

**CARCINOMA OF THE BONE-MARROW.**

By ALFRED PINEY, BIRMINGHAM.

- I.—INTRODUCTION.
- II.—ANATOMY OF THE BONE-MARROW.
- III.—BLOOD-VESSELS OF THE BONE-MARROW.
- IV.—LYMPHATIC CHANNELS OF THE BONE-MARROW.
- V.—DEVELOPMENT OF THE BLOOD-FORMING TISSUES.
- VI.—CHARACTERS OF THE BLOOD PICTURE IN CASES OF CARCINOSIS OF THE BONE-MARROW.
- VII.—MODE OF SPREAD OF CARCINOMA INTO BONE-MARROW.
- VIII.—EVIDENCES OF THE EMBOLIC ORIGIN OF METASTASES IN THE BONE-MARROW.

**I. INTRODUCTION.**

THE existence of deposits of malignant tumours in the bone-marrow had been realized by morbid anatomists and surgeons a very considerable time before any definite explanation of the fact was available.

The early conception of the formation of deposits of cancer in the bone-marrow depended upon a belief in the existence of a 'cancerous diathesis', which was capable of manifesting itself in different regions of the body, either at the same time or successively. Sanson<sup>1</sup> described a case in which a woman, with a scirrhus cancer of the breast of less than a year's duration, broke one femur while moving in bed. During the manipulations necessary for the reduction of this fracture, the other femur broke. At autopsy, there were many cancerous deposits throughout the skeleton; almost all the segments of the vertebral column were filled with tumour tissue, as were also the frontal bone and the medulla of each femur. In the last-named position, Sanson states that the tumour appeared to have grown from within the bone outwards. He sums up the case as follows: "qui a offert l'exemple peut-être le plus complet de ce qu'on nomme la diathèse cancéreuse".

The fundamental contributions to oncology which were made by Virchow made it necessary immediately to find some explanation of secondary cancerous deposits which did not depend upon the metaphysical conception of a 'cancerous diathesis'. It soon became obvious that the explanation of the process of formation of metastases was to be looked for in the blood or lymph. The conception of the formation of metastases by means of emboli consisting of cancer cells soon found abundant histological confirmation. The credit of pointing out the importance of a process other than embolism belongs to Sampson Handley. He has demonstrated that spread from a primary carcinoma of the breast is mainly by a process of 'lymphatic permeation'; that is to say, growth takes place along the lymphatic channels from the primary focus outwards. In the course of such permeation, the epithelial cells may be destroyed by a process of perilymphatic fibrosis, or they may proceed directly along these channels until they reach another organ, where obstruction to their onward course will result in the formation of a metastatic nodule which is large enough to be detectable macroscopically. Obstruction to onward proliferation may take place at any part of the lymphatic system, and where this occurs there will be formation of a cancerous nodule, e.g., in the skin.

The purpose of this paper is the detailed discussion of the evidence which relates to the problem of metastases in bone. In order to attack this much-disputed question, it is necessary to have a clear understanding of the anatomy of the bone-marrow, and a knowledge of the origin of this organ in the embryo. In a paper read before the British Medical Association at Glasgow in July, 1922, the present writer has described the macroscopic anatomy of the bone-marrow at different ages, and only a brief summary of this subject can be given.

## II. THE ANATOMY OF THE BONE-MARROW.

At birth all the bones of the skeleton except those of the cranium contain red marrow in which there is no fatty tissue either macroscopically or microscopically. As age advances, fatty tissue appears in the marrow, but is not present in equal amounts in all the bones.

The vertebræ, sternum and ossa innominata contain red marrow throughout life, and only microscopical amounts of fat are detectable even in advanced age. The ribs are also storehouses of cellular marrow throughout life, but in advanced age a patch of fatty tissue usually appears at the anterior end of each rib and extends for about one inch from the costochondral junction.

