ACUTE LYMPHATIC LEUKOCYTHAEMIA.

Being a Thesis for the Degree of M.D.,
Edinburgh University.

by

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April, 1906.

ACUTE LYMPHATIC LEUKOCYTHAEMIA.

As the name suggests the most striking feature of the condition consists in a marked preponderance of the white cells of the blood, and the term "lymphatic" must be used to denote the variety of leucocytes here found in excess and not held to indicate the origin of these cells solely in the lymphatic glands.

Cases of coincident enlargement of the lymphatic glands and spleen were noted by Malphighi in 1669 and by Morgagni in 1752.

Pallor of the blood in certain cases was commented on by Bichat at the beginning of the 18th century. In 1827 Velpeau observed the combination of pallor of the blood with enlargement of the spleen.

The dependence of this alteration in the appearance of the blood on an excess of white corpuscles was described by Donné in 1884 and interpreted by him as due to imperfect transformation of white into red corpuscles. In 1845 Dr Hughes Bennett described as "suppuration of the blood" two cases with enlarged spleen and suggested the term "leucocythaemia". Later in the same year Virchow independently published an account of the

condition ascribing the appearance of the blood to a large increase of leucocytes and called the condition leukaemia, he recognised the involvement of the spleen and lymphatic glands and Neumann in 1868 showed that the bone marrow is also involved. Mosler in 1872 gave an accurate description of the various kinds of white cells present in the blood.

In 1857 the acute nature of some of the cases was recognised when Friedreich described a case whose duration was only six weeks.

Leucocythaemia or Leukaemia is accordingly a disease of the blood forming organs and has been divided into two main groups.- splenic and lymphatic.

This division was based mainly on clinical differences and as knowledge of the condition increased it was found necessary to abandon this classification and to substitute for it another, having more regard for the pathological differences. The terms therefore "lymphatic" and "myelogenous" were used and indicated the chief kind of cell found in the blood and its place of origin.

With the increase of the number of cases examined and in view of recent work on the subject it would appear necessary to again alter this classification and to use the terms "lymphatic" and "myelogenous" as describing the type of leucocyte in

excess and not as indicating its seat of origin, since in some undoubted examples of lymphatic leucocythaemia changes have been found only in the bone marrow.

This class of lymphatic leucocythaemia may be divided roughly into two groups - acute and chronic.

Denys recognises three varieties:-

(1) A Chronic form with hyperplasia of lymphoid tissue.

(2) An acute form also with hyperplasia, its duration being three to four months.

(3) An acute form without hyperplasia.

The following two cases of acute lymphatic leukaemia occurred recently in the neighbourhood.

CASE I.

I first saw the patient on March 7th, 1906. He was a well developed man aged 58. He was then complaining of weakness, loss of appetite, pallor, swollen tender gums, some swelling of the neck and nose and a tendency to epistaxis.

He gave the following history. Towards the end of January he noticed that he became more easily tired and was not able to do his work as a labourer with his former energy. He felt that there was

something wrong with him but could not define what it was.

During the second week of February while at his work he was seized with a rigor and felt very ill; he was feverish that night and unable to go to work next day. He took to bed and called in his doctor. His temperature was found to be 102° but beyond pains in the back and limbs nothing further was to be made out. In three days his temperature became normal and he felt better; he was able to get up and come downstairs. A few days later he had epistaxis and also subcutaneous haemorrhage into the tissue of his nose which became very swollen and ecchymosed. About the same time he noticed his gums to be a little tender and swollen. After short intervals he again had epistaxis twice; the bleeding was not severe, being only a very slight trickle lasting from four to eight hours and he did not lose much blood. Instead of gaining strength he got weaker and lost all desire for food. On February 26th he felt some little lumps on the right side of his neck and also under the angle of both jaws.

Previous Health:

He stated that he had always enjoyed the best of health and had never had any serious illness or

accident; he did not remember to ever have been troubled with his throat or tonsils. There is no history of malaria or syphilis.

Family History:

This was negative. His father and mother were strong healthy people and lived to a good age, the father to over 80 and the mother to over 70. He had one sister who has always been healthy and no brothers. He was married but had no children, there was no history of miscarriages, the wife is alive and healthy.

General:

He lived in a dry, well-built house in a healthy locality. His habits were exemplary and he was a nonsmoker and total abstainer. He was always a hearty eater. He had never been out of England and spent almost his whole life in Wiltshire.

On Examination:

He was very pale with a slightly yellow tint, but no actual jaundice. The face had rather a puffy appearance, the nose was much swollen and ecchymosed and he breathed chiefly through his mouth. There was no apparent wasting, his body was well developed and well nourished, the skin had a waxy look, the neck appeared to be somewhat full.

Both submaxillary glands were enlarged to about the size of walnuts, a chain of glands could be felt on both sides of the neck, chiefly in the posterior triangle and far better marked on the right side. The enlarged glands were discrete, firm and freely movable on the surrounding structures, they were not tender and none could be felt elsewhere than about the neck.

The gums were much swollen and tender, they were pale but mottled with areas of a dark red colour. The teeth were pretty good and were not loose, the tongue was furred and the breath extremely foul. The tonsils were not enlarged. There was no tenderness of the bones.

Circulatory System:

The pulse was 110 full and easily compressible, regular in time and in force.

The heart was within normal limits, the apex beat was in the fifth interspace and the sounds were closed in all areas.

On making a puncture for the examination of his blood, the blood was observed to flow very freely from the wound, to be pale in colour, watery in consistence and to show very little tendency to clot. When allowed to do so, the clot formed was very

loose and showed little if any retraction, there appeared to be an unduely large proportion of serum.

Abdomen:

The spleen could only just be palpated.

The liver was found to be slightly enlarged, on percussion its upper limit in the mammary line was at the fifth rib and its lower border half an inch below the costal margin.

It felt smooth on palpation and there was no tenderness.

Respiratory System:

While at rest his respirations were 20 per minute, but the slightest exertion produced dyspnoea. He had an occasional cough which somewhat troubled him, especially at night. There was a little impaired resonance at the bases on percussion and on auscultation a few rales could now and then be heard.

The Urine:

Was normal in quantity, its specific gravity was 120. It was loaded with urates, there was no trace of blood or of albumen. Later in the case, the chlorides were found to be markedly diminished.

Fundi:

On examining the fundi numerous haemorrhages were found in both eyes, they were more marked and

numerous towards the periphery. They were irregularly oval in shape with their long axis parallel to the vessels, they appeared to be more intimately connected with the veins than with the arteries. The whole fundus was pale and had a hazy appearance which was especially marked roundabout the haemorrhages. The disc was very pale and its edges indistinct. The veins appeared to be enlarged. Sight was good.

Course:

The patient was confined to bed and became rapidly weaker. The swelling of the nose soon subsided. He had no desire for food and was unable to take solids, any attempt to do so brought on an attack of retching. His cough gradually left him and he had practically no subjective symptoms beyond weakness. The temperature was raised throughout and was irregular in character.

The heart became dilated, murmurs developed in all the areas and a venous hum could be heard in the neck.

The liver and spleen gradually increased in size until on March 22nd the lower border of the liver reached 1½ inches below the costal margin and the spleen could be plainly felt projecting for about

below the costal margin.
two inches. Some slight tenderness was present in the hepatic and splenic regions and he complained that he felt a pain in his left side on taking a deep breath or on attempting to turn in bed.

The tissues of his left cheek just behind the angle of the mouth became swollen and formed a firm painless swelling about the size of a florin. This was noticed on March 15th and after persisting a few days it gradually disappeared. After March 22nd the liver and spleen slowly diminished in size until the spleen was scarcely palpable and the liver reached only half an inch below the costal margin.

