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THE CONDITIONS THAT SIMULATE PERNICIOUS ANAEMIA.

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A STUDY of the literature of progressive pernicious anaemia leads us to the view that this disease is generally of cryptogenic origin, but nearly all writers on the subject admit that a number of cases clinically indistinguishable from progressive pernicious anaemia may occur as the result of such conditions as severe and prolonged haemorrhage, pregnancy, intestinal parasites, and cancer. Many of these cases were recorded before a detailed histological examination of the blood as an aid to diagnosis was customary. It now becomes an interesting and important question how far such cases can be distinguished by the condition of their blood from cases of Addison's anaemia as he defined it: "General anaemia occurring without any discoverable cause whatever, cases in which there was no previous loss of blood, no exhausting diarrhoea, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, or strumous enlargement."

The following case raises this question and shows, I think, that all such cases should be fully and carefully investigated not only on account of their rarity but because their detailed study is most likely to throw some important light on the much disputed pathology of Addison's anaemia.

Miss D., aged 42, professional nurse. In November, 1901, this patient was under the care of Dr. William Calwell, of Belfast, who, considering the interesting nature of the case, and that its clinical features closely resembled those of progressive pernicious anaemia, asked me to make several detailed examinations of her blood.

The history of the patient previous to this date was as follows: Two years ago a scirrhus tumour was removed with the right breast by Sir Thornley Stoker in the Richmond Hospital, Dublin. A recurrence in the neighbourhood of the clavicle of the same side was removed about a year ago by the same surgeon. While in hospital recovering from this operation she had several attacks of haemoptysis, but no physical signs of a lesion in her lungs could be detected. Haemorrhage was also detected coming at intervals from her throat and nose, and she stated that she frequently removed from her nostril a clot of blood, which was evidently a cast of the nasal cavity. She continued to bleed from the lungs, nose, and throat. At first there were no subcutaneous haemorrhages, but a few weeks previous to the period (November, 1901) at which the following observations were made she had noticed some petechial spots.

The following are my notes taken on the several occasions on which a blood examination was made:

November 7th, 1901. The patient is very anaemic-looking, and of a sallow, yellow colour. States that the haemorrhage coming from her nose has continued at intervals since the second time she was operated on (that is, about one year ago). Her sight is now dim owing to retinal haemorrhages; signs of gastric disturbance, nausea, and vomiting; heart dilated, systolic murmur.

Blood Examination.

Red cells = 2,300,000 per c.mm.
White cells = 6,700 per c.mm.
Haemoglobin = 49.0 per cent.
Colour index = 1.06

Differential Count of 500 Leucocytes.

Polymorphonuclear leucocytes = 54.0 per cent.
Small lymphocytes = 36.2 "
Large lymphocytes = 8.4 "
Transitional leucocytes = 0.8 "
Eosinophile leucocytes = 0.6 "

Twenty-nine megaloblasts and 16 normoblasts were found in counting 500 leucocytes. The films were stained with haematoxylin and eosine, so that possibly some of the cells classed as large lymphocytes were myelocytes (see examination on August 22nd, 1902). This blood picture, since it presented all the characteristic features of progressive pernicious anaemia and occurred in a case where the history pointed to

there being a secondary malignant deposit in some of the internal organs, marked the case as one of great interest. I therefore made several examinations of the blood.

November 28th, 1901.—Clinical condition much the same as before. The symptoms due to the anaemia are more marked.

Blood Examination.

Red cells = 1,600,000 per c.mm.
White cells = 6,000 per c.mm.
Haemoglobin = 33 per cent.
Colour index = 1.03

Differential Count of 500 Leucocytes.

Polymorphonuclear leucocytes = 56.4 per cent.
Small lymphocytes = 38.3 "
Large lymphocytes = 2.2 "
Transitional leucocytes = 3.0 "

Twenty-seven normoblasts and 13 megaloblasts were found in counting 500 leucocytes.

January 4th, 1902.—Patient apparently much worse; nervous, restless and sleepless; requires a hypodermic of morphine every night; almost blind with retinal haemorrhages; haemorrhages from the nose and throat still continue, but hardly so severe as formerly; dyspnoea very troublesome; appetite at present fairly good, as the sickness and vomiting have disappeared; one or two subcutaneous petechial haemorrhages on the shoulder; considerable oedema of the lower limbs with some ascites and hydrothorax.

Blood Examination.

Red cells = 1,070,000 per c.mm.
White cells = 5,500 per c.mm.
Haemoglobin = 27.6 per cent.
Colour index = 1.38

Differential Count of 500 Leucocytes.

Polymorphonuclear leucocytes = 67.2 per cent.
Small lymphocytes = 30.4 "
Large lymphocytes = 2.0 "
Transitional leucocytes = 0.4 "

Two megaloblasts and 6 normoblasts were found in counting 500 leucocytes.

The oedema which has been mentioned above disappeared, and she improved considerably, as cases of pernicious anaemia often do under similar circumstances. I have already pointed out that in a certain sense this oedema occurring in pernicious anaemia is to be regarded as "critical," and there often accompanies its disappearance a temporary improvement in the patient's condition, as if this oedema were an effort to concentrate the over-diluted blood.¹ This temporary improvement lasted for several months, and she went to the country, so that I had not an opportunity of making a blood examination at this time. Relapsing again, she returned to hospital, and I had then another opportunity of examining her blood. This was the last occasion on which a blood examination was made before her death, which occurred some months afterwards.

August 22nd, 1902. My notes at this date are: Greatly troubled with vomiting and sleeplessness; the oedema has entirely disappeared and she is greatly emaciated. Her appearance is now more like that of a cancer patient than ever it was before. Her liver is very large and slightly tender, but no nodules can be felt. The systolic murmurs are still well marked. There is no haemorrhage at present coming from the nose but a good deal from her throat.

