells. Many of the endothelial cells were quite flat, their bodies invisible and their nuclei projecting characteristically into the lumen of the capillary. Many others, however, were much thicker, occupying a large part of the capillary lumen, containing often pigment granules, apparently sending processes out into the capillaries.

All /

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1. Ewing : - N.Y.Med.Jour., March 2, 1895.

All stages of the so-called giant cells were seen, from a single well-defined leucocyte adherent to an endothelial cell to a long protoplasmic mass containing half-a-dozen nuclei. These appearances were too uniform and distinct to be regarded as artifacts, and were seen in every one of the nine, apparently normal, cases examined.

On comparing sections of normal livers with those of the animals killed after injection of bacteria, it was not easy to convince one's self that there was any increase in the number of leucocytes in the capillaries. Only once was such an increase unmistakable, when numerous small thrombi were found, each containing twenty to a hundred polynuclear leucocytes. But such thrombi having occured once in twenty cases examined, might reasonably be rejected as evidence of an invariable increase of leucocytes.

The swelling of the endothelial cells seemed more marked and more frequent than in the normal livers.

A comparison of the general appearance of the liver tissue before and after injection failing to give satisfactory evidence of a uniform increase of leucocytes /

leucocytes, Ewing decided to make a count of their numbers in the cubic millimetre of hardened tissue. According to the subjoined tables it will be seen that, with this method of estimate, there was a steady increase of leucocytes in the hepatic capillaries for at least two hours after the injection of Bacillus Pyocyaneus into the ear vein. In four instances two cubic centimetres of the sediment from a three-days-old broth culture of Bacillus Anthracis were injected, instead of the smaller quantity of Bacillus pyocyaneus.

LEUCOCYTES per CUBIC MILLIMETRE of LIVER TISSUE :

I. Normal Livers :

Ear vein before Injection	Ear vein after Injection	Leucocytes per Cubic Millimetre	Injection	Time of Examination after Injection.
7,500	...	23,000	...	...
12,000	...	12,500	...	...
8,000	...	20,000	...	...
8,000	...	16,000	...	...
6,500	...	20,000	...	...
7,000	...	10,200	...	...
8,500	...	12,600	...	...
8,000	...	19,600	...	...
11,000	...	22,800	...	...

II. /

II. After Injections :

Ear vein before Injection	Ear vein after Injection	Leucocytes per Cubic Millimetre	Injection	Time of Examination after Injection.
...	...	33,500	Anthrax	2 min.
...	...	35,000	"	6 min.
8,000	4,500	38,000	Pyocyaneus	7 m; thrombi.
8,000	4,500	34,000	"	10 min.
...	...	42,500	Anthrax	20 min.
8,000	5,000	29,400	Pyocyaneus	15 min.
12,500	5,000	26,600	"	25 min.
10,000	4,500	34,000	"	30 min.
7,000	2,000	35,000	"	30 min.
8,000	2,500	37,000	"	30 min.
10,000	5,000	51,000	"	30 min.
7,000	2,500	51,500	"	1 h.30 min.
8,500	3,000	58,000	"	1 h.30 min.
12,000	3,000	57,000	"	2 hours.
12,500	2,000	55,000	"	2 hours.
7,500	3,000	41,000	.....	2 hours.

From a general survey of sections from the lungs it appeared probable that the pulmonary capillaries contained many more leucocytes after the injections. The injections of Bacillus Anthracis affected the lungs more powerfully than did Bacillus Pyocyaneus, the former producing many minute thrombi in the distended capillaries. In the capillary endothelium no changes could be discerned as were constantly found in the liver : -

LEUCOCYTES /

LEUCOCYTES per CUBIC MILLIMETRE of LUNG TISSUE :

I. Normal Lung :

Ear vein before Injection	Ear vein after Injection	Leucocytes per Cubic Millimetre	Injection	Time of Examination.
7,000	...	40,600	...	...
8,000	...	42,000	...	...
8,000	...	37,800	...	...
11,000	...	41,000	...	...

II. Lungs after Injection :

Ear vein before Injection	Ear vein after Injection	Leucocytes per Cubic Millimetre	Injection	Time of Examination.
...	...	98,000	Anthrax	6 m, thrombi.
...	...	111,400	"	20 m, thrombi.
8,000	5,000	42,000	Pyocyaneus	15 min.
12,000	5,000	85,000	"	25 min.

