Leucocythaemia

Its Symptoms, Pathology and Treatment.
Aug. 2/95

Mr. Gladstone wishes to have the opportunity of addressing this Thesis. He is good as to allow him to have it for these days.

[Signature]
Leucocy thoeiria
Its Symptoms, Pathology and Treatment

This somewhat rare disease certainly deserves all the study, that has been bestowed on it since the time of its discovery by Bennet, when we consider how a correct interpretation of its morbid processes, followed by a more elaborate study of the same, would in all probability give its results which would be of value to us in fields of Pathology and Clinical Medicine wider in range and of more practical importance.

I intend to discuss the subject under the following heads.

I. The Symptoms and Physical Signs — To illustrate these, I shall describe the clinical history of two cases I had the opportunity of watching in the General Hospital, Nottingham; and am indebted to Dr. Hardford, under whom they were treated for permission to make use of the notes on their cases.

II. Pathology
I shall treat of this in two parts.
First considering the recent views of the normal functions of the structures affected in this disease; and then discuss the significance of the morbid appearances that are present and endeavour to find a theory which is capable of explaining them.

III. Treatment — Here I shall discuss the various kinds of treatment, that are employed, and give in a tabular form the results of these in the two cases at Nottingham.
I shall first relate the clinical history of the two cases I watched, to illustrate the symptomatology of the disease.

(a) J. M. 32. Waggoner. M., native of Reddington Holts was admitted to hospital on September 20th. He had never been abroad nor had acute or any serious illness previously.

Three months before, he began to have a voracious appetite; a month later he had sharp pain under the left lower costal margin, and soon began to notice a swelling growing from here into his abdomen. He began to suffer from dyspepsia and headache.

On admission, he had a good colour and seemed well. The abdomen was prominent and tense. It was entirely filled by a tumour, presenting deep splenic notches, nearly reaching the R. ant. sup. spine; extending 5½" to R. of umbilicus, 9" below rib margin. R. L. nipple line, the fact reaching the pubes. It was not tender to the touch but friction fremitus could be heard over it.
The cervical, thoracic axillary and L. femoral lymph glands were somewhat larger than normal and were freely movable.

The blood was bright red when drawn and contained 40% of haemoglobin.

At first the red cells numbered 3,600,000 per c.c.

and the leucocytes 500,000 "

On examining films of this blood, stained with Eosin and methyl blue — the colourless cells presented great varieties in size and shape, and the following kinds, of which I have made diagrams on the following page, could be seen:

(a) Large multinucleated cells, somewhat oval in shape, about 2-3 times the size of the "multinucleated" ones. The nucleoli presenting an indentation on one or both sides, having a distinct outline and staining faintly blue. The surrounding protoplasm in some cases stained blue, but in others was also stained with Eosin, becoming thus faintly purple — some indeed stained nearly as deeply as the red cells.

(b) Cells having protoplasm, deeply stained by Eosin, but, owing probably to imperfect preservation,
J. M. 32. Sept 26th 94.

Films fixed after drying by heat. Rested in alcohol and ether.

Stained with toluidin blue or eosin.

Crot. 1/6, 1895.

The appearances of the red bodies in the films examined were of doubtful significance. A large group of cells having what resembled a nucleus (f) or two nuclei (f'). These bodies were probably due to drying or some decomposition as when stained with hematoxylin they did not take a nuclear stain.
not showing the eosinophilous granules distinctly, they resembled in most cases the first group in size, but the nucleus usually contained its protoehromatin in fragments as if mitosis were about to commence. Some of these cells were smaller and evidence of mitosis could be seen in them.

(c) Ordinary "multinucleated" cells

(d) Small mononucleated cells or lymphocytes

The relative numbers of these various kinds, as 129 counted, showed that 67% were "multinucleated", 25% large mononucleated, 5% eosinophils, and 3% lymphocytes — the latter thus being present in small numbers. The appearance of the red cells are described on p. 14.

The urine contained a trace of albumen most of the three months he was under my observation. It would sometimes be absent for a few days, then gradually reappear, then disappear again gradually. The urine was often "muddy yellowish white" in appearance — containing urate crystals in large quantities. The deposit contained some
pus cells and occasionally hyaline casts and once a few uric acid crystals.

He never had any gastro-intestinal disorder except being laid up for two days from 4th Oct with vomiting nausea peronhea which were attributed to the arsenic he was taking.

He had slight epistaxis on Oct 18th and 22nd but never had a rise of temperature.
There was no retinal affection.

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6. 1. The second case is of H.B. Oct 22, miner, male, native of Claycross, Derbyshire, readmitted to General Hospital Nottingham on Oct 4th 1947. He had been abroad or lived in a mining district at home.

Four years ago he had inflammation of throat and "ague" directly after eating soup — further questioning however threw doubt on the latter statement. Two years ago he had inflammation of throat again.

His present illness began about July 1933 with diarrhoea and the frequent presence of blood in the motions. This apparently lasted for about three years and then ceased. About this time he first noticed the splenic enlargement and experienced pain
in the stomach after food.

He became an in-patient at the General Hospital, Nottingham in January 1944, remaining there till April 1944; he then attended as an out-patient until July 1944. During this time, under treatment, his spleen, which at first reached the umbilicus, because so reduced in size that it did not project beyond the rib margins; and his blood became changed—the ratio of white to red cells becoming as 1:366 instead of 1:716.