The long bones present changes which are rather more difficult to describe accurately and briefly. At birth the limb bones contain red cellular marrow in the diaphyses as well as in the epiphyses. The cellular tissue is divided into compartments by firm bony trabeculæ, and these take part in the series of changes which are normally associated with the attainment of the adult condition of the bone-marrow. Throughout childhood the marrow remains red, but fat is found in appreciable amount microscopically. It is not until the age of puberty is reached that macroscopically visible fat is found in the shaft. This first fat is visible just below the middle of the shaft in all the long bones and is surrounded by cellular marrow, which lies at the periphery of the medullary cavity. Extension of fatty change proceeds from this first formed mass of fat in both directions. The rate of spread in the distal direction is more rapid than in the proximal. Although the mode of fatty metamorphosis is the same in both the proximal and distal limb bones, there is one great difference, viz., the conversion into fat is complete more quickly in the distal bones. At the time when the whole of the radius, ulna, tibia and fibula are filled with fat, there is still a patch of red marrow at the upper end of each humerus and femur. This patch of red cellular marrow persists throughout life; microscopically it is obvious that there is a very considerable amount of fat even in this red patch.

The epiphyses of the long bones undergo a similar fatty metamorphosis, which is complete earlier than is the case in the shafts. The conversion of cellular marrow into fat is accompanied by disappearance of many of the bony trabeculæ in the shaft, but there is less disturbance of these structures in the epiphyses. The residual patches of cellular marrow at the upper ends of the diaphyses are practically free from bony trabeculæ.

The small bones of the hands and feet have not been examined sufficiently frequently to enable me to describe the changes in detail, but it is certain that conversion into fat is complete in them at an earlier age than is the case even in the radius and ulna, etc.

**Summary of the Distribution of the Red Marrow in the Adult.**—In the adult the vertebræ, sternum, ossa innominata and the greater part of each rib contain red cellular marrow.

The only red marrow in the long bones of the limbs is found in a small area at the upper ends of the diaphyses. Longitudinal section of the long bones gives an incorrect picture of the exact distribution of the red marrow, whereas transverse section demonstrates that the fatty tissue is mainly confined to the axis of the medullary cavity, while the periphery still contains some cellular marrow for a varying distance below the lower edge of the definite mass of red marrow which is so well seen on longitudinal section.

**Changes in the Distribution of the Red Marrow in the Adult.**—When one bears in mind the hæmatopoietic function of the bone-marrow in post-natal life, as demonstrated by Bizzozero<sup>2</sup> and Neumann,<sup>3</sup> it is obvious that any condition of the body which demands an increased supply of blood-cells, either red or white, will throw a large amount of extra work on the hæmatopoietic depôts. If such a demand be comparatively slight or of short duration, the existing tissue will suffice to produce the cells required: this is seen in the ordinary process of digestive leucocytosis. If, however, the demand is intense and long continued, it will be necessary for the cellular marrow to hypertrophy in order to supply an adequate number of cells to the circulation. Such hypertrophy is seen in

leukæmia, pernicious anæmia, and many other conditions. It is, therefore, correct to state that the red marrow can increase in amount even in adult life in response to many varieties of stimuli.

### III. THE BLOOD-VESSELS OF THE BONE-MARROW.

The gross anatomy of the blood-vessels of the bone-marrow is well known, but apparently the extreme importance of a comprehension of the finer anatomy has escaped general notice. The best method of demonstrating the distribution of the blood-vessels in the marrow is by means of specimens which have been injected with a carmine-gelatin mass; but even ordinary microscopic sections, stained with eosin, show the distribution of the blood channels quite distinctly. In the fatty marrow the blood channels are ordinary well-formed vessels, but as soon as the red marrow is reached the conditions become much more difficult to follow. The red marrow is essentially a tissue consisting of innumerable blood channels with extremely thin walls. Outside these channels are hæmatopoietic cells. *Fig. 176* shows the arrangement of the blood-vessels in the red marrow. It is obvious that the great widening of the stream-bed of the blood at the junction of the fatty with the red marrow must involve a great decrease in the rate of flow in this area. It is important to recollect that the veins in the medullary cavity possess no valves, although it would appear that those just outside the cavity possess more than the number usual in other vessels of the same size elsewhere. The anatomy of the vessels and lymphatics of the marrow was described in some detail by Schwalbe.<sup>4</sup>