In the kidney no changes could be discovered in the endothelial or fixed connective tissue cells, capillary vessels, Malpighian tufts or larger arteries or veins.

The multinuclear leucocytes were counted in 20 Malpighian tufts in each of five normal kidneys and in five cases after injection, with the following results : -

MULTINUCLEAR /

MULTINUCLEAR LEUCOCYTES in MALPIGHIAN TUFTS of KIDNEYS:

I. Normal Kidneys :

Ear vein before Injection	Ear vein after Injection	Leucocytes in Twenty Tufts	Injection	Time of Examination.
8,000	...	28	...	...
6,500	...	27	...	...
8,000	...	36	...	...
7,000	...	24	...	...
7,500	...	26	...	...

II. After Injections :

Ear vein before Injection	Ear vein after Injection	Leucocytes in Twenty Tufts	Injection	Time of Examination.
8,000	4,500	18	Pyocyaneus	10 min.
8,000	5,000	12	"	15 min.
12,000	5,000	18	"	20 min.
...	....	26	Anthrax	20 min.
7,000	2,500	30	Pyocyaneus	90 min.

In the marrow of the femur the leucocytes in the capillaries were often slightly increased in numbers, and rather more of the large uninuclear elements of the marrow appeared to be free in the circulation, but the extent and constancy of the changes were not very manifest. The examination of the spleen did not give convincing evidence either for or against an increase /

increase of leucocytes, although pulp cells, endothelial cells and sections of blood in vessels were carefully compared. The anaemic condition of the spleen found after the injection of bacteria must stand as strong presumptive evidence against any immediate increase of leucocytes in this organ.

LEUCOCYTOLYSIS : Most investigators have failed to find any trace of actual destruction of leucocytes in the blood after injections of bacterial products, and most are of opinion that the blood plates are not the result of disintegration of the leucocytes.

Among those who maintain that actual destruction of leucocytes is a factor in their disappearance in leucopenia are Löwitt, Roemer, S.S.Botkin, Holtzmann, and E. Botkin.[1] Those of the opposite opinion are Schulz, Rieder, Werigo, Medwedeff, Goldscheider and Jacob.[2] Since the publication of E. Botkin's paper on the solubility of leucocytes in peptone there is little doubt but that the injection of bacterial products directly into the circulation may destroy a considerable number of leucocytes.

Botkin /

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1. Botkin.E. :- Virchow's Archiv. Vol.CXXXVII,No.3,1894.
2. Goldscheider u.Jacob:- Zeitschr. f. Klin. Med. Bd. XXV, No.5, 1894.

Botkin treated pus with solutions of peptone and was able to follow, under the microscope, the changes that occurred in the leucocytes; they became translucent, finally invisible, while the nuclei lost their colour and gradually fell to pieces. In twenty-four hours eighty per cent of the leucocytes in the mixture had disappeared.

In Ewing's experiments he constantly found, after the injections, granular particles in the blood which might equally well have been regarded as deformed blood plates or as fragments of the nuclei of leucocytes. These granules were more abundant if the blood was allowed to stand in the mixer for an hour. In such specimens fragmentation and complete solution of the protoplasm of leucocytes could be plainly followed, while the nuclei, more difficult of solution, were seen to break up into irregular, faintly stained granules. At the end of two hours a diminution in the number of leucocytes was regularly noted. After four hours the diminution became marked, and in some specimens examined eighteen months after drawing, it was impossible to find a single leucocyte among the clumps /

clumps of developing bacilli. No such changes occurred in the blood drawn from healthy rabbits before injection.

Ewingl summarises his results thus : -

1. Within eight minutes after rupture of the medulla in rabbits very little change occurs in the number of leucocytes in the blood of the central vessels.

2. Ether narcosis in rabbits has very little effect on the location of leucocytes in the circulating blood.

3. The view of Rieder and Schulz that no change in the sum total of leucocytes in the blood ever occurs in leucocytosis is incorrect and may be disproved by an examination of rabbits' blood in the stage of hypoleucytosis, either after rupture of the medulla or, more conclusively, in ether narcosis.

4. After intra-venous injection of certain bacteria and their products, the majority of the leucocytes, especially the multinuclear forms, disappear uniformly from all parts of the arterial and venous circulation.

5. /

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1. Ewing :- N.Y.Med.Jour., Vol.LXI, p.262.

5. The leucocytes that disappear after bacterial injections are to be found more or less stationary, in the capillary vessels, especially in the lungs and liver.