He left off treatment however in June 1944. In July a slight enlargement of the spleen had occurred. In August 1944 he felt it growing in size, but kept on at his work in the pit.

On September 15th 1944 he was suddenly taken ill passing that day after a motion some liquid red blood and being obliged to go to bed. He sweated profusely, all the week, and said all his bones seemed to ache, his temperature was once 104°, where his doctor took it.

He was very weak and ill for a fortnight after this and was admitted again to the hospital in such a condition, on October 7th.
looked particularly anaemic, but his pupils were very widely dilated.

The spleen extended 1.5" to the R. of middle line 6.5" below ribs in L. nipple line, and its notch just exceeded the umbilicus — The measurements in January were slightly in excess of these — There was some enlargement and hardening of the femoral, thoracic, axillary, left genital and R. superficial clavicular lymphatic gland. No such enlargement was said to be present in January, this therefore developed after the leukaemia and splenic enlargement.

The Blood.
The blood was bright red when drawn and contained 45% of Hæmoglobin.

On Oct. 9th the red discæ numbered 2,670,000 or 54.2% the leucocytes 139,000 = 1:20.

Comparing this with an estimation of his blood on Feb. 26th when the red discæ were 3,670,000 or 69.4% and the leucocytes 280,000 = 1:11¾.

We note that the blood is in a more anaemic condition than at the earlier date, although there are also fewer leucocytes. Indeed the total number of cells in the blood has become reduced by about 1,000,000 per e. m. m.
The colourless cells of the blood.

On the following page I have made diagrams of the chief varieties of these cells, which were to be seen on examining the blood of this patient. They are as follows—

(a). Large, mononucleated cells with coarsely granular protoplasm which had distinct cell outline; a nucleus staining pale blue with methylene blue oval in shape, and having rather an undistinct nuclear membrane.

—The protoplasm of the cells was scarcely affected by staining reagents used—i.e., methylene blue and eosine—.

(b). One cell was seen with protoplasm resembling the former but having four nuclei with each a nucleolus—probably a giant cell.

(c). Large, mononucleated cells, having a more definite oval cell outline. The protoplasm faintly stained with eosin; the nucleus being indented at one or both sides having a distinct nuclear membrane.

(d). Large cells resembling (a) *th*, having no distinct cell outline, but containing large eosinophilic granules usually having a nucleus similar to those of (c). All were larger than lymphocytes of normal blood.
Stained with methyl-blue + Bismine

(Coomass 6, high ox. tube drawn out)

Stained with Haematoxylin (+ slightly with Bismine).

(Coomass 6, high ox. tube drawn out)
their size varied greatly. Occasionally they contained two nuclei.
(c) Lymphocytes
(f) Ordinary multinucleated leucocytes
Of 77 such cells counted —
There were 89% of (a), 17% of (b), 25% of (c),
8% of (d), 55% of (f), 8% of (e).
The lymphocytes were rather more numerous here than in J.M.'s case.

The Coloured Elements of the Blood.
These were very similar in appearance to those in the case of J.M.
A very large number of the dishes contained structures which somewhat resembled nuclei in various situations and of various shapes and sizes; see fig. (h). There were also similar fragments lying loose, between the cells (fig. i). A large no of the dishes did not contain these and seemed normal in appearance — fig. (j).
These bodies when stained with Hæmotoxylin (and also slightly with Eosin) became faint purple, not taking on a nuclear blue. I concluded that they were really due to some decomposition of the dried films (these being stained some months after preparation); a few cells
contained bodies which from round shape towards position in the cell itself. Much resembled nucleated red cells to they stained purple; they were far less numerous than the other kind. Some loose bodies (x) resembled extended nuclei.

A week after admission, diarrhoea began and lasted over a week. It was ushered in by vomiting. His temperature steadily rose to 102, he had headache, his face acquired a greenish pallor and he was laid up in bed, quite prostrate. He had a cough but no physical signs in the lungs. In fact the only objective symptoms was a cloud of albumen in the urine which was not present on admission. He was not free from pyrexia and was confined to bed from Oct 7th to Oct 16th. But during this time the coloured cells in his blood increased and the albumen diminished.

Evidently this illness was due to the entrance of some noxious material into the general circulation, whereas it was eliminated by the kidneys and alimentary canal probably, and associated with this improvement took place.
in blood formation.

After this attack of pyuria, of which he had a second in December, the urine usually contained a trace of albumen; and leucic acid crystals were seen every day for a fortnight in December.

Bacillus bodies perhaps prostatic casts were also seen from time to time in the deposit. They were three times the width of ordinary casts, and appeared to contain leucocytes mixed with fibrin.

Hyaline casts were also seen.
Pathology.

A.

The study of the Pathology of this disease necessitates in the first place a discussion of the nature, functions, life history, and mode of production of the cells of the blood, and a consideration of the haemopoietic organs—these subjects being viewed in the light afforded us by recent research. Let us consider first the leucocytes and the various kinds of adenoid tissue.

Leucocytes in Adenoid Tissue

In the leucocyte we have a cell, identical in structure with that most primitive of all animals, the amoeba; resembling it also in its power of independent motion, enabled it to move to neighboring particles, to wrap itself round & digest such bodies, and as gallbladder (1) has shewn, of retaining, when removed from the blood of an animal.