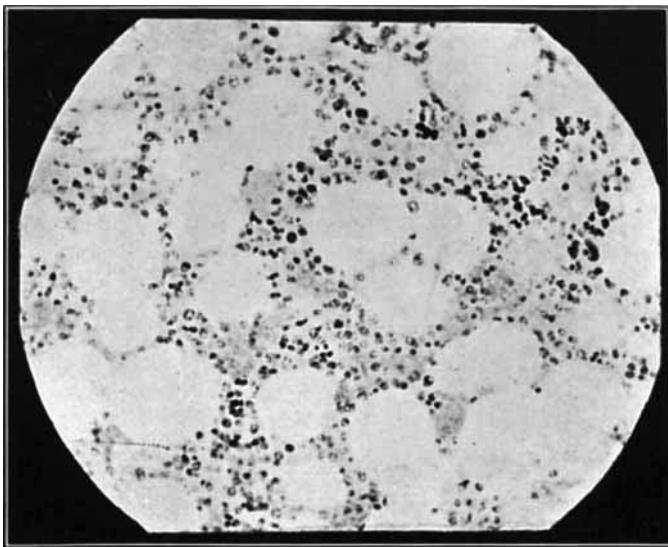


FIG. 176.—The pale areas in this figure represent the blood channels of the marrow: the white areas correspond to fat, while the dark elements are the marrow cells. This section was obtained from the marrow of the femur of a man, age 49. The extreme vascularity and the complicated arrangement of the course of the blood channels is well seen. ( $\times 100$ .)

### IV. LYMPHATIC CHANNELS IN THE BONE-MARROW.

It has been frequently stated that the bone-marrow contains no lymphatic channels, but I have been unable to find any reference to experiments relating to this matter. Ziegler<sup>5</sup> and Roger and Josué<sup>6</sup> state that there are no lymphatics in the marrow, but give no reasons for making this statement. The extremely careful work of Sampson Handley on the subject of lymphatic permeation has made it imperative to attempt to settle the matter. Dewey and Noyes<sup>7</sup> have used a very fine technique for the demonstration of lymphatic channels in teeth, and I have made use of this with slight modifications to make it applicable to such large objects as bones. The material used for injection was Prussian blue ground up with ether and turpentine in a mortar. I have found that it is possible to inject the lymphatic channels in the periosteum with comparatively little difficulty: the injection material passes from these channels into the bone and from it

into the endosteum, but I have been quite unable to find any evidence of a connection between these periosteal-endoosteal lymphatics and the marrow tissue. If an injection is made with the modified Dewey-Noyes cannula directly into the marrow tissue by screwing the cannula into the compact bone, the injection material passes into definite channels in the marrow tissue. The difficulty of regarding these as lymphatic channels was the fact that the injection material emerged from the veins at the large foramina.

The next step in the investigation of these channels was an attempt at a double injection, i.e., of both blood-vessels and lymphatics in the same specimen. The method adopted was as follows: The blood-vessels were injected with a carmine-gelatin mass, and when this mass had been completely solidified by cooling in iced water, an attempt was made to inject lymphatic channels through the Dewey-Noyes cannula. Even if considerable force was employed in the attempt to fill lymphatic channels, the Prussian-blue-ether-turpentine mixture could not be made to move along the marrow tissue. The necessary conclusion was that the channels, which were filled with the blue suspension in the previous experiment, were only blood-vessels. It appeared possible that a few lymphatics might enter the long bones along the tendons of attachment of the great muscles, but no communications could be detected between their fascial lymphatics and the marrow tissue.