Blood Examination.

Red cells = 1,000,000 per c.mm.
White cells = 7,500 per c.mm.
Haemoglobin = 25.6 per cent.
Colour index = 1.28

Differential Count of 500 Leucocytes.

Polymorphonuclear leucocytes = 53.4 per cent.
Small lymphocytes = 43.4 "
Large lymphocytes = 0.4 "
Transitional leucocytes = 0.8 "
Eosinophile leucocytes = 0.8 "
Neutrophile myelocytes = 1.2 "

Ten megaloblasts and 8 normoblasts were found in counting 500 leucocytes. The films on this occasion were stained with Ehrlich's triacid mixture and with eosine and methylene blue to demonstrate the granular leucocytes, and 1.2 per cent. of myelocytes were found in the films.

From these examinations it will be seen that the blood of this case all along maintained the character of that of progressive pernicious anaemia, and that too in spite of pretty severe haemorrhage, which might be expected to have the effect of lowering the colour index, and thus giving the blood one of the characteristics of anaemia of a secondary type.

Fortunately, owing to the request of the patient made before death, we were enabled to obtain a partial necropsy on this case.

Post-mortem Notes.—A few small nodules were found in the skin on the front of the chest. These were of recent development. The skin was dry and tense. A scar was noted over the position of the right breast

(which had been removed as before stated). A small scar was also noted above the clavicle corresponding to the position of the second operation. On opening the abdomen a quantity of serous fluid was found in the pelvic cavity and lumbar fossae. The great omentum was contracted in a flat band of about 1 or 2 in. broad by cancerous growth. The liver was studded by secondary growths and greatly enlarged. The spleen showed one or two secondary nodules and the mass of splenic tissue had the hard feeling of amyloid degeneration. It did not, however, in the fresh condition give the iodine mahogany-brown reaction. The spleen and liver were put in dilute hydrochloric acid and potassium ferrocyanide solutions, but gave only an indefinite iron reaction. (In this point, therefore, the case differed from true pernicious anaemia, but as the liver was one mass of cancerous growth we could hardly expect it to function as a normal liver would do under similar circumstances.) The heart muscle showed well-marked fatty degeneration (tabby cat striation). There was a large amount of fluid in the pericardium and in each pleura. The left lung was much congested, particularly at the base. Both lungs were intensely oedematous. The organs generally had not the pallor met with in pernicious anaemia. A piece of the shaft of the right tibia was removed and showed nodules of carcinoma throughout the marrow. On microscopic examination of the marrow it was found that round the areas of cancerous deposit the pale marrow had been converted into red, and this tissue contained a large number of nucleated red cells (megakoblasts and normoblasts) and some myelocytes—it was in fact identical in appearance with the condition of the marrow found in true cases of pernicious anaemia.

The two points in this case which deserve special attention are:

1. The condition of the blood; and
2. The condition of the bone marrow.

1. The characteristic blood picture of pernicious anaemia was simulated in every detail.

(a) The red cells were greatly diminished in numbers, and ran as low as 1,000,000 per c. mm.

(b) The red cells showed marked poikilocytosis, and many of them were of large size (megakoblasts); at the same time some very small cells (microcytes) were found.

(c) The blood was megaloblastic in type, that is there were generally more megaloblasts found in the films than normoblasts. Ehrlich regards this feature as the most essential characteristic of the blood of pernicious anaemia, and states that this megaloblastic condition never occurs in secondary anaemias due to haemorrhages, inanition, cachexias, blood poisons or cancer.² Most authorities agree that megaloblasts are excessively rare in other forms of anaemia, and that when they do occur they are not found in greater numbers than the normoblasts.

(d) The red cells showed signs of degeneration (polychromatophilia).

(e) The colour index was always high, increasing during the period of observation from 1.03 to 1.38. This high colour index is the most characteristic feature of pernicious anaemia, as will be shown in the sequel.

(f) The total number of leucocytes per c. mm. was about or slightly under the normal. There was a percentage increase of lymphocytes such as usually occurs in pernicious anaemia.

2. The second point of importance in this case was the condition found in the bone marrow. Unfortunately, it was impossible to make a complete examination of the marrow of all the bones, but as the portion of the tibia was taken at random, we may perhaps assume that this portion was fairly typical of the condition of the bone marrow generally. As has been already stated in the *post-mortem* notes, the marrow of the tibia was found infiltrated with secondary cancerous deposits, and the marrow in the neighbourhood of these deposits presented the appearance of red bone marrow, and microscopically was found to contain numerous megaloblasts, normoblasts, and myelocytes, and was in fact exactly similar to the condition of the marrow found in cases of progressive pernicious anaemia.

I have been unable to find an account of any case exactly similar to the case that has been recorded above. Several cases of tumours invading the bone marrow have indeed been recorded but none with similar blood changes.

The nearest approach to this case is one recorded by J. Epstein from Neusser's wards.³ It may be instructive to quote Ehrlich's summary of this case.⁴

In Epstein's case of metastatic carcinoma of the bone marrow there was found a considerable anaemia, with numerous nucleated red blood corpuscles, both of the normoblastic and megaloblastic type; their nuclei presented the strangest shapes, due not merely to typical nuclear division, but also to nuclear degeneration. The white corpuscles were much increased, their proportion to red was 1 in 25 to 1 in 40; the increase concerned in the main the large mononuclear forms, which bore for the most part neutrophile granulations, and were therefore to be

called myelocytes. In all the specimens only two eosinophiles were found. . . . The appearance of myelocytes is most readily explained in this case by a direct stimulation of the remaining bone marrow by the surrounding masses of tumour. . . . In explaining the presence of megaloblasts in the blood of Epstein's case we must keep before us what we have said elsewhere on this kind of cell: they are not present in the normal bone marrow; they arise, on the contrary, when a specific morbid agent acts upon the bone marrow, as we must assume is the case in the pernicious forms of anaemia.