These leucocytes are present in every member of the animal kingdom and have singularly similar characteristics wherever they may be found. They do not differ with the other parts of the structure of animals—maintaining the same size in
Such different organisms as useless, to the elephant and the mouse. Neither do they share the numerous structural modifications, which occur in the red cells of various animals; as for example, the in reptiles, the cells are large, oval and nucleated, in the yokes, those cells are of very minute size; and among the camel-like are oval in shape, yet all these animals have similar leucocytes. (Valier, 2.)

In fact these cells have not shared in the modifications which have been undergone by other cells, in the advance of evolution, and have reached to a very small extent to the changes which have, thro' the ages, taken place among them. Their presence is therefore evidence indispensable, in the animal kingdom: they are eminently fitted in their original form to perform the functions assigned to them. In specialization, cells lose many of the qualities of the amebas, become useless and unable to move to or unwrastle and destroy injurious bodies near them. They therefore need the help of cells, which have retained these primitive characters, to protect
there against such enemies and allow them to perform their several functions, on which the right working of the organism depend.

We may compare the leukocytes to the Fomes to on whose retention Photogena characters.

We come now to 

**Adenoid tissue**

which is a special tissue developed in the body that has the function of collecting leukocytes in its meshes and allowing of their multiplication by mitosis. This tissue consequently becomes crowded with adenoid cells, some as well be described later, being from their large size stationary here, others remaining only for a time. Wherever it is placed, it is capable of creating an intensification of the action of leukocytes. As would be expected from this consideration, adenoid tissue is found in large quantities in those places open to the attack of living or inorganic irritants.

1. **Thus in the Alimentary Canal** — The adenoid tissue of the tongue, nasopharynx, and the tonsils is placed to antagonise the irritants introduced with food or air.

The whole of the intestinal canal contains it in its walls, either diffusely or in special collections as *solitary follicles* or groups of these.

*Pepper's Patches.* The leukocytes are here
in large numbers close under the epithelium, defending the body from the multitude of irritants in the caecum.

II. The other exposed surfaces viz the skin and respiratory tract are not defended so directly as the alimentary canal is but, all the fluids returning to the blood from these must pass over the tree-like growth of adenoid tissue which is found in the lymphatic glands. Several times, before reaching the circulation and are thus freed from irritants.

There are two other organs containing adenoid tissue which have a position and function different from those we have just seen. These are the Thymus and the spleen. The Thymus is apparently a transitional organ to supply the blood and tissues of the young animal with a plentiful supply of leucocytes to defend it in its immature and vulnerable state from the numerous pernicious which attack it at this period of life. It atrophies when the body has become indifferent or immune to their attack and has also developed adenoid tissue elsewhere in larger quantities.
The Spleen.

The functions of the adrenoid tissue of the spleen are different from those of it elsewhere, from the fact that the organ is not located where it can prevent the entrance of irritants into the organism. There is however evidence to lead us to think that it removes irritants which have already entered the blood.

The spleen is not now deemed, during extraneous life, an organ for producing red dises—this statement being chiefly founded on the absence of Erythroblasts in any quantity in this organ. The presence of disintegrating red dises and the large quantities of pigment and Extractives normally found; the temporary enlargement of the spleen which occurs and the enormous quantities of Haemoglobin found in pernicious Anaemia, if death occurs during one of the attacks of blood destruction (H. Hunter[3]); and the number of breaking up dises found there after transfusion of blood or the injection of Tolyglandin—these three considerations indicate the spleen as the site of disintegration of damaged dises.
Further Galland (E. C.) has demonstrated the presence of disintegrating white corpuscles and of micro-organisms in the large stationary phagocytic leucocytes of the tonsil. We have no reason for doubting that the same phagocytic cells in the adenoid tissue of the spleen have the same function and we must consider the spleen as the site of destruction also of damaged leucocytes and micro-organisms. Its position favours such decomposing action since the products will immediately pass through the liver and the nervous compounds removed before entrance to the general circulation.

Now let us take the lymphoid tissue which is assigned to each of the 2nd arteries from which leucocytes can pass directly into the wide venous capillaries. This allows the blood to be thoroughly subjected to the phagocytic actions of these cells, which probably play a considerable part in the breaking up removing the abnormal elements which are here got rid of. We can see what an important defensive action the spleen must have in pathological conditions by discharging numbers of leucocytes into the
slowly flowing current of blood in the venous sinuses. These sinuses become more dilated and the adenoid tissue more hyperemic in cases of Septic Specific Malarial fevers (Woodhead[4]) which are cases in which poison have reached the blood—the spleen being found enlarged clinically then.

It would be interesting to discover how patients who had undergone the operation of splenectomy reacted to such diseases especially if attacks by them shortly after recovery from the operation when no compensating developments had occurred—one may mention a case of Koch's[5], where the spleen was congenitally absent, the cause of death in this case being typhoid fever.

Finally increased activity of adenoid tissue in any of the above situations leads to increase of leucocytes of the wandering or multinucleated variety in the tissue or blood. In the blood this is called leucocytosis.

It occurs physiologically from the hyperemia of the alimentary canal after meals, Pathologically in irritation of lymphatic glands and in fever in general where the spleen or the lymphoid tissue becomes
in a state of defensive activity.

In typhoid fever, its absence for the early stage, perhaps, is accounted for by the destruction of Peyers Patches. Leucocytosis would be a favourable sign indicating small affection of the tissue and also a healthy state of the leucocytes owing to the dose of the poison being small. It is well marked in tubercular meningitis (Bastian). I found in two such cases on careful examination, the leucocytes were 25,700 and 37,500 respectively. The cells of the former case showed also the retention of amoeboid characters 10 minutes after removal from the blood as to which is made a point of by Bastian (c.e).