On March 17th the submaxillary glands were noticed to be distinctly smaller and they continued to decrease in size until the left one could scarcely be felt at all and the right one was only half its former size.

The glands in the neck appeared to remain about the same size though on account of the progressive emaciation they could be more plainly felt. No enlarged glands were at any time felt elsewhere.

The gums remained very swollen throughout and towards the end necrotic areas developed in them, sordes collected on the teeth and the breath was very offensive.

The tonsils were never appreciably enlarged, there seemed to be some obstruction to breathing in the naso-pharynx and during his illness he breathed chiefly through the mouth. An examination of the naso-pharynx was not made as any attempt to do so caused retching and exhaustion.

On two occasions there was some vomiting but never any haematemesis - there was no diarrhoea.

There were no further haemorrhages of any sort until the 29th when his whole body was observed to be covered with small purple spots the size of a pin head; they were not thickly set.

During the last three days his face was frequently seen to twitch, the twitching was more pronounced on the right side of the face and was sufficient to draw up the angle of the mouth; there was no paralysis, the pupils were equal and reacted to light, there was no strabismus, his hearing remained good.

The urine at no time gave any evidence of blood or of albumen, it was always loaded with urates but towards the end the deposit became much less copious. The chlorides were estimated on the 22nd and found to be only 1·69 grammes, in the 24 hours while on the 28th and 29th they were entirely absent. There was no evidence whatever of pneumonia.

He died at 1 a.m. on March 31st, for a short time before death he is said to have been very restless and appears to have had considerable air hunger. For four days previous to his death he lay in a semi-conscious condition sleeping most of the time; he did not always recognise his friends but responded when spoken to.

Treatment:

He was given a mouth wash of euthymol and every effort was made to keep the mouth as clean as possible, but without much success.

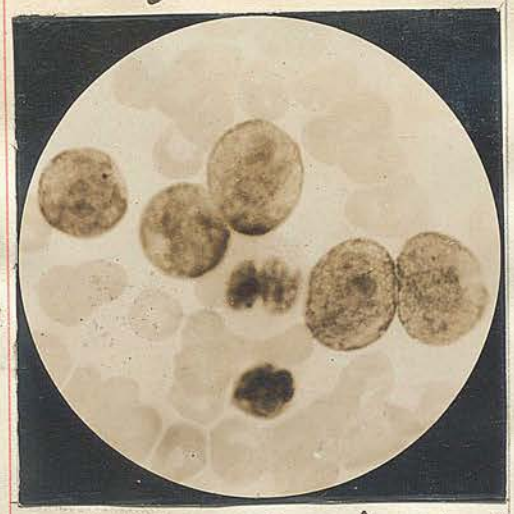
He was put on a mixture of iron and liquor arsenicalis, the strength of the latter was gradually increased from 3 to 10 minims three times a day, he was also given ½ gr. pill of opium at night in order to ensure him getting rest and also with the hope of warding off sickness, diarrhoea and haemorrhage from the bowel. After three weeks as his condition was steadily getting worse, the iron and arsenic was stopped and he was given Extract of bone marrow, but derived no benefit. He had a great loathing of anything solid, his diet consisted entirely of fluids and fruit. He was very thirsty and drank large quantities of liquid and was encouraged to do so, alcohol in the form of brandy was given somewhat freely and it appeared to help him.

It was unfortunately impossible to get a Post Mortem, but permission was obtained to remove one or two of the enlarged glands in the neck.

These were found to be red in colour, firm and perfectly discrete, on section they had a blotchy, red appearance and the medullary portion was considerably softer than the cortical. On one a few small haemorrhagic points were seen scattered through the gland. On microscopic examination no organisms could be found and no mitoses were seen. The stroma appeared to be unaltered in character; there were large numbers of lymphocytes and a fair number of what seemed to be large epithelioid cells.

The examination of the blood showed marked diminution of the red cells and increase of the white, this increase was due to the presence in large numbers of the large form of lymphocyte, the polymorphonuclears were greatly reduced, eosinophiles were not met with and myelocytes observed on only one occasion. Poikilocytosis was well marked and in the later stages of the disease nucleated red cells became fairly numerous, they were chiefly megaloblasts. The haemoglobin was obviously reduced. The large form of lymphocyte varied greatly in size, some being a little larger than a red blood corpuscle, others two or three times as large; in many, the nucleus was large and surrounded by a narrow rim of protoplasm which

No 1 × 1000



Group of large lymphocytes.

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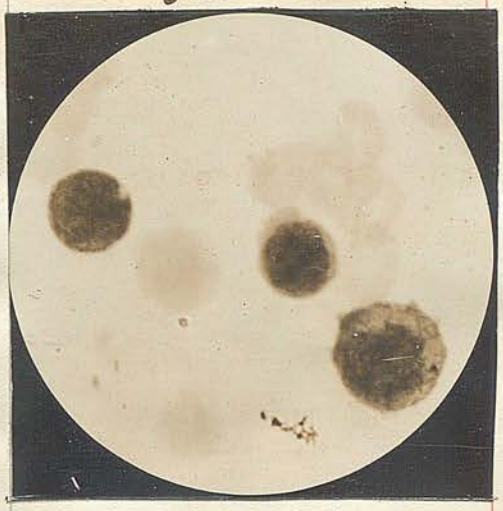
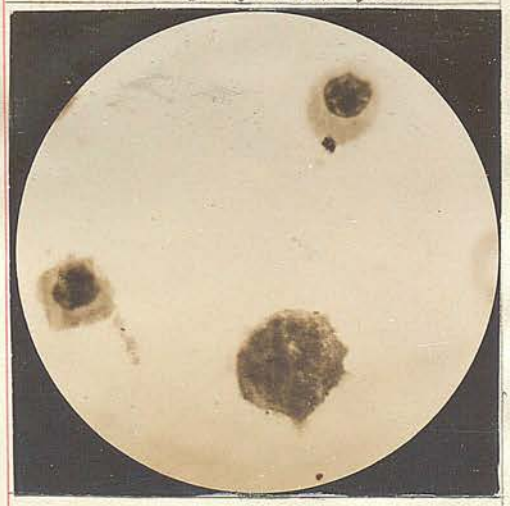


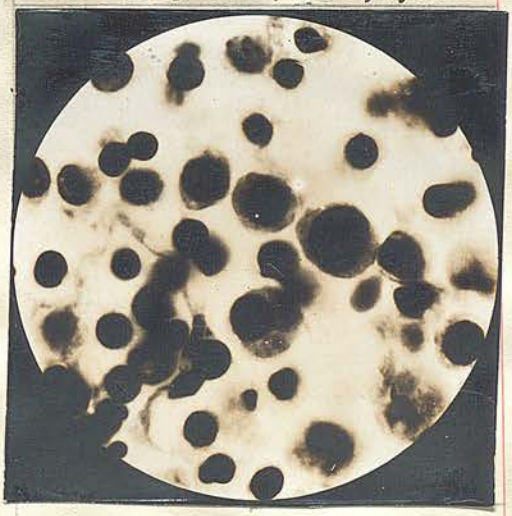
Degenerating lymphocytes

No: 3: × 1000



Two nucleated red cells and a degenerating lymphocyte

No: 4: × 1000



Section of lymphatic gland. 20 mitoses nuclei all in resting stage. Shows a few Large epithelioid? cells.

stained very deeply with basic dyes. In others, the nucleus was not so large and stained more deeply than the surrounding protoplasm which was more abundant; in many of these cells the nucleus was indented and in a few closely resembled a polymorphonuclear, save that the surrounding basophile protoplasm was entirely free from neutrophile granules. Many of the lymphocytes gave evidence of degeneration, in some the staining was very diffuse and they appeared as pale blue blotches, in others vacuoles could be seen both in the nucleus and in the protoplasm, one or two nuclei were seen surrounded only by jagged bits of protoplasm. No mitotic figures were seen. The following table gives the state of his blood, temperature, pulse and respirations from time to time during his illness.