6. The appearance of the endothelial cells of the hepatic capillaries indicates that these cells may take more than a passive part in detaining the leucocytes within that organ.

7. Leucocytolysis is apparently a secondary and unessential factor in the production of hypoleucocytosis.

8. It remains an open question whether hypoleucocytosis depends upon a simple mechanical sifting of swollen and cohesive leucocytes by the capillary endothelium or upon a determination of these leucocytes by chemiotactic influence, to specialised capillary endothelium in the viscera.

9. The appearance of the hepatic capillary endothelial cells, both before and after the injection of bacteria, points to a possible function of the liver as the physiological scavenger of the body, and in pathological conditions, as a special organ of phagocytosis.

Some /

Some writers believe that it is only by chemiotaxis that the cells are attracted, that the toxic substances exert an attractive influence on the wandering cells and remove them from the blood.

Thus Rieder[1] believes that the leucocytes are collected in some region of the circulation and are eventually again attracted into the blood by a process of positive chemiotaxis.

Goldscheider and Jacob[2] maintain that the leucocytes under such conditions are attracted to the lungs.

Löwitt[3] states that leucocytosis often occurs, without chemiotactic substances, or even with substances which are negatively chemiotactic and therefore ought to produce exactly the reversed condition.

Kanthack[4] says that if chemiotaxis explains the processes observed then, in many cases we have to deal with what we may call a "selective chemiotaxis".

Löwitt /

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1. Rieder:- Atlas der Klinischen Mikroskopie des Blutes - Leipzig.
2. Goldscheider and Jacob:- Ueber die Variationen der Leukocytose - Zeitschr. f. Klin.Med., Bd 25, Hft.5, 6.
3. Löwitt:- Studien zur Physiol. und Pathol. des Blutes und der Lymphe - Jena, 1892.
4. Kanthack:- Manchester Medical Chronicle Vol.I,1894, p.338.

Löwitt assumes that the diminution in the number of leucocytes is due to a destruction of the cells ("leucolysis") because, if you inject bacterial poisons or living organisms into the peritoneal cavity of an animal which contains a large number of cells you find a diminution of leucocytes is the immediate effect.

This "leucolysis", Löwitt[1] says, is the stimulus for the subsequent leucocytosis, the new cells being produced in the spleen and lymph glands, while, on the other hand, Römer[2] believes that we have a new formation of polynuclear leucocytes in the venous blood directly.

Whatever may be the destiny of the leucocytes in leucopenia, enough has now been said to show that the condition of leucopenia is one of exceptional interest and diagnostic importance and deserves much more than the comparatively scant attention which has hitherto been bestowed by observers upon it.

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1. Löwitt:- Studien zur Physiol und Pathol des Blutes und der Lymphe - Jena 1892.
2. Römer:- Uber den formativen Reiz der Proteine Buchniss auf Leucocyten - Berliner Klin,Wochenschr, 1891, No.36.

L I T E R A T U R E

REFERRED TO

in the PRECEDING PAGES.

Alexandre, G. : De la leucocytose dans les Cancers, (Thèse de Paris, 1887).

Afanassiew, M. : Ueber den dritten Formbestandtheil des Blutes im normalen und pathol. Zustande und über die Beziehung desselben zur Regeneration des Blutes. Deutsch Arch. f. Klin. Med., XXXV,1884, S.217.

Bignami : Atti della R. Accad. di Roma, XVl t.v.

Bastianelli : I leucocite nell' infezione malarica. Bull. del R. Acad. Med. di Roma, 27th March, 1892. Anno XViii fax V, 487.

Billings : The Leucocytes in Malarial Fever, Johns Hopkins Hospital 1894, Nos.43,105.

Botkin, E. : Virchow's Archiv. Vol.CXXXVii, No.3,1894.

Billings : The Leucocytes in Croupous Pneumonia, Johns Hopkins Hospital Bulletin, No.43, p.105.

Bouchut /

Bouchut and Dubrisay : Gazette Médicale de Paris,1878.

Bayer : Ueber die Zahlenverhältnisse der rothen und weissen Zellen im Blute von Neugeborenen und Säuglingen-Dissert., Bern, 1881.

Cabot, Richard C., M.D. : Guide to the Clinical Examination of the Blood for Diagnostic Purposes.

Coles, Alfred C., M.D. : The Blood, How to examine and diagnose its Diseases. London, 1898.