We thus have seen the important action of leucocytes in protecting the specialized parts of the organism against living or inorganic poisons and in removing effete substances produced in the body. We have also seen the organs which have been developed in the body, adapted by their position and structure to put to a useful end for the more complex highly developed animal economy, the primitive amoeboid properties of leucocytes. We have now to discuss, of most vital importance...
Do leucocytes become red dies?

That is, is it a fact that they are the antecedents of the nucleated red cells in the blood of the foetus and the marrow of the adult? The nucleated cells being, as will be shown later, taken as the antecedents of the red dies.

And we may also ask the question. Is it likely that the leucocytes, which have preserved with such tenacity their ancient character, all their animal kingdom and have their activities so fully taken up with their own work, should at a certain stage in the process of evolution, at the advent of fishes, have acquired the new property of extending their life history by changing all their former cell properties and becoming nucleated red cells which, as will be seen, have a definite life history of their own?

To answer these questions we must first consider the modifications which are now known to occur in leucocytes — changes which however will be seen to involve no radical alteration in cell structure or function. For this purpose we will follow the life-history of the white cells. Beginning with a cell that is just derived from the parent cell.
The lymphocytes, or small cells containing chiefly of
nucleus occur in all adenoid tissue especially
around the germ centres where mitosis is occurring
Resting in such a vascular tissue they naturally
increase in size. Pollard (c.e.) has found these cells
all stages of growth (in the tonsil) which process
consists in an increase in the quantity of their cell
protoplasm and unravelment of the chromatin of the
nuclear. If they reach a certain size without being washed out
of the adenoid tissue into the lymph channels by the serum
ordored by new cells formed behind them, they remain
there permanently playing the important part of phagocytes
which stop the passage into the body of irritants which
may attempt to enter. They also receive damaged
leucocytes from the lymph and perhaps damaged dises
from the blood — Bacelli breaking down leucocytes.
Red tissue being formed full and in such cells the tissue
If dislodged it reenters the lymphatics. In the case of the follicles
chiefly during the hyperemia of deflection when the
serum is great and these phagocytes break into little bodies which
may adhere to their growth. Passing into the veins, these cells are let
loose on the body wherever they are not of use to remove their
waste products. The nucleus during the changes of form assumed
by the cell in these migrations becomes moulded in various
directions and often seen in blood as the multilobular cell
or as it is usually called a multinucleated leucocyte. This change
however
Quilland (2) shows that this is not accurate and is only to be applied to those cells which are evidently dying— their nuclei remain homogeneous by death certainly does happen to cells in this stage—the large phagocytic adenoid tissue of are seen to contain dead leucocytes and probably great numbers are destroyed in the alimentary canal, where their enemies are so numerous.

Thus we see that there is no need for a special metamorphosis to account for their numbers not increasing the their reproduction is so active, this being simply due their death.

The multinucleated cells get caught in adenoid tissue and enlarge in their nucleus and protoplasm, undergo mitosis and give rise again to lymphocytes. We must now consider whether they may not be the antecedents of another set of cells found in another organ viz. the marrow cells of the medulla of bone. Muir & Drummond (3) others regard these cells as of the leucocyte orders on account of the structure of their nuclei and protoplasm. The eosinophile marrow cells are only different from the eosinophile tissue in being of larger size and showing evidence of multiplication.
The more numerous ones with neutrophile granules, also show evidence of active mitosis. This leads us to believe that these marrow cells are a source of the leucocytes in the blood. What their own origin is is uncertain. They may be a definite tissue developed from embryonic cells; but in birds we find ordinary leucocytes for their homologue, and there is more reason to suppose they are leucos, which, under the favourable surroundings, of the marrow affords them, have grown to a large size. Perhaps they arise from fusion of two individuals, such as occurs in animals before division. Eadward Hammonde (p. 8) have seen in the marrow of young animals cells with the nuclei constructed & considered the case as division by the direct process. May it not have been a stage in the fusion of two individuals?

We have now arrived at the organ which is the natural seat of the nucleated red cells or erythroblasts and it is here that if leucocytes are transformed to the latter the process must occur. It is here we might expect to have definite proof of the truth or falsity of the theory that leucocytes become erythroblasts by
Searching for transitional forms between the two cells. Recent research has failed to discover such forms in any sufficient numbers, if at all (Truax. H. Rust, and F.).

The life history of red cells also tends to establish the independent nature of the two. In the foetus at first leucocytes are very scanty in numbers according to Howe (9) and the red-nucleated cells arise then from mesoblastic cells included when the production of new blood vessels occurs. They therefore are not derived from ordinary leucocytes through which it cannot be disproved that these mesoblastic cells may have been of the leucocyte order.

With the development of the complex circulation in the liver this organ becomes the seat of the chief production of red cells and later on the spleen's developing circulation acts in a similar way. Lastly when the bones appear and require the great vascularity of their medulla for the rapid processes of growth this tissue takes on the erythropoietic function and here it is not transitional but when the red marrow has retreated to the flat bones of the epiphyses of long bones and to the short bone.
this tissue becomes during the whole life of the adult, the source of erythroblasts. That erythroblast produced by the spleen and arises has been quite established; it has been shown that this place by extrusion of the nucleus in a degenerate condition, and also that after this extrusion changes occur before the plate is ready to enter the blood. Howell (p. 16) has seen cells with the nucleus in all stages of extrusion that actually watched the process in one case. Meurthummond (p. 8) also have searched in vain for appearances supporting the theory that the nucleus dissolves in the spleen; free nuclei can be found and the fact that the nuclei, situated or extruded, never stain otherwise than homogeneously, showing their degeneration, show that the process is not an accidental or fortuitous one.