DIFFERENTIAL COUNT.

500 Leucocytes counted.

Date	Red Blood corpuscles	White Blood corpuscles	Proportion of white to red.	Lymphocyte per cent.		Polymorpho-nuclear per cent.	Myelocyte per cent.	Nucleated red blood corpuscles per cent.	Temperature		Pulse	Respirations
				Large	Small							
March 8	2,000,000	30,854	1 - 64.8	80	3	7	0	0	Afternoon.	100	115	22
10	2,000,000	28,000	1 - 71.4	91.4	4.8	3.8	0	0		101	120	23
12	1,600,000	30,687	1 - 52.1	93.4	4.6	2	0	0		100	110	20
15	1,424,000	35,000	1 - 40.6	90	5.8	3.8	0	0.4		101	122	24
17	1,200,000	53,125	1 - 22.5	91.2	4.4	3.2	0.4	0.8		100	120	22
20	1,232,000	56,875	1 - 21.6	89.4	5	4.6	0	0		101.8	120	22
22	1,440,000	89,375	1 - 16.1	83.8	10.4	4.8	0	1		M. 99.6 E. 102	110 130	20 24
24	880,000	75,000	1 - 11.7	80	9.2	8.6	0	2.2		M. 100 E. 100.8	98 108	20 20
26	828,000	59,375	1 - 13.9	88	6	4.8	0	1.2		M. 100.6 E. 100.4	112 100	20 18
29	700,000	37,500	1 - 17.6	80	8	6	0	2		M. 100.2 E. 101	100 115	16 20

CASE II.

Through the kindness of the Doctor in attendance I am enabled to give the notes of the following case.

The patient was a male aged 31, 5 feet 10 inches in height and of good muscular development.

On 22nd February 1906, he cycled from his home to a neighbouring town, a distance of seven miles to consult a Doctor.

He complained that four or five months previous he commenced to feel lethargic and was easily fatigued, he also had a tendency to shiver.

Beyond some gout on the mother's side, the family history was negative.

His previous health had been excellent. Ten years ago he had had an intermittent albuminuria when reading for his degree, but this completely passed off after a rest. He had been a total abstainer all his life but was a somewhat big feeder and was especially fond of meat. His work was hard and arduous mentally as well as physically.

On examination the backs of both hands and the heels were covered with what appeared to be "chilblains". There was no evidence of glandular enlargement anywhere, there was slight tenderness on palpation in the hepatic and splenic regions,

but no enlargement.

The urine was in every way normal. He was advised to rest and given aspirin and nux vomica with $\frac{1}{2}$ gr. calomel every other night.

On February 28th he wrote saying that he felt much better but on the next day he was seized with diarrhoea, and also passed blood by the bowel; his pulse varied from 96 to 106 and his temperature from 99 to 101·2°. One of his tonsils was ecchymosed and looked like a ripe grape.

On March 1st it was noted that the cervical axillary and inguinal glands were enlarged.

There was great prostration and he vomited his food.

The vomiting and diarrhoea mixed with blood continued until the 4th March; he was then able to retain his food and the diarrhoea ceased, but the prostration was very great.

He died on March 6th at 3-30 a.m. He was fully conscious to within 10 or 15 minutes of the end.

On two nights he was slightly delirious; his temperature varied from 100 to 103° and his pulse rate steadily rose until it reached 172.

A differential count of his blood made on March 3rd gave:-

Polymorphonuclears 0.75%.

Small & Large Lymphocytes 97.25%.

Myelocytes. 2%.

There was unfortunately no post mortem.

E T I O L O G Y .

Age and Sex.

The fact that many theories are put forward as to the cause of this disease is in itself sufficient to indicate that the actual cause has not yet been proven.

It may occur at any age but is more common in males than in females. In an analysis of 56 cases Fussel, Jopson and Taylor found the youngest subject to be $2\frac{1}{2}$ and the oldest 71 years; the great majority were males, most cases occurred between

the ages of 10 and 30 - nine were in the first decade.

It would appear to be more common in children than is generally supposed.

R. Hutchison remarks that the comparative frequency of this form in childhood is just as striking as the rarity of the myelogenous variety.

McCrae finds Leukaemia is a relatively rare disease in the first decade, but with regard to acute leukaemia believes there is ground for thinking that it occurs in a somewhat larger proportion.

Theodor collected 45 cases of acute leukaemia of which six were in the first decade.

The extent and activity of the adenoid tissue in childhood render it peculiarly liable to become the seat of pathological processes of all sorts. In them the disease has been divided into three types described by Guinon and Jolly:

1. Those exhibiting profound anaemia with general glandular enlargement with a haemorrhagic tendency in the later stages.

2. Those in which the haemorrhagic tendency is exhibited from the outset, petechiae appearing early so that the case may resemble one of the infective purpura.

3. Pseudo-scorbatic cases in which lesions in the buccal cavity are the most striking feature.

Heredity:

Heredity appears to have little or no influence. A case, however, is reported by Greene where the patient's sister died from chronic leukaemia at about puberty, while another sister had similar symptoms during pregnancy, but recovered after the induction of labour.

Malaria & Syphilis:

Malaria & Syphilis are commonly given as being possible predisposing causes, but acute leukaemia is a relatively rare disease, whereas malaria and syphilis are common. Moreover, in a large proportion of cases of acute leukaemia it is not possible to obtain a history of either.

Severe anaemia:

Cases have been described as following severe anaemias and it is possible that as Neumann suggests the exciting factor is the strain and irritation produced in the blood forming organs by their endeavour to keep pace with the demands made upon them. This theory has the support of Strauss who looks upon the relative lymphocytosis which occurs in pernicious anaemia as an indication that this disease may under certain circumstances develop into lymphatic leukaemia. This lymphocytosis is also noted by Da

Costa and Cabot. This theory, moreover, would not disagree with that put forward by Weber, Wolf and Pappenheim who assume that there is a cell of common origin for the various forms of leucocytes.

Organismal Origin.

Acute leukaemia in its rapid incurable course suggests a malignant disease, while its widespread nature, the irregular temperature and great increase in number of the white cells are not against an organismal infection.

From time to time, therefore, the finding of various micro-organisms in the blood or tissues has been reported by many, e.g. Obrastzow found cocci in the glands, Lowitt has described an intranuclear amoeba-like body, Fowler found a bacillus 6 or 7 in length, but admits that no special precautions to exclude organisms had been taken in the preparation of the films.

In the large majority of cases, however, observers have failed to find organisms.

The findings of Lowitt are not generally held and have been discussed by Turk. Lowitt, by means of a special staining method has claimed to find "intranuclear bodies or amoeba-like organisms" in the lymphocytes. He says that they occur more frequently in the lymph glands, bone marrow and spleen than in the blood itself, and that they are

usually found in young active cells while they are absent in those showing degeneration.

He also claims to have caused the myelogenous type in animals by the injection of leukaemic tissues but was not successful in the lymphatic variety.

Turk has concluded that the appearance of the supposed parasite is produced by products of cellular degeneration; he also denies that leukaemia can be transmitted to animals by innoculation with leukaemic tissues.

