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CASE OF CARCINOMA OF THE STOMACH WITH METASTASES IN THE BONE-MARROW, AND A BLOOD PICTURE SUGGESTIVE OF PERNICIOUS ANÆMIA.

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CASE OF CARCINOMA OF THE STOMACH WITH METASTASES IN THE BONE-MARROW, AND A BLOOD PICTURE SUGGESTIVE OF PERNICIOUS ANÆMIA.[1]

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It has long been recognised that cases of carcinoma of the stomach are frequently attended by a severe degree of anæmia. This anæmia is usually of the secondary type, and is likely to be more marked if numerous secondary growths are present. Erythroblasts are said to occur more frequently in it than in any other secondary anæmia, with the exception of that accompanying sarcoma (Da Costa). Other cases of cancerous anæmia have been described in which the blood picture was identical with that of pernicious anæmia. Many of these, however, occurred when our knowledge of the methods of examination of the blood and of its histology fell far short of modern requirements.

Metastatic cancerous deposits in the marrow of the bones have been frequently observed, but the blood in such cases has comparatively seldom been examined. Metastases in the bone-marrow secondary to cancer of the stomach have been noted by Frese, Goetsch, Ewing, Dickson, Parmentier and Chabrol, Schliep and Luzzato, and secondary to cancer in other organs by Houston (breast), Epstein (breast), Hirschfeld

[1] Read at a meeting of the Medico-Chirurgical Society of Glasgow held on 28th January, 1910.

(breast and uterus), Kurpjuweit (bile-ducts), and Braun (prostate). The cases fall into two groups.

In the first, there are no special changes in the blood. This class is illustrated by a case of Nothnagel (lymphadenia ossium), quoted by Ehrlich. In it the blood during life showed the features of a simple severe anæmia, but also isolated normoblasts, small marrow cells, and moderate leucocytosis. The bone-marrow showed complete atrophy, and was replaced by tumour masses. Nothnagel conjectured that the formation of the scanty erythroblasts occurred vicariously in the spleen, that of the leucocytes in the lymph glands. Ewing mentions two cases of carcinoma of the stomach with extensive bone metastases, in which he found "only moderate anæmia and but few nucleated red cells."

In the second group of cases there are striking changes in the blood. The most important change is the presence of numerous erythroblasts and myelocytes. Our case falls into this group.

Clinical report by Dr. A. R. Paterson.—The patient, a woman of 64 years, was admitted to the Glasgow Royal Infirmary on 9th August, 1909, complaining of pains in the back and legs. She had enjoyed fairly good health till about 28th June, when pain in the lower part of the back began to trouble her. The pain was sharp in character, and shot down the back of the legs. Pain was occasionally felt behind the right shoulder. She was never free from pain, but had not experienced any in the abdomen. During this time there was a tendency to constipation, and when the bowels moved after an interval of a day or two she noticed that the motions were of a black colour. At other times the motions were normal. Very occasionally she has had sickness and vomiting. On one or two occasions, about six months ago, she vomited brownish material. She was able to do a good day's work as cook on going to a situation on 28th June, but recently had rapidly failed. Her appetite has been very poor, and loss of flesh has been marked during the last month prior to admission.

Previous health.—Scarlet fever in childhood. "Indigestion" now and again during the last few years, with loss of appetite and occasional vomiting.

On admission, the patient is rather cold and exhausted. She complains greatly of pain, and seems to be in considerable discomfort. Emaciation is marked, and anæmia pronounced. The muscles are flabby, the skin is loose, and the eyes sunken.

There is a marked arcus senilis. The pupils are equal, and react normally. The tongue is furred. The fauces and pharynx are normal. There is pain on pressure over the sacral region, gluteal muscles, and down the back of the left thigh. In the calf pain is present in the region of the posterior tibial nerve. Sensation is normal. No enlarged glands can be felt. There is no œdema. Pulse is frequent (over 100 per minute), full, soft, and regular, but ill-sustained. A short, soft, systolic murmur is audible at the base of the heart. Nothing abnormal can be detected in lungs. Beyond slight distension, nothing abnormal was found on examining the abdomen. Rectal examination is negative. Ophthalmoscopic examination revealed nothing abnormal.