Cadet : Etude physiologique des eléments figurés du Sang. Dissert. Paris, 1881.

Chatenay, G. : Les réactions leucocytaires. Paris, 1894.

Deutsche Medicinische Wochenschrift 1895.

Dionisi /

Dionisi : Variazoni dei globuli rossi e dei globuli bianchi nell' infezione malarica in rapporto col Parassita della malaria. Lavoni del IIIº congresso della società italiana di medicina interna. Milan Oct.1890,169.
Also Lo Sperimentale, 1891, f.III and IV, 284.

Dane : Boston Medical and Surgical Journal, May 28th, 1896.

Dubrisay (Bouchut et Dubrisay) : Gazette Médicale de Paris, 1878.

Denis : Recherches expérimentales sur le Sang. Paris, 1880.

Eisenlohr : Virchow's Archiv. Vol.73.

Ewing : New York Medical Journal, Dec. 16th, 1893.

Ehrlich : Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes. Berlin 1891.
I Theil.

Fraenkel /

Fraenkel : Deut. Med. Woch. 1895, p.639.

Freudenstein : Ref. by Fraenkel, Deut. Med. Woch., 1895, p.639.

Fahrmann : Deutsch militätärtzliche Zeitschr., 1874, No.12.

Grawitz, P. : Maligne Osteomyelitis und sarkomatose Erkrankungen des Knochensystems als Befunde liei Fällen von Pernic Anamie, Virch Arch. Bd.76,1879.

Goldscheider and Jakob : Arch. f. exp. Path. u.Pharm, Vol.V.

Gibson, George A. : Edinburgh Medical Journal, October 1892.

Goldscheider and Jakob : Ueber die Variationen der Leukocytose. Zeitschr. f. Klin. Med. Bd.25, Hft.5, 6.

Golgi /

Golgi, C. : (1) Sur l'infection malarique. Arch italiennes di biologie, 1887, t.8.

(2) Fortschr. d. Med. 1889, 3.

(3) Sul ciclo evulotivo dei parasiti malarici nella febre terzana. Arch. per le scienze mediche 1889,Vol.XIII.

(4) Intern. Kongr. Berlin, 1890.

Gilbert (Hayem and Gilbert) : Arch. Gen. d. Med.p.257, 1884.

Gräber, E. : Zur Klinischen Diagnostik der Blutkrankheiten. Haematologische studien p.64, Leipzig, 1888.

Gundobin : Ueber die Morphologie und Pathologie des Blutes bei Kindern - Jahrb. f. Kinderheilk, Bd. XXXV, 1893.

Henck : Virchow's Archiv. Vol.78.

Heubner : Deut. Med. Woch. 1895, p.639.

Hayem /

Hayem : Du Sang et de ses altérations anatomiques. Paris, 1889.

Hewetson (and Thayer) : The Malarial Fevers of Baltimore: an Analysis of 616 Cases of Malarial Fever with special reference to the Relations existing between Different Types of Haematozoa and Different Types of Fever. Baltimore, 1895.

Hayem (and Gilbert) : Arch. Gen. d. Med. p.257,1884.

Halla : Ueber den Hämoglobingehalt des Blutes und die quantitativen Verhältnisse der rothen und weissen Blutkörperchen bei acute fieberhafte Krankheiten. Zeitschrift f. Heilk, 1893, Bd.IV S.198.

Hammerschlag : Ueber das Verhalten des spec. Gewichtes des Blutes und Krankheiten. Wien. Klin. Wochensch,1891, and Centralblatt für Klin. Med., 1891, No.44.

Hardy (W. B.) : Journal of Physiology, Vol.XIII, Nos. 1 and 2, p.183.

Hankin, E. H. : Über den Ursprung und das Vorkommen von Alexinen im Organisme - Centralblatt für Bakterial und Parasitenkunde, Vol. XII.

Jakob /

Jakob : (Goldscheider and Jakob) : Arch. f. exp. Path. u. Pharm. Vol. V.

Jakob and Goldscheider : Ueber die Variationen der Leukocytose - Zeitschr. f. Klin. Med. Bd.25, Hft. 5, 6.

von Jacksch and Cagney :- Clinical Diagnosis.

Kovács : Wien. Klin. Woch, 1893, p.701.

Kalindero : Les globules sanguins dans l'impaludisme. Jour. de Méd. et de Pharm. de l'Algerie 1889, XIV, 123, (June).