An infectious nature is suggested by Obrastzow's classical case where the patient died after a ten days" illness, and cocci were found in the glands - forty days later the attendant developed similar symptoms to the patient and died in fourteen days with purpura, haemorrhages, fever, albuminuria and a proportion in the blood of one white to nine red corpuscles. However, there is no record of this ever having been repeated even after the closest contact.

In contrast to this Askanazy has described a case of acute leukaemia in a pregnant woman where the child proved to be healthy. Cameron and Sanger also have published cases in which the children of mothers suffering from the chronic form were born healthy.

Packhard states that Westphal failed to obtain cultures from splenic puncture during life, and from the blood and bone marrow after death; that Gilbert was unsuccessful in his attempts to innoculate healthy dogs. That Mosler also failed to produce the disease by the injection of leukaemic blood into dogs and rabbits and that Bollinger who worked with leukaemic blood of animals of the same species got no better results.

P A T H O L O G Y .

The key to the pathology of this condition lies in the presence in the blood of the characteristic lymphocytosis.

Wherever the lymphocytes are capable of arising, there we may expect to find changes typical of the disease.

Though their mode of origin cannot yet be said to have been definitely settled, it would appear that they are capable of arising from lymphoid tissue wherever present.

It is in the lymphoid tissue, therefore, that the pathological changes are centred.

The striking enlargement of the glands gave rise to the belief that in them lay the starting point of the blood change and was largely responsible for the term "lymphogenous" in contra distinction to "myelogenous".

These terms are still used though in a less restricted sense.

Since that time, however, quite a number of cases have been described in which with the typical condition of the blood changes to account for it were found only in the bone marrow; e.g. Kelly, Reed, Denning, Pappenheim and others.

In the opinion of Walz, Pappenheim and Reed the bone marrow is the starting point of the disease in all cases.

Kelly shows that bone marrow is to be included among the lymphoid structures of the body and that it is accordingly able to form lymphocytes.

In a description of the pathology of the disease it would, therefore, be appropriate to start with the bone marrow.

Bone Marrow:

The extent to which the marrow may be affected varies with each case, but changes are invariably found in it and as we have seen may be present there when other organs do not show involvement.

This alteration has been found to be most marked in the tubular bones, most frequently the marrow is red in colour and of soft gelatinous consistence. Of the five cases described by Bradford and Shaw in one there was no post mortem, in three the marrow was red and gelatinous, in the other "puriform" not red anywhere.

In the case described by A. Dennig the bone marrow appeared to be normal macroscopically, a condition, as he remarks, probably unique.

Fussel, Jopson and Taylor in their analysis of 56 cases found that the lymph glands, spleen, bone marrow, liver, kidneys and alimentary canal seem to have been constantly affected by lymphatic haemorrhagic and parenchymatous changes.

In whatever portion of normal marrow that remains the natural function would seem to be retained since if suppurition should occur, the pus on examination would be found to contain the usual polymorphonuclear leucocytes.

On microscopic examination of the abnormal marrow large numbers of lymphocytes are found, the polymorphs are comparatively scanty and may be absent. In two cases Bradford & Shaw made films from the marrow of the shaft of the femur; the differential count gave:-

A.	Small lymphocytes	3·3%.
	Large lymphocytes	92.6%.
	Myelocytes	4·1%.
	Polymorphonuclears) Coarse Oxyphiles)	None found.
B.	Small lymphocytes.	16·8%.
	Large lymphocytes	82·2%
	Polymorphonuclears	0.2%
	Coarse Oxyphiles	0·6%
	Myelocytes	0.2%.

Muir speaks of a case in which the bone marrow showed almost an absence of the nucleated red corpuscles and of the cells which are believed to be their antecedents, the whole tissue being filled with smalluninucleated leucocytes.

The various stages of the red blood corpuscle are always present but apart from a possible decrease in number they show no change. The normal "marrow cells" are greatly reduced in number.

Lymphatic Glands:

In the majority of cases the lymph glands are enlarged, their degree of enlargement and number of glands involved varies within wide limits. The enlargement appears to be specially marked in the cervical region - this was so in four of Bradford & Shaw's cases and in the fifth there was universal enlargement.

Fussel, Jopson and Taylor found haemorrhage into the gland substance to be of frequent occurrence.

In contra-distinction to malignant disease the glands tend to be discrete and do not ulcerate through the skin or infiltrate surrounding structures; they are firm in consistence unless very large when in some cases they may become soft; they are slightly,if at all,tender.

On section they are most frequently reddish or mottled red and yellow - a colour distinct from the green of the glands in chloroma, though Bradford and Shaw describe a case in which the abdominal glands were found to be very soft and greenish in colour.

Byrom Bramwell reports a case in which with all the symptoms of acute lymphatic leukaemia some of the glands of the neck were green on section. A similar condition has also been reported by Linsay Stephen.

Microscopically the change is seen to be parenchymatous in nature; the stroma is not altered in character.

In the normal gland here and there are seen foci of cell proliferation - the germinating centres. In acute lymphatic leukaemia the whole gland becomes as it were a germinating centre and is crowded with lymphocytes (Benda).

Bizzozero found mitotic figures especially numerous in the lymphatic glands and spleen. A similar state has also been described by Gulland and found in Obrastzow's case.

Liver:

The lymphoid tissue shows hyperplasia and is packed with lymphocytes. This is especially marked in the portal tracts.

Spleen:

In the majority of cases the spleen is moderately enlarged. Enlargement was present in four-fifths of Bradford & Shaw's cases and in forty of these analysed by Fussel, Jopson and Taylor.

In children the enlargement of the spleen is more common than in adults and may reach a large size.

From the review of thirteen recorded cases McCrae found the spleen to have been enlarged in every case.

On section the colour is found to be greyish red to brownish red frequently mottled (Bradford & Shaw).

The appearance of the follicles is not constant, being sometimes sharply limited, but more often enlarged and ill-defined.

Consistence usually soft; haemorrhages are occasionally found (Fussel, Jopson and Taylor).

Histology.

The whole organ is packed with lymphocytes and the normal structure thereby obscured.

Kirk in his Handbook of Physiology states that the Malphighian corpuscles have the structure of lymphatic nodules.

It is mainly by the increase in size of the Malphighian corpuscles and by the accumulation of lymphocytes that the enlargement, when present, is brought about.

Wolff is of opinion that the spleen contains "indifferent cells" which under certain circumstances can develop along various lines according to the demand of the moment.

Kidneys:

The kidneys likewise may be enlarged according to the degree of the involvement of their lymphoid

tissue, this may occasionally form definite deposits.

On section they are usually pale, as in the post mortems on Bradford & Shaw's cases, and here and there haemorrhages may be found.

Histologically there is hyperplasia of the lymphoid tissue and general infiltration with lymphocytes.

Nephritis may occur, but is rare (Fussel, Jopson and Taylor).

Alimentary Tract:

Enlargement of the gums, tonsils and of the lymphoid tissue in the naso-pharynx is common and is often accompanied by ulceration.

Nodules of lymphoid tissue may be found in the stomach or intestines, more commonly Peyers patches are found to be enlarged and may be ulcerated.

Ulceration and Necrosis:

Ulceration and necrosis may occur in the skin and mucous membranes more commonly in the latter.

In the skin it may follow injury or be found at the site of a previous injury, pressure, or haemorrhage.

The condition is met with most frequently in the mouth, probably owing to the fact that here injury may most frequently occur and sepsis find

entry through the breach.

Haemorrhage:

Haemorrhage in various situations is common, it is very frequently observed in the retina. It may also occur in the skin and may arise from any part of the mucous membranes of the gastro-intestinal tract.