The fact that the case I have recorded in this paper presented the typical features of the blood of pernicious anaemia is another proof of the truth of Ehrlich's view that such changes are always the result of the stimulation of the marrow by a specific morbid agent.

My experience of other cases affords no justification for the attempt which has been made to show that it is impossible to differentiate between anaemias of the pernicious type and secondary anaemias of the gravest description.

The following table, compiled from my notebook, includes over 150 cases in which the haemoglobin was below 50 per cent.

(The number of corpuscles was estimated in these cases with the Thoma-Zeiss haemocytometer, and the haemoglobin by the Haldane-Lorrain Smith method.)

Date.	Hb.	Colour Index.	M*	N†	Type.	Diagnosis.
	%					
May 18, 1903 ...	16.00	2.66	6	0	×	Pernicious anaemia.
Mar. 22, 1902 ...	37.50	1.97	14	4	×	" "
Dec. 9, 1902 ...	16.00	1.81	—	—	×	" "
Dec. 24, 1902 ...	38.00	1.69	5	2	×	" "
June 2, 1900 ...	49.00	1.63	0	0	×	" "
April 16, 1902 ...	39.50	1.60	2	2	×	" "
Jan. 25, 1902 ...	22.20	1.54	14	0	×	" "
May 18, 1903 ...	27.36	1.50	0	0	×	" "
Dec. 14, 1901 ...	25.00	1.48	18	4	×	" "
Jan. 21, 1902 ...	23.70	1.48	12	2	×	" "
Jan. 31, 1903 ...	43.20	1.47	5	2	×	" "
Jan. 21, 1900 ...	31.00	1.40	0	0	×	" "
Aug. 1, 1903 ...	29.60	1.40	2	0	×	" "
Feb. 27, 1902 ...	25.60	1.38	6	4	×	" "
Nov. 30, 1901 ...	27.00	1.37	8	0	×	" "
Dec. 5, 1901 ...	26.00	1.30	10	2	×	" "
Dec. 31, 1901 ...	25.00	1.31	12	4	×	" "
Jan. 11, 1902 ...	29.60	1.37	2	0	×	" "
Jan. 28, 1902 ...	19.70	1.39	8	2	×	" "
Feb. 18, 1902 ...	15.80	1.35	12	54	×	" "
Mar. 4, 1902 ...	30.00	1.32	10	2	×	" "
Mar. 14, 1902 ...	29.00	1.31	8	0	×	" "
Mar. 22, 1902 ...	39.50	1.35	38	4	×	" "
Mar. 21, 1903 ...	24.48	1.31	15	0	×	" "
Mar. 9, 1901 ...	25.00	1.25	—	—	×	" "
Jan. 4, 1902 ...	27.60	1.29	2	6	×	Malignant disease, D.
Jan. 25, 1902 ...	22.70	1.27	12	6	×	Pernicious anaemia.
Feb. 4, 1902 ...	15.80	1.25	14	10	×	" "
Mar. 4, 1902 ...	35.00	1.25	0	0	×	" "
Mar. 22, 1902 ...	28.00	1.27	0	0	×	" "
Mar. 31, 1902 ...	25.60	1.28	18	16	×	" "
April 16, 1902 ...	23.70	1.23	4	4	×	" "
May 4, 1902 ...	39.50	1.23	6	2	×	" "
May 29, 1902 ...	35.00	1.26	2	0	×	" "
Aug. 22, 1902 ...	25.60	1.28	10	8	×	" "
Sept. 11, 1902 ...	30.00	1.28	12	0	×	Malignant disease, D.
Dec. 11, 1902 ...	21.70	1.20	27	10	×	Pernicious anaemia.
April 3, 1902 ...	33.00	1.10	75	300	×	" "
July 12, 1901 ...	18.70	1.10	22	10	×	" "
Dec. 20, 1901 ...	25.60	1.12	14	6	×	" "
April 2, 1901 ...	33.00	1.10	8	0	×	" "
April 19, 1902 ...	35.70	1.14	10	16	×	" "
April 18, 1900 ...	25.00	1.15	—	—	×	" "
April 2, 1901 ...	15.00	1.00	0	0	×	" "
Aug. 10, 1901 ...	40.00	1.04	0	0	×	" "
Aug. 21, 1901 ...	30.00	1.07	13	1	×	" "
Jan. 25, 1902 ...	49.50	1.05	0	0	×	" "
Nov. 7, 1901 ...	49.00	1.06	29	16	×	Malignant disease, D.
Nov. 28, 1901 ...	33.00	1.03	27	13	×	" "
Oct. 26, 1902 ...	19.80	1.03	3	0	×	Pernicious anaemia.
Feb. 17, 1901 ...	19.00	0.96	23	11	×	" "
May 12, 1903 ...	31.60	0.96	0	0	×	Acute lymphatic leukaemia.
Oct. 8, 1901 ...	37.40	0.90	—	—	×	" "
April 23, 1901 ...	45.00	0.85	0	0	×	Splenic leukaemia.
Aug. 8, 1901 ...	45.00	0.88	0	—	×	Lymphatic leukaemia.
Feb. 22, 1903 ...	38.80	0.88	0	2	×	Splenic leukaemia.
Aug. 12, 1901 ...	44.70	0.89	0	0	×	Lymphatic leukaemia.
June 26, 1901 ...	29.90	0.81	0	16	×	" "
July 9, 1901 ...	41.00	0.88	0	—	×	Splenic leukaemia.
Aug. 8, 1901 ...	44.00	0.88	—	—	×	Malarial cachexia.
May 20, 1902 ...	44.00	0.82	0	0	×	Splenic leukaemia.
Aug. 20, 1901 ...	43.00	0.82	0	12	×	Scurvy.
Jan. 29, 1902 ...	43.40	0.80	0	0	×	Splenic leukaemia.
Feb. 28, 1903 ...	38.80	0.80	0	0	×	Rheumatism and haemorrhage.
June 14, 1901 ...	35.00	0.82	0	0	×	Cancer of stomach.
Aug. 13, 1902 ...	41.40	0.82	0	0	×	Malarial cachexia.
Dec. 20, 1901 ...	35.00	0.81	0	0	×	Endothelioma (peritonitis).
May 20, 1900 ...	46.00	0.83	—	—	×	Haemoglobinuria.
Nov. 23, 1900 ...	22.00	0.79	0	0	×	Splenic anaemia.
						Septic fibroid.

