"THE MANIFESTATIONS OF LEUKAEMIA IN INFANCY AND CHILDHOOD WITH AN ACCOUNT OF INFECTIVE ANAEMIA AND LEUKAEMIA IN FOWLS."

Thesis

presented for the Degree of Doctor of Medicine

by

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PREFACE.

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The work described in this Thesis was begun in September, 1922, when I was awarded a Carnegie Research Scholarship in Pathology. The Scholarship was renewed for the year 1923-24, and the work has been continued up to date.

My thanks are due to Professor Leonard Findlay for his help and encouragement and for his kindness in allowing me to make full use of the wealth of clinical material under his care in the Royal Hospital for Sick Children.

I have taken the liberty of including in the series of cases of leukaemia a child which I saw in the Wards under the care of Professor T. K. Monro who kindly allowed me to examine the case.

The experimental work in connexion with Fowl Anaemia and Leukaemia was carried out in the Pathological Department of the University and Western Infirmary of Glasgow under the direction of Professor Muir and Professor Browning whom I should like to thank for their valuable help and criticism.

All the paintings and photographs were done by Mr./

Mr. J. Kirkpatrick, Senior Laboratory Assistant in Pathology, from specimens prepared by me. I wish to express my gratitude to him for the trouble he has taken.

PART I.

I. THE PHYSIOLOGY OF THE BLOOD AND HAEMOPOIETIC TISSUES IN EARLY LIFE.

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Having passed a more or less passive existence in utero during which time it derived from the parent all the nourishment necessary for the growth and development of its organs and tissues, the child, after it has drawn its first few breaths, begins life as a separate being who, in order to survive, must bring in to action all the physiological armament of which it is possessed. The respiratory apparatus ensures the aeration and the digestive apparatus ensures the nutrition of the tissues, while the excretory systems arrange for the removal of the waste products of katabolism. Further, the greater part of the healthy infant's life is passed in sleep which enables the body tissues to accumulate sufficient energy to meet the demands made upon them during the periods of wakefulness. In this way the sudden and abrupt change of estate which must come as no small shock to the organism is met by Nature who, in her wisdom, supplies the means for dealing with this, the first emergency which greets the birth of a new Soul.

After birth changes take place in every tissue and in none are they more interesting than in the blood: but before describing the changes in this vital material it seems/

seems advisable to give an account of the haemopoietic tissues in early life and to trace the development of the blood cells.

THE HAEMOPOIETIC TISSUES IN THE FOETUS AND INFANT.

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(1). LIVER. That the liver acts as a haemopoietic organ in the human foetus between the 8th week and the 8th month has been proved by a number of workers. (Browning,[1] Mollier,[2] Nathan,[3] and Schriddle[4] among others).

In sections of foetal liver one may observe, situated between groups of liver cells and lined by a single layer of flattened endothelium, sinuses which contain nucleated red cells, megaloblasts, a few normal red cells and varying numbers of Lymphoidocytes. These latter cells are about 20 microns in diameter and, when stained with polychrome methylene blue, show a large pale nucleus which is often slightly indented and which contains one or more small purple staining foci of concentrated chromatin. The protoplasm is deeply basophile and may be seen to contain an astrosphere situated near the indentation of the nucleus. This cell may be likened to the "negative of an ordinary lymphocyte." (Boudet).

In the liver, however, there is another source of blood formation besides the intravascular. In the substance of the liver tissue, between the liver cells and beneath the endothelium, areas may be seen containing lymphoidocytes, erythroblasts, erythrocytes and, to a lesser extent, early forms of granular cells (myelocytes). It is these areas which constitute the chief source of blood formation in the/

the foetal liver. The cells are probably born into the general circulation by ruptures occurring at various points of the endothelial lining. (Jolly).(5)

About the seventh or eighth month of intra-uterine existence this source of blood cells is no longer necessary and so, having fulfilled their purpose, these haemopoietic areas come to be destroyed by the liver cells themselves and by the endothelial cells, (Kupffer cells) which have active phagocytic properties. Nathan and Larier(#6) have observed red cell formation in the liver even after birth in certain infants who have died from various causes and some writers believe that in the severe anaemias of infancy the foetal organs again become active.

(2). BONE MARROW. The foetal marrow at first consists of a spongy network of connective tissue cells which later become replaced in greater part by large mononuclear cells identical with those already described as lymphoidocytes. Such cells are multipotential and from them are formed both the granular cells and the erythrocytes. The marrow also contains definite small areas of lymphocyte formation, but, apart from Lymphatic Leukaemia, this source of lymphocytes may be regarded as negligible. By the seventh or eighth month the bone marrow has developed sufficiently to be able to take over the blood formation for the whole of the body and it is about this time that the liver ceases to act as

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a haemopoietic organ. Browning,(1) in his study of foetal white cell production, states that "there can be little doubt that the function of granular leucocyte production exercised by the red bone marrow in the adult is nothing more than a survival in one suitable situation of a process which, in the embryo, was carried on widely throughout the perivascular connective tissue of the various organs."

In the infant the red marrow extends throughout the whole length of the long bones and contains a very small quantity of fat. It is only in later years that the marrow tissue at the ends of the bones is replaced by fat. On microscopical examination of the marrow one is struck by the tremendous activity of the leucoblastic elements in its structure. A smear of the bone marrow when stained shows a far greater proportion of myelocytes than is to be observed in the adult tissue.

Thus, in the young child, the whole of the marrow is acting at "full pressure" in order to maintain the physiological characters of the blood and, in consequence, the individual has no reserves upon which to fall back in case of emergency. The result of such a state of affairs is that, in the event of any deleterious influence tending to destroy the blood cells, immature forms will readily be thrown into the circulation. As will be shown later, this is exactly what does occur in infants who suffer from a great variety of disease processes.

At present I am engaged upon a study of the bone marrow in/

in infancy and childhood but the amount of work done does not justify any remarks or conclusions.

(3). SPLEEN, THYMUS & PLACENTA. There is reason to believe that haematogenesis takes place to a limited extent in these organs but such sources may be regarded as of very minor importance.

THE DEVELOPMENT OF THE BLOOD CELLS.

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Chiefly as a result of the work of Pappenheim, Wolff, Dominici and others on the human haemopoietic organs and in view of our knowledge of the comparative cytology of the lower vertebrates there seems to be a general agreement at the present time that all the somatic cells have a common ancestor in the undifferentiated connective tissue cell. This cell is multipotential and may give rise to osteoblasts, myoblasts, fibroblasts, haemoblasts, etc. It is with the haemoblast that we are concerned just now. The primitive haemoblast or Lymphoidocyte has already been described when considering haematogenesis in the liver, but let me repeat that it is a round cell, about 20 microns in diameter, with a large pale nucleus containing one or more small masses of concentrated chromatin and it is surrounded by a narrow ring of deeply basophile protoplasm in which an astrosphere may sometimes be seen. It will be noticed that this description applies exactly to that cell which is met with in the blood in myelogenous leukaemia and in cases of very severe anaemia in children and which is called a Myeloblast.(Naegli). In these diseases the myeloblast is looked upon as the primitive cell of the granular series and the parent of the myelocyte. An examination of the bone marrow in such cases confirms the accuracy of this view because every form of transition from the non-granular myeloblast (or lymphoidocyte) to the myelocyte containing either neutrophile, eosinophile or basophile granules may be observed.

On the other hand, it has already been shewn that the lymphoidocyte is the precursor of the erythroblasts in the blood - forming areas of the liver during foetal life. Characteristic changes occur in the conformation of the nuclear chromatin which first adopts the "wheel shaped" arrangement around the periphery and, later, becomes condensed to form a closely packed reticulum. These nuclear changes are associated with the appearance of haemoglobin in the protoplasm causing it to stain first in a polychromatic and then in an orthochromatic manner.

Finally, it is well known that in certain examples of acute leukaemia it is difficult to decide whether they are of myelogenous or lymphatic origin because the large cells present in the blood may either be primitive lymphocytes or myeloblasts. Shaw Dunn (7) has shown that, in a proportion of cases, the oxidase reaction may help to establish the exact nature of the cells; but this, however, does not alter the fact that the most primitive forms of lymphoblasts and myeloblasts cannot be differentiated by any known names. If the bone marrow from a case of acute leukaemia of the large cell type be examined a considerable proportion of these cells may be observed which do not give a positive oxidase reaction and, further, transition forms between such cells and large or small lymphocytes can be seen. The obvious conclusion is that the lymphoidocyte may also be the parent of the lymphocyte.

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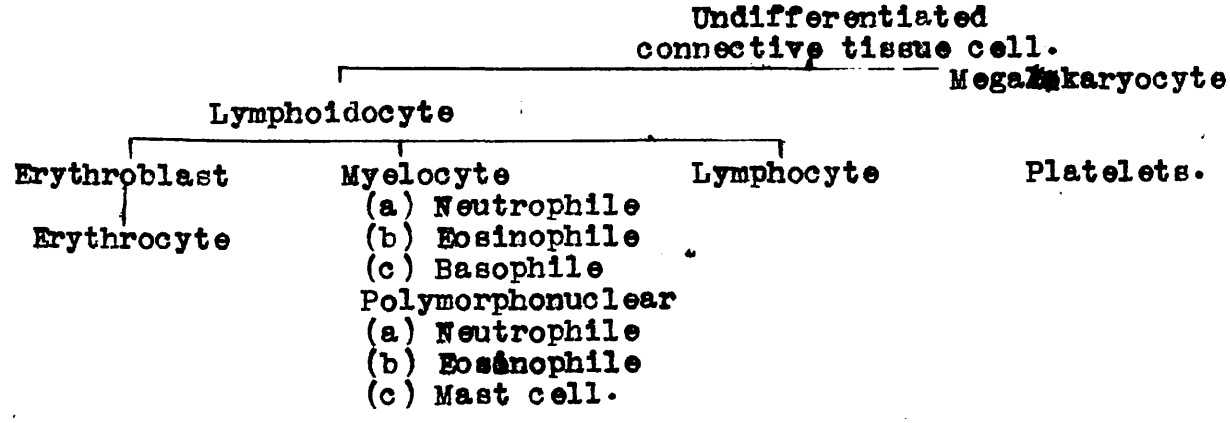
Owing to the multipotential character of the primitive blood cell it has been described in haematological literature under no less than 86 different names (8) but nowadays the term "Lymphoidocyte" has become more or less universal in connexion with this cell and because, in my opinion, none of the synonyms are more suitable, I have therefore retained it.

The following scheme describes the modern view of blood cell development and shows that the lymphoidocyte is to be regarded as the common parent of all the blood cells because, acting under the influence of forces as yet unknown to us, it may give rise to erythroblasts, myelocytes and lymphocytes.



THE BLOOD.

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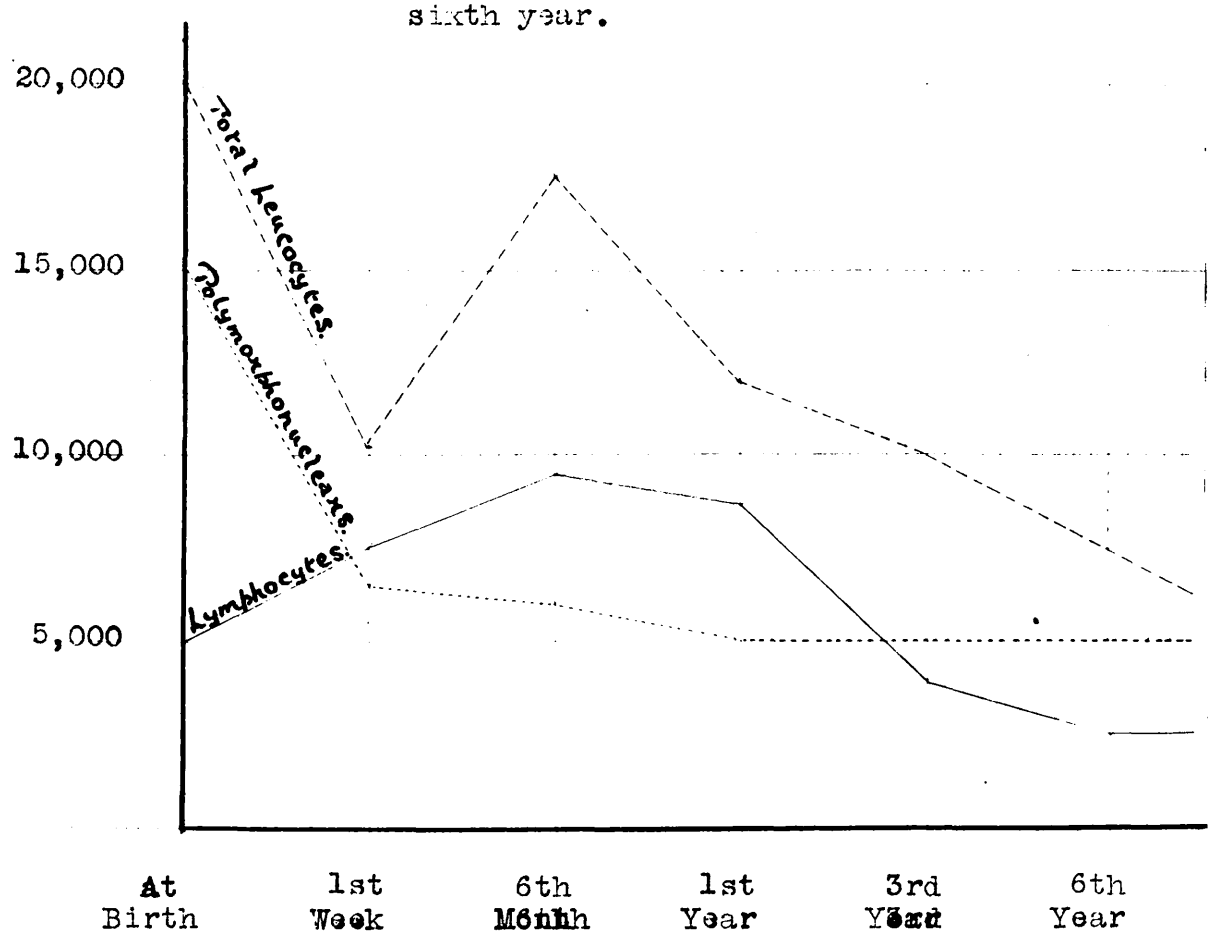
At birth there is a polycythaemia which is due to the increased activity on the part of the haemopoietic tissues and also to the loss of fluid from the body by evaporation. At this time the red cell count is between 6 and 7 million per c.mm. The haemoglobin is also high and the colour index is about unity. The leucocyte count is usually about 20,000 per c.mm. of which 60 per cent are neutrophil polymorphonuclears. On examination of film preparations the red cells are found to show a uniform degree of staining and there is very little abnormality regarding either their size or shape. A scanty number of normoblasts are present. The white cells show no unusual features and myelocytes are absent as a rule. During the first few weeks of life the red cells fall to between 4 and 5 million per c.mm. and within a very short time the nucleated red cells have all disappeared. This fall in the erythrocyte count is probably due partly to the dilution of the blood resulting from the balance between the intake and output of fluid, and partly to the destruction of red cells which is taking place at this time, as is manifested by the rapid disappearance of the nucleated forms, and the slight degree of jaundice which is so common shortly after birth. At first the haemoglobin falls in proportion to the erythrocytes, but, instead of being arrested/

arrested when the red cells find their normal level, it continues to fall very slowly until about the sixth month when the average reading is about 70 per cent. The haemoglobin usually remains at this level until the fifth year after which it begins to rise. The adult reading of between 90 and 110 per cent is probably reached sometime between the ninth and twelfth year. I am not aware of any theory which will explain satisfactorily this chlorotic state of the blood in infancy. That the diet of the infant is relatively poor in iron does not afford an adequate explanation unless it is assumed that the liver cells do not store up the greater portion of the iron derived from the physiological destruction of the red cells.

Simultaneously with the decrease in numbers of the erythrocytes the leucocyte count falls from about 20,000 to 10,000 per c.mm. This decrease occurs entirely at the expense of the neutrophil polymorphonuclears. Meanwhile the lymphocytes show a steady increase both relatively and absolutely. The following chart (after Hutchison (9)) shows the proportion of polymorphonuclears to lymphocytes at various ages.

Chart showing the physiological variations in the number of white cells from birth to the sixth year.



From the above chart it will be seen that the average white cell count varies between 15,000 at six months and about 10,000 at the third year. After the first week of life the variation in the white cell count depends entirely on the number of lymphocytes which are present because the/

the polymorphonuclears remain very constant at about 5,000 per c.mm.

The adult ratio of polymorphonuclears to lymphocytes is reached by the sixth year of life, but I have observed cases in which it was delayed until several years later. It would appear that just as abnormalities of certain tissues produce the various conditions which are grouped together under the general heading of Infantilism, so may the haemopoietic and adenoid tissues retain their infantile features and reflect them in the blood as shown by a persistence of its two chief characteristics as emphasized by Hutchison, viz. (1) Its chlorotic state and (2) The preponderance of the cells of the non-granular series. This latter phenomenon is due to the intense activity on the part of the adenoid tissues throughout the body. The reason for this adenoid hyperplasia is unknown, because, unless the lymphocytes subserve some purpose vital to the growth of the organism as a whole, it is difficult to understand why all this energy is being liberated.

LEUCOCYTIC REACTIONS TO ACUTE INFECTIVE PROCESSES.

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In most cases of infection with pyogenic organisms the bone marrow reacts by throwing in to the circulation an increased number of cells of the granular series. The leucoblastic apparatus is called upon to supply an increased demand for polymorphonuclear leucocytes and it seems to do this with considerable ease. On the other hand, these cells are carried off into the blood stream before they have reached maturity. This, however, is just what is to be expected when it is recalled that the marrow has no reserves upon which to fall back in the event of an emergency. When a film of the blood is examined the nuclei of the granular cells are usually found to have only two lobes and this is significant of the youth of these cells. Such cells may be called Meta-myelocytes or Transitionals. In examples of simple leucocytosis in children myelocytes are quite common but they are rarely present in a proportion of more than 3 per cent.

If we turn our attention to the behaviour of the lymphocytes in examples of simple leucocytosis it will generally be found that they are either normal or diminished in/

in number.

In a critical review of the more recent literature in which it is stated that sepsis may be an occasional cause of an absolute lymphocytosis, Tidy (10) concludes that there is no satisfactory evidence of such being the case. Tidy gives no criteria showing what he would regard as sepsis but, it must be admitted that the examples he quotes from the literature would tend to support his conclusion.

If, however, pneumonia in infancy may be regarded as a septic condition; I have observed four cases in which there was an absolute lymphocytosis. The cases are detailed in the following table, along with a number of others which show what is regarded as the normal reactions to such infective processes.

Table: showing difference between calculated and expected number of Lymphocytes in various conditions.

No.	Age in months.	Disease.	Total Leucocytes	Calculated Lympho-cytes.	Expected Lympho-cytes.	Difference.
26	13	Marasmus	14,500	6,856	9,000	Minus 2,200
29	13	Diarrhoea	14,800	4,633	9,000	4,400
73	14	Marasmus	20,000	3,720	9,000	5,300
40	13	Pneumonia	17,200	3,440	9,000	5,600
38	9	Pneumonia	23,100	6,930	9,000	2,100
15	11	Marasmus	25,400	7,874	9,000	1,200
18	3	Pneumonia	17,900	4,117	9,000	4,900
105	26	Bronchitis	15,600	1,762	6,000	4,300
41	25	Pyelitis	14,600	4,614	6,000	1,400
112	33	Pneumonia	20,400	3,590	5,000	1,500
1	17	Pneumonia	21,000	8,060	7,500	-----
32	24	Pneumonia	23,400	6,084	6,000	-----
100	31	Abscess of Lung.	19,600	6,272	5,500	-----
2	17	Pneumonia	22,700	14,775	7,500	Plus 7,200
23	18	Pneumonia	19,000	9,785	7,500	2,200
6	19	Purpura simplex.	16,700	10,955	6,500	4,400
13	30	Pneumonia	29,200	10,220	5,500	4,700
90	14	Pneumonia	49,600	13,392	9,000	4,300

The following are the average figures obtained from an analysis of the four cases which show an absolute lymphocytosis.

Total White Cell Count	30,125.
Expected No. Lymphocytes.	7,375.
Calculated No. Lymphocytes.	12,063.
Difference.	4,688.

It will be observed from the Table that there is a case of Purpura Simplex in which there is a lymphocytosis. I can make no comment on the phenomenon because we are very much in the dark regarding the explanation of lymphocytosis in general.