After escape of the nucleus the cells undergo further changes, as shown by the different staining reactions they present, in different parts of the marrow, and, after liver haemorrhage, in the blood (Meurthummond p. 8). Which condition favours the entrance therein of immature cells as is further exemplified in Peripneumonic Accidents.
We have now seen firstly how leucocytes are continually being reproduced, that they have definite and hazardous duties of their own, in the performance of which their numbers become reduced (that this is sufficient to explain why they do not accumulate in the blood). Secondly how the spleen is not regarded as an erythrocytopoiesis organ in the adult but is to remove waste products and irritants from the blood; Thirdly how the weight of evidence of research lately has gone to establish the independent nature of red dise leucocytes.

On these three considerations and aided by the recent researches in the histology of normal bone marrow we are able to view the pathology of this disease very differently from what was possible a few years ago. I will now pass to discuss the pathology proper of the disease.
Pathology.

Increase in the number of leukocytes in the blood does not constitute leukocythemia. It depends on the quality of the white cells present. There are three conditions presenting different appearances as to the quality of leukocytes. These are as follows:

a. Increase in the multinucleated cells, together with the presence of 3 abnormal elements derived from the bone marrow. This occurs in the common myelogenous form of leukocythemia.

b. Increase in the lymphocytes and probably decrease in the multinucleated cells which we may call lymphocythemia.

c. Increase in the multinucleated cells only or leukocytes which phenomenon has been seen to have a physiological significance in normal or pathological conditions of the body.

The first two conditions of which the latter is the rarer form constitute the disease leukocythemia.
Let us first discuss the condition of the spleen. The enormous enlargement of the spleen suggests what is proved by microscopic examination viz. that it increases in size due to a dilatation of the already existing blood spaces. (Woodhead 19)

The question now comes up: is this due to a passive distension or an active dilatation? In favour of the former view we may argue that the structure of the spleen is certainly fitted, more than that of any other organ or tissue in the body, for retaining leucocytes killed in the blood and have thus lost their amoeboid power of leaving it and consequently that this collection is the reason the spleen enlarges before any other tissue becomes infiltrated.

The appearance of the endothelial cells lining the sinuses is against the theory of passive dilatation as they do not appear atrophied by pressure but are swollen and multinucleated, having large cell budding from them and evidently seem in a state of increased activity. This would make it seem more likely that an active dilatation has
taken place to meet the demands, it is explained for increased activity in blood purification. So as to subject the blood more thoroughly to the action of phagocytes to remove the dying cells of the blood and attack the agent causing that destruction. It is therefore probable that early in the disease the malpighian bodies are in a state of increased activity and that a large number of Benecks in the sinuses may have been produced from the adherent tissue and are busy acting as phagocytes.

It is certain, possible that the rôle may be partly accounted for by this active dilatation or hypertrophy, and also partly by passive distension owing to the former process being inadequate to dispose of all the dead cells, which therefore collect and distend the organ.

We may with probable correctness therefore look upon enlargement of the spleen at an early stage as an indication of the great capabilities the body has of defending itself against the morbid processes present here.—Thus the enormous enlargement present in T. M. case see p. 22. was probably the cause of his
absence of symptoms. And in a case of Wathen quoted by Muri (9) of medullary leukemia running an acute course its enlargement the spleen was not great, perhaps we may say instead of Muri's comment ("this may possibly be accounted for by the short duration of the disease") "The short duration of the disease may possibly be accounted for by its slight enlargement with it.

At first there is certainly no permanent damage done the spleen since in H. B.'s case (page 7) the spleen almost returned to its normal size when its increased activity was reduced unnecessary by the arsenic when the no. of leucocytes was lessened. In the later stage it certainly becomes diseased with limited functional activity from the occurrence of infarctions and a limitation of supply of phagocytes.

Adenoid tissue is also hypertrophied as seen in the lymph glands and tonsils clinically and in Peyer Patches fest making.

But the essential or rather primary pathological change is not in the spleen or adenoid tissue.
But, in the commoner form of leucocytosis, leucocytes are not found in the bone marrow only. Yet I maintain that the occurrence of the adenoid hypertrophies both explains the increased number of multinucleated leucocytes present; that subsidiary to the peculiar features in the blood this disease we have a process of leucocytosis actively progressing for the purpose of antagonising abnormal agents in the blood.

We must now consider what are these abnormal agents, the cause of the disease? We must accordingly come to the three abnormal elements in the blood viz. large cells, mononuclear with either neutrophilic or eosinophilic granules and nucleated red cells. We have called these the peculiar features of the blood in leucocytosis and are justified in doing so since in the conditions known as leucocytosis they are never present—they cannot therefore be explained by increase of leucocytes in the blood, leading to increase in number in the marrow cells, by being present in excessive numbers and delayed in the already formed.
Such an increase in leucocytes does not ever give rise to marrow cells in the blood in any other condition and accordingly it is not likely that it should do it here. We must conclude that these cells, which are shown by Muir to have the same characters as cells in the bone medulla, known as "marrow cells," that these cells appear in the blood in engravings of some pathological condition in the marrow. This is demonstrated also by morteure—the marrow being crowded with marrow cells undergoing mitosis (vide Owen's Atlas). These cells are further always present in this form of the disease, even when the no white cells has reached normal times. In a case related by Muir the patient, several condition was not improved by such reduction of the white corporals in number, marrow cells were.