Date.	Hb.	Colour Index.	M*	N†	Type.	Diagnosis.
Mar. 13, 1903 ...	40.30	0.76	0	0		Tuberculous peritonitis.
Feb. 16, 1901 ...	38.00	0.79	0	0		Chlorosis.
June 7, 1901 ...	37.40	0.74	0	0		Puerperal sepsis.
July 5, 1901 ...	45.00	0.72	0	32		Splenic leukaemia.
Jan. 6, 1902 ...	47.40	0.71	0	0		Bleeding piles.
July 3, 1902 ...	49.30	0.77	0	0		Tuberculosis.
Oct. 12, 1902 ...	28.00	0.79	0	0		Malignant disease.
June 12, 1901 ...	33.70	0.73	3	18		Splenic leukaemia.
Feb. 12, 1900 ...	45.40	0.71	—	—	—	Sarcoma.
Feb. 25, 1900 ...	34.00	0.72	0	0		Chlorosis.
Mar. 20, 1900 ...	30.00	0.70	—	—	—	"
Mar. 19, 1900 ...	30.00	0.75	—	—	—	"
June 2, 1900 ...	27.00	0.67	0	30		Splenic anaemia.
April 18, 1900 ...	34.00	0.68	—	—	—	Chlorosis.
May 27, 1901 ...	41.00	0.64	0	0		"
April 27, 1900 ...	40.00	0.66	—	—	—	"
Mar. 28, 1902 ...	32.00	0.61	—	—	—	"
Feb. 26, 1903 ...	34.00	0.69	0	0		"
June 21, 1902 ...	42.00	0.67	0	0		"
Aug. 25, 1902 ...	48.00	0.64	0	0		Bleeding piles.
Aug. 27, 1902 ...	40.00	0.60	—	—	—	Anaemia following pregnancy.
May 1, 1902 ...	28.00	0.61	—	—	—	Uterine haemorrhage.
Mar. 22, 1902 ...	19.90	0.61	0	4		Uterine sepsis (haemorrhage).
Jan. 17, 1902 ...	49.30	0.61	0	0		Chlorosis.
Jan. 9, 1902 ...	29.60	0.60	0	0		"
Dec. 20, 1901 ...	35.00	0.65	0	0		Haemoglobinuria.
Sept. 28, 1901 ...	20.00	0.61	0	0		Bleeding piles.
Nov. 13, 1900 ...	37.00	0.61	0	0		"
Sept. 17, 1900 ...	36.00	0.61	0	0		"
Oct. 16, 1901 ...	38.00	0.61	0	2		Hodgkin's disease.
Oct. 5, 1901 ...	29.96	0.65	0	0		Chlorosis.
April 17, 1901 ...	16.00	0.66	0	3		Lymphatic leukaemia.
Mar. 2, 1901 ...	33.00	0.61	0	0		Chlorosis.
Feb. 28, 1901 ...	37.00	0.61	0	1		"
Sept. 14, 1901 ...	15.00	0.58	0	2		Splenic anaemia.
May 7, 1901 ...	30.00	0.65	—	—	—	leukaemia.
Mar. 9, 1901 ...	25.00	0.56	—	—	—	Chlorosis.
Oct. 1, 1901 ...	29.90	0.56	0	0		"
Mar. 12, 1901 ...	24.00	0.51	0	0		"
May 18, 1903 ...	28.80	0.55	0	0		Cancer of stomach.
June 25, 1900 ...	22.40	0.54	0	0		Chlorosis.
Oct. 8, 1901 ...	29.90	0.53	0	0		"
Mar. 14, 1901 ...	40.00	0.50	0	0		Splenic anaemia.
May 29, 1901 ...	30.00	0.50	0	0		Chlorosis.
Oct. 17, 1901 ...	31.40	0.52	0	0		"
Sept. 24, 1900 ...	45.00	0.56	0	0		Splenic anaemia.
Nov. 2, 1900 ...	41.00	0.56	0	0		Prolonged diarrhoea.
Jan. 18, 1901 ...	38.90	0.58	0	0		Anaemia after pregnancy.
Jan. 22, 1901 ...	40.00	0.50	0	0		Splenic anaemia.
Aug. 16, 1903 ...	18.00	0.50	0	2		Splenic anaemia of infancy.
Dec. 28, 1901 ...	24.60	0.50	0	0		Chlorosis.
Jan. 6, 1902 ...	21.70	0.51	0	0		Malignant disease.
Jan. 24, 1902 ...	41.40	0.57	0	0		Sepsis.
Feb. 18, 1902 ...	34.50	0.58	0	0		Chlorosis.
Mar. 17, 1902 ...	35.50	0.54	0	0		"
Mar. 26, 1902 ...	37.50	0.58	0	0		"
Nov. 22, 1902 ...	46.00	0.55	0	0		Uterine haemorrhage.
Dec. 2, 1902 ...	38.80	0.53	0	0		Faulty feeding (baby).
Dec. 4, 1902 ...	36.00	0.51	0	0		"
Feb. 10, 1900 ...	34.00	0.51	—	—	—	Chlorosis.
Mar. 2, 1900 ...	38.00	0.52	—	—	—	"
May 26, 1900 ...	22.00	0.55	0	0		"
Jan. 26, 1902 ...	30.00	0.45	0	0		Sepsis.
April 23, 1901 ...	35.50	0.49	0	0		Chlorosis.
May 27, 1901 ...	35.00	0.49	0	0		Splenic anaemia.
Feb. 19, 1901 ...	16.00	0.45	0	0		Chlorosis.
Oct. 1, 1901 ...	37.40	0.43	0	0		"
Oct. 15, 1901 ...	33.70	0.47	0	0		"
Oct. 22, 1901 ...	38.90	0.40	0	0		"
Oct. 10, 1900 ...	15.00	0.47	0	0		"
Jan. 15, 1901 ...	18.70	0.43	0	0		Haematuria.
Jan. 2, 1902 ...	24.60	0.41	0	0		Chlorosis.
Jan. 21, 1902 ...	34.50	0.49	0	0		"
Jan. 19, 1902 ...	22.00	0.40	0	0		Malignant disease.
Jan. 28, 1902 ...	39.50	0.47	0	0		Chlorosis.
Mar. 1, 1902 ...	36.00	0.47	0	0		"
Feb. 22, 1902 ...	35.50	0.46	0	0		"
Mar. 14, 1902 ...	34.80	0.49	0	0		"
Feb. 26, 1900 ...	42.00	0.43	—	—	—	Haematemesis.
May 26, 1900 ...	32.00	0.44	—	—	—	Chlorosis.
May 20, 1900 ...	29.00	0.44	—	—	—	Splenic anaemia.
Aug. 16, 1902 ...	15.80	0.39	6	14		Anaemia in pregnancy.
May 12, 1900 ...	23.00	0.30	—	—	—	Chlorosis.
Sept. 25, 1900 ...	14.90	0.36	0	2		"