With reference to the four cases of pneumonia, it is not clear what is the explanation of this reaction to infection on the part of the lymphatic apparatus. If it were due to some unknown chemiotactic influence exerted by the infective agent (as in Whooping Cough, for instance) the phenomenon should be almost general in cases which are clinically identical. Such, however, appears not to be the case.

I cannot help thinking that it must come to be explained by a hypersensibility of the lymphatic system present in certain individuals and somewhat closely related to that loosely defined condition known as the Status Lymphaticus. It is known that in many examples of sudden death in children while asleep or under the influence of narcotics an abnormal hyperplasia of the thymo-/

thymo-lymphatic system is the only pathological feature detected at the autopsy: and, further McNeil (11) has shown that a similar finding may be made in certain cases of pneumonia in which the patient died suddenly without showing the usual reactions to the disease.

SUMMARY.

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1. A short description is given of the haemopoietic tissues in the foetus and young child and it is observed that they are working at such a high pitch that the organism has virtually no reserves upon which to fall back in the event of any toxic process tending to destroy the blood cells.

2. The development of the erythrocytes, granular cells and lymphocytes is described and it is explained how they all come to be regarded as the offspring of the Lymphoidocyte which, in its turn, is derived from the Undifferentiated Connective Tissue Cell.

3. A description is given of the changes which take place in the actual and relative numbers of the various blood cells from birth until about the sixth year. It is shown that in infancy the blood is chlorotic and that the colour index seldom reaches unity. There is also an unexplained adenoid hyperplasia which is manifested in the blood by a reversal of the adult ratio of lymphocytes to polymorphonuclears.

4. The leucocytic reactions to pyogenic infective processes are described and it is shown that in most cases the bone marrow throws into the circulation an increased

number/

number of granular cells, a varying proportion of which have not reached maturity. In certain instances, in addition to a neutrophile leucocytosis, there is an absolute lymphocytosis; and it is suggested that an explanation for this phenomenon may be found by assuming a hypersensibility of the lymphatic system and thus considering it as one of the less grave manifestations of the Status Lymphaticus.

II. LEUKAEMIA IN INFANCY AND CHILDHOOD.

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Leukaemia must be regarded as a relatively uncommon disease and, therefore, in order to gain a reasonably comprehensive idea of its symptomatology and haematological features I have collected 100 cases of the disease occurring in children under 8 years of age. (See Appendix).

In this series there are 70 cases of Lymphatic Leukaemia, 19 of Myelocytic Leukaemia and 11 of the so-called Myeloblastic Leukaemia.

The greatest care has been taken in selecting the cases so that there could be little or no doubt as to the diagnosis. This was especially difficult in regard to examples of Myelocytic Leukaemia because a number of cases reported under this diagnosis would almost certainly appear to be examples of severe anaemia in childhood or the so-called von Jaksch's Anaemia.

However, I believe the series of cases here quoted to be genuine and to give a reasonably accurate account of the symptomatology and blood changes in the various forms of Leukaemia in infancy and childhood.

In view of the fact that the symptoms of all forms of leukaemia in childhood are very similar they will be treated together and when there is any marked difference it will be clearly shown. The blood changes will be described separately.

ETIOLOGY.

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It is not proposed at this point to enter into a discussion on the special etiology of leukaemia but in Part II of this Thesis there is an account and discussion regarding the observations which have been made with reference to the etiology of this disease. Only the general features in the etiology of leukaemia will be considered here.

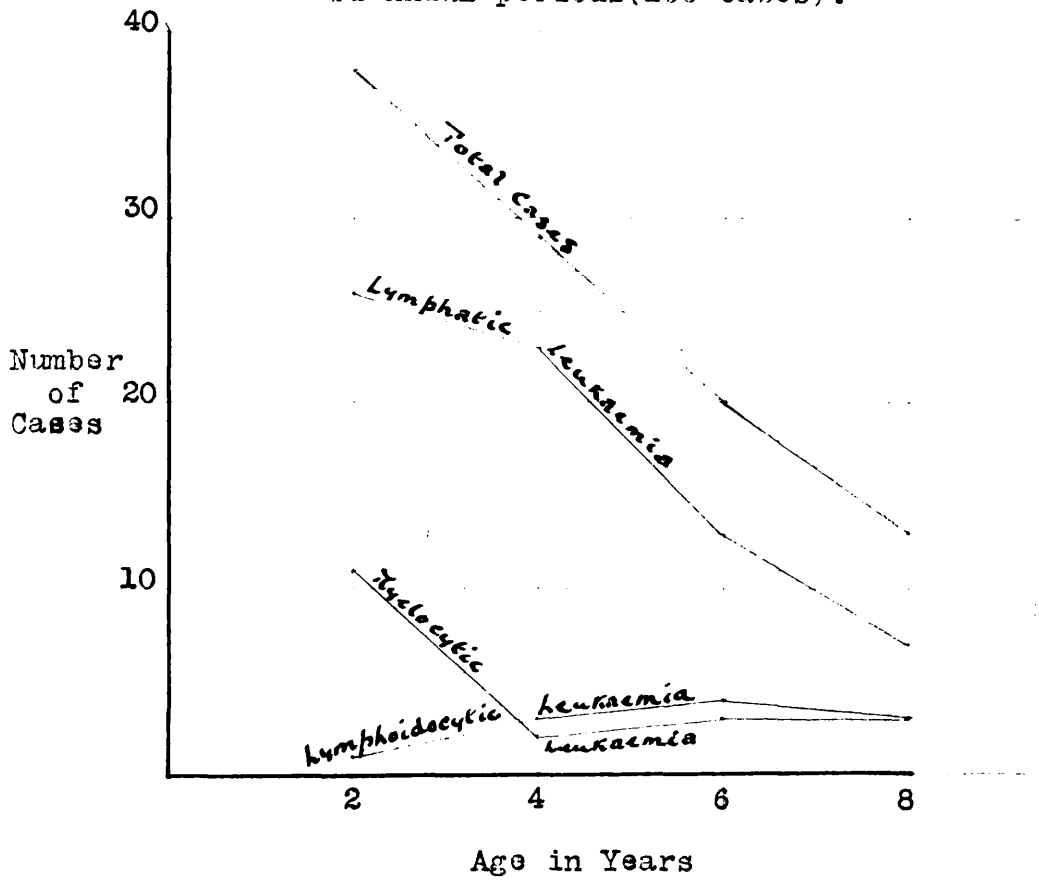
Age. The following Table shows the result of an analysis of the ages of the cases in this series.

Table I.

Age in years.	1st.	2nd.	3rd.	4th.	5th.	6th.	7th.	8th.
Lymphatic.	12	13	8	16	8	6	5	2
Myelocytic.	7	4	2	0	0	3	0	3
Lymphoido-cytic.	0	1	2	1	2	2	1	2
Total:-	17	18	12	17	10	11	6	7

From this table there is one interesting fact to be learned: namely that there are roughly twice as many cases of leukaemia occurring in the first four years of life as there are in the subsequent four years. This is well demonstrated in the following chart in which the cases are arranged in biennial periods.

Chart showing age incidence of Leukaemia in biennial periods(100 cases).



In nos. 4, 41, 48 and 65 the age of the infant when it came under examination was below two months and it seems probable that these may be regarded as examples of congenital leukaemia. The latter case came under my own observation in Professor Findlay's wards and the history seemed to date back to the time of birth. In each it was stated that the mother was not suffering from leukaemia and this may be expected because there are several cases on record in which women who were the victims of leukaemia have given birth to normal children. These facts have been brought/

brought forward against the theory that leukaemia is infective in origin and they seem to support the view that it is related to the malignant processes; "a sarcoma of the blood." (Banti).

Sex. In 94 of this series the sex was known and of these 62.87 per cent were males. This is in accordance with the statements generally made that the disease is more common in the male subject.

Social Conditions. There is no evidence that leukaemia is relatively more common among the poorer classes than the wealthy. The only observation which I have made in this connexion is that, in so far as my limited experience goes, the disease appears to be more common among country dwellers than among those who live in the large towns. I make this observation with every reservation but it would be interesting if accurate statistics could be furnished on this point.

SYMPTOMATOLOGY.

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Onset. The onset of leukaemia may be insidious or abrupt. In the former case the patient gradually becomes less active; he may be lethargic and somnolent; he is frequently irritable and suffers from loss of appetite; he tends to lose weight and, as a rule, he becomes pale. This stage may last for one or two months and the diagnosis of the disease is difficult, but, sooner or later, increasing pallor, haemorrhages, enlargement of the spleen or superficial lymphatic glands will appear and suggest the existence of some grave disorder of the blood. These symptoms may occur independently of any previous illness or they may follow such diseases as malaria (nos. 34 and 36), pneumonia (no. 18), or mumps (no.58).

When the onset is abrupt the patient may be suddenly stricken down with fever and great prostration. On examination neither the spleen, liver, nor superficial lymphatic glands may show any palpable enlargement and the only symptom likely to suggest the possibility of leukaemia may be either a purpuric rash or a severe attack of epistaxis. However, even in the cases with the most acute onset the patient generally lives long enough for the majority of the main clinical features of the disease to manifest themselves.

Symptoms. The following table illustrates the symptoms of leukaemia in infancy in the order of their frequency. In a regrettable number of instances no note has been made to indicate the presence or absence of a particular symptom, but/

but such is to be expected in any analysis of this kind.

TABLE II.

Analysis of symptoms.	Present.	Absent.
Enlarged Spleen.	82	7
Enlarged Glands.	84	13
Haemorrhages.	78	8
Fever.	70	7
Enlarged Liver.	70	19
Digestive disorders.	44	3
Gingivitis and Stomatitis.	37	7
Cardiac Murmurs.	30	9
Enlarged Tonsils.	24	11
Albumenuria.	20	20
Oedema.	19	13
Dyspnoea.	17	3
Pain.	16	11
Retinal changes.	12	6

It will be observed that there are five principal symptoms, namely enlargement of the spleen, liver and lymphatic glands; haemorrhages and fever. The other symptoms, although they may constitute an important part of the general picture in given cases, are of relatively infrequent occurrence.

We shall now consider these and other features of the disease in detail.

(1). Splenic enlargement. Enlargement of the spleen per se during the first four years of life is of little significance for it is well known that in many examples of pneumonia, tuberculosis, syphilis and gastro-enteritis in infancy the spleen becomes palpable and may even appear as a very large mass/

mass in the abdomen.(1) In the more severe forms of anaemia the spleen is almost constantly palpable although the degree of enlargement bears no relation to the severity of the anaemia.(2) Enlargement of the spleen, however, appears to be the most constant symptom in leukaemia during childhood and it is advisable to make a blood examination in every case presenting this feature, because, although there may be no evidence of leukaemia, there is always something to be learned from a study of the appearances of the blood. The spleen often fluctuates in size to a small extent during the course of the disease and when the volume diminishes, as it does after a haemorrhage or an attack of diarrhoea, the parents sometimes offer the opinion that the child is looking better and that the appetite has improved. During the last few days of the illness it is often noticed that the spleen decreases in size and this may be associated with a similar decrease in the size of the superficial lymphatic glands and with a fall in the white cell count.

(2). Glandular Enlargement. From the table it will be observed that in all but 13 cases there was some degree of glandular enlargement, although in a number of the children the increase was either very slight or limited in extent. The significance of the occasional absence of glandular enlargement is interesting in that it seems to show once and for all that the primary lesion is in the bone marrow. Nowadays it appears to/

to be an accepted fact that the blood is never leukaemic until definite changes characteristic of the disease have taken place in the bone marrow, and the occasional instances of leukaemia which arise from time to time showing no enlargement of the glands "go to prove that acute leukaemia, whether lymphoid or myelocytic, is due to changes in the bone marrow, the other haemopoietic organs being involved, if at all, secondarily."(3) This is in accordance with the opinions expressed by Neumann,(4) Walz,(5) Pappenheim,(6) Brandenburg(7) and others.

In the cases presenting enlargement of the glands the most common group appears to be the cervical glands. The mesenteric glands are almost always enlarged but it is not often that they can be palpated with certainty. The mediastinal and bronchial glands are also frequently involved and may give rise to distressing symptoms.

(3). Haemorrhages. Bleeding may occur in three forms; (a) a purpuric rash, (b) ecchymoses and (c) bleeding from the mucous membranes.

(a). Purpura. This is one of the commonest symptoms of leukaemia. The rash may appear all over the body or it may be limited to a small area. Frequently it occurs in the form of successive crops of small petechial haemorrhages coming on for no apparent reason and bearing no relation to the severity of the disease.

(b)/

(b). Ecchymoses. The parents may have noticed that the child "bruised easily" and during the course of the illness large extravasations of blood may take place. Probably the commonest site for these haemorrhages is over the sacrum but they may be found almost anywhere.

(c). Bleeding from mucous membranes. In the large majority of cases of leukaemia bleeding from the gums takes place. Such haemorrhage occurs as a persistent oozing of blood and may be a prominent factor in the production of the anaemia. It may be the principle symptom and lead to a faulty diagnosis of Barlow's Disease. Epistaxis is another common symptom and when it occurs it is usually severe and prolonged and it is likely to recur from time to time during the course of the illness. Melaena is quite common and haematemesis occurs in a few cases. Haematuria is rare.

The following table shows the relative frequency of haemorrhages in the various forms of leukaemia.

TABLE III.

	No. of cases in which note regarding Haemorrhages was made.	Percentage of cases in which Haemorrhages were present.
Lymphatic	65	93.8%
Myelocytic	14	78.6%
Lymphoidocytic	8	75.0%

The explanation of this tendency to haemorrhage in leukaemia is not far to seek. The platelets, as has been shown, are formed from the megakaryocytes in the bone marrow, and, when the extensive changes which take place in this tissue in leukaemia are considered, it is obvious that the normal processes by which the platelets are manufactured are generally upset, and, consequent on their decrease in number in the blood stream, the physiological methods for the control of haemorrhage are in abeyance. Further, the greater tendency to haemorrhage in lymphatic leukaemia can be explained by the almost complete annihilation of the normal activities of the bone marrow by the rapid proliferation of the lymphatic elements in its structure.

(4). Fever. Some degree of fever was present in 70 cases, in 7 it was stated to be absent and in 23 it was not mentioned. There is nothing characteristic about the temperature chart of a case of leukaemia. Sometimes the fever is of the continued type, sometimes of the swinging type, but speaking generally, it is capricious and irregular. The temperature may be normal for days on end and then, for no apparent reason, it may rise to about 100°F., only to fall again sooner or later. Occasionally the temperature may go up to 105°F. At the beginning of this illness in children there is usually, however, some form of fever, and this is one of the points which make the clinical picture of leukaemia so/

so similar to that of many acute infectious diseases. At the termination of this disease the temperature may fall and be accompanied by a decrease in size of the spleen, liver and lymphatic glands and a fall in the number of leucocytes in the blood. On the other hand, the patient may die with hyperpyrexia suggesting some toxic action on or a leukaemic infiltration of the pons varolii.

The etiology of the disease being unknown, it is impossible to explain the fever, but there are four possibilities: namely, (1) that it is a manifestation of the systemic reaction to a specific infection, (2) that it is the result of some secondary infection with pyogenic organisms, (3) that it is due to the digestive disturbances which occur during the course of the illness and (4) the possibility suggested by Treadgold,(8) that it is due to the action of degenerated leucocytes on the heat centres.

(5). Hepatic enlargement. Enlargement of the liver was present in 70 of this series and in 19 it was stated not to be enlarged. In how far these figures are accurate as regards the enlargement of the organ it is difficult to ascertain because in young children the lower border of the liver can usually be palpated half to one inch below the costal margin, and it is quite possible that this has been recorded as an actual enlargement in a proportion of cases in which there was really no increase in its weight. However, it is quite certain that in the majority of cases in/

in which a post mortem examination is performed the liver is found to be definitely enlarged. The relative frequency of hepatic enlargement in the three varieties of leukaemia was as follows:- Lymphatic leukaemia 80.6%; Myelocytic leukaemia 75.0%; Lymphoidocytic leukaemia 66.6%.

(6). Digestive disturbances. Symptoms referable to the gastro-intestinal system were present in 44 cases and in 58 no note was made; probably because these symptoms were considered too insignificant. Such symptoms are anorexia, diarrhoea, vomiting and constipation. Haematemesis and melaena were present in a few patients. The tongue is generally furred and the gums are frequently swollen and bleeding. 37 children in this series suffered from stomatitis or gingivitis. The tonsils were enlarged in 24 cases; in 11 there was stated to be no enlargement and in 65 no note was made.

(7). Cardio-Vascular Symptoms. In a considerable number of cases a note has been made of the condition of the heart and pulse. The pulse is generally soft and of low tension. Tachycardia and Bradycardia are not mentioned as being present although the heart's action is often rapid when associated with pyrexia. The organ is sometimes found to be enlarged and a murmur or bruit coincident with ventricular systole is to be heard in a porportion of cases (30 in this series). Post mortem examination seldom if ever reveals the/

the presence of an endocarditis and it must, therefore, be supposed that the explanation of the dilatation and of the murmurs is to be found in the impaired state of nutrition of the myocardium.

(8). Genito-urinary symptoms. In 3 cases it was stated that the kidneys were large and easily palpated (nos. 25, 28, 32) but with these exceptions there is no note of the size of the organs in any of this series. In several instances the post mortem findings showed a considerable enlargement of the kidneys. Albuminuria is not uncommon but seldom appears to be present in the same quantity as in acute nephritis. The uric acid output is increased due to katabolism of the excessive endogenous protein associated with the leucocytosis. Haematuria is rare.

(9). Respiratory symptoms. Dyspnoea is not an uncommon symptom in leukaemia. It may be due to enlarged glands in the neck pressing on the trachea or larynx, as was the case in No. 4, and from which cause the child died. Again, dyspnoea may be due to enlarged bronchial and mediastinal glands pressing on the recurrent laryngeal nerves or on one of the larger bronchi. In infants with leukaemia the tonsils are often enlarged and it is to be presumed that the naso-pharyngeal adenoid tissue is also hypertrophied, and it is quite possible that these factors may play a part in the production of dyspnoea. Finally, dyspnoea may exist as

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a manifestation of the severe degree of anaemia which is so constantly present.

A mild bronchitis is probably present in the majority of cases but it causes no symptoms of importance. Some degree of oedema of the lungs is always present and is associated with the anaemia. Pneumonia may occur at any time during the course of the disease, but, as a rule, it is not associated with the usual reactions seen in the healthy subject, and, in some cases, it may only be discovered at the post mortem examination.

(10). Skin. One of the most constant features of lymphatic leukaemia is the occurrence of haemorrhages either into or beneath the skin. These phenomena have already been described. Sweat rashes are not uncommon in childhood and when present in cases of leukaemia probably bear no relation to the disease. Herpes occurred in one of this series (no.20) and it may be accounted for by haemorrhage taking place in or some toxic process acting on the posterior root glanglia. Ulceration of the skin occurred in one case (no.17). Oedema of the skin and subcutaneous tissues was present in 19 of this series. It may be generalised and associated with ascites or it may be limited to the face or ankles. In a porportion of cases Nodules may be present and the condition has been called Nodular Leukaemia by Ward (9) who has collected a number of cases. According to Ward the nodules probably arise from the scattered foci of lymphoid tissue which occur throughout the meso- and hypoblastic tissues. The nodules do not appear

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in the epiblastic tissues such as the epidermis or the central nervous system although they frequently grow from the subjacent fibrous tissue of the skin (no.54) and the dura mater. The cutaneous nodules differ greatly in size and in colour. They may be as small as a pin's head or as large as a cricket ball and their colour is dependent upon the depth from the surface and may be modified by interstitial haemorrhages. The nodules may be present throughout the alimentary tract. Finally, the nodules may occur in connexion with the bones; particularly the bones of the head; and it is these tumours which frequently have the green colour characteristic of Chloroma. (nos. 89, 95). In some cases, however, the colour may be absent or it may fade very rapidly after removal of the tumour, but it can often be brought back by immersing the tissue in hydrogen peroxide.(10) The nodules, wherever placed, may become smaller in size or even disappear suddenly.(9)

(11). Retinal Changes. It is unfortunate that in 82 of this series no mention has been made of the appearances of the fundus oculi. In 6 it was stated that there was no abnormality and in 12 certain changes were observed. The commonest lesion consisted of one or more small retinal haemorrhages (11 cases). In one case pallor of the disc and fundus was noted and in another, in addition to retinal haemorrhages, there was a neuroretinitis.

THE BLOOD.