In conclusion, the only statement possible at the present time is that modern methods of injection do not demonstrate the existence of any structures in the bone-marrow which resemble lymphatics in structure or distribution. The writer well realizes that negative evidence of this character is not necessarily of value, but the absence of lymphatic channels from the marrow is only a minor portion of the evidence upon which the present paper rests.

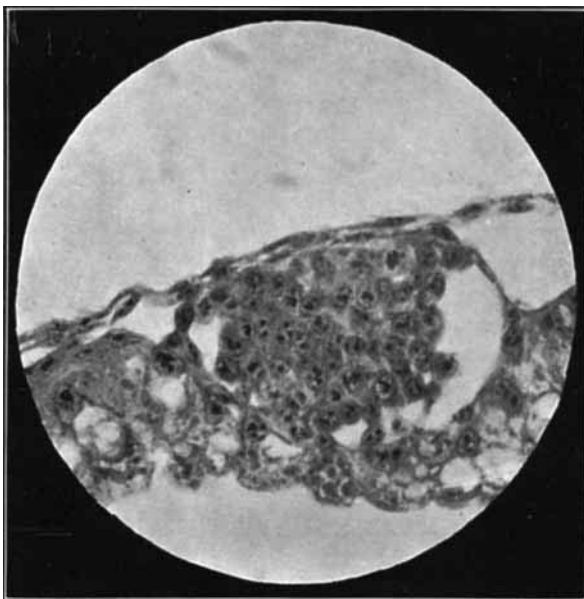


FIG. 177.—This figure shows one blood island from the wall of the yolk-sac of the embryonic canary. The clear portion in the upper part of the photograph represents the extra-embryonic cavity. The circumscribed cellular mass is the blood island which is surrounded by the primitive endothelium of the vessel, while the red cells are in process of differentiation in the interior. The cells around the blood island belong to the yolk-sac. ( $\times 150$ .)

#### V. DEVELOPMENT OF THE BLOOD-FORMING TISSUES.

For the purposes of the present discussion there is little advantage in giving the well-known details of the development of the blood in the embryo, but although no thorough consideration is necessary, it is essential to refer to a few of the finer details of the histogenesis of the blood-cells.

There appears to be little doubt that Weidenreich<sup>8</sup> was perfectly correct in his contention that the white cells of the blood are not primarily true blood-cells, but are really specialized developments of the primitive amœbo-cytes, that is, cells formed in the primitive body cavity and only secondarily invariable components of the blood picture. When the development of the erythrocytes is considered, a very different

arrangement is obvious. *Figs. 177 and 178* show blood islands on the wall of the yolk-sac of the canary embryo and the human embryo respectively. It will be noted that the development of the red cells is an entirely intravascular process. Dantschakoff<sup>9</sup> and

other observers have noted that the process of erythropoiesis in birds is purely intravascular, while leucopoiesis is extravascular.

The reason for this peculiar arrangement will be obvious from the description of the different mode of the origin of these two types of cells. The conception of two types of hæmatopoiesis does not involve the conception of two ancestral cells for the two types of blood-cells; the lining cells of the marrow produce red cells on the side towards the lumen, while white cells are produced on the other side. In this way an explanation of the ordinary hyperplasia of the red marrow is available: under no conditions does one find a spread of the leucoblastic tissue without a contemporaneous spread of the erythroblastic: the converse is also true. Similarly, no injury to one process can leave the other completely intact. The present writer has dealt with this subject more fully in a paper read to the Pathological Society, in July, 1922, with W. T. Hillier.