Urine.—Amber, acid; specific gravity, 1028; haze of albumen, no blood, bile, sugar, indican, urobilin, or albumose.

The stools on the 10th, 13th, and 15th August were very offensive and tarry. Blood was evidently abundant in them. There was no further melæna after 15th August. Patient was rapidly losing ground. She gradually sank, suffering greatly from pain.

On 10th September there was a good deal of catarrh in the chest, and the pulse was very poor. She died on 15th September.

Blood examination (see table, p. 4).—*23rd August, 1909:* Erythrocytes, 1,600,000; leucocytes, 14,000; hæmoglobin (Haldane's method), 35 per cent; colour index, 1·09. The differential counts of the leucocytes are shown on table, with the numbers of megaloblasts and normoblasts. Films were stained by Leishman's or Jenner's stains. The red cells show moderate poikilocytosis and considerable anisocytosis, megalocytes being numerous. Polychromatophilia is fairly marked, especially in the erythroblasts. Many erythrocytes show granular basophilia, and numerous very ill-formed and poorly staining cells are present. Numerous megaloblasts and normoblasts are seen, many of the megaloblasts being very large. Evidence of division of the nucleus is fairly frequent in the normoblasts. Many atypical leucocytes are seen, so that the cells are difficult to classify. Myeloblasts as well as myelocytes are present.

1st September.—Erythrocytes, 1,900,000; leucocytes, 8,000; hæmoglobin (Haldane's method), 42 per cent; colour index, 1·1. Poikilocytosis is slight, but megalocytosis notable. Polychromatophilia and granular basophilia are marked. Numerous megaloblasts and normoblasts are present. Myelocytes are more numerous.

9th September.—Erythrocytes, 1,800,000; leucocytes, 8,000; hæmoglobin (Haldane's method), 35 per cent; colour index, 0·9. Erythroblasts and megalocytes are still numerous. Polychromatophilia is still notable, but granular basophilia is not so marked.

Films examined on 14th September, the day prior to death, showed the same characters, and the percentage of myelocytes had increased.

DIFFERENTIAL COUNTS OF 500 LEUCOCYTES (LEISHMAN'S STAIN).

	Aug. 23.	Sept. 1.	Sept. 9.	Sept. 14.
	Per cent.	Per cent.	Per cent.	Per cent.
Polynucleated neutrophiles, . .	63·0	52·2	59·0	54·6
,, eosinophiles, . .	0·7	0·6	0·1	0·8
,, basophiles, . .	...	0·2	...	...
Lymphocytes, ...	16·7	13·8	13·5	17·2
Large mononucleated and transitionals, ...	18·8	28·2	25·5	21·4
Myelocytes, ...	0·8	5·0	1·25	6·0
Megaloblasts } total number in count	29	55	45	46
Normoblasts } of 500 leucocytes,	4	11	25	20

Report of post-mortem examination (17th September, 1909).—The body was extremely anæmic and emaciated. There was a hard mass of lymphatic glands infected with tumour in the root of the neck on the left side.

Thorax.—The heart showed signs of fatty degeneration, and there was marked atheroma of the aorta. There were no tumours in heart or pericardium. Both pleural sacs showed old fibrous adhesions, and numerous white plaques of tumour on the parietal and visceral layers. The pleura stripped cleanly from the ribs, and there appeared to be no connection between the tumours in it and the underlying bone. There were no tumours in the lungs or in the bronchial lymphatic glands. Both surfaces of the diaphragm showed widespread injection by white tumour in lines converging towards the œsophagus.