* Number of megaloblasts found in counting 500 leucocytes.

† Number of normoblasts found in counting 500 leucocytes.

‡ Type: The symbol x indicates that the blood was megaloblastic.

This table clearly supports the view that secondary anaemias can always be distinguished from pernicious anaemia by their low colour index and generally by the absence of megaloblasts. The case which I have detailed stands out as a clear exception to the rule (this case is marked D in the table). Before considering further the various forms of secondary anaemia which are supposed to simulate pernicious anaemia I wish to emphasize the fact that, as far as my experience goes, I have found the high colour index the most reliable and charac-

teristic feature of the blood of pernicious anaemia. Hayem was the first to demonstrate this high colour index, and Laache afterwards showed that this feature was probably due to the presence of many megalocytes with increased haemoglobin.

As Ewing points out⁵ the megalocyte is derived from the megaloblast of the bone marrow. Hence the high colour index has the same significance as the presence of megaloblasts, and, as the table shows, is a much more constant feature of the pernicious anaemia type of blood. It further not only indicates the megaloblastic origin of the erythrocytes in this disease, but also that this is the predominant type. The presence of one or two megaloblasts without a high colour index in the corpuscles is not indicative of pernicious anaemia, nor does the absence of megaloblasts indicate in cases presenting a high colour index that the condition is not pernicious anaemia. I have examined the blood of some cases of undoubted pernicious anaemia again and again, and made an exhaustive search for nucleated reds but found none. Bearing this in mind, we may briefly consider the conditions which are said to simulate pernicious anaemia. These are:

1. Haemorrhage.
2. Intestinal parasites.
3. Pregnancy.
4. Cancer.

1. *Haemorrhage*.—I have examined a number of cases of profound anaemia, evidently the result of severe and prolonged haemorrhage, which, as far as their clinical symptoms were concerned, presented the features of pernicious anaemia with the exception that they were the result of haemorrhage, generally repeated small haemorrhages, as, for instance, bleeding piles, or bleeding from cancer of the stomach. The following is a list of such cases:

Date.	Red Cells per c.mm.	White Cells per c.mm.	Hb.	Colour Index.	Pmn.	Lymph.	Eosines.	*N.	†M.	Diagnosis.
11/9/00	2,920,000	8,000	36.00	0.61	63.04	33.00	3.80	0	0	Bleeding piles.
25/9/00	2,050,000	5,600	14.98	0.36	53.00	43.00	4.40	0	0	Haematemesis.
13/11/00	3,090,000	8,000	37.00	0.61	66.00	28.80	5.00	0	0	Bleeding piles.
15/1/01	2,140,000	6,300	18.72	0.43	54.00	44.60	1.30	0	0	Haematuria.
27/8/02	3,330,000	6,300	40.00	0.60	—	—	—	—	—	Uterine haemorrhage.
27/11/02	4,170,000	10,000	46.00	0.55	67.00	32.00	1.00	0	0	Uterine haemorrhage.
28/10/02	1,680,000	6,000	20.00	0.61	58.40	40.60	0.00	2	0	Bleeding piles.
6/1/02	3,320,000	4,100	47.40	0.71	50.86	49.20	0.00	0	0	Bleeding piles.
19/1/02	2,760,000	11,000	22.00	0.40	81.00	17.00	2.00	0	0	Melaena (cancer?).
29/1/02	1,550,000	9,000	23.40	0.78	81.00	19.00	0.00	2	0	Melaena (cirrhosis of liver).
22/3/02	1,600,000	16,000	19.75	0.61	70.00	30.00	0.00	4	0	Uterine haemorrhage.