Kelsch : Arch. de Physiol. 1875.

Kikodse : Path. Anat. d. Blut. b. croup, Lungenentzündung. Inaug. diss. Petersburg, 1890.

Kanthack : The Histological Changes of the Blood in Diseased Conditions - Manchester Medical Chronicle, Vol.I, 1894.

Leslie /

Leslie, R. Murray : Case of great Enlargement of the Spleen and Liver of remarkable nature, with Diminution of Leucocytes - Oligo-leucocythaemia. Edinburgh Hospital Reports, Vol.II, p.258.

Lanciani : "Des Hungern". German Translation by O. Frankel, Hamburg, 1890.

Litten : Zur Pathologie des Blutes (Berlin Klin. Wochenschr.) 1883.

Löwitt : Studien zur Physiologie und Pathologie des Blutes und der Lymphe. Jena, 1892.

von Limbeck : (1) Klinisches und Experimentelles über die entzündl. Leukocytose. Zeitschr. f. Heilk., Bd.X, 1890, S.392.

(2) Grundriss einer Klinischen Pathologie des Blutes. Jena, 1896.

Müller : Deut. Archiv. für Klin. Med. 1892,Vol.50, p.47, and 1891, Vol.48.

Maragliano /

Maragliano : Zeit. f. Klin. Med. Vols 14 and 17;also Berlin Klin. Woch. Nos 36 and 51, 1891.

Muir : "Contribution to the Physiology and Pathology of the Blood." Jour. of Anat. and Phys. Vols XXV, XXVI and XXVII, 1891

Ortner : Wien. Klin. Woch. 1890, p.832.

Osler : The Principle and Practice of Medicine

Pepper : Theory and Practice of Medicine, Vol.II.

Pohl : Archiv für exper. Pathologie u. Pharmakologie XXV, 87, 1888.

Quincke : Ref. in Munch Med. Woch. No.1, 1890.

Richter /

Richter : Deut. Med. Woch. 1895, p.639.

Rotch : Hygienic and Medical Treatment of Children, Vol.I.

Reinert : Die Zahlung der Blutkörperchen, Leipzig, 1891.

Rieder : (1) Beiträge zur Kenntniss der Leukocytose, Leipzig, 1892.

(2) Atlas der Klinischen Mikroskopie des Blutes. Leipzig.

Reinecke : Fortschritte der Medicin IX, 1891. Virchow's Archiv. CXViii, 148, 1889.

Römer : Über den formativen Reiz der Proteine Buchniss auf Leucocyten - Berlin Klin.Wochenschr., 1891, No.36.

Stewart, Sir T. Grainger : Notes of Lectures on Clinical Medicine.

Stintzig : Ref. in Munch.Med.Woch. No.1, 1890.

Stengel /

Stengel : Article on Diseases of the Blood in Twentieth Century Practice of Medicine Vol.VII.

Schulz, George : D.Archiv. f. klin.Med.B. 51,1893, S. 234.

Sörenson : Jahresbericht über die Fortschritte der Physiologie und Anatomie, S.192 - 197.

Sadler : Fortschritte der Medicin Bd.IX, 1891.

Schiff : Ueber das quantitative Verhalten der Blutkörperchen und des Hämoglobins bei neugeborenen Kindern - Zeitschrift für Heilkunde Bd.XI, 1890.

Sherrington : Notes on some changes in the Blood of the General Circulation consequent upon certain inflammations of an acute local character - Proc. of the Royal Society - Vol.IV,No.332, 1894.

Thayer /

Thayer (and Hewetson) : The Malarial Fevers of Baltimore : An Analysis of 616 cases of malarial fever, with special reference to the relations existing between different types of haematozoa and different types of fever. Baltimore 1895.

Tchistovitch : Ann. d. l'Inst. Pasteur Vol V. p 7.

Thayer : Bulletin of Johns Hopkins Hospital, Baltimore Vol IV. p. 30.

Uskow : Centralbl. f.d. Med. Wissl897 S.499.

Winternitz : Imperio Royal Medical Society Vienna, February 1893.

Warthin : Medical News 1895.

Winiarski : Petersburgher Medicinische Wochenschrifte 1892.

Wyssokowitsch : Zeitschrift für Hygiene Bd. I.

Werrigo : Annal. de l' Institut. Pasteur 1892.

Zeissl : Wein Klin. Woch. May 14th 1896.