Abdomen.—The stomach was small, and there was an hour-glass contraction about the middle. It was drawn close up to the liver, and firmly attached to it by hard white fibrous tissue. About 2 inches of the lesser curvature was occupied by a deep ulcer having the character of a simple chronic ulcer, but there was permeation of the gastrophrenic ligament and gastrohepatic and great omentum by hard white tissue, which

was clearly of the nature of tumour. In addition, all round the ulcer there was a hard flat tumour with raised margins, extending so as almost to encircle the stomach. This was the cause of the hour-glass deformity. The tumour did not extend to the œsophagus, but there were small secondary nodules in the œsophageal mucous membrane for about 3 inches above the cardiac orifice. The intestines showed nothing of note. The lymphatic glands behind the stomach, and in the root of the mesentery and down the aorta as far as the bifurcation, were also involved. The inguinal glands appeared to be free from tumour.

The liver was of normal size, and showed slight fatty infiltration. There were a few flat tumours in the capsule, but none in its substance. The spleen was somewhat enlarged with red soft full pulp. There were no tumours in it. The condition appeared to be largely due to venous congestion. The kidneys were slightly cirrhotic, and contained a few minute white tumours. The pancreas contained numbers of small tumours.

The bones.—Ribs: No nodular thickening could be felt, but the ribs were very brittle, and broke in removal. Definite tumours were not recognised in the fractures. The bony walls everywhere appeared to be thin. On squeezing the ribs only a little fatty fluid escaped. The cancellous tissue was uniformly occupied by a pale, rather fibrous-looking material, with the exception of a few small areas, which were of red colour, but this appeared to be due to hæmorrhage rather than to the presence of red marrow. Subsequent microscopic examination showed the white tissue to be tumour. The calvarium was noted as being free from tumours, but this statement only excludes definite nodules, the colour of the diploë not having been particularly observed. Both femora and the right humerus were examined. The heads of the bones were filled with white tissue in many parts forming rounded nodules, which were taken to be tumours; the rest of the cancellous tissue was occupied by a less white and more fibrous-looking tissue, with red areas here and there. The lower ends of the femora seemed to be occupied by yellow marrow. The medullary cavities of all three bones were occupied by firm, bright red marrow, in which were embedded numerous yellowish-white translucent tumours, ranging in size from pin-points up to the size of peas. They could be picked out of the marrow as fairly well-defined globular bodies. This bright red marrow filled the cavity in the upward direction as far as the cancellous tissue, but in the

downward direction it gave place gradually to ordinary yellow marrow, with which the lower 2 inches or thereby of the cavity were filled.

Portions were sawn from the front of several of the lower dorsal and lumbar vertebræ. The bony tissue seemed to be very dense and of a red colour, mottled with yellowish-white areas, which, however, were quite hard, and were not recognised as tumours. There were small tumours in both psoas muscles, principally on the surface, and no involvement of the lumbar nerves could be made out. There were no tumours in the brain.

Microscopic examination.—Microscopic examination was made of the primary tumour, the bone-marrow from the femur, the liver, the kidney, the lung, and the lymphatic glands by the paraffin process, and the ribs, the head of the femur, and parts of the vertebral bodies were decalcified and embedded and cut in celloidin. The spleen, unfortunately, was not examined. Films were also prepared from the bone-marrow in the femur. Only a little fatty juice could be squeezed out of the ribs, and films could not be prepared from it.

Stomach.—The tumour of the stomach proved to be a carcinoma. The ulcer, microscopically, appeared to be a simple chronic ulcer, the tumour not appearing in the floor or edges, but being visible at no great distance from both. At the growing edges the tumour was fairly cellular. It was composed of small processes of polyhedral cells occupying the meshes of a somewhat scanty fibrous stroma. In such parts many of the cells presented the characteristic appearance of colloid degeneration, but in the more central parts of the tumour this was replaced by a shrunken appearance affecting both nucleus and cell body, so that at no point were the usual large colloid masses to be found. The tumour cells seemed to disappear from the older parts of the growth, and great thickening of the fibrous stroma took place, so that the greater part of the bulky mass occupying the lesser curvature of the stomach was very dense connective tissue, with comparatively little apparent tumour in it.