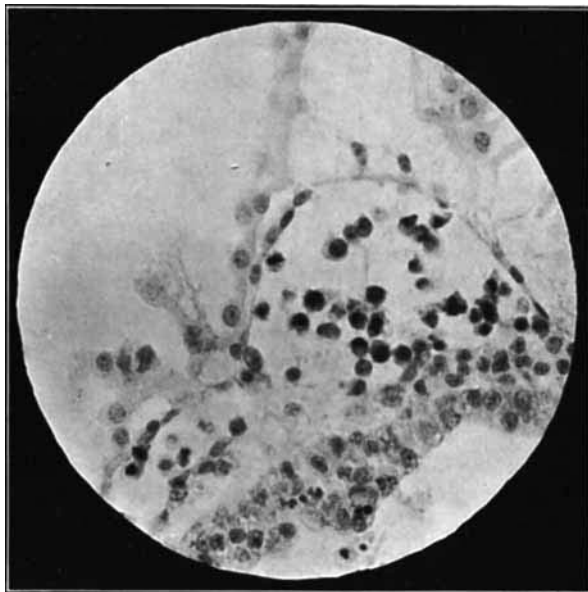


FIG. 173.—This figure shows similar appearances to those depicted in the previous one, but this specimen was obtained from a human embryo. ( $\times 150$ .)

#### VI. THE CHARACTERS OF THE BLOOD PICTURE IN CASES OF CARCINOSIS OF THE BONE-MARROW.

The realization of the hæmatopoietic function of the adult bone-marrow was soon followed by a partial comprehension of the grave alterations in the character of the blood picture which were observed to follow the presence of metastases in the marrow. The blood picture in such cases was found to resemble that of 'pernicious anæmia' in many particulars, and in fact the first description of such a case by Ehrlich<sup>10</sup> was that of pernicious anæmia with incidental formation of a sarcoma.

The literature of hæmatology now contains details of many cases of this description, and it would appear that the alterations in the blood picture are independent of the site of the primary growth, and are only related to the presence of metastases in the marrow. Alterations of this 'pseudo-pernicious' type have been described in cases where the primary growth was in the stomach by Schleip,<sup>11</sup> Parmentier and Chabrol,<sup>12</sup> Harrington and Teacher,<sup>13</sup> and Harrington and Kennedy;<sup>14</sup> in cases of cancer of the breast by Epstein,<sup>15</sup> Houston<sup>16</sup>; and a case reported by G. R. Ward<sup>17</sup> was almost certainly of the same character, although no confirmation was possible, as an autopsy was not permitted. Grawitz<sup>18</sup> reported a case of this type in which the primary growth appears to have been in the suprarenal gland; Reichmann<sup>19</sup> described a case with similar alterations in the blood picture and a primary growth in the œsophagus; Schleip<sup>11</sup> gives details of such a case where the primary tumour was a colloid cancer of the appendix, and also reported another where the primary focus was in the jaw. There are doubtless other cases recorded in the literature, but I think that sufficient evidence has been presented to make it clear that there is no close relation between the site of the primary tumour and the character of the blood change.

It must be borne in mind that almost every case of cancer shows a definite degree of anæmia, but this is not of a specific character. Although the ordinary anæmia of cancer is not dependent upon the presence of metastases in the bone-marrow, it is dependent upon changes in that organ. The chronic anæmia of protracted cases of cancer leads to an increase in the amount of red cellular marrow in the bones.

It would appear from the work of McMaster and his collaborators<sup>20</sup> that hæmoglobin or one of its decomposition products is the essential stimulus to increased hæmatopoiesis after destruction of red corpuscles in the body. The cases of cancer in which the liver does not give a 'free iron' reaction are very rare, and are always those in which there is little or no increase in the amount of red marrow in the bones.

This increase in the amount of the red marrow is of great importance in connection with the present subject, as I propose to demonstrate that the red marrow is the site of deposition of cancer in bones. A brief description of the alterations in the character of the blood picture in these cases is necessary, because they are not usually quite easy to interpret, and also because some recent writers appear to be unaware of them, and thus are led to publish misleading interpretations of a blood picture. In a recent controversy arising out of a paper by Izod Bennett and Dodds<sup>21</sup> on the nature of the achlorhydria of pernicious anæmia, there has been an example of this misinterpretation. Dr. A. E. Hurst<sup>22</sup> suggested that the development of 'pernicious anæmia' in four cases of carcinoma of the stomach after total gastrectomy was evidence of the primary character of the achlorhydria of pernicious anæmia. Unfortunately, no detailed account of the blood picture was published, and therefore no definite statements can be made, but when one notes the great similarity between the condition of the blood in cases of carcinosis of the marrow and in pernicious anæmia, one would be chary of accepting the evidence of the true 'pernicious' character of these cases.