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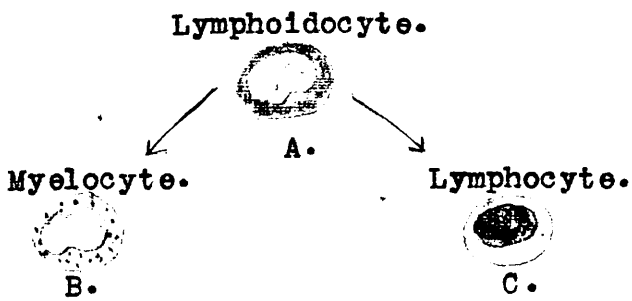
(a). GENERAL CONSIDERATIONS.

The lymphoidocyte has already been described as the common parent of the blood cells and it is obvious that the variety of leukaemia which will occur depends on whether the unknown influence responsible for the disease causes differentiation along myelocytic or lymphocytic lines. In the leukaemias, however, differentiation of the cells is always incomplete and it is this lack of complete differentiation which constitutes the difference between a simple leucocytosis and leukaemia.



A glance at the above diagram shows that if differentiation ceases at B there must obviously be a Myelocytic leukaemia and if at C a Lymphatic leukaemia. But there are cases in which there is an almost complete absence of differentiation and in which the majority of cells observed in the blood are lymphoidocytes. Such cases constitute the so-called Myeloblastic or, better, Lymphoidocytic leukaemia.

(b). LYMPHATIC LEUKAEMIA.

The blood flows easily from a prick in the ear, finger or in the lobe of the ear. It is paler and more watery than in the healthy subject and as a rule it does not show the normal tendency to rapid coagulation.

Serum. The serum may appear quite normal or it may contain a moderately large quantity of fat, as it did in no. 56. In none of the cases of this series was the Wassermann reaction said to be positive. A positive Widal was obtained in no. 6. In some cases the serum may be frankly jaundiced and the Van den Bergh test may give a diphasic reaction, presumably indicative of compression of the small intra-hepatic bile channels by round cell infiltration. This was recently observed by me in a boy of 9 years in the Royal Hospital for Sick Children. The case is not included in this series. In 7 cases a streptococcus was said to have been cultivated from the blood and in no. 57 I isolated a streptococcus which multiplied rapidly under anaerobic conditions but which, although it survived under aerobic conditions, grew less freely. Streptococci, however, may be isolated quite frequently during the terminal stages of many illnesses in childhood.

Red Cells. The total red cell count is always decreased and towards the end of the illness it may fall below a million per cubic millimetre (nos. 8, 13, 40, 54, 64). The average red cell count was 1,946,000. Irregularity in size and shape of/

of the corpuscles is present and polychromasia and basophile stippling are common features. Nucleated red cells are generally present but, as a rule, they are scanty in number. The erythrocytes stain well and the average Haemoglobin was 31 per cent, which gives a Colour Index of 0.816. The platelets are decreased in number.

White Cells. In this series there was a leucocytosis in 58 cases; in 8 the total white cell count was either decreased or within normal limits; and in 4 no note was made. The average leucocyte count was 210,245 per cubic mm.

It would appear that in the cases in which the onset is not very sudden and in which the patient does not seem to be seriously ill the white cell count is high and may even exceed a million per cubic millimetre (nos. 10, 31, 41, 52). When the onset is abrupt and the patient is prostrated and obviously in a perilous condition the white cell count may not be raised and there may even be a frank leucopenia. During the last few days of the illness the leucocyte count almost always falls and this is regarded as a grave factor in the immediate prognosis.

The one constant feature about the blood in lymphatic leukaemia is the high relative increase of the lymphocytes. Whatever the total white cell count may be the lymphocytes are always relatively in excess of normal and in this series averaged 94 per cent.

Characters of the Lymphocytes. The type of lymphocyte which dominated the blood picture was noted in 52 of this series. In the majority of cases (61.54%) the micro- and mesolymphocytes were the predominating cells. In these forms the nucleus stains deeply and the cytoplasm is scarcely visible. In some examples, however, the large lymphocytes are present in the greatest proportions.(38.46%). Such cells have a rather paler nucleus than the small forms and in it one or two nucleoli may be observed. The cytoplasm is not abundant and, so far as my experience goes, seldom if ever, contains the azurophil granules which are so commonly encountered in the lymphocytes of healthy blood.

In films from every case of lymphatic leukaemia lymphoidocytes may be found. Sometimes they are present in quite large numbers and the blood picture represents an intermediate stage between Lymphatic leukaemia and Lymphoidocytic (myeloblastic) leukaemia.

A large number of the lymphocytes seen in a film of lymphatic leukaemia present some abnormality which leads to their being regarded as pathological cells in contradistinction to the healthy lymphocytes which appear in a simple lymphocytosis. Such abnormalities consist of extreme scantiness of the cytoplasm, vacuolation of the cytoplasm, changes in the nucleus indicative of karyolysis and the familiar "shadow" or "basket" cells which are found so often in cases of leukaemia with a high cell count. These latter forms represent the/

the penultimate stage of the lymphocytes which have undergone cytolysis, although a certain proportion of them are due to a breaking up of the already fragile lymphocytes in the making of a very thin film.

(c). MYELOCYTIC LEUKAEMIA.

Red Cells. The average total red cell count in this series was 2,114,800 which is about the same as that observed in the lymphatic variety. The average Haemoglobin was 31.8 per cent, giving a Colour Index of 0.76. The blood platelets are usually somewhat increased but they may be diminished in number.

White Cells. The average white cell count was 139,020 per cubic millimetre. This figure is much lower than that obtained in the cases of lymphatic leukaemia in this series. In no case was there a leucopenia.

Apart from the clinical features of these cases, the characteristic which compelled a diagnosis of leukaemia was the high proportion of myelocytes present in the blood films (average 32 per cent). Such a myelocytosis is not observed in any other condition in infancy or childhood. Further, post mortem examinations were performed in 58 per cent of the cases and the diagnosis was stated to have been confirmed by the appearances observed.

The following figures represent the average differential count/

count of the white cells obtained from this series:-

Polymorphonuclears	38.7%
Eosinophiles	3.6%
Lymphocytes	25.0%
Myelocytes	32.0%

There is one interesting fact to be learned from these figures, and that is that in Myelocytic Leukaemia in infancy and childhood there is a large absolute lymphocytosis which accompanies the increased output of the normal and abnormal cells of the granular series.

(c) LYMPHOIDOCYTIC LEUKAEMIA.

Red Cells. The average red cell count in the 11 cases of this series was 2,066,400 per cubic millimetre. The Haemoglobin was 31 per cent and the Colour Index was 0.775.

White Cells. In this form of leukaemia the white cell count is low in comparison with the other varieties; the average here being 47,962 per cubic millimetre. The average proportion of lymphoidocytes (or Myeloblasts) present in a differential count was 58 per cent.

An average differential count gives the following figures:-

Polymorphonuclears.	9.3%
Eosinophiles.	2.0%
Lymphocytes.	22.5%
Myelocytes.	4.6%
Lymphoidocytes.	58.0%

Comparative Table of the Haematological features in the three varieties of Leukaemia.

TABLE IV.

	Lymphatic Leukaemia.	Myelocytic Leukaemia.	Lymphoidocytic Leukaemia.
Total Red Cells.	1,946,000	2,114,800	2,066,400
Haemoglobin.	31%	31.8%	31%
Colour Index.	0.816.	0.762	0.775
Total White Cells.	210,245	139,020	47,962

Course of the Disease. The course of leukaemia in infancy is always a short one, and, therefore, the disease must be regarded as a uniformly acute process at this time of life. Seldom, if ever, are remissions of the symptoms observed. Once the disease has developed, the patient passes steadily down hill and within 2 or 3 months death takes place. The following figures show the average duration of the illness in 73 per cent of this series:-

Lymphatic Leukaemia. 2.0 months.
Myelocytic Leukaemia. 4.3 months.
Lymphoidocytic Leukaemia. 2.1 months.

The apparent relative chronicity of the disease in the Myelocytic form is largely to be accounted for by the protracted course of No. 78 in which it is stated that the child/

child lived for 2 years after leukaemia had developed.

The figures in this series seem to show that in children the average duration of the illness varies but little irrespective of whether the large or small lymphocytes dominate the blood picture or whether the case is even a definite Lymphoidocytic Leukaemia.

RELATIONSHIP BETWEEN INFANTILE SPLENIC ANAEMIA AND LEUKAEMIA.

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Before discussing the question of the relation between Infantile Splenic Anaemia and Leukaemia it would appear advisable to consider the clinical features of this condition.

The symptom complex was first described by von Jaksch (11) and called by him Anaemia Pseudo-leukemica Infantum. Von Jaksch believed it to be a disease sui generis and held that, although it bore certain resemblances to leukaemia, it was not related to such a grave disorder.

Other writers (12) have since described the condition and have supported von Jaksch's view, but it would seem that the majority of workers (13) believe it to be a form of simple anaemia occurring secondary to a number of causes. Its clinical features have been summed up under the title of Infantile Splenic Anaemia.

CLINICAL FEATURES.

The clinical features may be summarised by saying that the condition is characterised by enlargement of the spleen associated with the presence of anaemia, degenerate and embryonic red cells and myelocytes in the peripheral blood, and that it rarely, if ever, appears after the fourth year of life. The liver and lymphatic glands may be enlarged;

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a leucocytosis may or may not be present: rickets is almost always present; and Hutchison (14) pointed out that the condition tends to occur in more than one member of a family and that it is especially frequent in twins. Haemorrhages may occur although they do not constitute nearly so prominent a feature as in leukaemia.

With regard to the appearances of the blood, in my series (see appendix) of 27 cases which presented all the features characteristic of the disease the following were the averages obtained:-

Age	18 months.
Red Cell Count.	3,390,000.
Haemoglobin.	44 per cent.
Colour Index.	0.7.
White Cell Count.	17,200.

In 9 cases the cells of the granular series were in excess of the lymphocytes, but in the remainder the proportion of lymphocytes to polymorphonuclears was within normal limits (about 3 to 2). The average percentage of myelocytes observed in differential counts of 300 cells was 2.3.

DISCUSSION.

Three theories have been postulated with the object of bringing this condition into relation with leukaemia. They are as follows:-

1. That it is an aleukaemic stage of true leukaemia. (15), (16), (17)
2. That it is midway between simple anaemia and leukaemia. (18)
3. That it is a transition between Pernicious Anaemia and Leukaemia. (19)

With regard to the first theory that Infantile Splenic Anaemia is an aleukaemic stage of true leukaemia, it is true that the blood picture, in so far as the white cells are concerned, is not typical of leukaemia although there may be a fairly high leucocytosis, but it is difficult to understand why a proportion of the cases should not, at some time in their course, become frankly leukaemic. Such, at least not infrequently, happens in the examples of aleukaemic leukaemia which are occasionally encountered in the adult. Further, no authentic cases of a transition from Infantile Splenic Anaemic to leukaemia appear to have been recorded.

Again, it has been said that Infantile Splenic Anaemia represents an intermediate stage between simple anaemia and leukaemia. Certainly, the appearances may be suggestive of such being the case, but there is no evidence that it bears any etiological relationship to the latter disease, because, as has been mentioned, the transition is never complete and the sequence, Simple Anaemia, Infantile Splenic Anaemia, Leukaemia has never been observed.

Finally, let us consider the theory that Infantile Splenic Anaemia is a transition stage between Pernicious Anaemia and Leukaemia. The appearances of a blood film from certain examples of the disease are very similar to the so-called Leukanaemia in the adult, and, doubtless, this resemblance is responsible for Engel's conception of the disease. An examination of the red cells in many cases

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of Infantile Splenic Anaemia shows them to have all the features which, in the adult, would justify a diagnosis of pernicious anaemia. It must be remembered, however, that in the infant such a blood picture has not the same significance as in the adult. In the infant a megalocytosis with a high colour index and the presence of numbers of megaloblasts signifies no more than a grave disorder of the haemopoietic tissues from which the patient may recover completely if the cause of the anaemia is eliminated. Even although the cause of the condition cannot be definitely ascertained; with hygienic surroundings and good nursing, recovery may be said to be the rule. Further, if a pernicious anaemia ever occurs in infancy, it must be excessively rare, and, certainly, I have never seen a case which could be given such a diagnosis.

With regard to the white cells, it has already been shown that the appearances encountered in a blood film are by no means typical of the leukaemic state. (20) Again, Thursfield has shown that the histological appearances of the organs do not show the features considered characteristic of leukaemia. Finally, in my series of cases the symptom complex was associated with a number of known toxic processes, e.g. tuberculosis, pneumonia, syphilis, etc.

In the light of these obdervations it seems justifiable to conclude that the so-called Infantile Splenic Anaemia bears no etiological relationship to the leukaemic processes.

SUMMARY.

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A hundred cases of leukaemia in children under 8 years of age have been analysed and the following observations have been made:-

(1). The relative frequency of the three forms of leukaemia at this period of life may be taken as follows:-

Lymphatic Leukaemia.	70 per cent.
Myelocytic Leukaemia.	19 per cent.
Lymphoidocytic Leukaemia.	11 per cent.

(2). Leukaemia is about twice as common during the first 4 years of life as it is in the subsequent 4 years.

(3) 62.87 per cent of cases of leukaemia occur in male subjects.

(4). An analysis of the symptomatology of leukaemia has been made and it shows that there are five principal features of the disease, namely; enlargement of the spleen, liver and lymphatic glands; haemorrhages; and fever. Other symptoms which are of relatively less frequent occurrence are described. Most of the symptoms are considered in some detail.

(5). An account is given of the blood picture observed in each variety of leukaemia and the relationship between the types of leukaemia is explained by reference to the physiological development of the blood cells.

(6). It is shewn that all forms of leukaemia in early life must be regarded as being acute and that the expectation of life, once the disease is established, is but a matter of a few weeks.

(7). The theories suggesting that Infantile Splenic Anaemia bears an etiological relationship to leukaemia are discussed and the conclusion submitted that no such relationship exists.

REFERENCES TO PART I. Section 1.

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1. BROWNING. Jour. of Path. and Bact., 1905. X. p.145.
2. MOLLIER. Arch. f. mikr. Anat. 1909. LXXIV. p. 474.
3. NATHAN. Jour. de l'Anatomie, 1908. XLIV. p. 208.
4. SCHRIDDE. Centralblatt f. allg. Path. 1909. XX. p. 433.
5. JOLLY. Traite de Haematologie, Paris. 1923.
6. NATHAN and LARIER. Soc. de Biologie, 1900.
7. DUNN. Quarterly Jour. of Med. 1913. 6. No. 23.
8. For complete list of synonyms see Gruner, O.C., "The Biology of the Blood Cells," 1913.
9. HUTCHISON. Lancet. 1904. vol.1. p. 254.
10. TIDY. Quart. Jour. Med. 1924. XIV. 66. p.210.
11. McNEIL. Edin. Med. Jour. 1914. XII. p.25.

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REFERENCES TO PART I. Section II.

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1. RAMSAY. Brit. Jour. Child. Dis. 1924. XXI. p.48.

2. CARPENTER. Reports of Soc. for Study of Dis. in Child. 1902-3. III. p. 343.

3. REED. Amer. Jour. Med. Sci. 1902. CXXIV. p.653.

4. NEUMANN. Berl. klin. Wochenschr. 1878. nos.6,7,9 and 10.

5. WALZ. Arbeiten aus dem path. Inst. Tubingen. 1899. II. p.1.

6. PAPPENHEIM. Zeitschr. f. klin. Med. 1900. XXXIX. p. 171.

7. BRANDENBURG. Charite Annalen. 1900. XXV. p.85.

8. TREADGOLD. Quart. Jour. of Med. 1908. I. p.239.

9. WARD. Proc. Roy. Soc. Med. 1912. V. 2. p.73.

10. TREADGOLD. Lancet. 1913.

11. von JAKSCH. Wiener. klin. Wochenschr. 1889, II.pp.435,456.

12. ALT and WEISS. Centralb. f.d.med.Wissensch.1892.XXX.p.433.
FOWLER. Brit. Med. Journ.1902. II. p.694.
MELLAND. Brit. Med. Jour. 1902. II. p.698.
POYNTON, THURSFIELD and PATERSON, Brit. Jour. Child. Dis. 1922. XIX. p.57.

13. ASHBY. Practitioner. 1912. LXXXVIII. p.675.
EVANS AND HAPP. Bull. Johns. Hopkins Hosp. 1922.XXXIII.p.1.
FISCHL. Zeitschr. f. Heilk. 1892. XIII. p.277.
FLESCH. Ergebn. d. inn. Med.u.Kinderheilk. 1909.III.p.186.
HUNTER. Lancet. 1909. I. p.230.
LICHENSTEIN. svenska lak-sallsk.handl.1917.XLIII.p.1533.
MARSI. Pediatrica. 1922. XXX. p.652.
NAEGLI. Blutkrankheiten und Blutdiagnostik, 1923.
OSTROWSKI. Jahrbuch.f.Kinderheilk. 1911. LXXIII.p.690.
RIVIERE. Lancet. 1903. II. p.1419.
STENGEL. 20th Century Practice, New York. 1896. VII.p.460.
WENTWORTH. Boston Med. and Surg. Jour. 1901. CLXV. p.374.
RAMSAY. Brit.Jour.Child.Dis. 1924. XXI. p.48.

14. HUTCHISON. Goulstonian Lectures. Lancet. 1904.I.p.1323.

REFERENCES TO PART I. Section II. Contd.

15. LEHNDORFF. Jahnb.f.Kinderheilk. 1904.LX.p.194.

16. LUZET. Archiv.gen.de med. 1891. I. p.579.

17. PAPPENHEIM. Folia Haematologica. 1904. I. p.188.

18. HUTCHISON. Lancet. 1904. I. p.1323.

19. ENGEL. Virchow's Arch. f. path. Anat. 1894. CXXXV. p.369.

20. THURSFIELD. Brit. Med. Jour. 1921. II. p.873.

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CASES OF LYMPHATIC LEUKEMIA.

TABLE I.

No.	Author.	Sex	Age in months	Duration in mths.	Enlarged spleen.	Enlarged liver.	Enlarged glands.	Fever.	Haemorrhages.	Retinal changes.	Dyspnoea.	Digestive Symptoms	Albuminuria.	Heart Murmurs.	Stomatitis.	Pain.	Oedema.	Enlarged tonsils.	P.M. Examination.	Red cell count.	Hb. %	White cell count.	% Lymphocytes.	Predominant Type of Lymphocyte
1	Savory	M	54	1½	-	-	+	+	+	+	+	+			+			+	-	2,157,000	35	356,000	96	Large
2	Geissler, Japha,	M	60	3	+	+	+	+	-											1,580,000		34,250	97	
3	Chisholm.	M	42		+		+		+														98	
4	Larabee.	F	1½	1	+	-	+		+		+	+							-	4,392,000	60	918,000	99	Small
5	Babonneix, Tixier.	F	18	2	+		+	+	+		+	+	+		-			-	+	2,950,000	70	43,600	91	Large
6	Rocaz.	M	48	1	+		+	+	+			+			+			+	+	1,816,000	30	244,000	96	
7	McCaw.	F	20	1½	+	+	+	+	+				+						-	2,200,000	38	818,000	99	
8	Glinski.	M	12		+	-	+		+			+			+		+		+	918,760	21	180,416	94	
9	Churchill.	M	48	1	+	+	+	+	+		+	+	-	+				+	+	2,740,000	40	52,000	99	
10	Veeder.	F	17		+	+	+	+	+				+	-	+			+		3,370,000	55	1,330,000	99	Small
11	Bezy.	F	84		+	-	+	+	+		-	+	-			+			+	3,000,000		20,000	95	Large
12	Strauss.	M	13	1	+	+	+	+	+			-	-					-	+	2,008,000	25	208,000	97	
13	Condat.	F	48		+	+	-	-	+			+			+		+		-	660,000	20	148,000	91	Small
14	Hutchison.	F	72	3	+	+	+	+	+	+					+					1,200,000	10	170,000	98	Small
15	Carpenter.		42	1	+	+	-						+							1,568,000	15	130,000	99	Small
16	Surmont, Debon.		42	4	+	-	+	+	+		+		+		+		+	+		2,433,500		14,375	99	Small
17	Nobel.		18		+		+	+	+											1,700,000	25	6,400	79	

CASES OF LYMPHATIC LEUKAEMIA

TABLE I. (Contd)

No.	Author.	Sex	Age in months	Duration in mths	Enlarged Spleen	Enlarged liver.	Enlarged glands	Fever.	Haemorrhages.	Retinal changes.	Dyspnoea.	Digestive symptoms.	Albuminuria.	Heart murmurs.	Stomatitis.	Pain.	Oedema.	Enlarged tonsils	P.M. Examination.	Red cell count.	Hb. %	White cell count.	Lymphocytes. %	Predominant Type of Lymphocyte.
18.	Comby.	F	48	4	+	+	+	+	+					+			+		-	2,164,000		70,680	97	
19.	Johnson.	M	24	1	+	+	+		+				+		+				+	1,200,000		517,000		Large
20.	Whipham, Leathem.	F	24	1	+	+	+	-	+			+			+	+			+	3,000,000	42	20,000	98	Large
21.	do.	M	57	½	+	+	+	+	+	+		+		+	+				+	2,196,000	58	22,800	72	
22.	Moussous.	M	42	4	+	+	+	-	+	-	+		+	+						1,143,600	21	5,580	99	Small
23.	McCrae.	M	36	1	+	+	-	+	+			+		-	+		-	+	-	1,760,000	32	60,800	99	Small
24.	Forbes, Langmead.	M	18	1	+	+	+	+	+				+				+	+	+	1,106,000	15	83,000	91	Small
25.	do.	M	15	1	+	+	+	+	+	-		+	+	+	+			+	+	1,000,000	30	29,000	92	Small
26.	do.	M	24	1	+	+	+	+	+			+							+	1,200,000	20	196,840	98	Small
27.	do.	F	12	1½	+	+	-	+	+			+						-	+	1,000,000		60,000	93	Small
28.	do.	F	7		+	+	+	+	+			+	+						+	2,000,000		321,000	99	Large
29.	do.	M	36	2	+	+	+	+	+	+			+		+			+	+	1,340,000	32	14,000	96	Small 1
30.	do.	F	42	6	+	-	+	+	-										+	2,550,000		7,500	96	Small
31.	do.	M	30	2½	+	+	+	+	+	+	+		-		+			-	+	3,000,000	35	1,000,000	97	Small
32.	do.	F	39	1	+	+	+	+	+		+	+	+				+	-	+		38			
33.	do.	F	48	2	+	+	+	+	+	+		+	-	+			+		+	2,284,000	45	61,000	99	
34.	Chaney.	F	60	6	+	+	+	+	+				-	+				+	-	1,500,000	21	19,000	100	Small
35.	do.	M	54	1½	+	-	+		+		+	+				+		-	-	2,500,000	45	304,000	96	Small

CASES OF LYMPHATIC LEUKAEMIA.