The secondary growths in the kidney, bone-marrow, and lymphatic glands showed a similar tendency to atrophy of the epithelial element and development of fibrous stroma. The white tissue filling the ribs and the cancellous heads of the long bones proved also to be tumour. Some parts of the tumour in the bones showed young cellular carcinomatous tissue, but the greater part was more or less degenerated,

showing shrunken cells and a large amount of fibrous stroma. Many large areas consisted of fibrous tissue only, but the nature of this was easily made out by tracing the stages in the transformation between it and the young tumours. Most of the red areas in the ribs were found to represent hæmorrhage, but a few were red marrow. The head of the femur likewise contained much more tumour than red marrow; and the veretebral bodies showed a large proportion of marrow, but, on the whole, rather more tumour. The red marrow had, in fact, almost entirely disappeared from its normal sites.

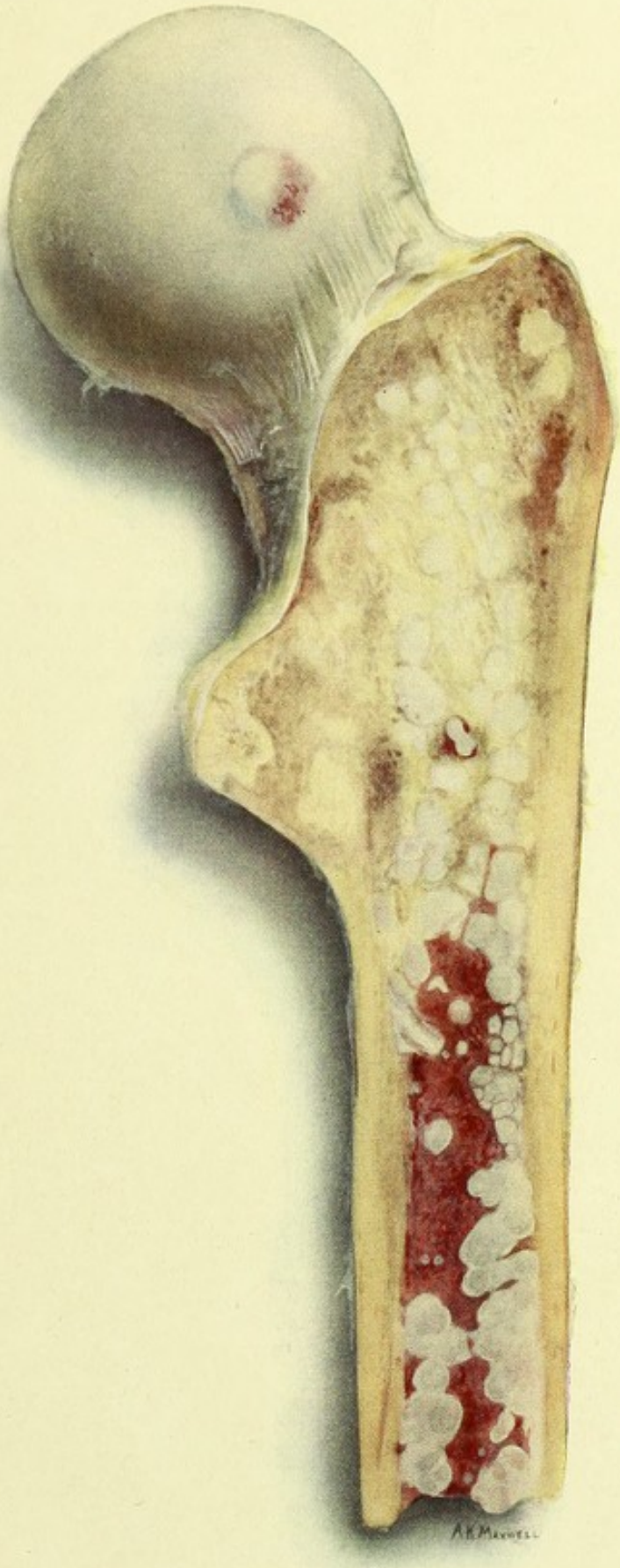
The bright red tissue occupying the medullary cavities of the long bones was red marrow containing all the normal elements, but with rather an excess of the red elements. Owing to the length of time which elapsed before the *post-mortem* examination, the preservation was not very good, which made it difficult to estimate the exact condition. The granular cells were not well preserved, but the neutrophile and eosinophile forms were abundant, and there were also numerous non-granular cells which were not tumour cells. The nucleated red cells varied greatly in size and nuclear character. Many were larger than normal, and had large pale nuclei; others were large, but had nuclei of the normal type, and normoblasts were also fairly numerous. On the whole, the condition corresponded with that of the blood, and the marrow might be called megaloblastic in type. No difficulty was experienced in distinguishing the tumour from the bone-marrow, the cells of the former being very much larger than those of the latter. The tumour also contained very few blood-vessels, whereas the bone-marrow was highly vascular.