In this section I shall consider some of the cases of this type which have been published during the last fifteen years. One of the most carefully described cases with which I am acquainted is that published by Harrington and Teacher.<sup>13</sup> The patient was a woman, age 64, who suffered from vague pains in different parts of the body; the most noticeable abnormality which was detected was a very definite anæmia; melæna was frequent. The authors report several blood-counts, of which the following is a typical example :—

Red corpuscles .. ..	1,600,000 per c.mm.
Hæmoglobin .. ..	35 per cent.
Colour index .. ..	1·09
Leucocytes .. ..	14,000 per c.mm.

A differential count of the leucocytes gave the following result :—

Neutrophil polymorphonuclear cells ..	63·00 per cent.
Eosinophil .. ..	0·70 "
Basophil .. ..	0·00 "
Lymphocytes .. ..	16·70 "
Large mononuclears and transitionals ..	18·80 "
Myelocytes .. ..	0·80 "

In counting 500 leucocytes they noted 29 megaloblasts and 4 normoblasts. The authors state that myeloblasts were present, but no figures are given.

Three weeks later the most marked change in the blood picture was a rise in the number of myelocytes up to 6 per cent of the total number of leucocytes. Polychromatophilia and punctate basophilia were well shown, but there was only slight poikilocytosis, while megalocytosis was very marked.

In this case the autopsy showed that they had been dealing with a case of scirrhus cancer of the stomach with numerous metastases in the ribs, vertebræ and femur.

Harrington and Kennedy<sup>14</sup> reported a similar case in which the total number of leucocytes per cubic millimetre was 10,000 and the primary tumour was in the stomach. The leucocytes were present in proportions somewhat similar to those in the first case; thus there were 2 per cent of myeloblasts, while the myelocytes formed 0·5 per cent of the total number of leucocytes. The colour index was above 1.

Parmentier and Chabrol<sup>12</sup> reported a similar case in which the primary tumour was also in the stomach. Only one blood-count was performed just before death, and, although there was a very definite anæmia with a high colour index, there were only 3500 leucocytes per cubic millimetre.

Schleip<sup>11</sup> has reported blood changes of this type in three cases, in which the primary tumours were in the stomach, appendix, and jaw respectively.

Houston's case<sup>16</sup> of carcinoma of the breast with metastases in the bones showed a colour index of 1.28.

Reichmann's case of carcinoma of the œsophagus<sup>19</sup> showed a colour index of only 0.66, but the blood picture was of the same character in other respects.

No good purpose would be served by referring in detail to the large number of other cases which can be found in the literature. It may perhaps be serviceable to give a summary of the changes of the constitution of the blood picture which can be regarded as sufficiently characteristic for the diagnosis of carcinosis of the bone-marrow to be made during life.

#### CARCINOSIS OF THE MARROW.

1. Reduction in the number of red corpuscles.
2. High colour index, not always above 1.
3. Slight leucocytosis.
4. Leucocytosis due to increase of neutrophil polymorphs.
5. Anisocytosis, etc., well marked.
6. Nucleated red corpuscles present, both normoblasts and megaloblasts.
7. Myelocytes and myeloblasts present.

#### 'PERNICIOUS ANÆMIA'.

1. Similar reduction.
2. Colour index usually above 1.
3. Usually slight leucopenia.
4. Relative lymphocytosis.
5. Similar appearances.
6. Always present, but vary in number at different times.
7. Myelocytes are not uncommon, myeloblasts are rare.