TABLE I. (Contd).

No.	Author.	Sex.	Age in months.	Duration in mths	Enlarged spleen.	Enlarged liver.	Enlarged glands.	Fever.	Haemorrhages.	Retinal changes.	Dyspnoea.	Digestive symptoms	Albuminuria.	Heart murmurs.	Stomatitis.	Pain.	Oedema.	Enlarged tonsils.	P.M. examination.	Red cell count.	Hb. %	White cell count.	% Lymphocytes.	Predominant Type of Lymphocyte.
36.	Cheney.	M.	84	4	+	+	-	+	-			+		+				-	-	2,000,000	15	480,000	96	Small
37.	Bradford, Shaw.	M.	84	2	+	-	+	+	+			+	+		+	+	-	-	+	1,480,000	31	34,400	99	Large
38.	Muller.	M.	48	1	+	+	+	+	+						+	+			+			109,600	97	Large
39.	do.	M.	48	1	+	+	-	+	+						+				-			209,000	98	Large
40.	Vermehren.	F.	3	3	+	+	+		+			+	-						-	739,000		260,000	99	Small
41.	Lommell.	M.	1	1	+	+	+										+		+	1,282,000		1,240,000		Small
42.	Mennacher.	M.	11	5	+	+	+	+	+			+					-	-	+	4,900,000	40	258,000	73	Small
43.	McWeeney, Farnan.	F	36		+	-	+	+	+				-	-		+	+	-	-	1,540,000		136,400	97	Large
44.	Kakels.	M	18		+		+		+				+	+	+				-	2,046,000		682,000	94	Small
45.	Morse.	F	36	½	+	+	+	-	+			+		+		-		+	-	2,024,000	25	87,400	94	Small
46.	Myers.	M	51	2	+	+	+	+	+		+	-	-	+	-	-	-	+	+	1,424,000	25	32,000	97	Small
47.	Holscaw.	M	11	1	+	+	+	+	+			+	+	-	+	-		+	+	3,200,000		109,000	99	Small
48.	Smith.	M	1½	½	+	+	+	+	+			+		+					-	2,624,000		189,000	91	Small
49.	Lehndorf.	M	48	1	+	+	+	+	+						+			+	+	1,690,000	27	69,000	92	Large
50.	do.	F	16	2	+	+	+		+										+	2,800,000		80,500	92	Large
51.	Flesch.	M	48	½	+	+	+	+											-	3,000,000		380,000	96	Large
52.	Berghinz.	F	84	2	-	+	+	+	+						+		+		-	1,300,000		1,100,000	92	
53.	Bradley.	M	96	2	+	+	+		+						+				-	1,850,000		85,000	97	Large

CASES OF LYMPHATIC LEUKAEMIA.

TABLE I. (Contd.)

No.	Author.	Sex.	Age in months.	Duration in mths.	Enlarged Spleen.	Enlarged liver.	Enlarged glands.	Fever.	Haemorrhages.	Retinal changes.	Dyspnoea.	Digestive symptom	Albuminuria.	Heart murmurs.	Stomatitis.	Pain.	Oedema.	Enlarged tonsils.	P.M. examination.	Red cell count.	Hb %	White cell count.	% Lymphocytes.	Predominant Type of Lymphocytes.
54.	Gunewardene.	M.	36	6	+	+	+	+	+			+	+	+	+	-		+	+	760,000	11	8,400	85	Small
55.	Haushalter, Richon.	M.	90	2	+		+	-											+	1,829,000		36,000	83	
56.	Prof. Monro.	M.	54		+	+	+	+	+	+	+		-	+	+	+	-	+	-	1,360,000	18	22,900	97	Small.
57.	R.H.S.C.	F.	18		+	+	+	+				+		+	+				-	1,230,000	32	10,200	96	
58.	R.H.S.C.	F.	54	2	-	-	+	+	+			+		+		+		+	+	2,080,000	30	9,600	96	
59.	R.H.S.C.	M.	7	3	+	+	+	+	-	+		+	+	+	+				+	1,490,000	14	42,400	88	
60.	R.H.S.C.	F.	7		+	+	+	-	+			+		+					-	1,630,000	20	47,000	92	
61.	R.H.S.C.	F.	72	3	-	-	+	+	+		+		+	+		+	+	+	-	1,312,000	35	40,000	96	Large
62.	R.H.S.C.	M.	66	3	+	+	+	+	+					+	+			+	+	1,260,000	30	3,200	78	Large
63.	R.H.S.C.	M.	1½	1	+	-	+	+	+	-	-	+	-	-	-	-	-	-	-	3,120,000	70	713,000	94	Large
64.	Bartlett.		14	2½	+	+			+										+	824,000	20	57,100	94	Large
65.	Bass.	M	48		+	+	+	+	+	+		+				+			-	1,912,000	32	4,000	96	Small
66.	Strauch.	M.	48	3	+	+	+	+	+		-	+	-	+	-	-	-	+	+	2,200,000		40,000	93	Small
67.	Cooke.	F.	36	¾	+	+	-		+	+									+				89	Small
68.	Do.	M.	30	1	+	+	+		+						+			+	+				99	Small
69.	Ross.	M.	78		+	+	+	+	+		+			+		-	+					60,000		Large
70.	Acuna.	M.	72	½	+	+	+	+	+			+	-	-	+	+	+		+	1,500,000	40	250,000	93	Large

CASES OF MYELOCYTIC LEUKAEMIA.

TABLE II.

No.	Author.	Sex.	Age in months.	Duration in months.	Enlarged spleen.	Enlarged liver.	Enlarged glands.	Fever.	Haemorrhages.	Retinal changes.	Dyspnoea.	Digestive symptoms.	Albuminuria.	Heart Murmur.	Stomatitis.	Pain.	Oedema.	Enlarged tonsils.	P.M. examination.	Red cell count.	Hb %	White cell count.	% Polymorphs.	% Eosinophils.	% Lymphocytes.	% Myelocytes.	% Lymphoidocytes.
71.	Morse.	M.	12	1	+	+	+		+										-	2,900,000		48,000	46	6	31	21	
72.	Lehndorf.	M.	18	2	+	+	+	+	+				+	+	+		+		+	1,600,000	22	32,000	53	1	33	12	
73.	Berghinz.	F.	96	4	+	+	+	+									+		-	2,000,000		800,000	59	2	9	27	
74.	Karsner.	M.	30	6	+	+	+		+	+	+	+	-	-	-	-	-		+			19,000					
75.	Falconer.	M.	72		+	-	+	+	-	-				+		-			-	2,260,000	45	146,970	47	5	2	36	
76.	Stewart, Campbell.	M.	72	3	-		+	+	+							+			+	750,000		40,000	45	3	25	27	
77.	Whipham.		18		+	+	+	+	+											4,080,000	80	63,400	32	2	5	26	19
78.	Charon, Gratia.	F.	96	24	+	+					+								+	880,000	39	305,000	49			37	
79.	Ginsberg.	M.	30	4	+	+	+		+										+		55						
80.	Cassell.	M.	96		+	-	-		-			+				+	-		-	3,550,000	40	500,000	30	12		69	
81.	Goodall.	F.	2½		+	+	-		+			+		-	+				+	1,100,000		75,000	26	1	24	48	
82.	Carpenter.		12		+	+	-		+											2,900,000		48,000	47	1	31	21	
83.	Zylberlast.	M.	6	3	+	-	-		-		+	+	-			-			+	2,720,000	35	39,370	32	3	49	26	
84.	Menetrier, Aubertin.	M.	4		+	+	-												-	Whites to reds = 1 : 1			24		25	42	
85.	Weil, Hutinel & Clerc	M.	14	½	+	+	+	+											+	3,317,000		28,000	9	4	41	17	
86.	Hirschfeld.	M.	72	¾	+		+	+		+		+	-	+	+		-		+	800,000		59,000	60		18	23	
87.	Benjamin & Sluka.	M.	6	1	+	-	+	+	+			+					+	+	+	1,500,000	30	120,000	27		31	42	
88.	Delfosse.	F.	12		+		+	+	+											1,400,000		25,000				33	
89.	R.H.S.C.	F.	14	2½	+	+	+	+	+	-			+	+		+	+	-	+	2,080,000	20	115,000					

CASES OF LYMPHOIDOCYTIC LEUKAEMIA.

TABLE III.

No.	Author.	Sex.	Age in months.	Duration in months.	Enlarged spleen.	Enlarged liver.	Enlarged glands.	Fever.	Haemorrhages.	Retinal changes.	Dyspnoea.	Digestive symptoms.	Albuminuria.	Heart Murmurs.	Stomatitis.	Pain.	Oedema.	Enlarged tonsils.	P.M. examination.	Red cell count.	Hb %	White cell count.	% Polymorphs.	% Eosonophils.	% Lymphocytes.	% Myelocytes.	% Ltmphoidocytes.
90.	Panton, Tidy.	M.	60	1½	-		-	+				+				+	+			1,930,000	20	13,800	1		1		98
91.	Ross.	M.	72	3½	+	+	+	+	+	+		+		+	+				+	2,377,000	30	6,900	1		23		75
92.	do.	M.	39		+	+	+	+	+	-				+	-	-				1,800,000	28	17,200	19		38		43
93.	do.	F.	66	1	+	+	+	-	-			-		+	+	-			+	2,650,000	30	1,132	2		10	2	86
94.	Dallas.	F.	20	3	+	-	+	-	-			-					-		-	2,253,000	25	36,452	30		49		21
95.	Esser.	M.	96		+	+	+	+	+				-	+			-	+	+	840,000	35	8,700	21		1	5	24
96.	Horwitt.	M.	60		+	+	+	+	+				-		-		-			1,000,000		140,000	2				98
97.	Bass.	F.	96		+	+	+	+			+		-							2,080,000	41	134,400	5	2	15		80
98.	Furser.	M.	36				+	+							+					2,800,000	50	78,000					
99.	Nanta and Loubet.	F.	84		+	-		+	+			+	-	-	+	+			-	2,900,000		20,000					77
100.	Stirnimann.	F.	36	2½	-	-	+	+	+			+			+			+	+	2,100,000	20	70,000	3	2	43	7	44

CASES WITH COMPLETE PICTURE OF INFANTILE SPLENIC ANAEMIA.

Case No.	Sex.	Age in months.	Total red cell count.	Hb per cent.	Colour Index.	Total white cell count.	Ratio of polymorphs to lymphocytes.	Remarks.
1	F	17	4,790,000	58	0.6	21,000	R*	Unresolved pneumonia of 3 wks.duration.
4	F	17	3,840,000	64	0.8	22,800	N	History of melaena.
13	M	30	4,440,000	62	0.7	29,200	R	Repeated attacks of broncho-pneumonia.
22	M	5	4,090,000	66	0.7	18,200	R	Tuberculous meningitis. Died.
28	F	26	3,870,000	40	0.5	13,500	N	-
48	M	18	3,820,000	48	0.6	35,200	R	Miliary Tuberculosis. Died.
57	M	25	2,120,000	29	0.7	9,600	N	Sudden onset and rapid recovery.Lead poisoning.
67	M	18	4,160,000	46	0.6	18,600	N	-
68	M	13	1,760,000	20	0.6	18,200	N	Oozing of blood from mouth and nares. Wassermann reaction positive. Died.
72	M	34	3,870,000	64	0.8	8,000	N	-
77	M	5	2,570,000	56	1.1	11,000	R	Miliary tuberculosis with cavity in the lung. Died
79	M	10	3,660,000	46	0.6	21,600	N	-
81	M	11	2,310,000	32	0.7	18,600	N	Irregularly discharged.
83	F	45	2,140,000	28	0.6	7,900	R	Cardiac case.
84	M	18	1,080,000	24	1.2	13,800	N	-
90	M	14	5,500,000	48	0.4	49,600	R	Broncho-pneumonia. Removed against advice.
92	M	18	3,940,000	60	0.8	8,400	R	Discharged well 3 mths.later.
93	F	13	3,000,000	25	0.4	10,000	R	Died 4 days after admission. P.M.:- Lungs nil. mesenteric glands enlarged.
94	F	24	3,500,000	48	0.7	12,500	N	History of repeated rectal bleeding.No local cause detected.6 weeks later discharged well.
95	M	13	2,920,000	30	0.5	14,500	N	Died of rub.broncho-pneumonia. 5 wks.aft.adm.
96	M	18	1,820,000	18	0.5	16,400	N	Splenectomy performed.Gradual improvement.
97	F	12	4,080,000	45	0.5	26,000	N	Discharged with chickenpox.
98	M	44	3,280,000	50	0.8	16,000	N	Splenectomy performed.Gradual improvement.
99	F	10	3,920,000	35	0.6	16,400	N	" " " "
100	M	31	3,380,000	65	0.5	8,400	N	History of Purpura.
101	M	12	3,010,000	44	0.6	8,000	N	History of severe umbilical bleeding at birth.
108	M	5	4,700,000	50	0.5	12,200	M	-
Average		18	3,390,000	44	0.7	17,200		

* N—Normal R - Reverse.

REFERENCES TO CASES OF LYMPHATIC LEUKAEMIA. Table I.

ACUNA. Archives de med. des Enfants. 1906. IX. p.321.

BABONNEIX and TIXIER. Ibid. 1909. XII. p.662.

BARTLETT. Amer. Jour. Dis. Child. 1924. XXVIII. p.256.

BASS. Amer.Jour.Med. Sciences. 1921. CLXII. p.647.

BEDFORD and BATTY SHAW. Trans.Med.Chir.Soc.London, 1898. LXXXI. p.343.

BERGINZ. Paediatria, 1904, 1905. Quoted by BENJAMIN and SLUKA, Jahrb. f. Kinderheilk, 1907. LXV. p. 251.

BEZY. Archives de med. des Enfants, 1915. XVIII. p.224.

BRADLEY. New York Med. Jour., 1899. LXX. p.923. Quoted by HUTCHISON (vide infra.).

CARPENTER. British Medical Journal, 1903. II. p.469.

CHENEY. Amer. Jour. Med. Sciences, 1912, CXLIII. p.22.

CHISHOLM. Australian Med. Gazette, 1910, March 21st., Abstract:- Folia Haematologica 1911, X. 2. p.12.

CHURCHILL. Amer.Jour. Med. Sciences, 1904. CXXVIII. p.563.

COMBY. Archives de med. des Enfants, 1909. XII. p.131.

CONDAT. Ibid. 1923. XXVI. p. 286.

COOKE. Lancet, 1923, I. p.382.

FLESCH. Quoted by BENJAMIN and SLUKA, (Vide supra.). Jahrb. f. Kinderheilk 1907. LXV. p.87.

FORBES and LANGMEAD. Proc. Roy. Soc. Med., 1909. II.1. p.129.

GEISSLER and JAPHA. Jahrb. f. Kinderheilk. 1900. LII. p.572.

GLINSKI. Arch. f. path. Anat. 1903. CLXXI. p.101.

GUNEWARDENE. Brit. Jour. Child. Dis. 1920. XVII. p.9.

HAUSHALTER and RICHON. Archives de med. des Enfants. 1899. p.356.

HOLSCLAW. Archives of Pediatrics, 1918. XXXVI. p.151.

HUTCHISON. Lancet, 1904. I. p.1332.

References to Cases of Lymphatic Leukaemia. (Contd.)

-------oOo-------

JOHNSON. Brit. Jour. Child. Dis. 1909. LXI. p.10.

KAKELS. Archives of Pediatrics, 1902. XIX. p.443.

LARABEE. Boston Med. Jour. 1905.II. p.40.

LEHNDORF. Wien. med. Wochenschr. 1906. VII. p.311.

LOMMEL. Munch. med. Wochenschr. 1905. XIX. p.904.

McCAW. Practitioner. 1903. LXXI. p. 575.

McCRAE. Johns Hopkins Bulletin. 1900. CX. p. 102.

MEYERS. Archives of Pediatrics, 1915. XXXII. p.188.

MORSE. Ibid. 1898. XV. p.330.

MENNACHER. Munch. Med. Wochenschr. 1906. XLIII. p.2108.

MOUSSOUS. Jour. de med. de Bordeaux, 1908. XXII. p.341.
Abstract:-Arch. de med.des Enfants, 1909. XII. p.298.

MULLER. Jahrb. f. Kinderheilk. 1896. XLIII.p.130.

NOBEL. Gessellsch. f. innere Med. v. Kinderheilk, 1914. XXV.
Abstract:- Folia Haematologica, 1916. XVII. 2. p.62.

ROCAZ. Revue mensuelle des mal.d'Enfance, 1902. XX. p.120.

ROSS. Proc. Roy. Soc. Med. 1914. VII. 1. P. 129.

SAVORY. Lancet, 1904. I. p. 365.

SMITH. Amer. Jour. Dis. Child. 1921. XXI. p. 163.

STRAUSS. Arch. f. Kinderheilk. 1900. XXX. p. 272.

SURMONT and DEBON. L'Echo med. du Nord, 1904.
Abstract:- Glasgow Med. Jour. 1905. LXIII. p.149.

VEEDER. Archives of Pediatrics, 1911. XXVIII. p.43.

VERMEHREN. Quoted by BABONNEIX and TIXIER (vide supra).

WHIPMAN and LEATHEM. Lancet, 1906, II. p.367.

REFERENCES TO CASES OF MYELOCYTIC LEUKAEMIA. Table II.

--------oOo--------

BENJAMIN and SLUKA. Jahnb. f. Kinderheilk. 1907. LXV. p.87.

BERGHINZ. Quoted by BENJAMIN and SLUKA (vide supra).

CARPENTER. British Medical Journal, 1903. II. p.469.

CASSELL. Berliner klin. Wochenschr. 1898. IV. p.76.

CHARON and GRATIA. Quoted by HUTCHISON, Lancet, 1904. I. p.1332.

DELFOSSE. La Pediatrie pratique, 1911. XXI. p.538.

FALCONER. Lancet, 1906. I. p.1320.

GINSBERG. Quoted by KARSNER (vide infra).

GOODALL. Edin. Med. Jour. 1912. VIII. p. 500.

HIRSCHFELD. Berliner klin. Wochensehr. 1907. XXV. p.772.

KARSNER. Pennsylvania Med. Bull. 1910. XXVI. p.325.

LEHNDORF. Jahrb. f. Kinderheilk. 1904. 60. p.194.