It has been observed in the pericardium epicardium pleura peritoneum pelvis of the kidney and in the bladder.

According to Benda the haemorrhage follows injury of the vessel wall which is brought about by the formation in its wall of lymphomata. He claims that wherever haemorrhage occurs an accumulation of leucocytes may be observed around the vessel.

Thymus:

It is interesting to note that the Thymus has frequently been found to be enlarged.

Beard in the course of a systematic investigation of the development of Scyllium canicula found that for a comparatively long period of the development the blood contained only nucleated red blood corpuscles. Almost as soon as leucocytes arise at

all some of them make their way into the blood.

Working with the Raja Balis he came to the conclusion that the first place of origin of the leucocytes is the thymus.

He is of opinion that the same will hold good for man.

It would, therefore, appear that the thymus may play an important role in the formation of leucocytes and it is not surprising to find it enlarged in a disease where an excess of leucocytes is such a conspicuous and essential feature.

S Y M P T O M S .

The symptoms complained of by the patient may in the majority of cases be divided into two groups.

(1) Those due to the anaemia.

(2) Those peculiar to the type of disease from which he is suffering.

The symptoms most commonly complained of by the patient are:-

Group (1). Great weakness.
Shortness of breath.
Loss of appetite.
Pallor.

Group (2) Lumps in neck, etc.
Tenderness & swelling of the gums.
Haemorrhages.

A number of symptoms common to the anaemic state are accordingly met with - dyspnoea on exertion, oedema, rapid pulse, haemic murmurs, weakness.

The appearance of the patient is often striking; the neck looks full, the face somewhat bloated and of a dirty grey or slightly lemon colour.

Dyspnoea added to that due to anaemia is frequently met with and may be due to enlargement of lymphoid tissue in the naso-pharynx, to enlargement of the thymus or mediastinal glands limiting the area of the chest and perhaps pressing on the trachea or bronchi. Bronchial catarrh, moreover, frequently occurs and lobar or broncho-pneumonia may be a terminal affection.

The heart and circulatory system present the symptoms usual to anaemia, haemic murmurs develop, endocarditis has sometimes been found as described by Pollmann. The pulse is inclined to be rapid.

The onset is commonly insidious but may be sudden. Sometimes there is a history of vague prodromal symptoms of general malaise, weakness or

a febrile attack, occasionally there may be pains in the region of the spleen and a few have commenced with a swelling of the joints resembling acute rheumatism (A. Frankel). There may be but little to draw attention to the disease, McCrae reports the case of a boy aged three who on admittance to hospital had enlarged tonsils and adenoids; he otherwise seemed to be in good health and but for the blood examination no suspicion of leukaemia would have been entertained. In other cases a profuse haemorrhage may be the first sign which draws attention to the possibility of a blood disease.

Blood:

The all important feature of the disease is the change in the blood.

The main feature of this change consists in a leucocytosis of such a nature that the lymphocytes are greatly in excess, their increase being both absolute and relative.

The number of red blood corpuscles is reduced, a few nucleated reds are sometimes observed. R. Muir says he has not observed any nucleated red corpuscles in this variety of leukaemia until the number of red cells has fallen below 1,500,000. Bradford and Shaw found not only a great diminution

in the amount of blood. The blood is frequently stated to have a cafe au lait colour. The haemoglobin is reduced. Many authorities, e.g. Bradenburg, Bramwell, Gilbert and Weil, are of opinion that the disease may be well advanced and the leukaemic condition established while the red blood corpuscles are only slightly diminished. The blood also clots in a somewhat characteristic way, the clot is loose, does not show the same amount of retraction as the normal and there is a relative increase in the proportion of serum.

Of all the features of the blood, the increase of the lymphocytes is the most marked and the most striking. The proportion of the small to the large variety does not appear to be at all constant; Osler states that in acute lymphatic leukaemia the large form of lymphocyte is frequently present in considerable percentage and that in the more chronic cases the small form usually predominates.

Cabot observes that in some cases gradation from the smallest to the largest may be got.

In Bradford and Shaw's cases the large form was in excess, but in Fussel, Jopson and Taylor's and in McCrae's the small variety was most numerous.

Fraenkel describes the predominating cell as varying greatly in size from that of a red blood corpuscle to those twice as large and showing every

every grade of transition between the two. The large cells contain voluminous nuclei which fill the cell leaving only a narrow rim of protoplasm. The nuclei are usually round or oval, but may show indentations and some are even polymorphous. The typical small lymphocytes are much less numerous than these large elements, but are still absolutely increased.

He notes the absence of myelocytes and eosinophiles and the relative and even absolute decrease of the polymorphonuclear cells.

The average normal proportion of one white blood corpuscle to 700 red is greatly altered, the lowest being 1 to 65 and the highest 1 to 5. Cabot gives an average of 1 to 40 and observes that the numerical increase of white cells is not so marked as in myelogenous leukaemia where it reaches a high grade and averages 1 to 7.

McCrae in reporting a case of acute lymphatic leukaemia observed that there was a marked tendency for the lymphocytes to disintegrate and appear in the stained specimen as shapeless blotches with a pale blue stain. He is of opinion that this may be a feature of the lymphocytes in acute cases.

The polymorphonuclear leucocytes in striking contrast to most other forms of leucocytosis are present only in a small percentage, they may show

an absolute reduction (McCrae - R. Muir).

Iodophilia has been described as sometimes occurring. Durham, discussing iodophilia, says that he finds it in connection with suppuration that has not been walled off and is not tuberculous in character. He has found it also in pneumonia and in leukaemia.

Hofbauer, too, found it in pernicious anaemia and leukaemia. Locke and Cabot consider iodophilia to be an indication of a general tonaemia such as may occur in a great majority of diseases and is most commonly coincident with pus.

Fowler was unable to find a typical polymorphonuclear cell in any of the films examined in his case.

Myelocytes may occur in small numbers. Muir found them to be generally absent, though in one of his cases (Case 4) some were present in the blood, especially towards the end of the disease.

Myelocytes were present in two of Bradford & Shaw's cases to the amount of 0.6 and 0.4%.

Eosinophiles may also occur in small numbers but are rare.

Mast cells are never numerous and are generally entirely absent.

The following table will give a general idea of the condition found and the relative proportion of the several constituents of the blood.

Name of observer	Red Cells	White Cells	White to red	Haemoglobin per cent	Lymphocytes		Myelocytes	Eosinophiles	Polymorphs	Nucleated red cells
					Small	Large				
Bradford & Shaw Case 3.	2,500,000 to 2,000,000	74,000 to 280,000	1 to 35 1 to 7	40 to 30%	6.9%	90.4%	0.6%	1.6%	0.5%	
Bradford & Shaw Case 4.	2,500,000 1,500,000	34,500 68,000	1 to 43 1 to 25	36 to 26	13.4 12.2	61.8 64.3	0	26 -	22.3	
Do. Case 5.	-	-	-	-	0.88	98.49	0.4	0.23	0	
Fowler.	510,000	100,000	1 - 5	15						
Cabot. Average of 5 cases.	-	-	-	-	95.9		0.7	0.36	3.04	
McCrae. May 12. " 15 " 19 " 24	1,680,000 - 1,760,000 -	26,000 - 60,800 21,800	1 - 65 - 1 - 29	35 - 32	41.5 78.9 96.6 89.2	45 16.7 2.6 9.4	0.2 - -	 1 1	13.3 4.4 4 9	
Fussell, Jopson & Taylor.	1,273,000	362,000	1 - 35	32	79.37	5.54	-	0.9	11	
Do. do.	800,000	134,000	1 - 6		88.84	5.48	-		1.52	
Osler. Average of cases.	2,294,000	144,800	1 - 16	37	-	-	-	-	-	
Gilbert & Weil.	4,500,000 to 1,840,000	22,010 to 46,400	1 - 205 1 - 39	-		100	-	-	-	
Phear.	1,384,000	404,000	1 - 3	-	11.1	80.9	-	.24	6.9	
Middleton	-	30,000	-	-	4.2	93.3	-	-	2.5	
Bradley	1,850,000	85,000	1 - 22	-	28	69	-	-	3	

To sum up, therefore, the chief changes found in the blood are briefly:-

Reduction in number of the red cells, poikilocytosis may be present, nucleated reds are as a rule absent, the haemoglobin is reduced, but may be relatively high when the number of red corpuscles present are considered. In one of McCrae's cases the colour index remained at about 1.