* Number of normoblasts found in counting 500 leucocytes.

† Number of megaloblasts found in counting 500 leucocytes.

Several of these cases were supposed before the blood was examined to be cases of pernicious anaemia. For instance, the case marked § in the table was admitted to the Belfast Royal Victoria Hospital presenting practically all the clinical features of pernicious anaemia, that is, extreme pallor (lemon yellow tint), flabbiness of all the tissues, slight pyrexia, dilated heart with haemic murmurs. He had, however, a history of prolonged bleeding from piles. His blood was found to have the characteristics detailed in the table. This blood picture is quite distinct from that of pernicious anaemia for the following reasons: (1) The blood is chlorotic in type, the colour index being 0.61; (2) the differential count shows an increase in the polymorphonuclear elements; (3) the blood was not megaloblastic, only a few normoblasts being found in the films. The rapid and permanent recovery of this case confirmed the diagnosis.

The contention of Stockman that pernicious anaemia is always the result of repeated small haemorrhages is not, so far as my experience goes, supported by the examination of the blood of cases of severe anaemia resulting from haemorrhage. It will be seen from the above table that all the cases showed the characteristic features of a secondary anaemia. Stockman, however, states that there is no characteristic feature of pernicious anaemia. He does not even admit Addison's definition of the disease, but claims "that pernicious anaemia is preceded in a large majority of

cases by exhausting conditions, and that it results directly or indirectly from these conditions."

After a careful study of the history of over 50 cases of progressive pernicious anaemia, I have been struck by the fact that it is almost impossible in any case to assign any obvious cause for the anaemia. This, indeed, is one of the most characteristic features of the disease. Stockman also states that the haemoglobin of the red corpuscles is rich in the majority of cases of pernicious anaemia (that is, the colour index is high) but not in all cases. The cases which he quotes to prove that notable exceptions occur are open to very serious criticism. For instance, he gives as an undoubted case of pernicious anaemia the following:

A woman, aged 51, who presented the clinical features of pernicious anaemia, including yellow skin and stoutness. The anaemia was due to a bleeding polypus. The haemoglobin was 10 per cent., and the red corpuscles were 1,000,000 per c.mm., that is, the colour index was 0.5. There was marked poikilocytosis and several nucleated red cells. Again, he mentions that cases due to infection by ankylostoma duodenale often become cases of pernicious anaemia but with a low colour index. Such cases, however, cannot now be admitted as true cases of pernicious anaemia, as they neither correspond with Addison's definition, nor does their blood conform to the type characteristic of this form of anaemia.

Stockman offers an ingenious explanation of the high colour index which he admits usually occurs in pernicious anaemia. He infers that the haemorrhage usually occurs into the tissues, and that the extravasated blood is quickly absorbed and supplies the remaining corpuscles with iron, so that their normal amount of haemoglobin is thus kept up. From analogy I think it can be shown that this explanation is not correct. If in the cure of a secondary anaemia we give iron medicinally, the effect is to raise the number of red cells, and much more slowly the colour index. It may indeed occasionally be noticed that in the cure of chlorosis the red corpuscles may be found to exceed the normal while the haemoglobin is still low. Thus, in chlorotic or secondary anaemia, it would be impossible by means of iron to raise the haemoglobin without raising to a much greater extent the number of corpuscles, and therefore the colour index would still be below unity, at least, while any anaemia remained.⁶ In this connexion it may be mentioned that iron is generally regarded as useless in the treatment of pernicious anaemia.

From these considerations it seems certain that haemorrhage, directly at least, is not the cause of the blood condition so characteristic of pernicious anaemia. Haemorrhage, however, is a frequent symptom of this disease and may sometimes be of considerable severity. The following cases in which severe haemorrhage from the stomach was the first symptom that made the patient call in medical aid will exemplify this fact:

His blood on examination was as follows:

Red cells	=	1,400,000 per c.mm.
White cells	=	5,500 per c.mm.
Haemoglobin	=	30 per cent.
Colour index	=	1.07
Differential Count of 500 Leucocytes.		
Polymorphonuclear cells	=	66.4 per cent.
Small lymphocytes	=	24.2 "
Large lymphocytes	=	8.6 "
Transitional cells	=	0.6 "
Eosinophile cells	=	0.2 "

Thirteen megaloblasts and 1 normoblast were found in counting 500 leucocytes.

This case shows the typical picture of pernicious anaemia in spite of the occurrence of severe haematemesis, which might be supposed to have the effect of lowering the colour index. The after-history of this case verified the diagnosis of pernicious anaemia. In some cases, therefore, if a careful examination of the blood be not made, the haemorrhage may erroneously be supposed to be the cause of the severe anaemia and not, as it is in this case, merely a symptom of the disease.

2. *Intestinal Parasites.*—There is a widespread idea that the changes in the blood produced by infections with ankylostoma and bothriocephalus are frequently indistinguishable from those occurring in progressive pernicious anaemia. With regard to ankylostomiasis, A. E. Boycott and J. S. Haldane have recently given an interesting account of a number of cases of anaemia occurring in the Dolcoath Mine in Cornwall,⁷ the result of infection of the intestine by ankylostoma duodenale. They state that the essential alterations in the blood consist in an anaemia of the chlorotic type, with an increase in the total volume of the blood, a varying increase

in the leucocytes, and a marked relative and absolute increase in the eosinophile cells. Quoting several severe cases they say, "The actual highest and lowest colour indices occurring among these cases are 0.81 and 0.53. The lowest colour indices appear to be associated with the lower percentages of haemoglobin; thus the average index for those cases with 30 to 39 per cent. of haemoglobin is 0.64, from 40 to 49 per cent. is 0.68, and from 50 to 59 per cent. is 0.75. Thus the more profound the anaemia the less does it show the high colour index characteristic of the pernicious type."