MENETRIER and AUBERTIN. Quoted by BABONNEIX and TIXIER, Archives de mal. des Enfants, 1909. XII. p.662.

MORSE. Boston Medical Journal, 1894. II. p.133.

STEWART and CAMPBELL, Quoted by KARSNER (vide supra).

WHIPHAM. Proc. Roy. Soc. Med. 1910. III. 1. p.92.

WEIL and CLERC. Revue des mal. de l'Enfance, 1903.

ZYLBERLAST. These de Geneve, 1907. No.147. Quoted by BABONNEIX and TIXIER.

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REFERENCES TO LYMPHOIDOCYTIC (Myeloblastic) LEUKAEMIA.

Table III.

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BASS. Amer. Jour. Med. Sciences, 1921. CLXII. p.647.

DALLAS. Archives de med. des Enfants, 1910. XIII. p.213.

ESSER. Munch. med. Wochenschr. 1912. XL. p. 2148.

HORWITT. Archives of Pediatrics, 1922. XXIX. p. 819.

NANTA and LOUBET, Folia Haematologica, 1913, XVI. p.75.

PANTON and LOUBET. Folia Haematologica, 1913. XVI. p.75.

PANTON and TIDY. Ibid. 1914. XVII. p.400.

PURSER. Lancet, 1921. D. p.124.

ROSS. Lancet, 1916. II. p.940.

STIRNIMANN. Jahrb. f. Kinderheilk. 1907. LXV. p.609.

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PART II.

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INFECTIVE ANAEMIA AND LEUKAEMIA IN FOWLS.

PART II.

INFECTIVE ANAEMIA AND LEUKAEMIA IN FOWLS.

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During the past twenty years knowledge regarding the pathology of Leukaemia has undergone little change. The etiology of the disease in the human subject remains obscure, but there are two theories, neither of which can be taken as proved; (1) that it is of the nature of a tumour; a "sarcoma of the blood" (Banti);[1] and (2) that it is due to some infective agent.

The first attempt to transmit human leukaemia to lower animals was made by Mosler[2] in 1872 and since that date a multitude of experiments have been performed with the same object in view and the results have been uniformly negative.

Ellermann and Bang[3] and Hirschfeld and Jacoby[4] in 1909 each inoculated material from fowls suffering from Leukaemia in to rabbits, guinea pigs, doves, guinea fowl and turkeys but did not get any "takes." From these experiments it would appear that heterologous inoculations are unable to reproduce the disease, even when the experimental animals are subject to spontaneous leukaemia.

The first homologous transmission experiment was done in 1874 by Bollinger[5] who inoculated material from a leukaemic dog in to other dogs. Several workers in later years/

years repeated Bollinger's experiments but no positive results appear to have been recorded. The first successful transmission of leukaemia was done in 1908 by Ellermann and Bang [3] who used material from leukaemic fowls with which they were able to pass on the disease through several generations. Since that date Ellermann has transmitted at least 8 strains of the disease; one of them (Strain H) having gone through 12 generations. [6] Ellermann's observations were confirmed by Hirschfeld and Jacoby in 1909, [4] by Schmeisser in 1915 and by Magnusson [7] in the same year. [8] Thus, although leukaemia is met with among other animals, e.g. cats, dogs, cattle and horses, it is only in fowls that transmission experiments have been successful. However it would be well to remember that experiments of this nature may fail, and that for no apparent reason. Ellermann states that after 3 successive inoculations with different material, each in to 8 animals, he got a negative result. Not until the fourth inoculation did he succeed; after having used 32 animals.

The work which is here described was undertaken with the object of studying the appearances met with in fowl anaemia and leukaemia and in the hope that by this means some light might be shed upon the etiology of the similar diseases in the human subject.

THE BLOOD.

In order properly to understand the morbid appearances of the blood and haemopoietic tissues in fowls suffering from anaemia and leukaemia it is essential that one should be familiar with the morphology of these tissues in the healthy bird.

Samples of blood for examination are taken from the comb by snipping a piece off with a pair of scissors.

Method of counting the blood cells. To 15 c.c. of Gower's solution add one drop of a 0.5% solution of Crystal Violet and, after shaking, filter. This is used as the diluent. An ordinary red cell counting pipette is used. After the blood is drawn up in the pipette and diluted with the above solution it should be allowed to stand for 10 minutes and then shaken for a minute, after which the cells are counted in a Thoma-Hawksley haemocytometer chamber. The lymphocytes and thrombocytes stain deep blue while the nuclei of the red cells are very faintly stained. The polymorphonucleears can be recognised by their highly refractilegranules. It has been suggested that, owing to the cells adhering to the sides of the pipette, the above method is not accurate when counting the white cells. That such is not the case is proved by the constancy of the readings and by the close agreement between the figures so obtained and the results of a differential count in a film preparation; in which case the average reading is one white

cell to every 100 red cells.

The following figures represent the average of 14 blood examinations in different healthy hens between the ages of one and three years. The extreme variations are also noted.

Erythrocytes.	3,070,000	2,190,000 to 3,850,000.
Haemoglobin.	60%(Sahli).	45% to 84%.
Thrombocytes.	31,000.	22,600 to 40,600.
Leucocytes.	30,000	17,000 to 35,500.

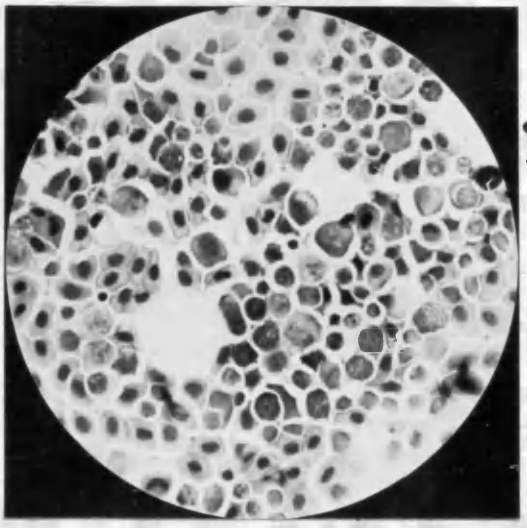
Stains. I have found Leishman's stain to give the most satisfactory results for the study of smears of fowl blood. The pure stain is left on the coverslip for 1½ minutes and then diluted with twice the quantity of distilled water, after which it is allowed to stand for 15-20 minutes. The film is then washed in water until the granules of the polymorphonucleears are bright red. After drying in the air (not over a flame) the film is mounted in neutral balsam. On the other hand, Jenner's stain is very useful, if not essential, in the study of pathological blood and I have made it a routine to use both these stains. Other stains which may be mentioned are Ehrlich's Triacid stain, Pappenheim's Panoptic stain and dilute Giemsa's stain, but, although each has its own particular merits, it is doubtful whether more information is to be obtained from these methods than from a satisfactory Leishman or Jenner preparation.

MORPHOLOGY OF THE BLOOD CELLS.

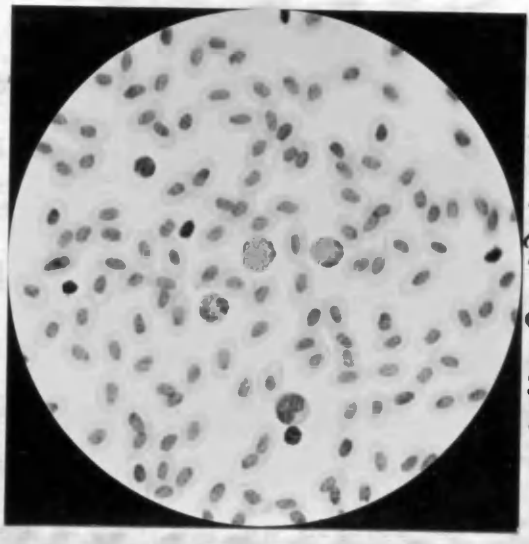
Erythrocytes. These are flat elliptical biconvex discs, about 7.5 by 13.5 microns in size, containing haemoglobin and a small round or ovoid nucleus with a closely set deeply staining chromatin network. The cells are very uniform in size but occasionally a large round cell with an excentric nucleus may be observed. These megalocytes are present in the blood of every fowl. With eosin the staining of the protoplasm is exactly the same as in the red cells of man. Disintegrated free nuclei which stain diffusely of a light violet colour are found in considerable numbers in some film preparations. These forms are not to be observed when the fresh blood is examined unfixed, and, therefore, it is probable that their appearance is largely an artefact associated with the making of a thin film. I have repeatedly observed that in the thicker parts of a film these disintegrated nuclei are not present.

Thrombocytes. These occur in the blood as pear shaped or almond shaped cells of about the same size as the erythrocytes and have a clear haemoglobin-free protoplasm and a round or oval nucleus containing dense chromatin granules. The protoplasm often contains a few azurophil granules. According to the observations of Werzberg (9) and Bedson (10) it would appear that the/

Normal Fowl.



Bone Marrow Smear.



Blood showing a lymphocyte, three Polymorphonuclears, a Monocyte and several Thrombocytes.

the thrombocytes have the same function as the mannalian platelets but that they are not morphologically related to the same; rather do the thrombocytes throw off fragments of material which correspond to the mammalian platelets.

Lymphocytes. These cells resemble very closely the human lymphocytes. The large and the small varieties are met with. Azurophil granules may frequently be observed in the cytoplasm.

Monocytes. These cells are larger than the lymphocytes and possess a feebly basophile protoplasm. The nucleus occupies the greater part of the cell, is kidney shaped and its structure consists of a rather pale chromatin network which does not stain so deeply as the closely packed network in the lymphocyte. The monocytes are comparable to the large mononuclear (large hyaline) leucocytes recognised in human blood.

Polymorphonuclears. These cells occur in two distinct forms:-

(1). Eosinophiles with rod shaped granules. These cells are crowded with spindle shaped highly refractile eosinophile granules arranged, as Gruner aptly puts it, like iron filings before a magnet is placed near them. The nucleus of such cells is rather dark and lobed and resembles in structure that of the mammalian neutrophile leucocyte. These cells correspond in number to the neutrophil/

neutrophil leucocytes in the mammalia and they are increased, as the following experiment proves, when pyogenic organisms are introduced into the body.

Experiment. 100 million living staphylococcus pyogenes aureus from a 24 hours culture were inoculated subcutaneously into the anterior abdominal wall of a healthy fowl on 4th August, 1923. The following table shows the changes which took place subsequently in the blood.

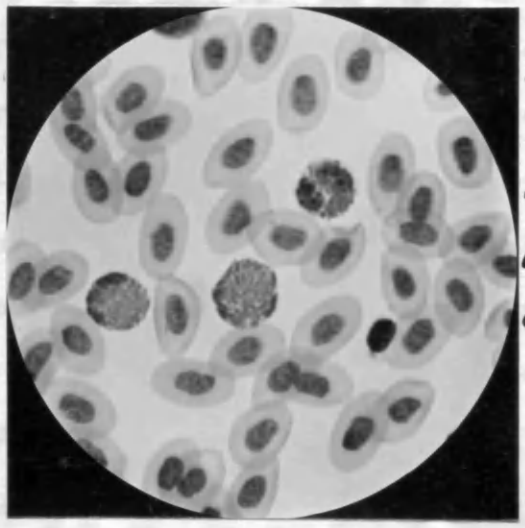
Date.	White cell count.	Polymorphs, with rods.	Polymorphs with grains.
Before expt.	33,190	30.0%	6.3%
5.8.23.	66,400	61.3%	1.3%
6.8.23.	50,000	50.3%	2.3%
7.8.23.	49,200	48.6%	3.6%
8.8.23.	44,100	39.6%	3.6%
9.8.23.	34,100	33.0%	4.3%

This experiment along with the other facts considered before appears to justify the opinion of Kasarinoff (11) according to whom these cells, which he calls the "pseudo-eosinophils of t he bird," correspond with the polymorphonuclear series of mammalian leucocyte. These pseudo-eosinophils, however, do not give the oxidase reaction.

(2). Eosinophils with fine round granules. These cells are found in much smaller numbers than the above type of cell. They give a positive oxidase reaction. The nucleus is lobed and stains deeper than that of the pseudo-eosinophile. These cells have been called the "true eosinophiles of the bird." (Kasarinoff).

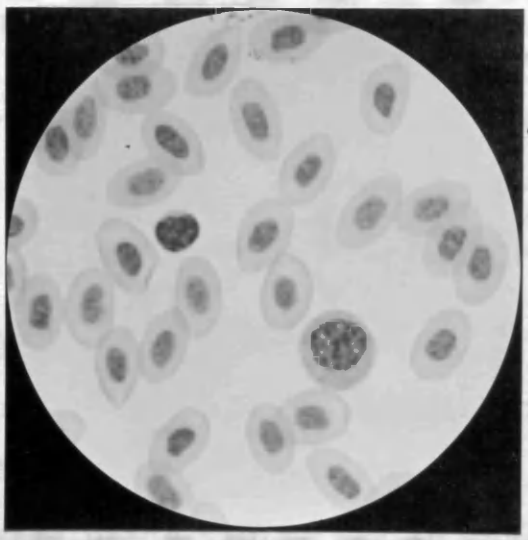
Mast/

Normal Fowl



Blood

Showing Eosinophile with grains and two Eosinophiles with spindle-shaped granules.



Blood

Showing two lymphocytes.

Mast Cells. These correspond to the mast cells as they occur in man. The protoplasm is foamy and often vacuolated and the granules appear to be situated in the vacuoles. The granules are more numerous, coarser and of less constant size than in the human mast cell; and they do not stain in the same metachromatic manner but rather of a deep violet colour. The nucleus is usually rounded and is of the lymphocyte type.

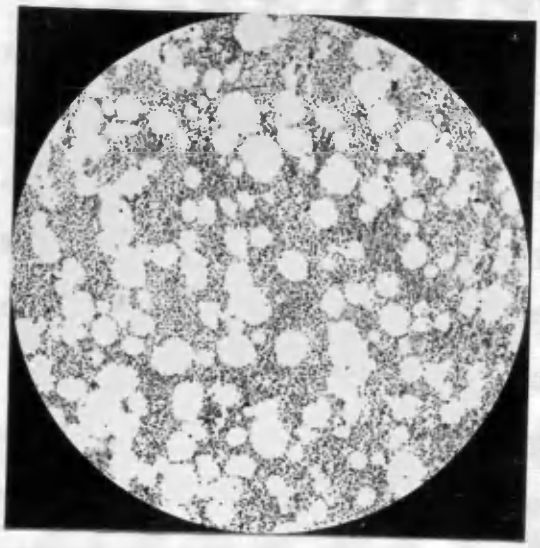
Differential Count of Leucocytes. In each case at least 300 cells were counted. The following figures represent the average differential count in 14 different healthy hens and show the extremes that were encountered.

Polymorphonuclears	Rod bearing.	27%	(22 to 46%)
	Grain bearing.	4%	(1 to 8%)
Lymphocytes.		57%	(46 to 72%)
Monocytes.		10%	(5 to 14%)
Mast Cells.		2%	(1 to 8%).

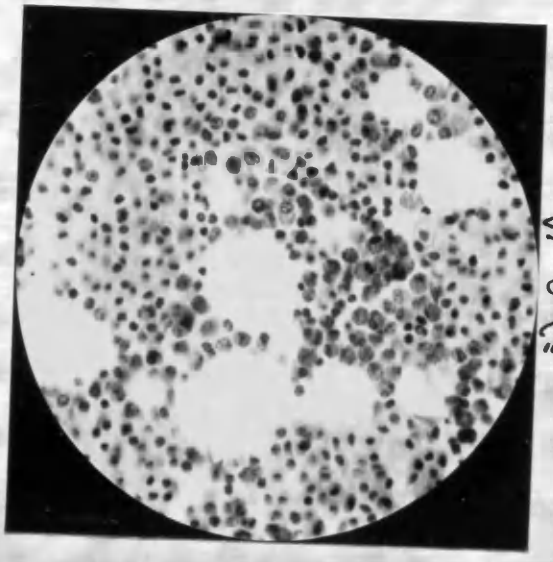
THE HAEMOPOIETIC TISSUES.

Bone Marrow. The marrow of the femur and tibia is red throughout except in birds over two years of age in which it is often fatty in the tibia. As in man, the marrow tissue is intersected by a number of fine cancellous bony spicules which make it rather difficult to shell out without damage. In the tibia the spicules are much fewer in number and, therefore, since I have noticed no difference between/

Normal Fowl



Bone Marrow



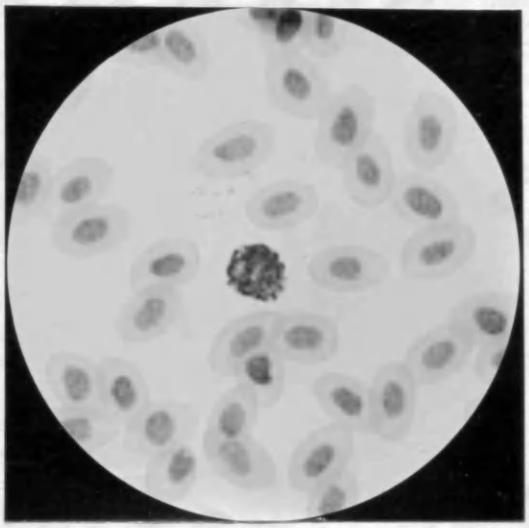
Bone Marrow

Showing Myelocytes and adult Polymorphonuclears.

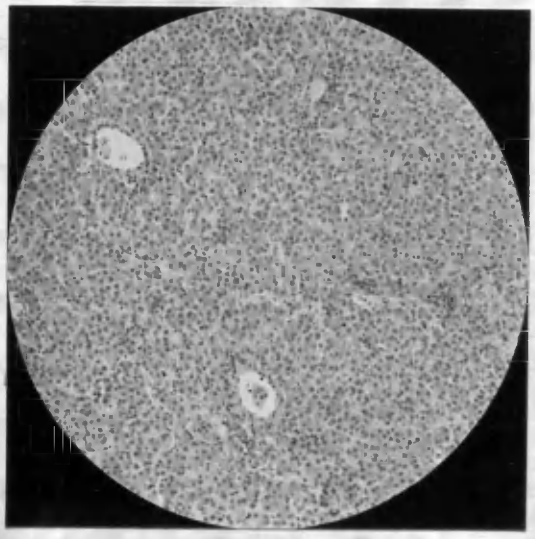
between marrow taken from the femur and that taken from the tibia, I usually take from the latter situation.

Under the low power of the microscope the marrow tissue is found to consist of (1) vascular areas completely filled with red cells; (2) a delicate fibrous connective tissue framework in which are to be seen (a) cells belonging to the granular series; (b) scattered foci of lymphocytes and (c) fat cells, the number of which is inversely proportional to the activity of the particular piece of bone marrow under observation. On examination with the high power the vascular areas are found to be venous sinuses enclosed by a single layer of epithelium, and in them the process of erythropoiesis may be observed. A number of large round basophile cells are seen in the sinuses and the trabeculae. The trabeculae contain the cells of the granular series and scattered foci of lymphocyte formation. Megakaryocytes are not present in the marrow of the fowl. On examination with the oil immersion lens the basophile cells referred to above are found to be lymphoidocytes (vide infra). These cells are present in the sinuses along with adult red cells and some of their progenitors. Mitotic figures are present in a number of the erythroblasts and occasionally among the lymphoidocytes. The cells in the trabeculae are myelocytes and metamyelocytes having a single oval or lobed nucleus and a number of large round granules which often stain uncertainly, i.e. neither frankly oxyphile nor frankly basophile. Groups of adult/

Normal Fowl



Mast Cell.



Livex.

adult polymorphonuclears with lobed nuclei and spindle shaped oxyphile granules are present in smaller numbers. Mast cells are very rarely seen. Mitotic figures are not common among the granular cells.

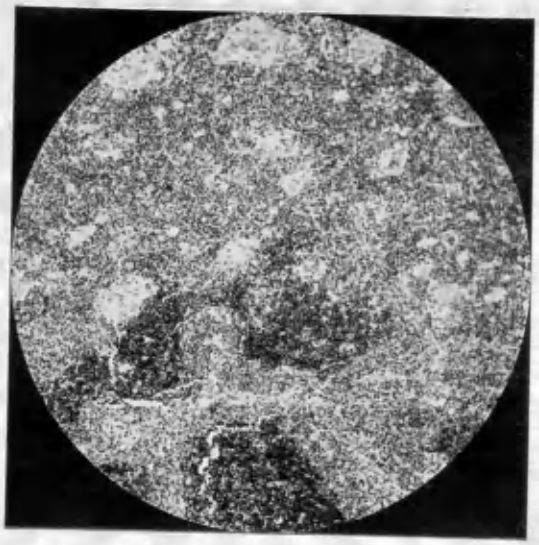
Liver. Weight 30-40 grammes. The general structure is similar to that of the human organ. Normally, however, accumulations of lymphocytes or of myelocytes are to be found in relation to some of the portal tracts. There is no evidence of red cell formation in the liver of the adult fowl. Advanced fatty degeneration of the liver is often found in birds which have ceased to lay and which have not led an active existence.