There is great increase of the white cells due to an increase of the lymphocytes, the large or small variety may predominate, but one is inclined to think that the large variety is more numerous in the more acute cases. Von Limbeck has pointed out that the lymphocytosis sometimes does not appear until shortly before death. The polymorphonuclears are relatively reduced - often absolutely - and in some cases may be entirely absent. Eosinophiles and myelocytes may occur, but are scanty.

The importance of the blood examination cannot be overestimated; without it a positive diagnosis is impossible.

Gulland cites a case where a woman aged 25 was anaemic, slightly feverish and had a markedly enlarged spleen and enlarged cervical glands. Her heart was enlarged and there were slight systolic and diastolic murmurs.

Her condition, therefore, was suggestive of leucocythaemia, but on examining the blood the leucocytes were found to number 18,000 and the vast majority were polymorphonuclears. Endocarditis was diagnosed and proved to be correct.

Enlargement of various lymphatic structures is common and may be widespread. The most obvious and perhaps most common is enlargement of the lymphatic glands.

Very rarely is this sign wanting, the degree of enlargement varies considerably, it is common to find the cervical glands most involved often more so on one side than on the other. In consistence they are usually hard, they are discrete and movable on themselves and on the surrounding structures; though commonly painless, they may be tender - as found in case 4 of Bradford & Shaw.

From an analysis of thirteen cases in children McCrae found enlargement of the cervical lymph glands associated with affection of the mouth and tonsils occurred in half the cases, while general glandular enlargement was present in a smaller proportion.

Swelling of the gums and tonsils frequently accompanied by ulceration and necrosis is common.

The naso-pharyngeal lymphoid tissue may also be enlarged and obstruct breathing through the nose. Stomatitis was present in all of Bradford & Shaw's cases and in all there was distinct evidence that it was not an initial symptom.

Tenderness is frequently complained of and together with pain on swallowing may render the taking of sufficient nourishment difficult.

Enlargement of the spleen is present in most cases; it is usually moderate in amount and frequently cannot be palpated during life. Out of 56 cases Fussel, Jopson and Taylor found the spleen to be enlarged in 40. It is more constantly enlarged in children and tends to reach a relatively larger size than in adults. It was enlarged in all of McCrae's cases. There may be tenderness on palpation or on taking a deep breath or making certain movements, in some cases this may be due to a perisplenitis since in post mortem reports of cases adhesions are frequently described as occurring between the spleen and diaphragm.

Enlargement of the liver is frequent; it is said to be more often met with in children than in adults (half of McCrae's cases).

Tenderness of the bones may occur but is rare, it was present in case 5 of Bradford & Shaw.

Haemorrhage, a striking and characteristic feature, was present in 39 of the cases analysed by Fussel, Jopson and Taylor; it was usually in the form of petechial though there was sometimes free subcutaneous bleeding. Epistaxis and haemorrhage from the nouth and other mucous membranes were common.

Purpuric haemorrhages in the skin and to a slighter extent in the serous membranes were present in four-fifths of Bradford & Shaw's cases and melaena present in two-fifths.

Haemorrhage may be so severe as to cause death either directly by the amount lost or by its position - as in some regions of the brain. It may cause paralysis of the peripheral cranial nerves, e.g. facial, auditory (Stockman).

Retinal haemorrhages should always be looked for since they are very common and may be of help in the diagnosis.

The haemorrhages vary in size, are situated more commonly towards the periphery of the fundus and at the macula lutea. Frequently they appear as round white elevated spots with a haemorrhagic

halo. There is also often a slight diffuse retinitis the papilla is pale and its margin indistinct. The vessels look pale and the veins may be much enlarged.

Vision may be but little affected if the macula lutea be fairly free from haemorrhage, but complete blindness may be produced by bleeding into the vitreous (Swanzy).

Fever is frequently present and is irregular in character. It may resemble typhoid but most commonly is of a septic type; and considering the frequency with which ulceration and necrosis occurs in the alimentary tract, it is evident that there is abundant chance for septic absorption to take place and cause disturbances of temperature in addition to that produced by the disease itself.

Fussel, Jopson and Taylor found fever in 31 cases, in one of which it resembled typhoid, in the others it was septic in character. McCrae is of opinion that fever accompanies most cases, but as a rule is not high. In Fowler's case, it ranged from 98° to 101°F., in those of Bradford & Shaw the maximum temperature ranged from 100.2° to 105.4°, but in the latter broncho-pneumonia with purulent secretion in many of the bronchides was found post mortem. The temperature may drop as death approach-

es; in a case published by Craig it ranged from 99° to 103°, but dropped to 97° just before death.

Urine:

The urine frequently shows traces of albumen and in a few cases nephritis has been found post mortem, but is comparatively uncommon. In other cases the albumen present may possibly be due to impaired nutrition of the epithelial cells of the kidney. Haematuria may occasionally occur. The uric acid is said to be always increased (Stockman) and may be derived from the nucleo-albumin of the leucocytes; its presence is frequently commented on in the reports of cases.

Josue discussing the leucocytosis of pneumonia says that Loeper has observed during the maximum leucocytosis an increased elimination of peptone and uric acid - the products of destruction of the nuclei of leucocytes. I can find no mention of the amount of chlorides present in leukaemia; in Case I. they were found to be much reduced, but the observation unfortunately extended only over a short period. Priapism is occasionally met with. Ward describes a case where it followed a thrombosis of the corpora cavernosa; it has also been noted by Craig.

DIAGNOSIS.

The most important step towards the diagnosis is the examination of the blood and should the changes already described as characteristic be found this alone might suffice.

Bradford & Shaw confess that their first case was recognised, almost by accident, by means of an examination of the blood. But their first case being thus recognised, detection of the others was easy.

As in all other diseases it is most unwise to have to rely on one factor alone; confirmatory signs, therefore, from whatever quarter are to be sought for. The value of these is apparent when one remembers that the presence of some intercurrent disease may have a marked influence upon the blood.

The evident anaemia, enlargement of the lymphatic glands, swelling soreness and perhaps ulceration of the gums, haemorrhages, enlargement of the spleen and liver, and the irregular fever must be sought for, and when found all go to make an unmistakable picture.

As might be expected, the diseases from which it is to be distinguished are those in which, together with anaemia, there may be included one or more of the prominent signs of acute lymphatic leukaemia.

The following list of diseases are those perhaps most liable to be confused with it:-

Chronic lymphatic leukaemia.
Myelogenous leukaemia.
Chloroma.
Hodgkins disease.
Tubercular adenitis.
Lymphosarcoma.
Typhoid.
Purpura.
Scorbutus.
Malaria.
Leucocytosis.

Chronic lymphatic leukaemia.