Since this account of ankylostomiasis in Cornwall was published Dr. Stockman has recorded in the JOURNAL of July 25th, 1903, an interesting case of the same disease occurring in a Lanarkshire miner. The disease was probably contracted in India. The red cells numbered 3,200,000 per c.mm., the leucocytes 9,000 per c.mm., and the haemoglobin was 28 per cent. The colour index was therefore 0.43. The eosinophile cells varied from 12 per cent. to 43 per cent. of the total leucocytes at different counts. Dr. Stockman states that this case is probably the first that has been observed in Scotland.

I am indebted to Dr. R. M. Beatty for the following details of the blood examination of a patient in the Victoria Barracks, Belfast, suffering from ankylostomiasis. This is, I believe, the first case of the kind observed in Ireland. The patient believed he had contracted the disease in Dinapur, India. Numerous ova and worms were found in the faeces. When the patient was most anaemic his blood count was as follows:

Red cells	=	2,710,000 per c.mm.
White cells	=	13,000 per c.mm.
Haemoglobin	=	24 per cent.
Colour index	=	0.44.

The eosinophile cells varied from 15 to 35 per cent. of the total leucocytes at different counts. Dr. Beatty also estimated the coagulation time of the blood with Wright's coagulometer, and found it considerably increased. A deficient coagulability of the blood in such cases might possibly account for the occurrence of the "bunches" or urticarial eruptions which are so characteristic of this disease.

In both these cases it will be observed that the anaemia was the secondary type, as the colour indices in both cases were under 0.5.

From these results it would appear that the characteristic blood features of pernicious anaemia, if they ever occur as the result of ankylostomiasis, must be an extreme rarity. It may also be mentioned that the eosinophilia which constantly occurs in ankylostomiasis is not a feature of the blood of pernicious anaemia. With regard to bothriocephalus anaemia, Ehrlich admits that in some cases the blood presents the typical megaloblastic features of pernicious anaemia,⁸ but he regards this as due to the direct stimulation of the marrow by a specific toxin produced by the parasite.

3. *Pregnancy.*—Pregnancy is occasionally accompanied by a severe or even fatal anaemia, which from its symptoms closely simulates progressive pernicious anaemia. I had recently occasion to examine a case of profound anaemia occurring evidently as the result of the pregnant condition. The patient in a previous pregnancy had developed a similar anaemia. This patient had all the symptoms of profound anaemia—extreme pallor (lemon-yellow tint) general flabbiness of the tissues with considerable oedema, dilated heart, and cardiac murmurs. Her mouth was not in a septic condition, although she had several bad teeth. Her blood was as follows:

Red cells	=	2,000,000 per c.mm.
White cells	=	14,000 per c.mm.
Haemoglobin	=	15.8 per cent.
Colour index	=	0.39
Differential Count of 500 Leucocytes.		
Polymorphonuclear cells	=	75.6 per cent.
Small lymphocytes	=	21.6 "
Large lymphocytes	=	2.0 "
Transitional leucocytes	=	0.8 "

Seven normoblasts and one or two doubtful megaloblasts were found in the films in counting 500 leucocytes.

This, then, was not a case of true pernicious anaemia, but a secondary anaemia of a very grave type. Although her haemoglobin was below 16 per cent. she made a good recovery, and is alive and well at present. It will be seen on reference to the foregoing table that all the cases of anaemia occurring in association with pregnancy were found to be of the secondary type. The fact that pregnancy seems to have no peculiar influence in producing the blood changes of pernicious anaemia is borne out by all the recent work on this

subject. Ehrlich could find only one case of this description in recent literature.⁹ At Sloane Maternity Hospital from 1892 to 1899 Ewing states that he saw many cases of severe anaemia but none of the progressive pernicious type.¹⁰ Ahlfeld, with a wide experience, could not report a single case following pregnancy (1898).¹¹

4. *Cancer*.—It has been often stated that cancer, especially cancer of the stomach, may give rise to the blood changes characteristic of progressive pernicious anaemia. Hunter, however, who has gone very fully into the literature of this subject, comments on the extreme rarity of such a connexion, as he was able to find only the following cases:—Quincke, 1 case; Eisenlohe, 2 cases; Letten, 1 case; Grawitz, 3 cases. He also states that these cases from the accounts given are not entirely free from question as to the character of the anaemia present.¹²

The following cases of severe anaemia associated with malignant disease will show that the blood changes are, as a rule, totally different from those of true pernicious anaemia.

Date.	Red Cells, per c.mm.	White Cells, per c.mm.	Hb.	Colour Index.	Pmn.	Lymph.	Eosines.	*N.	†M.	Diagnosis.
19/1/02	2,760,000	11,000	22.0	0.40	81.0	17.0	0.2	o	o	Cancer of stomach.
6/1/02	2,120,000	3,100	21.7	0.51	76.8	23.2	0.0	c	o	Cancer of stomach.
12/2/00	3,190,000	7,000	45.4	0.71	—	—	—	—	—	Lymphadenoma.
12/9/02	1,760,000	6,000	28.0	0.79	62.0	36.0	2.0	o	o	Malignant epulis.
13/8/02	2,480,000	9,000	41.4	0.82	65.5	34.5	0.0	o	o	Endothelioma (peritoneum).
28/2/03	2,180,000	6,900	38.8	0.89	70.0	30.0	0.0	o	o	Cancer of stomach.
17/10/00	2,060,000	38,500	37.0	0.90	92.2	7.4	0.4	o	o	Malignant disease of lung.
16/10/01	3,090,000	10,100	38.0	0.61	76.0	23.6	0.4	o	2	Hodgkin's disease.