Large areas of the tumour consisted of groups of small cells with very dark nuclei, which, on superficial examination, resembled badly stained nucleated red blood corpuscles, but closer investigation showed this to be a stage in the degeneration of the carcinoma cells. This tissue did not come into close relation with the red marrow, which was seen only in proximity to young tumour nodules, with the following exception:—Some of the red areas in the pale cancellous bones were found to consist of red bone-marrow. These were situated, not at the edges of young tumours, but at the edges of the most fibrous nodules, a position which suggested that they represented areas in which a new development of marrow was taking place after the tumour had passed its active stage and degenerated into an inactive condition.

Bone metastasis appears to be relatively common in cancer of the stomach.

In most of the published cases the cancer has been pyloric, of small size, and circumscribed. Thus, in most cases the primary growth has been latent. Gastric symptoms have been absent and no tumour could be felt. In our case the emaciation of the patient and the melæna, with a history of occasional dyspepsia, and on one or two occasions of vomiting of brownish material, were sufficient to arouse suspicion. Still the gastric symptoms were not clamant, and on examination of the abdomen nothing abnormal could be made out beyond some distension. No enlarged glands could be felt. The patient's general condition vetoed gastric analysis. Her only complaint was of pains in the back and thighs. There was some tenderness in the sacral region and over the left thigh. Any movement of the body or lower limbs appeared to cause great pain. The appearance of the patient on admission was that of a woman who had been losing blood and weight for some time, and her emaciation during her residence was rapid. Carcinoma of the stomach seemed a very probable diagnosis. The blood examination threw fresh light on the case. A low red cell and hæmoglobin estimate, a slight leucocytosis, and a high colour index were found. Films showed a severe anæmia with poikilocytosis, megalocytosis, polychromatophilia, and granular basophilia. A small percentage of myelocytes was found, and erythroblasts were numerous, the megaloblasts predominating. Such a blood picture was quite foreign to that usually seen in the anæmia of cancer of the stomach, and was suggestive of pernicious anæmia. But there were points of difference. It is very unusual to meet with large numbers of erythroblasts in pernicious anæmia. Much more often they have to be carefully sought for. When large numbers do occur, it is only for a short period, and they are not constantly present. Films were made of our patient's blood on many occasions, and erythroblasts were always present in large numbers. Again the leucocytosis with a considerable proportion of polymorphonucleated neutrophiles, although there was a relative increase of mononucleated cells, did not favour the diagnosis of pernicious anæmia.

With regard to the high colour index, Von Noorden states that while megalocytes and a high colour index are of almost constant occurrence in pernicious anæmia, they are exceptional in the anæmia of cancer. This is a fact admitted



Illustrate the paper by Dr. A. W. Harrington
Dr. J. H. Teacher.)

by most observers, although not by Aubertin and others in France.

Dr. John Shaw Dunn suggested the possibility of bone metastases, and with the bone pains this seemed very probable. A diagnosis of cancer of the stomach with bone metastases was therefore made.