In many of its features the chronic form of lymphatic leukaemia resembles the acute. The symptoms, however, are not so severe, the prostration is not so great, fever is rarely met with and when present is probably due to some complication or to an acute exacerbation. The lymphocyte in excess is stated usually to be of the small variety.

Myelogenous leukaemia.

So characteristic are the changes in the blood that an examination of this alone would suffice to differentiate it. An increase in the number of white cells is evident and commonly reaches a higher grade than in lymphatic leukaemia, they may even reach so high a proportion as one white to one red cell (Osler). There are present in large numbers mononuclear neutrophile cells varying much in size, known as myelocytes, they commonly average about 30% of the white cells present.

Mast cells are found in increased numbers and there is a great total increase of eosinophiles. The polymorphonuclear cells may be present in normal proportion or relatively diminished. Nucleated red cells are present in considerable numbers and vary in size, usually they are normoblasts. The average number of red cells is 2,850,000 per c.m. and the average amount of haemoglobin 42% (Osler).

The myelogenous also differs from the lymphatic form in the rarity of glandular enlargement and the great increase in size of the spleen commonly present. (Neumann describes a case of myelogenous leukaemia in which certain groups of glands were enlarged.)

Chloroma:

This disease runs a rapid course and is scarcely to be distinguished during life from acute lymphatic leukaemia.

Since the condition of the blood and many other features in each may be identical. Melville Dunlop, Byrom Bramwell, Rosenblath and Risel and others have described cases closely resembling acute lymphatic leukaemia.

The points of resemblance then may be found in the blood change, the anaemia, cachexia and haemorrhages and in the hyperplasia of the lymphoid tissue of the lymphatic glands, bone marrow, spleen and liver.

The points in which it differs are:-

(1) The green colour of the lymphoid collections which, however, may only be discovered post mortem; the cause of this green colour is unknown.

(2) The lymphoid collections in the orbits, temporal fossae and periostium of the skull and the resulting alterations of which exophthalmos is characteristic.

Dock and A. S. Warthin have come to the following conclusions concerning chloroma:-

(1) Chloroma is a tumour-like hyperplasia of the parent cells of the leucocytes, primarily in the bone marrow the periostium being involved only secondarily. The possibility of a primary chloroma in any part of the body in which white cells are formed, must be considered.

(2) As a result of this leukoblastic hyperplasia atypical leucocytes may appear in the circulating blood in varying numbers. Chloroma is, therefore, to be classed with the leukaemias.

(3) The cells resulting from the atypical proliferation may in different cases attain different stages of differentiation. In some cases they may be of the large lymphocyte type, in others of the type of neutrophile or eosinophile myelocytes.

(4) It is therefore evident that as in the cases of other leukaemias the blood picture may be very varied and if this be used as a basis of classification, it is possible to designate different varieties of chloroma.

(5) The essential difference between chloroma and other leukaemias is its more marked neplastic character and the form of green infiltrations or metastases.

(6) Chloroma is probably to be regarded as a more malignant form of leukaemia.

Hodgkins Disease bears a resemblance to acute lymphatic leukaemia in that along with anaemia the lymphatic glands are enlarged and discrete, but differs from it in its usually chronic course, the character of the blood and its morbid anatomy. R. Hutchison states that it is the supporting tissue of the glands which is mainly affected, whereas in lymphatic leukaemia the change is parenchymatous in nature.

He has neither seen nor read of any case either in children or in adults in which leukaemia appeared

to pass into Hodgkins disease or vice versa.

Middleton describes a case where enlargement of the lymphatic glands had existed for two months at the time of admission. The blood was examined but nothing abnormal noted beyond a slight increase in the leucocytes and the diagnosis of Hodgkins disease was made. Shortly afterwards the glands rapidly increased in size, there was a marked increase of the white cells in the blood, 87% were a large form of lymphocyte.

The patient died four days later. Here was a case then where apparently acute lymphatic leukaemia had developed out of Hodgkins disease, but on further examination it may be noted that there is no record of the variety of white cell predominating in the blood on his admission. Hutchison is of opinion that in cases of leukaemia where there is no absolute increase of the total leucocytes, there will be found a marked absolute increase of lymphocytes and the normal count is due to a reduction of the polymorphonuclears.

In Hodgkins disease the blood is normal or at most shows a moderate leucocytosis (Cabot).

Tubercular Adenitis:

This affection may bear a superficial resemblance to acute lymphatic leukaemia; there is usually anaemia, enlargement of the glands, most commonly in the cervical region and often pyrexia.

The glands, however, tend to become matted together and to suppurate. It is common in the young and there is most frequently a marked family history of tubercle.

The blood examination will show none of the characteristics of leukaemia, it is usually of normal character but sometimes there may be marked leukopnia (Cabot).

Lymphosarcoma:

In this condition also there is overgrowth of the adenoid tissue, but it is not confined to the organ primarily involved but may spread into and infiltrate the surrounding tissues. It, therefore, differs considerably from leukaemia and also from Hodgkins disease.

The blood occasionally may show a lymphocytosis. Sometimes the leucocytes are present in about normal proportion and it may be only when a differential count has been made that the increase of lymphocytes is realised. Da Costa found a lymphocytosis in

three out of a series of ten cases. Cabot in 32 cases found lymphocytosis in eleven - of the rest some showed a polymorphonuclear leucocytosis with a reduction in the number of lymphocytes,in others the white cells were present within normal limits. Lymphocytosis cannot, therefore be considered at all a constant feature.

Typhoid:

The possibility of typhoid has sometimes to be considered. Phear's case sought advice on account of an attack of diarrhoea with abdominal pain. The spleen was enlarged. The absence of rose-coloured spots, negative reaction to Widals test and the results of a blood examination enabled typhoid to be excluded and the diagnosis of acute lymphatic leukaemia to be made.

It is to be noted that epistaxis and bronchitis, common early symptoms in typhoid,are also common in acute lymphatic leukaemia, occasionally also the temperature of the latter may resemble that of typhoid.

Gulland finds that in typhoid and less frequently in tuberculosis the tendency is for the lymphocytes to increase in number.

Josne mentions that the number of leucocytes in typhoid is generally subnormal and the count may reach as low as 2000 or 1000. The polymorphonuclears are diminished in number and the lymphocytes increased, the latter may reach 24 to 35% during the second week and 28 to 45% during the fourth week.

As a rule therefore there should not be much difficulty in excluding typhoid.

Purpura:

Although purpura cannot correctly be termed a disease it is convenient to group under this heading a number of affections having as their chief feature haemorrhages into the skin.

In all cases where haemorrhage spontaneously occurs the blood should be examined. The changes found in the blood in leukaemia are unfortunately so well marked that the group should thereby be easily eliminated. In all varieties of purpura Coles found little alteration in the blood save that of anaemia, the result of haemorrhage.

Scorbutus:

From the condition of the mouth, the anaemia debility enlargement of the spleen and tendency to haemorrhages a clinical resemblance to acute lymphatic

leukaemia may be met with. Bradford & Shaw found their cases somewhat to resemble scurvy. In this disease Osler states the blood to be dark and fluid, microscopically the changes due to severe anaemia are seen; there is no leucocytosis. Again, therefore, the blood examination should settle the diagnosis.

T R E A T M E N T .

No treatment hitherto applied can claim to arrest the course of the disease to its fatal termination. In our present state of knowledge, therefore, the treatment unfortunately occupies a relatively unimportant position.

The surroundings of the patient must be made as comfortable as possible; he must be kept absolutely at rest in bed in a pleasant, dry, well-ventilated room and endeavour to avoid mental worry. The diet should be as nourishing as possible and if possible

he should be encouraged to take ripe fruit and vegetables.