Spleen. Weight 1.5-2.5 grammes. The structure of the spleen is similar to that in man. The organ contains a number of Malpighian follicles of various sizes composed of lymphocytes and surrounded by an abundant pulp tissue which is divided up in to lobes by fibrous trabeculae running inwards from the capsule. In the normal adult fowl follicles with active germ centres are not usually seen although such is quite common in young birds. The pulp tissue contains lymphocytes, erythrocytes and polymorphonuclear leucocytes.

Kidney. Weight 5.0-6.5 grammes. Microscopically the organ is the same as the human kidney. I have not observed any evidence of red cell formation in this organ but in the pelvis of the kidney areas of active white cell production are a fairly constant feature.

Normal Fowl.

Thymus



Thymus. The gland extends on each side of the neck from the upper attachment of the pericardium to the angle of the jaw. It lies in the same anatomical position as the cervical lymphatic glands in man. Thus the thymus of the fowl, instead of being a single gland mass, may be considered as having been unraveled. Hassal's corpuscles are present in fair numbers and polymorphonuclears are frequently found in them. The pulp of the gland is composed of lymphocytes along with a few red cells and polymorphonuclears. I have not observed any lymphatic glands in the fowls examined; and this is in accordance with the statement of Ellermann that lymphatic glands are absent in all birds except ducks and geese.

DEVELOPMENT OF THE BLOOD CELLS.

Wera Dantschakoff (12) has described in considerable detail the method of blood formation in the chick and in the fowls which I have examined I have been able to observe most of the stages which she describes. All the blood cells may be traced back to the undifferentiated connective tissue cell which is multipotential; being capable of becoming a fibroblast, an osteoblast or a haemoblast. It is with the haemoblast that we are concerned. The undifferentiated connective tissue cell becomes spherical, the protoplasm becomes deeply basophile and surrounds, as a narrow ring, the nucleus which is round, pale and contains a small central deeply staining mass of chromatin. This cell is about 20 microns/

microns in diameter and may be called the primitive haemoblast or lymphoidocyte. The lymphoidocyte, in its turn, may be the parent of either erythrocytes, lymphocytes or cells of the granular series. In the adult bone marrow lymphoidocytes are quite common and cells representative of the various steps in the formation of the normal blood are to be seen. The central chromatin mass is found to break up in to a number of particles and to be distributed throughout the nucleus; the astrosphere, which is present in the most primitive haemoblasts, disappears and the cell substance becomes relatively more abundant. Polychromatophile erythroblasts showing scanty haemoglobin formation in the protoplasm and a radial arrangement of the nuclear chromatin are present in moderate numbers and it is among such cells that mitotic figures are most commonly observed. Finally, forms having smaller nuclei with less of the wheel shaped structure and a more oxyphile cell body of elliptical shape are present along with the normal adult erythrocytes.

I have not been able to observe the development of the thrombocytes but it is almost certain that they are derived from the lymphoidocytes in the same way as the red cells, only no haemoglobin is formed in the cell substance. (10), (12).

Turning to the cells of the granular series; in the adult bone marrow a very scanty number of cells may be found showing all the characters of the lymphoidocyte but having, in addition, a few oxyphile granules embedded in the cytoplasm around

the astrosphere. Present in much larger numbers are the true myelocytes in which the central chromatin mass has broken up in to two or more particles, the astrosphere has disappeared, the cytoplasm has become much less basophile and the granules have increased in number and size. The granules in these cells are often mixed; some being oxyphile and others basophile. Other cells are present in which the nucleus is lobed and the cytoplasm contains both round and spindle shaped granules. These cells may be called metamyelocytes. Finally, adult polymorphonuclears are found having the characteristic spindle shaped granules of uniform size embedded in their cytoplasm. The mast cells and the true eosinophiles are almost certainly formed in exactly the same manner as has been indicated for the pseudo-eosinophiles.

TECHNIQUE OF TRANSMISSION EXPERIMENTS.

Owing to the rapid onset of post mortem change in birds it is advisable to kill the diseased animal in agony by wringing its neck. After portions of the haemopoietic tissues have been placed in fixing material for histological purposes an emulsion of part of the liver or spleen is made with silver sand in normal saline and then centrifugalised for a short time. The supernatant fluid is decanted and may be inoculated intravenously or intraperitoneally at once or after filtration through a Berkefeld candle. Cultures of the organs may be made on various media. In my experiments I used nutrient agar slopes, bouillon, Bulloch's meat medium and/

and Noguchi's kidney and ascitic fluid medium aerobically and anaerobically. All my culture tubes after incubation at 37°C. for varying periods up to one month remained sterile with the exception of one tube of Noguchi's medium (aerobic) in which a coliform bacillus was found after a few days.

LEUKAEMIA AND ANAEMIA IN FOWLS.

Up to date, I have not seen an example of leukaemia in fowls and the following description of the disease is taken from Ellermann's "Leucosis of Fowls," London, 1921.

Myeloid Leukaemia. As in man, the disease may come on very rapidly or in an insidious manner. The animal suffers from lethargy, anorexia and a varying degree of anaemia. Once the condition has manifested itself in the blood the bird loses weight rapidly, and, in the course of a few days, perishes. As a rule the red corpuscles are reduced in number and embryonic forms are present. The haemoglobin is deficient. The white cells are very much increased in number, even reaching as high as 1,000,000 per cubic millimetre. The predominant element is a cell with an irregularly shaped nucleus containing a delicate chromatin network and having a rather basophile protoplasm in which there are no granules. These cells are called "poikilonuclears" by Ellermann and they would appear to correspond to the non-granular polymorphonuclears occurring in human leukaemia and referred to by Pappenheim as "Die leucoblastische Riederzellen." Cells similar to these but having a round nucleus and a scanty protoplasm/

protoplasm are also numerous and they are not dissimilar to the lymphoidocytes or myeloblasts (Naegli) which occur in man in cases of acute myeloid hyperplasia. The myelocytes are large cells with a faintly basophile protoplasm containing round granules of irregular size. In contradistinction to leukaemia in man the typical polymorphonuclears are not absolutely increased in number. Thus it would appear that an abnormal form of hyperplasia is taking place, thus:- Lymphoidocyte (myeloblast) - Metamyeloblast - Poikilonuclear In some examples of myelogenous leukaemia in fowls the normal form of myeloid hyperplasia occurs, thus:- Lymphoidocyte - Myelocyte - Metamyelocyte - Polymorphonuclear. Aleukaemic cases are very rare but have been observed. Finally, examples of the disease in which myelocytic tumours were present have been seen. These tumours would appear to be analogous to the chloromata.

Regarding the appearance of the organs, we find changes identical with those observed in leukaemia in man, i.e. enlargement of the spleen, liver and kidneys, all of which show mottled areas of various sizes which on microscopical examination prove to be islets of myeloid metaplasia. The bone marrow shows a hyperplasia of the myeloid elements and the sinuses are frequently found to be packed with embryonic red cells.

Lymphatic Leukaemia. Clinically there is no evidence of disease but the bird dies suddenly and unexpectedly. The lymphatic hyperplasia is entirely extravascular and the blood shows/

shows no leukaemic change. The liver, spleen, kidneys, and often the thymus and lymph nodes in the intestine are enlarged. Nodules of varying sizes are present throughout the tissues and these, on microscopical examination, prove to be masses of large lymphocytes. In some cases there are definite tumours suggestive of Sternberg's leucosarcomatosis. The bone marrow in this disease may be normal or it may contain small scattered accumulations of large lymphocytes.

Pernicious Anaemia. All my experiments have been performed with material from fowls which have been suffering from this disease. The condition begins insidiously with lethargy, anorexia, loss of weight and anaemia. As the condition progresses the bird becomes distinctly jaundiced and the anaemia becomes severe. Remissions may occur during which the bird appears healthy and the blood shows little or no abnormality. Eventually, however, the animal dies and the characteristic changes are found in the organs. In film preparations of the blood one may observe every form of immature and degenerating erythrocyte. There is a large proportion of lymphoidocytes and basophile erythroblasts. The white cells are usually within normal limits both absolutely and relatively but an occasional myelocyte is by no means infrequent. The thrombocytes are diminished in number. On examination of the organs, the liver and spleen are usually found to be enlarged but this is not always

the/

the case. The Prussian blue reaction is positive. On microscopical examination, the capillaries of the various organs are seen to be uniformly packed with primitive red cells. The Malpighian bodies of the spleen are very small or, in some cases, quite atrophied while the pulp is densely infiltrated with all forms of erythroblasts. In the bone marrow the trabeculae are atrophied and very little myelogenous tissue is observed. The marrow fat is very much diminished or even entirely absent. The sinuses are dilated and filled with lymphoidocytes and other primitive red cells. Occasionally scattered areas of myeloid metaplasia may be seen in the liver.

As examples of this disease I shall quote my own cases.

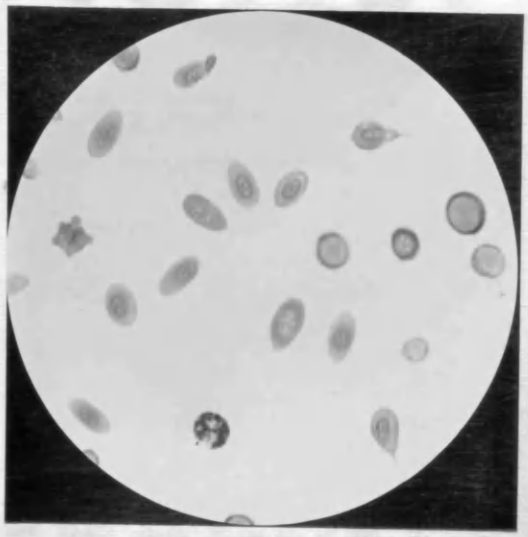
Fowl 6. White Leghorn. Received on 1st May, 1923, from a poultry keeper in the north of England.

Blood examination:-	Red cells.	519,000.
	Haemoglobin.	10%.
	Colour index.	0.96.
	White cells.	31,200.
	Thrombocytes.	12,100.
Differential count:-	Polymorphonuclears.	19.3%.
	Lymphocytes.	68.6%
	Monocytes.	4.3%
	Mast cells.	3.0%
	Myelocytes.	4.3%

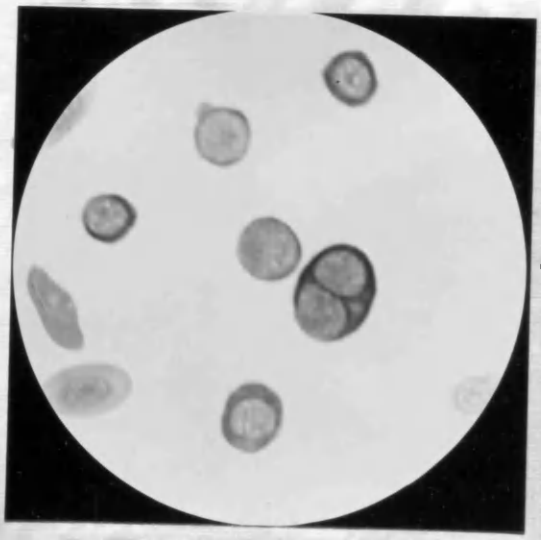
The bird was very jaundiced and it remained lying on the ground and could not be enticed to take either food or drink. On 5th May, 1923, the bird was killed.

Liver/

Row C. 6.



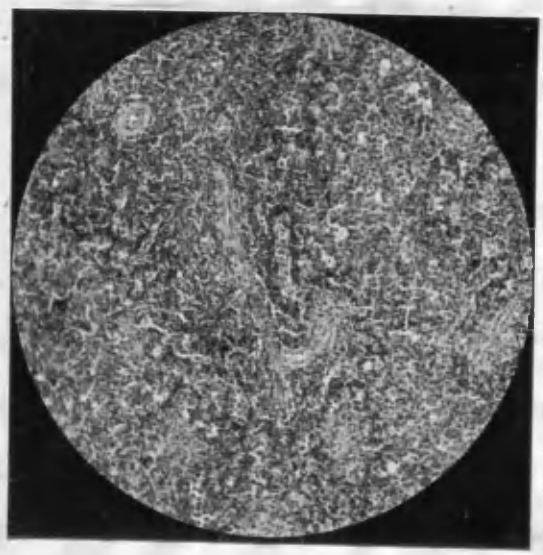
Blood.



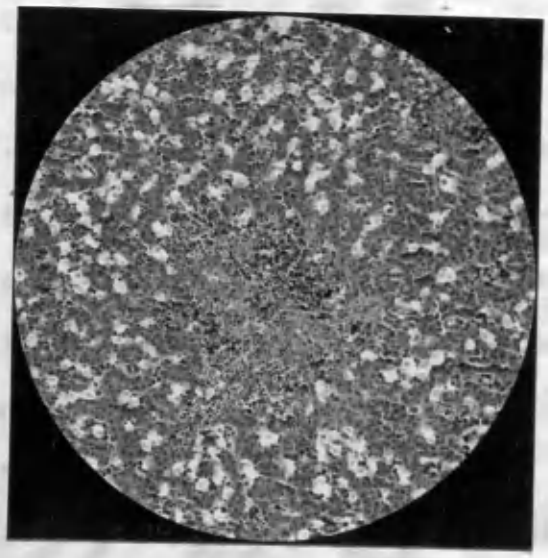
Blood.

showing a lymphocyte in mitosis.

row 6.6.



Spleen.



Liver

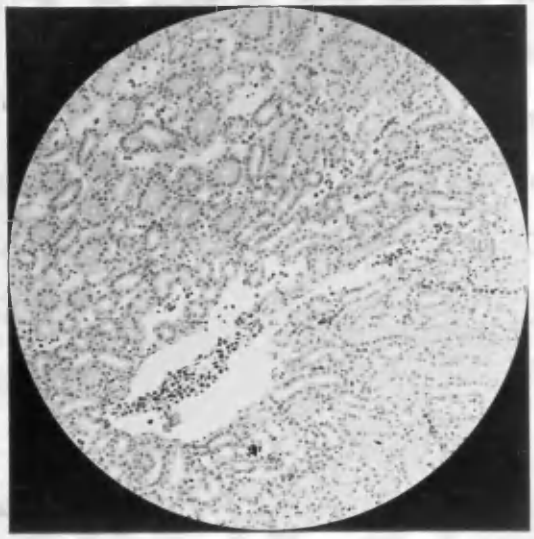
Liver. Weight 51.4 grammes. The organ appears normal and there are no nodules on the surface or on section. The cut surface is reddish in colour. The Prussian blue reaction is strongly positive. The gall bladder is full of bile and no calculi are present. On microscopical examination, the capillaries are dilated and filled with lymphoidocytes and erythroblasts. There are numerous areas of myelogenous hyperplasia scattered throughout the organ but they are found chiefly around the portal tracts. There is much haemosiderin present in the liver cells. The Prussian blue reaction is well marked and it is observed that the iron is almost entirely localised to the liver cells and endothelial cells, being present only in the smallest quantity in the areas of hyperplasia or infiltration.

Spleen. Weight 6.7 grammes. The organ is very soft. On section it is dark in colour and the Malpighian bodies are not visible. The Prussian blue reaction is positive. On microscopical examination, the Malpighian bodies have entirely disappeared and the pulp is densely packed with cells, chiefly primitive erythrocytes.

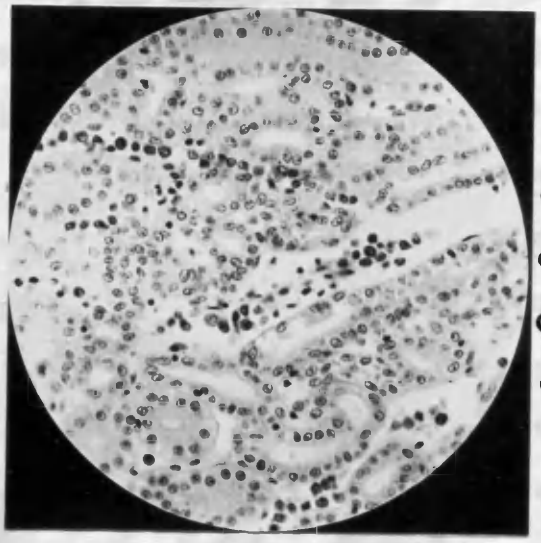
Kidneys. Weight together 13.2 grammes. No abnormality is detected on naked-eye examination. On microscopical examination the capillaries are found to be considerably dilated and filled with erythroblasts. Occasional myelocytes are to be seen. The Prussian blue reaction is positive.

Bone

Fowl . 6.



Kidney



Kidney

showing many erythroblasts and lymphocytes in the capillaries.

Bone Marrow. The marrow is very red but no definite abnormality is noticed on naked-eye examination. Microscopically the fat is found to be very much decreased. The trabeculae are almost entirely atrophied and the myelogenous tissue is conspicuous by its absence. The sinuses are greatly enlarged and are uniformly densely packed with lymphoidocytes and other primitive types of the red cell series. Occasional mitotic figures are observed.

EXPERIMENT. An emulsion of the liver and spleen from the above fowl was inoculated at once in to a (a) 2 rabbits with a negative result (one rabbit died 2 weeks later from some laboratory infection and the other died of coccidiosis 3 months after inoculation); 4 healthy fowls of the same breed (White Leghorn) and each about one year old with one positive result (vide infra); and (c) in to tubes of Noguchi's medium in which it was incubated for 3 weeks under aerobic and anaerobic conditions. On examination the tubes appeared sterile. The medium was then inoculated in to 2 rabbits and 2 fowls. The result of this inoculation was negative in the case of the rabbits after 9 weeks and in the fowls after 6 months.

The following is the history of one of the fowls inoculated directly from Fowl 6.

FOWL F.	Total Red Cells.	Hb. %	C.I.	Total White Cells.	Remarks.
4.5.23.	2,770,000	54	1.	25,900	Weight 3 lbs. 10 ozs. Inoculated the following day.
6.6.23.	2,780,000	54	1.	26,300	Appeared quite healthy.
15.8.23.	2,190,000	35	.8	30,100	Appeared healthy. No abnormality detected in film preparations.
25.10.23.	890,000	12	.7	34,000.	Jaundice of 2 days' duration. Films showed many abnormal red cells.
9.11.23.	740,000	10	.7	33,400	Condition unchanged. Weight 3 lbs 6 ozs. Killed.

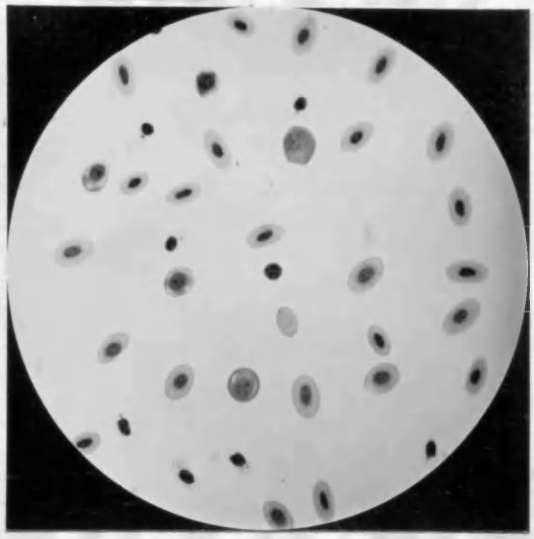
The thrombocytes were counted just before the bird was killed and were found to number 12,300 per cubic millimetre. In this connexion it is worthy of note that the fowl bled profusely and for an abnormally long time whenever its comb was snipped in order to obtain blood for examination. This was never noticed until the bird had developed definite signs of disease.

On examining stained preparations of the blood the chief feature is the relatively very large number of embryonic red cells. Every stage in the development of the red cell may be observed from the lymphoidocyte to the adult erythrocyte.