The proliferation of marrow cells is evidently the primary lesion, the process of leucocytes, which antagonist, this is secondary.

I will now quote a sentence from Muir's Observations (15):

"It is as I believe that the changes in leucocytes cannot be explained on any other theory than..."
that of an excessive indefinite proliferation of a certain kind of cell, in its nature resembling that seen in the growth of many tumours.

and I will now endeavour to show how a theory that the cause of leucocytosis is neoplastic growth of one or other of two cells of the leucocyte order i.e. the either of the marrow cells or of the lymphocyte is considered capable of explaining all the phenomena seen in every variety of this disease. As I have not myself seen this theory stated in the above form anywhere else, I will now proceed to demonstrate its applicability to the facts observed in leucocytosis.

Firstly in the more common form where their proliferation of marrow cells and their entrance into the blood — median leucocytosis.

Secondly in the rare form where indefinite proliferation of lymphocytes occurs in the body — lymphatic leucocytosis.
Medullary Leucosthenia

In the first variety the tissue affected by neoplastic growth is the orderly large mononuclearated cells found in the marrow of bones. In marrow cells, by this means their development into leucocytes (which we have previously seen to be probably seen) is arrested, they multiply rapidly, but retain their original force, and appear them in the blood.

Either their abnormal presence or the product they give off here excites activity in adenoid tissue in order to afford phagocytes to remove both of these factors and to clear the blood of dead phagocytes which have previously succumbed to their injurious effect.

The battle is at first waged most actively with spleen which assists the purifying action of the liver. For by reason of its peculiar structure according to just these are no symptoms from impurities retained in the blood but great hypertrophic enlargement of the spleen which often able to cope with the enemies.

The slight affection of the spleen in some cases of medullary leucosthenia may be accounted for by some previous disease having destroyed its functional activity; a by some congenital abnormality affecting rendering it of no use as a defense to the body.
When arsenic is administered which keeps down the muscarinic neoplastic cells the spleen has less work to do and may almost return to normal proportions (Ch 1B's case p. 7).

Arsenic however does not seem like able to ever entirely banish marrow cells from the blood nor with long run to prevent a fatal issue. Perhaps because its action although damages the body's tissues besides checking the morbid growth so that its administration has either to be stopped the disease left to progress or if persisted in has only the effect of aggravating the symtoms.

So at length the neoplastic become unchecked and advance. The spleen must eventually suffer - it dilated vascular tissues being liable to thrombosis and cause infarctions (these are seen in all stages of degeneration. P.M.

The supply of leucocytes must therefore gradually become insufficient to replace the number that become killed and to afford enough large stationary phagocytes to remove their dead companions from the blood.

The adenoid tissues which had become hypertrophied consequently will shortly coalesce in that tissue in the spleen. P.M. or else
perhaps be made destroy from a deficient no.
of phagocyte to protect them--this may perhaps explain the ulceration Meyer Patton fund. 1917.
Let us now consider how the red cells are affected by these processes. The proliferation of cells in
the marrow evident interfaces with the growth by the blasts and so deficient supply by erythrocytes to the blood and the former also become
dislodged and appear in the circulation.
When the neoplastic cells reach the blood
they probably are detrimental to the health of red cells already formed. Also the cells
may suffer from a prolonged absence in the
spleen may see over the delay in the
dilated \& packed Venoms Scheme. After Spleen. These considerations explain the dehumanization of the
red cells. Hemoglobin carrying anemia
Symptoms observed clinically of dyspnea, headache,
fillingness, tendency to hemorrhage and the
appearance seen P.M. of extreme paleness,
afflagment in the spleen.
The reason why then form wille disease in men
prolonged over years is due to the action of
of multinucleated cells which keep the process
check. It is therefore of little importance to
Estimate the mere total number of white cells present in the blood, but we should note the proportionate number of marrow cells of active multinucleated leucocytes.

Increase in the total number of white cells may be either a sign that the disease is being competently resisted by numerous active leucocytes or an indication of advance in the disease when the numbers will be mainly made up of marrow cells and dead leucocytes, which cannot be destroyed removed.

Decrease in the total number may either be due to stoppage of the morbid process or else to failure in the supply of active leucocytes to antagonise it.
Lymphocytocemia.

We will now consider the less common variety which Muir finds to run a much more rapid fatal course. This fact which can be fully explained when we consider the neoplastic growth here affects lymphocytes. Consequently the supply of multinucleated cells which would keep the morbid process in check is lost. The first force is there to a large extent cut off at its source. Lymphocytes are arrested in their development into multinucleated leucocytes (as described earlier) they are seen to be undergoing active mitotic division cells lymph glands and also within tissues to which they have migrated. Histories normally occur in this early stage of the life history of the cell some evidence of the primary pathological change here. Most of the adenoid tissue become affected, as seen by the lymphatic enlargement due to their collecting after being rapidly reproduced here, consequently the marrow cells perhaps the spleen become the only organs for producing "multinucleated cells". Sometimes the adenoid tissue sometimes becomes affected too and perhaps from its qualified use...
appearance to the idea that there were some cases of lymphoeythenia in Hodgkin's Disease, implying that perhaps this is not the case and that microscopic examination of the enlarged lymphatic bodies in such cases would prove them to be undergoing lymphoid change of Hodgkin's disease, but to be crowded with lymphocytes. In fact, that this appearance is really due to the extension of the process of leucocytes multiplying while occurring in the cases, only with lymphocytes.