The teeth and gums must be kept clean and one of the many antiseptic mouth washes should be used.

Special treatment will vary according to the outstanding features of the case and to the observer's ideas as to the causation of the disease.

Iron and arsenic,so beneficial in many other conditions of severe anaemias, should be tried with the hope that they may stimulate the blood forming tissues to normal action, but hitherto they appear to have been powerless to effect much.

The possibility of arsenic causing gastric irritation - vomiting and diarrhoea must be remembered and where there is any fear of this occurring, it may be well to give in addition some form of opium.

Purgatives must be carefully avoided; where there is constipation and it is considered necessary to open the bowels, a glycerine suppository or the injection of two or three ounces of olive oil per rectum which are allowed to be retained, are to be preferred to more violent measures. It is probably better to allow the patient to be constipated than to risk bringing about diarrhoea or haemorrhage so liable to occur without any interference.

If malaria is thought to have been a factor in the case quinine is indicated (Osler).

Oral sepsis should be carefully looked to and Hunter is of opinion that in some cases this may be a starting point for the disease.

Should we hold with Webers "tumour formation theory" of the various forms of leukaemia, we may with some show of reason employ agents reported to have proved beneficial in other forms of leukaemia.

Oxygen inhalations have been tried by many. Burney Yeo mentions that Da Costa has given as much as 100 gallons daily with benefit and that with oxygen Sticker of Cologne found a large and absolute increase in the reds with an actual and relative decrease in the number of white corpuscles, this improvement was not however maintained.

Cowen has reported a case of myelogenous leukaemia which recovered under oxygen inhalations but a differential count was not made.

Its employment in acute lymphatic leukaemia has not been attended with any encouraging results.

X Rays also have been tried especially in America, but no definite good has resulted. Bruce considers they may have a bactericidal action and notes their beneficial action in some cases of sarcoma.

Capps & Smith found that the acute cases did not seem to receive any benefit from the X Rays.

Bone marrow, spleen, lymphatic glands and extracts made from them have now been pretty extensively used, but without any benefit (Stockman).

P R O G N O S I S.

The prognosis is invariably bad, there is no history of recovery in any recorded case.

Rapid increase in the white corpuscles or decrease in the red, fever and diarrhoea are bad symptoms (Stockman).

Von Limbeck has pointed out that lymphocytosis sometimes does not appear until shortly before death, on the other hand Fussel, Jopson & Taylor found the excess of lymphocytes disappeared just before death in a notable number of cases.

The duration varies from a few days to three months; cases much exceeding this limit must be looked on as probably belonging to the more chronic variety of lymphatic leukaemia. Osler found three of his cases to run a course of less than two months.

In an uncomplicated case death most frequently occurs from exhaustion or as a result of haemorrhage. A few are carried off by some intercurrent affection to which their low state of vitality renders them specially liable.

NATURE OF THE DISEASE.

As previously stated, the direct cause or causes of acute lymphatic leukaemia have not yet been determined. It is only by carefully examining the blood and tissues in a number of cases and by observing other conditions in which lymphocytes appear in excess, that we may expect to arrive at some idea as to its nature.

The nature of the lymphocytes themselves must also be considered. Thus they are sommonly held to be devoid of amoeboid movement and so far as has yet been determined are not attracted into the blood in direct response to some stimulus. The liability of some other forms of leucocytes to be acted on by chemiotaxis is well known; to give a few examples, eosinophile cells can be found in the blister of phemphigus, in the sputum of asthmatical patients and the poison of the bothriocephalus can give rise to a condition similar to pernicious anaemia, while nothing is more common than the increase of polymorphs in septic conditions.

The presence of an excess of lymphocytes in the blood may therefore be assumed to be probably due to a mechanical process; they are washed out from the tissues in which they are formed or in the case of acute lymphatic leukaemia may be pushed out by

the pressure of cells behind them. Pilocarpine when injected into the body causes a flushing of the surface of the body and an increase of the lymphocytes in the blood. Irritation also of lymphoid tissue may bring about a lymphaemia it has been described by Weiss in gastric and intestinal catarrhs,by Mennier in whooping cough and attributed by him to the irritation and swelling of the tracheo-bronchial glands.

R. Muir is of opinion that there is strong evidence for believing that the changes found in both forms of leukaemia are due to the indefinite proliferation of a certain kind of cell in a manner analogous to that found in the growth of certain tumours.

In this connection the "tumour" theory of Weber is worth quoting, he says:- "If we admit that a nongranular cell of the large lymphocyte type normally seen in the germinating centres of the lymphatic glands is the predecessor in the lymphatic glandular tissues of the ordinary lymphocytes and in the bone marrow of the granular myelocytes (and thus indirectly of the polymorphonuclears) the following "tumour-formation" theory of the various kinds of leukaemia appears to be the most probable.

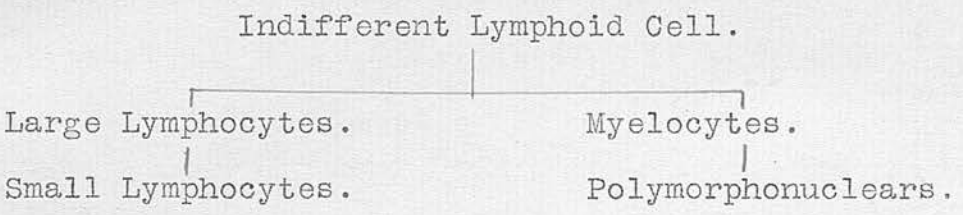
All forms of leukaemia are to be regarded as due to a hyperplasia like tumour formation in the leucocyte producing tissues of the body, the tumour cells overflowing or being attracted out into the blood stream.

If in this tumour formation the less differentiated cells, viz. the nongranular cells of the large lymphocyte type either those of the lymphatic glandular tissues or those of the bone marrow or of both be the cells chiefly involved, the result will be a condition of lymphatic leukaemia and in most acute cases the blood generally contains more cells of the large lymphatic type than of the small."

This theory is also favoured by Wolff who states that in early embryonic life the blood cell is a large mononuclear lymphoid cell similar to the one found in the lymph glands, spleen, bone-marrow and leukaemic blood of the adult. This cell, wherever found, he classes as the "indifferent lymphoid cell" its destiny depending on its environment.

In post embryonic life the haemopoietic organs become differentiated so that there is a division of labour, the marrow being concerned in the production of the granular leucocytes, the lymph glands of the nongranular lymphocytes and the spleen principally concerned in phagocytosis. The "indifferent

lymphoid cell" is found in all these organs and from these cells the mature ones are produced and under some conditions they may functionate vicariously. Wolff gives the following scheme for the leucocytes.



Pappenheim agrees with this theory in the main, but gives the large lymphocyte as the mother cell.

R. Hutchison discusses the relationship between lymphosarcoma and acute lymphatic leukaemia, in both there is an overgrowth of the parenchymatous elements of the adenoid tissue, but in lymphosarcoma the growth is not restricted to the organ primarily involved but breaks through into the surrounding tissues. He notes in both the profound general anaemia with an absolute increase in lymphocytes more constant and of higher degree in lymphatic leukaemia.

He considers chloroma to form a connecting link between the two processes.

The view that the leukaemata are of the nature of a malignant disease has therefore much in its favour and renders the consideration of them at

any rate less confusing. Their indefinite aetiology and the hitherto unsatisfactory treatment are not against the theory, while the fact that the less differentiated form is the more acute is in harmony with what is found in malignant tumours and may be applied as a general rule throughout nature, viz. the simplest and most primitive type of cell is the one most easily propagated.

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