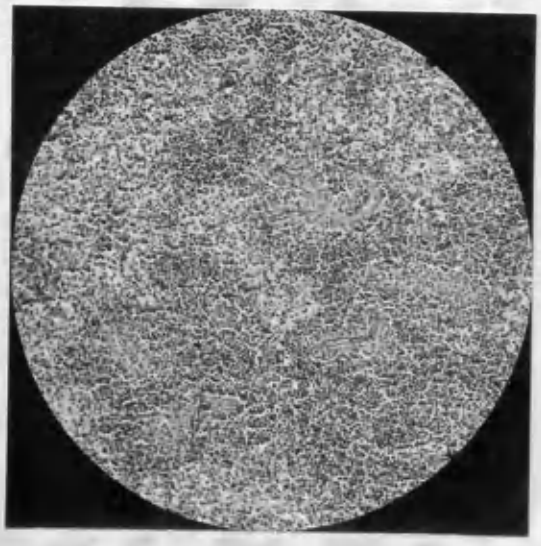
Differential Count.	Polymorphonuclears	27.3%
	Lymphocytes	57.6%
	Mast Cells	6.3%
	Monocytes	5.6%
	Myelocytes	3.0%

Bone Marrow Smear. The predominant cell is the same as is seen in the blood films in such large numbers, i.e. the lymphoidocyte/

Fowl F.

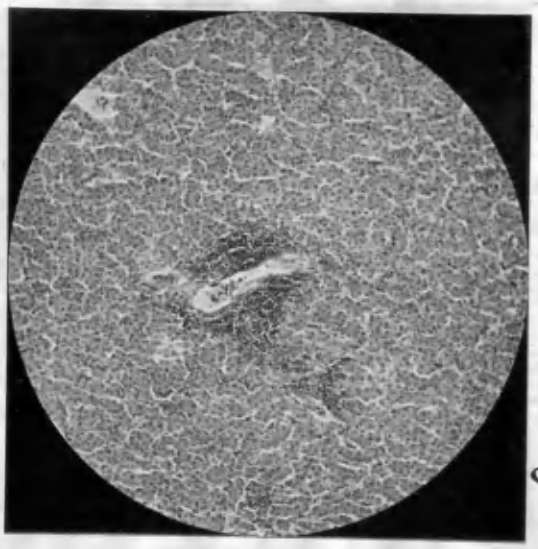


Blood film.



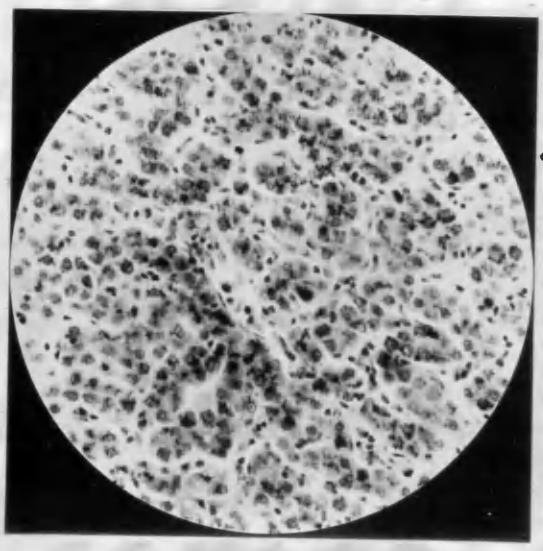
Spleen

Fowl. r.



Liver

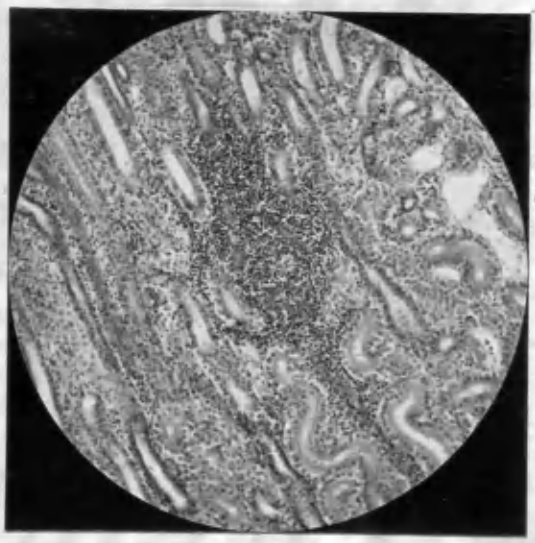
Showing moderate accumulation of erythroblasts in the capillaries. The peribortal accumulation of cells is physiological



Liver

Showing deposit of Haemosiderin.

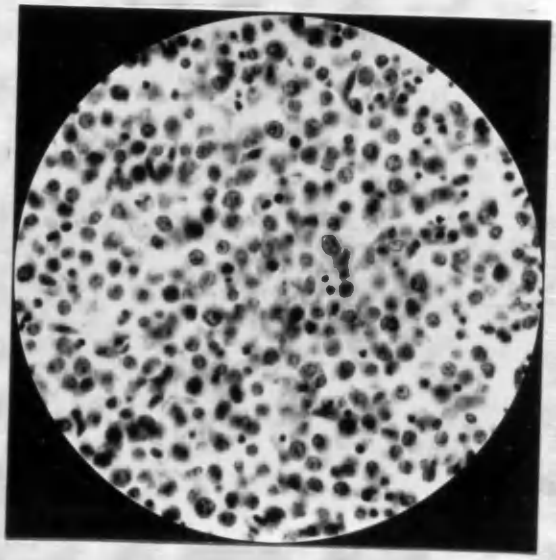
Fowl F.



Kidney

Showing the capillaries dilated and filled with normal and embryonic red cells.

Fowl 6.



Bone Marrow

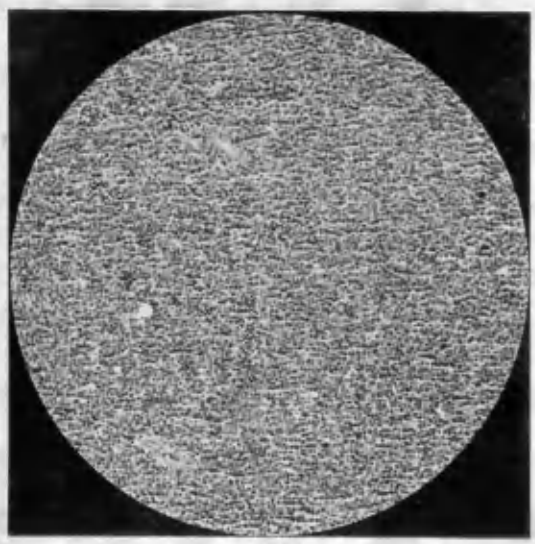
lymphoidocyte. Every stage from this early form to the normal erythrocyte is to be observed. Mitotic figures are quite common and a few large erythrocytes are to be seen with two distinct nuclei. Myelocytes and polymorphonuclears are present in relatively small numbers.

Liver. Weight 49 grammes. The lower part of the right lobe shows some slight mottling on the surface. The organ is dark red in colour. The gall bladder is rather distended and full of bile but no calculi are present. The Prussian blue reaction is positive. On microscopical examination the capillaries throughout the organ are seen to be dilated and filled with red cells and their precursors. Patches of myelogenous hyperplasia are scattered through the section. A considerable quantity of haemosiderin is visible in the liver cells.

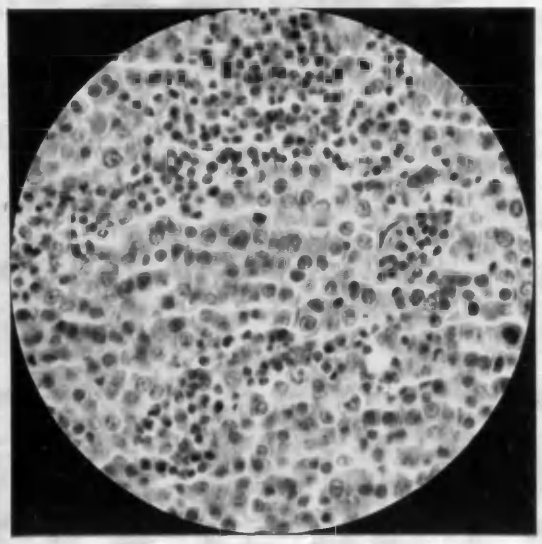
Spleen. Weight 14.6 grammes. The organ is slightly mottled on the surface. On section it is dark red in colour but is quite firm in consistence. The Malpighian bodies seem scanty and are difficult to detect. The Prussian blue reaction is weakly positive. On microscopical examination the Malpighian bodies are not well defined and seem to be atrophied and diminished in number. The pulp is pakced with cells; chiefly primitive erythroblasts. Mitotic figures, although scarce, are present among the cells in the pulp tissue.

Kidneys. Weight together 13.8 grammes. No abnormality is detected on naked-eye examination. Microscopically, a number/

Fowl. 1



Bone Marrow



Bone Marrow.

number of the capillaries are dilated and filled with many forms of red cells. This "capillary stasis" occurs as scattered patches and is not evenly distributed throughout the organ. The glomeruli appear to contain more cells than normally; many having the same morphological character as the lymphoidocytes.

Bone Marrow. The naked-eye appearances suggest nothing abnormal. Stained preparations show that the fat is very much diminished and that the sinuses are dilated and closely packed with red cells in all stages of formation. The trabeculae are atrophied; the general appearances suggesting that they have been crushed out of existence by pressure from the dilated sinuses. The myelogenous tissue is considerably diminished and only exists in the form of a few scattered foci. Mitotic forms are to be found among the primitive red cells and myelocytes.

EXPERIMENT. An emulsion from the liver and spleen from the above animal was inoculated at once in to 8 healthy fowls of the same breed (White Leghorn) and each about one year old. Part of the emulsion was filtered through a Berkefeld candle and each of 3 fowls received 5 c.c. of the filtrate, the others receiving an equal quantity of the unfiltered material. Cultures made in bouillon, in Noguchi's kidney and ascitic fluid medium and on the blood agar plates both before and after filtration showed no growth after 7 days.

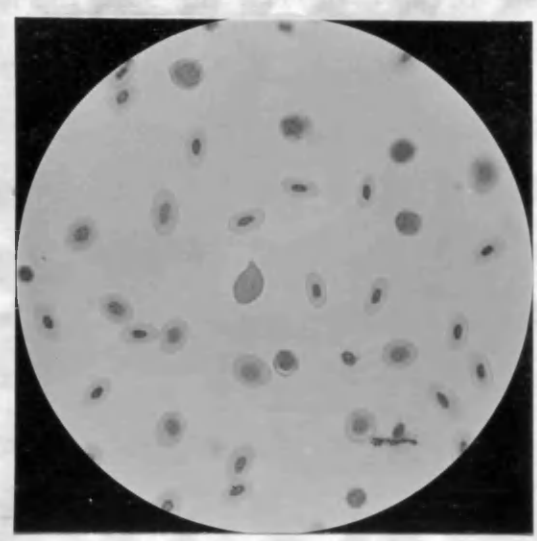
The following is the history of one of the fowls inoculated from Fowl F.

Fowl 1.h. white Leghorn. On 9th November, 1923, the bird was inoculated intravenously with 5 c.c. of the unfiltered emulsion of liver and spleen from Fowl F. On the day of inoculation the bird weighed 3½ pounds and the haemoglobin was 67% (Sahli). A month later the weight was 3 lbs 10 ozs and the haemoglobin was 64%. On 11th Feb., 1924 the weight had increased by 3 ozs. and the haemoglobin was 65%. On the 20th March the weight was 4 lbs 2 ozs and the haemoglobin had not altered. On 30th April the bird was found lying dead. Previous to this no jaundice, lethargy or loss of weight significant of illness had been observed and it was assumed that the animal was healthy. This fowl could not have been dead for more than half an hour before it was discovered and a post mortem examination was performed at once. The weight was 4 lbs. The skin was not jaundiced and the fat throughout the body appeared to be normal in quantity. The heart, lungs and alimentary tract appeared healthy. The following is a description of the appearances found in the blood and organs.

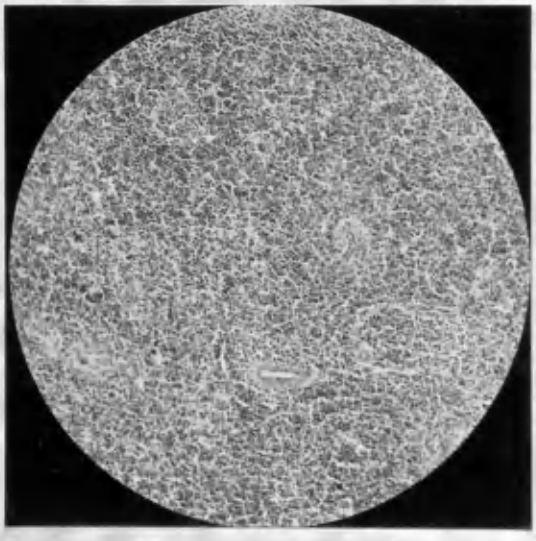
Blood films. The films were made from the heart blood immediately the thorax had been opened. The blood picture is that of a megaloblastic anaemia. There are

a/

Fowl 1. h.



Blood Film.



Spleen.

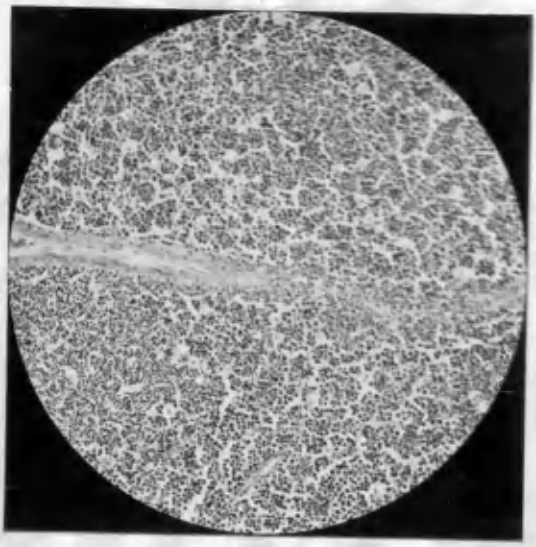
a large number of erythroblasts in all stages of maturity but mitotic forms are scarce. The majority of the primitive red cells contain no haemoglobin and appear to be basophil erythroblasts or lymphoidocytes. There is a considerable decrease, both absolutely and relatively, in the number of cells of the granular series. The following is a differential count of 300 white cells:-

Polymorphonucleears.	10.0%
Lymphocytes.	79.0%
Mast cells.	1.3%
Monocytes.	6.3%
Myelocytes.	3.3%

Bone Marrow Smear. Dry films and wet films fixed at once in Zenker's fluid are made. The films are stained with Leishman's stain, Ehrlich's triacid stain and with haemalum and eosin. The striking feature, on examining these preparations, is the scanty number of adult erythrocytes and of granular cells. The large majority of the cells are primitive erythroblasts. Mitotic forms are not common but occasional megaloblasts with twin nuclei are present.

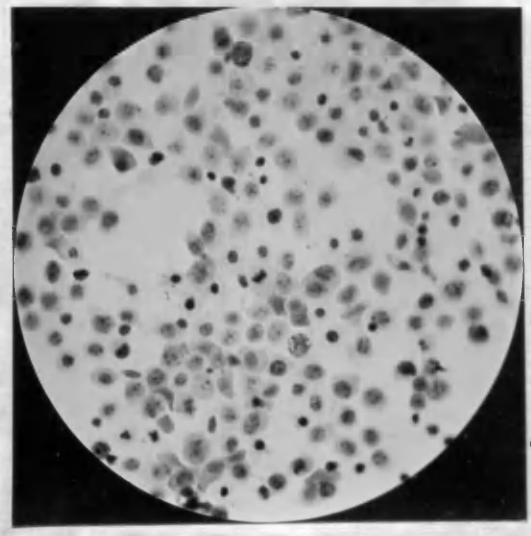
Bone Marrow. The colour of the marrow appears to be a slightly darker red that is usual in the healthy fowl and the fat is almost entirely absent. On microscopical examination/

Fowl. I. h.



Section of Bone Marrow.

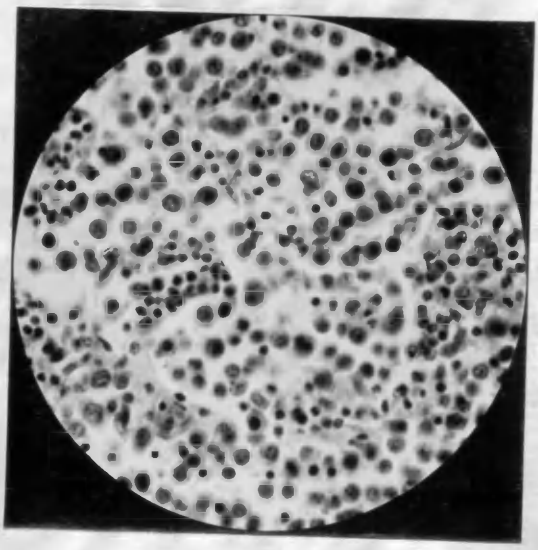
Note the absence of fat.



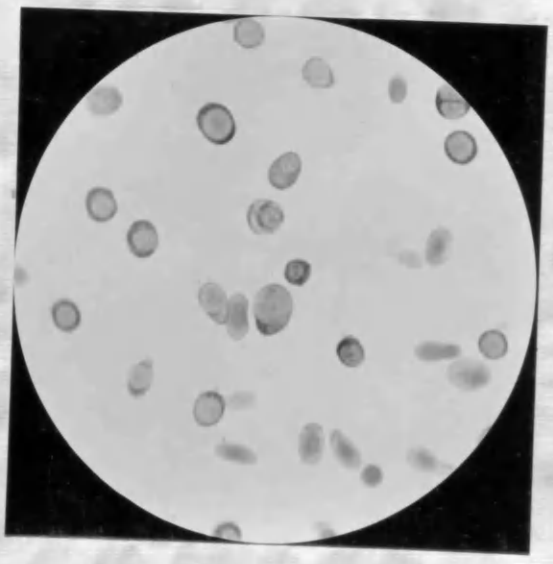
Smear of Bone Marrow.

Showing numerous erythroblasts, a megaloblast with twin nuclei, and a very scanty number of granular cells.

Fowl I.h.



Bone. Marrow

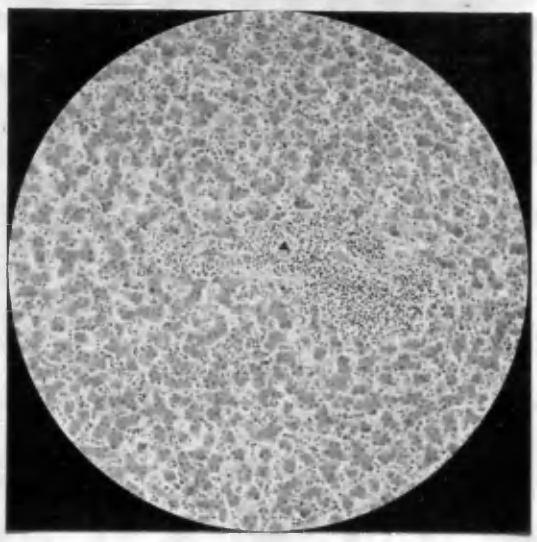


Blood

examination, the tissue is found to be almost free from fat and to consist of greatly dilated sinuses which are densely packed with lymphoidocytes. Adult erythrocytes and even polychromatophil erythroblasts are very scanty. The dilatation of the marrow sinuses appears to have crushed out of existence by far the greater part of the trabecular framework, and, in consequence, the granular cells are present only in a few scattered foci. Mitotic figures are present in small numbers.

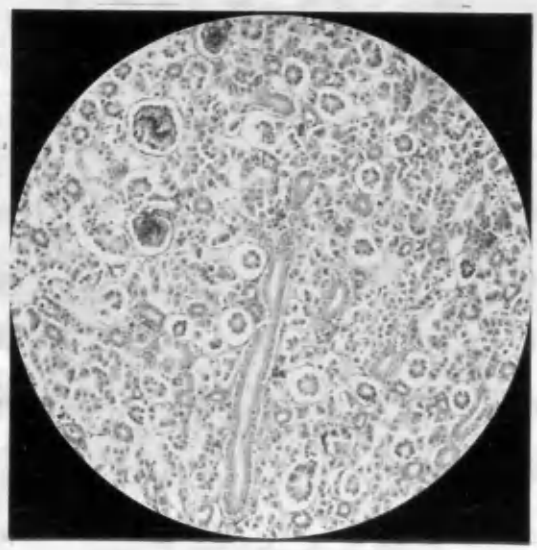
Liver. Weight 50.2 gms. The organ is smooth and red, and it shows no mottling on the surface or on section. There is slight fatty change. The gall bladder is not distended and it contains no calculi. On microscopical examination the capillaries between the groups of liver cells are found to be distended and packed with lymphoidocytes and erythroblasts. Adult erythrocytes are also present in fair numbers. The areas of myelogenous tissue around the portal tracts are not hypertrophied or increased in number, but surrounding a number of the vessels small densely packed foci of lymphoidocytes may be seen. Beneath the endothelial lining of the capillaries and in the substance of the liver cells there are a few areas consisting of lymphoidocytes, erythroblasts and myelocytes similar in appearance to the haemopoietic foci to be seen in the foetal organ. These appearances are not normal and/

Fowl. 1. h.