The literature of the subject is as yet rather scanty, and few of the cases have been fully worked out. The case recently published by Parmentier and Chabrol was one of latent scirrhus of the stomach with bone metastases. The erythrocytes numbered 1,040,000; leucocytes, 3,500; hæmoglobin (Tallquist), 60 per cent; colour index, 3. Films showed poikilocytosis, anisocytosis, megalocytosis, and slight polychromatophilia. The differential count of the leucocytes was —polynucleated neutrophiles and transitionals, 60 per cent; neutrophile myelocytes, 8 per cent; polynucleated eosinophiles, 4 per cent; mononuclears, 15 per cent; large mononuclears, 6 per cent; lymphocytes, 6 per cent; "cellules de Turck," 0·6 per cent; erythroblasts, 44 per cent. Two-thirds of the erythroblasts were normoblasts and one-third megaloblasts. The megaloblasts were very polychromatophilic and showed basic stroma degeneration. Only one blood examination, and that two hours prior to death, is recorded. The bacteriological examination of the blood was negative. Coagulation time was six minutes. This case differs from ours in showing a leucopænia, and in the fact that the majority of the erythroblasts were normoblasts.

In a case of very limited carcinoma of the stomach with numerous bone metastases recorded by Schliep, the hæmoglobin was 40 per cent; erythrocytes, 1,084,000; leucocytes, 16,400; colour index, 2. Erythroblasts numbered 120 per 500 leucocytes, and were chiefly megaloblasts. A differential count of the leucocytes showed neutrophiles, 82 per cent; lymphocytes, 8·2 per cent; "formes intermediares," 2·9 per cent; eosinophiles, 1·2 per cent; neutrophile myelocytes, 0·7 per cent; "formes cellulaires (cellules neoplasique?)," 4·9 per cent. No such cells as those last mentioned were seen in the films from our case.

Houston's case of bone metastases secondary to cancer of the breast is of considerable interest, as four blood examinations are recorded, the last being fully nine months after the first. There was great diminution of the red cells and marked poikilocytosis, many megalocytes and some microcytes and polychromatophilia. Megaloblasts

and normoblasts were present throughout, the megaloblasts predominating. The colour index was high, the leucocytes about or slightly under the normal proportion with relative lymphocytosis and presence of myelocytes. These findings were practically the same at all examinations.

In Epstein's case, quoted by Ehrlich, there were "many nucleated corpuscles of both normoblastic and megaloblastic type, the nuclei of which showed the strangest figures, due not only to typical nuclear division, but also to nuclear destruction. The white corpuscles were decidedly increased, showing a relation to the reds of $\frac{1}{25}$–$\frac{1}{40}$. The increase was most evident in the large mononuclear forms, the great number of which showed neutrophile granulations, in other words were myelocytes. Only two eosinophile cells were found in all the preparations." No such striking loss of eosinophiles occurred in our case, and the myelocytes were not so numerous.

It would thus appear that the features which such cases have in common are the marked diminution in red cells, high colour index, megalocytosis, and the *constant* presence in the blood of myelocytes and of erythroblasts in considerable numbers, many of the latter being megaloblasts. The megaloblasts are usually said to predominate, but Naegeli states that three-fourths of the erythroblasts are normoblasts. All authors agree that in most cases the blood shows a strong myeloid reaction, numerous erythroblasts and myelocytes being found. Parmentier and Chabrol's case showed 8 per cent myelocytes and 44 per cent erythroblasts, of which two-thirds were normoblasts. In Wolfer's case, quoted by Parmentier and Chabrol, 25,900 erythroblasts per cubic millimetre were seen. Houston estimated that there were 45 erythroblasts, mostly megaloblasts, per 500 leucocytes, and a small percentage of myelocytes in his case. Large numbers of both occurred in the blood of Epstein's case. Schliep counted 120 erythroblosts per 500 leucocytes, these being chiefly megaloblasts, and 0·7 per cent myelocytes. Kurpjuweit records 17 per cent of myelocytes. In our case, 70 erythroblasts per 500 leucocytes, with a preponderance of megaloblasts, and 6 per cent of myelocytes, were the highest counts obtained.

Does such a blood picture render it possible to diagnose bone metastases? One must first enquire whether such findings occur apart from metastases.