The spleen certainly enlarges but, owing to the defective production of mature lymphocytes in the body, is far less effective in stopping the disease than in the former type.

The marrow cells probably become exhausted in numbers owing to the same cause. Since they are probably reinforced by new leucocytes from the blood.

In consequence of this the lymphocytes breed without being satisfactorily resisted by the lymphocytes in the blood. They here probably injure red cells and by infiltrating, clogging all the places where the circulation is slow they interfere with the growth of the tumours in the marrow hence the profound anaemia the rapidly fatal issue to the disease.
A few points yet remain to be explained. The enlarged mulberry-shaped infiltration of the organs is probably due to the collection of the marrow cells and dead leukemia which are not properly removed by the spleen in the latter stages of the disease.

The gastric intestinal attacks attended with fever may be due to sudden expulsion of various wastematter from the spleen which enters the alimentary canal by the bile duct, the blood by the hepatic vein — thus explaining the diarrhea and the toxemia. In this case, the increased expulsion of these wastematerials was accompanied by improvement in the blood, etc., p. 49.

and perhaps consisted in an excessive destruction of its enemies, their disintegration in the spleen.

In conclusion, I think we are justified on those grounds in defining Leucosthenia as a neoplasm of Leucocytic cells, which are either marrow cells or else Lymphocysts.
III Treatment.

If the preceding views be correct as to the pathiology of Leucocytoma, our hopes of finding a permanent cure for the disease must become fancier. We must wait for the discovery of some agent capable of stopping the growth of neoplasms in general. Still the extended study of the blood in this disease may indirectly favour such a result by adding to our knowledge on the pathiology of new growths.

Let us first consider the drug which is universally admitted to have great powers of arresting the disease but not, in the present development of its administration and to ultimately prevent a fatal issue of arsenie. The truly extraordinary improvement it produces in these cases is well shown by the succeeding tables of the result of its administration in the two cases I have mentioned.

The blood observations were made with Pooser's Hemoctometer.

Arsenie has lately been recommended (10) for the cure of Sarcoma, and if Leucocytoma is really a neoplasm of the blood cells we can see why arsenie should have such pronounced
effect here since the abnormal growths are present in the blood and consequently are more in contact with the drug than if they were in the tissues. They receive its full effect. The arsenic has not yet permanently cured the disease, it not follow that it would not do so, where our knowledge as to dosage and duration of administration and other clinical points has improved.
There are probably stages in the disease when its admin-istration should be temporarily suspended. The onset of diarrhoea + amenorrhoea is probably an indication for it to be left off, as at such times the alimentary canal is not in a fit state for it to be administered.
Accurate+prolonged records as to dosage, improvement in the condition of the blood and the onset of exacerbations of the disease during treatment are what are now required to enable us to use arsenic in the best way for antagonising the disease.
Argon inhalations have been recommended by Dr. Frederick Taylor (11) in addition to arsenic as causing more rapid improvement than the latter alone. It is difficult to understand the advantage
of oxygen beyond it improving the vitality of the red cells and increasing the resisting power of the multi-nucleated leucocytes.

While arsenic is the only thing has any effect here we must consider finally two other modes of treatment whose value has not been confirmed by clinical experience.

1. When the discovery of abnormal marrow elements in the blood was made, the treatment by bone marrows was suggested on somewhat vague grounds. Its use has however not confirmed its value. It has apparently no effect on the course of the disease.

It was tried in both the cases I mentioned and was not found to have any pronounced action in them (vide tables pp. 43, 44, 50).

A case is also mentioned in the Practitioner (12) where the blood deteriorated when arsenic was stopped and bone marrow substituted for three weeks. There is certainly a case in the Lancet (13) treated with apparent benefit with bone marrow (raw). But here arsenic had been pushed to a nearly fatal result—full doses being continued while the patient was
Suffering from prolonged diarrhoea. It was probably the cessation of the administration of the arsenic, aided by the mental effect of the new treatment that allowed of the patient's recovery by its stopping the diarrhoea. This patient seems to have made a lasting recovery which may have been the effect of the excessive doses of arsenic. No mention is made of the condition of the blood but only of the spleen and tumor, we cannot therefore be sure it was a case of leucocytosis.

In conclusion there is the operation of Splenectomy. It uniformly fatal issue as is shown in H. Collin's table of 17 cases (14) would alone render it unjustifiable - but if the preceding remarks on the Pathology be correct it would, if performed in the Early Stage simply deprive the patient of his best means of keeping the disease in check and in the later stages increase the patient's suffering, and shorten his life for no purpose whatever.

The next three pages will finish this thesis. I regret that I have been unable to record the progress of these cases after return from India December 1894.
Since completing this thesis I have learnt the after history of the two cases T.M. and H.B., from the House Physician, who had been away for some weeks and so unable to answer my inquiries. The details I have received are somewhat meagre but are to the following effect.

The first case T.M. steadily improved after December under arsenic; his enormous spleen became so reduced in size that it's lower border was covered by the rib margin. He was dismissed cured and, as an Out-Patient, is continuing to take arsenic.

The second case H.B. did not improve in his general health remained weak. He was attacked with pyrexia and after six weeks of continued high temperature (102°-103°) the disease ended fatally.