* Number of normoblasts found in counting 500 leucocytes.

† Number of megaloblasts found in counting 500 leucocytes.

Considering, therefore, the extreme rarity with which the blood changes which are characteristic of progressive pernicious anaemia are associated with such causes of anaemia as haemorrhage, intestinal parasites, pregnancy, and cancer, and considering the fact that in the vast majority of cases such conditions produce an entirely different type of anaemia—namely, the secondary type—the question naturally arises, Are such cases, when they do occur, to be regarded as the direct result of the apparent cause, or is there not some additional factor which accounts for the departure of the condition of the blood of such cases from the secondary type of anaemia? The case which has been detailed seems to show that this additional factor was to be found in the malignant deposits in the bone marrow, and that there was a direct connexion between these deposits and the peculiar condition of the blood found in this case. In Epstein's case, which has already been referred to, Ehrlich has explained the condition of the blood as due to the direct stimulation of the remaining bone marrow by the tumour deposits. He also believes that the pernicious type of anaemia found in some cases of bothrioccephalus infection is the result of the action on the bone marrow of some specific poison generated by the parasite. I think that a similar explanation applies to the case that is now recorded, and probably to all secondary cases associated with the pernicious type of blood.

If this explanation be the correct one, this case has an important bearing on a much disputed point in the pathology of progressive pernicious anaemia; for, by inference we are forced to conclude that the changes found in the bone marrow in cases of progressive pernicious anaemia are an essential lesion of the disease directly accounting for the condition of the blood, and not, as some have supposed, of a secondary nature—the result of the severe anaemia.

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- 7 *Journal of Hygiene*, vol. iii, No. 1, pp. 95 to 156.
- 8 Loc. cit., p. 165.
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- 10 Loc. cit., p. 178.
- 11 *Lehrbuch d. Geburtshilfe*, Leipzig.
- 12 *Pernicious Anaemia*, Hunter, p. 39.

MEDICAL MAGISTRATE.—Captain J. Booth-Clarkson, Reserve of Officers, District Surgeon and Health Officer, Alexandra County, has been appointed Justice of the Peace for Alexandra County, Natal, South Africa.

NOTE ON THE BODIES RECENTLY DESCRIBED BY LEISHMAN AND DONOVAN.

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IN May, 1903, Major Leishman, R.A.M.C., described¹ certain small oval bodies occurring in smear preparations made *post mortem* from the spleen of a soldier suffering from low fever, chronic dysentery, and cachexia. The observation was made in London at the Military Hospital, and the patient had contracted his illness at Dum-Dum, near Calcutta. Leishman gave a very accurate description of these bodies. He said that they existed in large numbers among the spleen cells and red corpuscles; that they were round or oval, and 2 μ to 3 μ in diameter; that on staining with Romanowsky's method they were found to contain two masses of chromatin—a large circular mass or ring, and another smaller mass, "usually in the form of a short rod set perpendicularly or at a tangent to the circumference of the larger mass." The outline of the bodies containing these two masses of chromatin was faintly visible with this stain. The bodies were usually isolated, but occasionally aggregated into "clumps composed of twenty to fifty members." Regarding their nature, he thought it probable that they were the residue of trypanosomes of which the vibratile membrane had disappeared after death, leaving behind the nucleus and micronucleus shrunk together in a small mass, and quotes in support of this view the occurrence of similar *post-mortem* changes in the trypanosomes of dead rats.

In July Captain Donovan, I.M.S., stated² that he had already found the same bodies on April 9th, 23rd, and 24th in *post-mortem* smears from the spleens of three consecutive cases said to have died from chronic malaria in Madras. At first he thought that the bodies represented the long-sought-for resting stage of the malaria parasite, but, after finding them in two other cases, began to think that they were *post-mortem* degenerations of spleen cells. On reading Leishman's paper he recognized their similarity to the bodies described by that observer; and next was able to recover them in blood taken *intra vitam* from the spleen of a boy suffering from irregular pyrexia (June 17th). He remarks that this case excludes the possibility of the bodies being due to *post-mortem* changes, and adds that nothing resembling trypanosomata could be found in the boy's blood.

Captain Donovan was good enough to send me three preparations well stained by the Romanowsky method—namely, one preparation from his case of April 9th (*post mortem*), one from his case of June 17th (*intra vitam*), and a third dated July 4th from the splenic puncture (*intra vitam*) of yet another case. I have examined these carefully, and as there has already been considerable delay over them I think that the following brief notes should be recorded at once as a verification of the previous papers:

1. All these preparations contain bodies agreeing exactly with Leishman's description, and he himself admits the similarity after having been so kind as to examine the specimens.

2. In Donovan's specimen of April 9th (*post mortem*) the bodies number about 30 in a field and measure about 2.5 μ . They are disconnected from each other, but often lie fairly close together in groups of 10 or more. In the specimen of June 17th (*intra vitam*) they number only about 1 in 12 fields, but are slightly larger—up to 3.25 μ . In that of July 4th they are also large, and number about 1 in every field or so; while groups of from 2 to 12 of them can often be found embedded in what seems to be some kind of matrix which stains a faint bluish-grey colour, and which has an oval contour measuring up to 8 μ in the long diameter. Some of the bodies appear even to be intracorpuseular, but this may be due to accidental superposition.

3. Both large and small nuclear masses are almost invariably present, and both are always stained a deep vivid crimson. The smaller one is very often rod-like and pointed at the large one, just as Leishman describes, and stains somewhat deeper than it. The bioplasm is generally colourless, but its contour is reddish in the specimens made *intra vitam*.

4. In none of the specimens can I find either entire trypanosomes or the remains of dead ones, such as the characteristic flagella.

It is to be hoped that Major Leishman and Captain