Stienon reports a case of latent adeno-carcinoma of the stomach in which the erythrocytes numbered 1,580,000 to

1,420,000; the leucocytes, 6,400 to 8,700; and the hæmoglobin was 25 to 35 per cent. The differential count of the leucocytes was at first almost normal. There were no nucleated red cells, and only 3 per cent of myelocytes. Some days before death the count showed 15 per cent polynucleated neutrophiles, 47 per cent small lymphocytes, 26 per cent myelocytes; normoblasts, 4 to 24 per cent; megaloblasts, 1 to 3 per cent. The marrow of the femur was in full reaction, but no mention is made of metastases. The change in the character of the blood is striking, and although no metastases was found in the marrow of the femur, they may have been present in other bones not examined.

That grave anæmia in cancer may exist without metastases has been fully shown by the work of Aubertin and others. It is, however, difficult to understand why one case of grave anæmia in cancer should differ so notably in its blood findings from another, unless some definite cause, such as metastases in the bone-marrow, can be found. The case of latent gastric carcinoma with extreme anæmia recently published by Clerc and Gy illustrates this point well. In this case the erythrocytes numbered 650,000, the leucocytes 6,000, and the hæmoglobin was 7 per cent; colour index, 0·5. The differential count of the leucocytes was normal, and 1 normoblast per 4,000 leucocytes was seen. The marrow was in full reaction, but there were no metastases. The case forms a very striking contrast to those in which bone metastases were present, and many similar cases could be detailed.

In most instances, therefore, the occurrence of metastases in the bone-marrow is followed by the appearance of large numbers of erythroblasts and myelocytes in the blood. In a case in which there is reason to suspect the presence of cancer, the constant presence of large numbers of erythroblasts and myelocytes in the blood should certainly suggest the probability of bone metastases. Even when the primary growth is latent the occurrence of such blood changes ought to make one keep in mind this possibility. If such a blood picture occurs in the anæmia of cancer apart from metastases, it must do so very rarely. Further observations are necessary upon this point.

The presence of bone pains would favour the diagnosis. They were a striking feature of our case. In Frese's case, pressure on the iliac bones, the bones of the lower limbs, and on the third left rib elicited severe pain. Kurpjuweit reports a case secondary to cancer of the gall-bladder, with palpable swellings and spontaneous fracture of the bone. But pains

appear to be more often absent, or so slight as not to attract attention.

Parmentier and Chabrol consider enlargement of the spleen valuable as an indication of bone metastases. In our case there was no enlargement clinically, and only slight enlargement found at the autopsy.

Greatest importance must be attached to the blood condition. It is the most constant feature, while bone pains and splenic enlargement may or may not be present.

In causation of this grave anæmia the insufficient alimentation of the patient and the hæmorrhages must have played a considerable part, as, apart from the metastases in the marrow, the secondary growths were inconsiderable. With such extensive destruction of marrow, hæmogenesis must have been defective. It is difficult to say whether or not hæmolysis took part in the production of the anæmia. No direct observations were made on this point, but the liver showed no iron reaction, and there was no urobilin in the urine. The condition in Parmentier and Chabrol's case was very similar. The spleen showed a small amount of *débris* of red cells. Siderosis was absent in glands, marrow, and kidney. Luzzato's case contrasts with this. In a cancer of the stomach with grave anæmia, myeloid reaction of the blood, and metastatic nodules in various parts of the bone-marrow, he found the signs of hæmolysis well shown in the spleen, less intense in the liver, and almost absent from the bone-marrow. He concluded that the anæmia was due to increased hæmolysis, and not to the presence of metastases in the bone-marrow. Probably both defective hæmogenesis and hæmolysis play a part in the production of the anæmia.

There seems to be little doubt that the presence of large numbers of erythroblasts and myelocytes in the blood is due to the stimulation of the bone-marrow by the metastatic tumours.

Summary.—The principal features of the case were as follows:—

I. Anæmia of a peculiar type showing marked diminution of the red cells, high colour index, granular basophilia, polychromatophilia, slight poikilocytosis, megalocytosis, and the *constant* presence of numerous myelocytes and erythroblasts, the majority of which were megaloblasts. The symptoms pointed somewhat indefinitely to cancer of the stomach, and in view of the peculiar type of anæmia and the presence of

some bone pains, cancer of the stomach with metastatic invasion of the bone-marrow was diagnosed.