Liver.

showing primitive cells in the liver capillaries and at the centre of the lobule.



Kidney

and suggest that active blood formation is occurring and that the liver has returned to its foetal function of haematogenesis. There is no cirrhosis. The Prussian blue reaction is very weak and is limited to the cells of the endothelial lining of the liver capillaries.

Spleen. Weight 2.8 grammes. The organ is firm and it is dark red in colour both on the surface and on section. The Malpighian bodies are visible but are not very clear. On microscopical examination, the pulp is densely packed with lymphocytes, lymphoidocytes and red cells. Granular leucocytes are scanty. Some of the Malpighian follicles show active germinal centres. There is no cirrhosis and the Prussian blue reaction is not present.

Kidneys. The organs are pale but no gross abnormality is to be detected on naked-eye examination. Microscopically, very little infiltration of the capillaries is observed, but, here and there, scattered throughout the section dilated capillaries are seen containing lymphoidocytes and other erythroblasts. There is no hyperplasia of the myelogenous element which is present in the pelvis of the kidney and the granular cells which are found in the section are not in excess of normal.

THE VIRUS OF FOWL ANAEMIA AND LEUKAEMIA.

It has been shewn that the pernicious type of anaemia in fowls can be transmitted to healthy birds by the inoculation of an emulsion of tissue from the diseased bird. In my experiments the disease has been passed through two generations as follows:-

Fowl 1.
↓
Fowl F.
↓
Fowl 1.h.

Further, Ellermann has reproduced the disease even after the emulsion has been passed through a Berkefeld or Reichel filter. This experiment disproves the suggestions made that the reproduction of the condition is due to the grafting of tumour cells, or that what is called leukaemia in fowls is really a form of tuberculosis. (Burchardt)[13]. From this the conclusion may be drawn that the causal agent is either of the nature of a toxin or a living filterable virus. But Ellermann has shewn that the incubation period of the disease is progressively shortened by passage through animals until a certain point is reached at which it remains constant. On the other hand, however, many passages may be made the proportion of "takes" remains very constant (30 per cent). It is very difficult to imagine, therefore, how this noxious agent/

agent can be a toxin while the proof that it is of the nature of a living virus is almost conclusive.

It has been abundantly proved that this virus is not strictly specific because it may cause pernicious anaemia in one fowl, myelogenous leukaemia in another and lymphatic leukaemia in a third. The following figures show the relative frequency of the various forms obtained by Ellermann;(14) Anaemia 69 per cent, Myelogenous Leukaemia 18 per cent, and Lymphatic Leukaemia 13 per cent.

Nothing is known regarding the natural transmission of the disease among fowls but it has been suggested that some blood sucking insects perform the role of disseminating agents. While experimenting with certain of these insects Ellermann(14) recently had one positive result when using Cimex lectularius, but until this observation has been repeated many times no definite conclusion can be drawn.

DISCUSSION ON THE ANALOGY BETWEEN LEUKAEMIA AND PERNICIOUS ANAEMIA IN FOWLS AND IN THE HUMAN SUBJECT.

Myelogenous Leukaemia. In fowls this condition occurs in a myelocytic form; a myeloblastic form; an aleukaemic form, and finally, as a leukaemia associated with tumour formation. The disease is uniformly fatal and is not usually associated with a marked degree of anaemia. Histological examination reveals a proliferation of the parent/

parent cells of the granular series throughout the haemopoietic tissues; and this proliferation is not associated with the normal nuclear and cytoplasmic differentiation which occurs in a simple leucocytosis. Thus the clinical manifestations of this disease in the fowl correspond very closely, if not identically, with human myelogenous leukaemia, while the morbid anatomy of the two conditions is strikingly similar.

Lymphatic Leukaemia. In this disease the analogy is not so close because there is no leukaemic change in the blood. However, the morbid anatomy of this condition presents very similar features to human lymphatic leukaemia.

Pernicious Anaemia. A description has been given and examples cited of an anaemia which is progressive and uniformly fatal in its course, although remissions may occur during which the fowl is apparently healthy. It has been shown that there are primitive and pathological forms of red cells in the blood corresponding with a pathological form of erythrogenesis in the bone marrow, and that there is an abnormal deposit of iron in the organs. The parallel between this anaemia in fowls and the cryptogenic pernicious anaemia in man appears to be very close.

It has been shewn, however, that this anaemia and leukaemia in fowls are infective in origin and are caused by the same agent. If it be accepted that these diseases

in/

in fowls are analogous to the similar pathological processes occurring in man it may, therefore, be justifiable to continue the analogy further and to suggest that pernicious anaemia and the two forms of leukaemia in the human subject are closely identified with one another in their etiology and that this is of the nature of an infective process. The toxic nature of pernicious anaemia in man appears to be accepted by all clinicians and pathologists.

The pathological evidence in favour of this was afforded by Muir (15) in his study of the bone marrow in several cases of the disease. "In the marrow there is a return to a sort of embryonic condition..... This reversion is not a primary pathological condition, but a process compensatory to the long standing drain. These changes are chiefly of the nature of degenerations, and are to be referred principally to direct toxic action." With regard to leukaemia Muir (16) again has summed up our knowledge of the etiology of the disease as follows: "In the absence of knowledge regarding the agent producing the excessive proliferation of leucocytes we cannot definitely assign the place of leukaemia in the category of disease. On the whole it presents most points of analogy to the growth of tumours, the analogy being especially striking in the lymphatic variety but, on the other hand, it is not absurd to suppose that it may yet prove to be due to a microparasite." Goodall and Alexander (17) discussing/

discussing examples of acute myelocythaemia and chloroma, while adhering to the view that the leucoblastic proliferation is more closely allied to tumour growth than to any other condition, make the suggestion "as something more than a mere speculation than leukaemia is closely allied to a malignant process, and that both leukaemia and malignant disease may yet prove to be the result of infections."

In this connexion examples in which the disease was apparently contagious may be quoted. Obrastow (18) in 1892 described a case of acute leukaemia occurring in a male nurse who was attending a patient suffering from the same disease. Bie (19) in 1910 described a similar case in which a servant girl who was responsible for cleaning the patient's bedroom developed the disease shortly before the patient died. Arnsperger (20) investigated a small area near Heidelberg where leukaemia was apparently endemic. Finally, Arnsperger and Weiss (21) quote examples in which there was an undoubted family tendency to leukaemia.

If then one goes so far as to say that the experiments with leukaemia in fowls seem to lend a certain amount of support to thetheory that human leukaemia is due to some infective process, one is immediately faced with the second part of the analogy, viz. that human leukaemia and some cases of pernicious anaemia are each different manifestations of one and the same pathological process. Fundamentally, each

of/

of these diseases consists of a pathological form of hyperplasia occurring in response to some unknown influence acting on the marrow. Here, however, the similarity between the two conditions seems to end. On the other hand, it is interesting to note that, speaking generally, lymphatic leukaemia is most common in early childhood at which period the lymphatic elements in the body are most active; that myelocytic leukaemia is chiefly a disease of young adult life when the myeloid tissues are working at "full pressure;" and that pernicious anaemia is a disease of senescence during which the whole haemopoietic system is liable to react in a pathological manner to any prolonged destructive agent. Thus when the blood forming tissues are in a vigorous state of activity a proliferative process tends to take place; whereas after this stage has been passed and the tissues have entered upon a period of relative quiescence a destructive process is the rule. Anomalous appearances of the blood, such as the so-called Leukanaemia, in which it is hard to say whether myelocytic leukaemia or pernicious anaemia is the primary condition, lend some support to the theory that these diseases are related to one another. Against this there is the fact that only one case appears to have been recorded of leukaemia developing in a patient infected with the bothriocephalus latus, (22) a parasite which is not infrequently associated with an anaemia of the pernicious type. The explanation of this/

this may be what is at present no more than an hypothesis, viz.: that leukaemia is caused by a specific agent which in its turn is only one of the several agents capable of producing a pernicious anaemia.

SUMMARY.

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1. The appearances of the Blood and Haemopoietic Tissues in the healthy young fowl are described.

2. A detailed account is given of the appearances of the Blood and Haemopoietic Tissues in three examples of fowl anaemia and experiments are described showing that from the original Fowl 6 the disease was transmitted to the second generation at which point the strain died out.

3. The analogy between Leukaemia and Pernicious Anaemia in fowls and in the human subject is discussed. The analogy appears to be very close and in view of the fact that these conditions are of an infective nature in fowls the possibility that they are of a similar nature in the human subject is discussed. Further, since the virus in fowls is capable of giving rise to each variety of leukaemia and to pernicious anaemia, the question of whether or not leukaemia and pernicious anaemia in the human subject are related to one another is discussed.

CONCLUSION.

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It is obvious that no final conclusions can be drawn regarding either the infective nature of leukaemia or the etiological relationship between leukaemia and pernicious anaemia; but it seems reasonable to believe that the experimental work which has been done on leukaemia in fowls gives some added support to the infective theory of the similar disease in man. That some close etiological relationship exists between the cryptogenic pernicious anaemia and leukaemia can be looked upon as but a theory, postulated as the result of argument by analogy, but at the same time worthy of some consideration.

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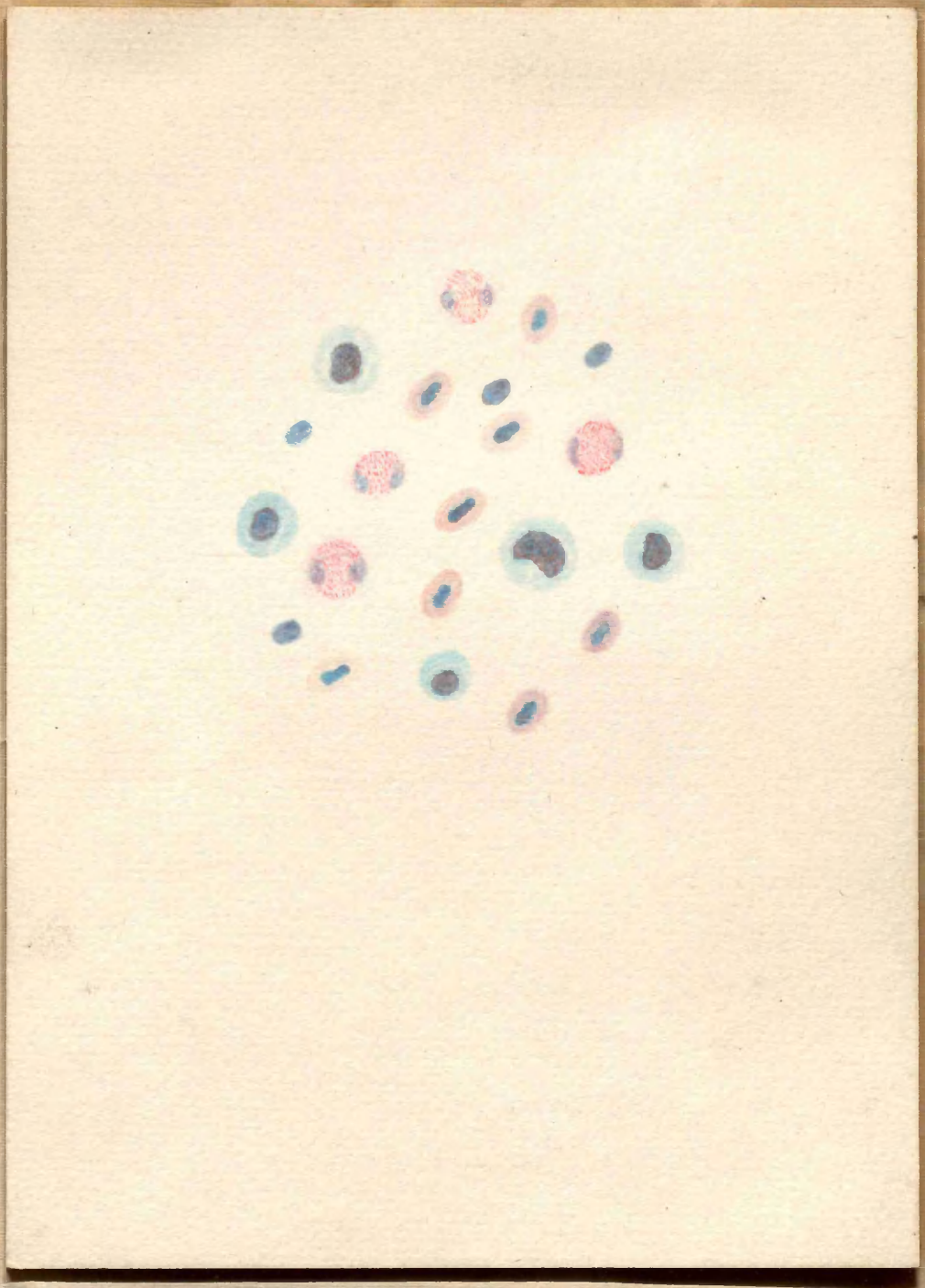
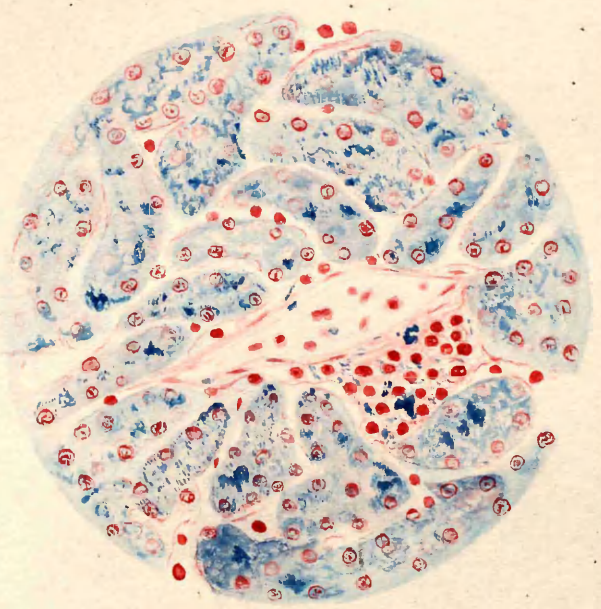
Normal Fowl.



Composite Drawing showing the various types of Blood Cells.

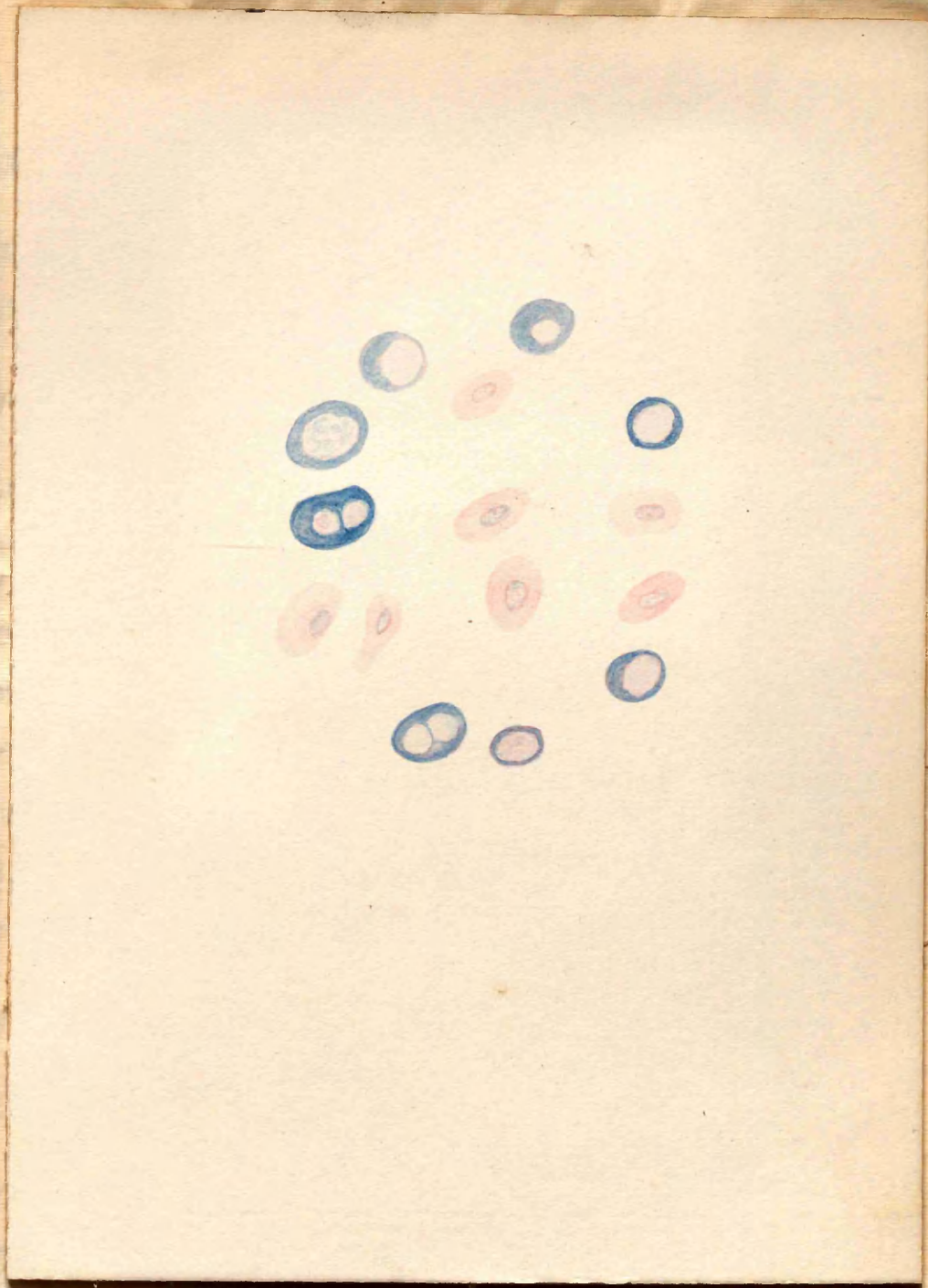
Fowl 6.



Liver.

Showing Prussian Blue Reaction.

Fowl 6.



Blood.

Showing a number of lymphoidocytes, two of which have twin nuclei.

REFERENCES TO PART II.

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1. BANTI. Centralblatt. f. allgemeine Path. 1904, XV. 1. p.1.

2. MOSLER. Die Path. u. Therapie der Leukamien. 1872.

3. ELLERMANN & BANG. Centralblatt. f. Bact. 1908. XLVI. Heft 1 (Orig.). p. 4.

4. HIRSCHFELD & JACOBY. Berliner klin. Wochenschr. 1909, IV. p. 159.

5. BOLLINGER. Virchows Archiv. 1874. LIX. p. 341.

6. ELLERMANN. The Leucosis of Fowls and Leukaemia Problems, 1921.

7. SCHMEISSER. Jour. of Exper. Med. XXII. p. 820.

8. MAGNUSSON. Zeitschr. f. Krebsforschung. 1915, XV.

9. WERZBERG. Folia Haematologica. 1910. X. 1. p. 301.

10. BEDSON. Jour. Path. and Bact. 1923. XXVI. p. 145.

11. KASARINOFF. Folia Haematologica. 1910. X. 1. p. 391.

12. DANTSCHAKOFF. Arch. f. mik. Anat. u. Entwickelungsch. 1909, LXXIV. p. 855.

13. BURCHARDT. Zeitschr. f. Immunitatsforschung. 1912. XIV. Orig. p. 544.

14. ELLERMANN. Jour. de Physiologie et de Path. gen. 1923. XXI. p. 117.

15. MUIR. Jour. Path. and Bact. 1894. II. p. 354.

16. MUIR. Allbutt's Sytem of Medicine. 1910. V. p. 852.

17. GOODALL & ALEXANDER. Quart. Jour. Med. 1924. Vol. XVII. No. 66. p. 118.

18. OBRASTOW. Deutsch. med. Wochenschr. 1892. p. 641.

19. BIE. Ugeskrift. f. Laeger. 1910. LXXII. p. 1607.

20. ARNSPERGER. Munchen. med. Wochenschr. 1905. I. p. 9.

21. ARNSPERGER & WEISS. Quoted by Ellermann, Leucosis of Fowls. London, 1921.

References to Part II. (Contd.)

22. STUKOWSKI. Klin. Wochenschr. 1922. n. 2527.

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