In the first case we have a good illustration of the marvelous improvement that may occur at first, after treatment with arsenic. In the second we see such an improvement followed, after several months, by a relapse in which arsenic proved unable to stop the fatal course of the disease.

We may also note in the latter case how little the spleen varied in size, from October 9th to the end - it's lower border being never far distant from the umbilicus.
<table>
<thead>
<tr>
<th>Date</th>
<th>% of Full White Deer</th>
<th>Ratio</th>
<th>Observations</th>
<th>Date</th>
<th>Treatment (per dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sept 26th</td>
<td>72 1/72</td>
<td></td>
<td>Splene reaches beyond diaphragm to right cost. sup. spine.</td>
<td>Sept 25th</td>
<td>Lig. Arsenie 49.6g 9m</td>
</tr>
<tr>
<td>Oct 4th</td>
<td>7/2 1/6</td>
<td>Epistaxis again</td>
<td></td>
<td>Oct 4th</td>
<td></td>
</tr>
<tr>
<td>7/15</td>
<td></td>
<td>Vomiting occurred &amp; nausea &amp; anorexia occurred till 6.9 Oct.</td>
<td></td>
<td>Oct 5th</td>
<td></td>
</tr>
<tr>
<td>Oct 7/6</td>
<td>1/112</td>
<td></td>
<td>Urine milky yellow from coarse meconias (stark aligae), scarce &amp; yellowish tint in dependent portion, not beyond the right iliac line.</td>
<td>Oct 7th</td>
<td></td>
</tr>
<tr>
<td>Nov 2nd</td>
<td>69.8 1/105</td>
<td></td>
<td>Spleen as large?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nov 21st</td>
<td>69.8 1/18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec 3rd</td>
<td>7/8 1/24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec 8th</td>
<td>7/8 1/25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec 10th</td>
<td>79.8 1/71</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td>Pulse Rate</td>
<td>Ratio of White to Red Cells</td>
<td>Spleen</td>
<td>Observation</td>
<td>Haemo.</td>
</tr>
<tr>
<td>-------</td>
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<td>--------</td>
</tr>
<tr>
<td>3 Oct</td>
<td>32 1/2</td>
<td>1:20</td>
<td>6 1/2&quot;</td>
<td>Below ribs</td>
<td>4.5%</td>
</tr>
<tr>
<td>5 Oct</td>
<td>52 1/2</td>
<td>1:32</td>
<td>Yes</td>
<td>Pyrexial attack began</td>
<td></td>
</tr>
<tr>
<td>12 Oct</td>
<td>59 1/2</td>
<td>1:24 1/2</td>
<td>3&quot;</td>
<td>Pyrexial attack</td>
<td>4.5%</td>
</tr>
<tr>
<td>25 Oct</td>
<td>70 1/2</td>
<td>1:30</td>
<td>5 1/2&quot;</td>
<td>Patient now convalesce from pyrexial attack.</td>
<td></td>
</tr>
<tr>
<td>2 Nov</td>
<td>86 1/2</td>
<td>1:54 1/2</td>
<td>3&quot;</td>
<td>Patient is still weak, albumen in urine, been present.</td>
<td></td>
</tr>
<tr>
<td>10 Nov</td>
<td>84 1/2</td>
<td>1:37</td>
<td>3&quot;</td>
<td>Spleen distant from umbilicus, beginning to rapidly decrease, now, in</td>
<td></td>
</tr>
<tr>
<td>22 Nov</td>
<td>88 1/2</td>
<td>1:14</td>
<td>3&quot;</td>
<td>Patient feeling better</td>
<td></td>
</tr>
<tr>
<td>1 Dec</td>
<td>78 1/2</td>
<td>1:36</td>
<td>3&quot;</td>
<td>Spleen distant from umbilicus, beginning to rapidly decrease, now, in</td>
<td></td>
</tr>
<tr>
<td>4 Dec</td>
<td>88 1/2</td>
<td>1:29 1/2</td>
<td>3&quot;</td>
<td>Patient feeling better</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td>% Ratio</td>
<td>Ration</td>
<td>Date</td>
<td>Observations</td>
<td>Daily Treatment</td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
<td>-----------</td>
<td>--------</td>
<td>--------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Feb 4</td>
<td>67.4:1:1</td>
<td>60%</td>
<td>Feb 1</td>
<td>Spleen 7 1/2&quot; below rib margin in L sphincter line; 2 1/2&quot; below navel; no rise to R of middle line. No enlargement palpable.</td>
<td>Arsenic and quinine - does not recorded at first.</td>
</tr>
</tbody>
</table>

- **Feb 5**
  - Spleen 5" below rib margin.

- **Mar 8**
  - Spleen 4 1/2" below rib; 6" horizontally at base of rib margin.

- **Mar 15**
  - Spleen 4" below rib; 6" horizontally at base of rib margin.

- **Mar 22**
  - Spleen 2 3/4" below rib. 4" at upper base.

- **Apr 6**
  - Spleen 2 1/2" below rib. 3" at lower base.

- **Apr 12**
  - Spleen 2 1/2" below rib. 3" at lower base.

- **May 9**
  - Edge of spleen receding just under the 6th rib. Left of spleen.

- **July 16**
  - Patient felt spleen pressure. Her 18th pyrexial attack.
Literature.


2. Rule & Staunton. "Lectures on the Blood and Vertebrae"
   Med. Times 11, 162, p. 270


5. London Medical Record 1879 p. 178.