II. *Post-mortem* examination revealed a large carcinoma of the lesser curvature of the stomach. Secondary to this there was very widespread lymphatic permeation extending from the primary tumour in the stomach, but there were very few nodules in the solid viscera. In addition, there was very widespread dissemination through the bone-marrow, which could hardly have occurred by any other route than the blood-stream.

III. The almost complete disappearance of red marrow from its normal situations, and its replacement by tumour tissue, and the development of large quantities of red marrow in the medullary cavity of the long bones. The marrow showed a megaloblastic type of red corpuscle formation.

Conclusions.—1. The occurrence of cancer metastases in the bone-marrow is followed in most instances by the appearance of large numbers of erythroblasts and myelocytes in the blood, usually associated with a high colour index and megalocytosis.

2. Where there is reason to suspect the presence of cancer, the constant presence of large numbers of erythroblasts and myelocytes in the blood, with megalocytosis and a high colour index, should suggest bone metastases.

3. The presence of bone pains favours the diagnosis, but the greatest importance is attached to the condition of the blood.

4. The blood picture is due to the stimulation of the bone-marrow by the metastatic tumours. The manner in which they act cannot at present be determined.

5. Probably both defective hæmogenesis and increased hæmolysis take part in the production of the anæmia.

6. The very widespread distribution of tumour through the skeleton, with its absence from the viscera, suggests a selective affinity on the part of the tumour for the bone-marrow, and the following is believed to have been the sequence of events. The tumour developing in the red marrow in its normal situations destroyed it, and a compensatory hypertrophy took place in the same situations in which this has been noticed in septic conditions and after severe hæmorrhage, viz., in the medullary cavities of the long bones. There the ordinary yellow marrow was to a very large extent replaced by red marrow rather of the erythroblastic type; and in this new

marrow the secondary tumours had developed to a greater or less extent.

While the bone-marrow and the blood present evidence of disordered (megaloblastic) red corpuscle formation, the marrow is particularly free from degenerative changes, and is not the bone marrow of a pernicious anæmia.

REFERENCES.

Aubertin, "Les Anémies par l'anhematopoièse," *Semaine Méd.*, 15th July, 1908.

Braun, *Wien. med. Woch.*, 1896, No. 12.

Clerc and Gy, *Bull. et Mémoires de la Société Médicale des Hôpitaux de Paris*, 5th August, 1909.

Cabot, *Clinical Examination of the Blood.*

Da Costa, *Clinical Hæmatology*, 1906.

Dickson, *The Bone-Marrow*, 1908.

Epstein, *Zeitschrift für Klin. Med.*, 1896, Band xxx.

Ehrlich, *Nothnagel's Encyclopædia*, "Diseases of the Blood," English edition.

Ehrlich and Lazarus, *Histology of the Blood*, translated by W. Myers.

Ewing, *Clinical Pathology of the Blood.*

Frese, *Deutsch. Archiv f. Klin. Med.*, 27th September, 1900.

Goetsch, *Ziegler's Beiträge*, 1906.

Houston, *British Medical Journal*, 14th November, 1903.

Hirschfeld, *Fortschritte der Medicin*, Bd. xix, 1901, No. 29.

Israel and Leyden, *Berlin. Klin. Woch.*, 1890, No. 10.

Kurpjuweit, *Deutsch. Archiv f. Klin. Med.*, Bd. lxxvii, 1903.

Luzzato, *Acc. Méd. de Parma*, 28th February, 1908.

V. Noorden, *Mediz. Klinik.*, 25th October, 1908.

Parmentier and Chabrol, *Bull. et Mémoires de la Société Médicale des Hôpitaux de Paris*, 5th August, 1909.

Schliep, *Atlas der Blutkrankheiten.*

Stienon, *Société d'anat. pathol. de Bruxelles*, 19th February, 1909.

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