It will be obvious that the essential feature of the blood picture in these cases of carcinosis of the bone-marrow is the evidence of a grave disturbance of the erythropoietic organs while, in addition, there appears to be some interference of a stimulating nature acting on the leucopoietic mechanism.

At this point it might be instructive to refer to a different type of case which I had an opportunity of examining both before and after death.

The patient was a man, age 40, with well-developed Hodgkin's disease. Examination of his blood revealed the following surprising picture :—

Red corpuscles	..	4,650,000 per c.mm.
Hæmoglobin	..	90 per cent
Leucocytes	..	45,000 per c.mm.

A differential count of the leucocytes revealed the following proportions :—

Neutrophil polymorphonuclear cells	75 per cent
Neutrophil myelocytes .. ..	4 "
Myeloblasts .. ..	15 "
Lymphocytes .. ..	6 "

A second count a week later showed little change in the blood picture. In this case the blood shows no evidence of any interference in the process of erythropoiesis, but there is evidently much alteration in the mechanism of leucopoiesis.

I am able to find only two cases of secondary carcinosis of the marrow in the literature in which the blood picture was of this extraordinary character. The first case was that of Dieballa and Entz,<sup>23</sup> in which the leucocytes reached the surprising number of 112,600 per c.mm., and it is stated that there was no myeloid metaplasia in the liver and spleen. The second case was that of Bizarri,<sup>24</sup> in which there appears to have been a definite leukæmia of the myelogenous type with the well-known anatomical changes in the liver and spleen, in addition to a cancer of the stomach. The second case is of little importance in the present discussion, but the first presents some difficulty. Dieballa and Entz stated that both the liver and the spleen were enormously enlarged in their case,

and, as they offer no explanation of this phenomenon, it seems fair to leave their case out of consideration, and it has only been included in order to give completeness to the account of the varieties of blood change which have been known to be associated with cancer in bone-marrow.

Blood changes of the 'pseudo-pernicious' type have aroused considerable interest, mainly from the point of view of diagnosis, but it appears to me that there is another and wider interest, as affording evidence of the mode of spread of cancer into the medulla of bones. In the section which deals with the development of the blood-forming tissues, I have pointed out that erythropoiesis is an intravascular process, while leucopoiesis is extravascular. If the very equivocal case of Dieballe and Entz be disregarded, it will be noted that the essential change in the blood picture in cases of carcinosis of the marrow is a grave disorder of the distribution and appearances of the red corpuscles in the circulation, while the leucocytes show a far less intense degree of change.

It is usually admitted that lymphadenoma (Hodgkin's disease) is of the nature of a chronic granulomatosis rather than neoplastic in character. The mode of infection is quite unknown, and even the means by which deposits in foci distant from the primary granuloma develop is uncertain. There is no evidence pointing to a transfer of cells in these cases from one organ to another. Occasionally it is possible to see the lymphadenomatous process invading the walls of veins, but there is no evidence that cells capable of growth elsewhere are disseminated in this manner. Although the unknown virus of this disease may be carried in the blood-stream, there are no histological appearances which would lead one to suppose that the granulomatous tissue develops primarily in the blood-vessels. As all the evidence shows that lymphadenoma is an extravascular process, it is not surprising that deposits of this granuloma in the bone-marrow lead to alterations

in the distribution of the circulating leucocytes. The case which is partly described above showed large masses of lymphadenomatous tissue in the marrow of many of the bones, and these were regarded as the cause of the strange blood picture which had been noted during life.

This case is, therefore, an example of the effect of an extra-vascular lesion in the bone-marrow. It would appear perfectly justifiable to presume that the changes in the number and distribution of the red corpuscles in cases of carcinosis of the marrow are due to intravascular lesion.

At this point it must be admitted that cases of carcinosis of the marrow are on record in which there was no pseudo-pernicious blood picture. Middleton<sup>25</sup> has published such a case, where the primary growth was in the stomach. He remarked on the absence of reaction in the marrow

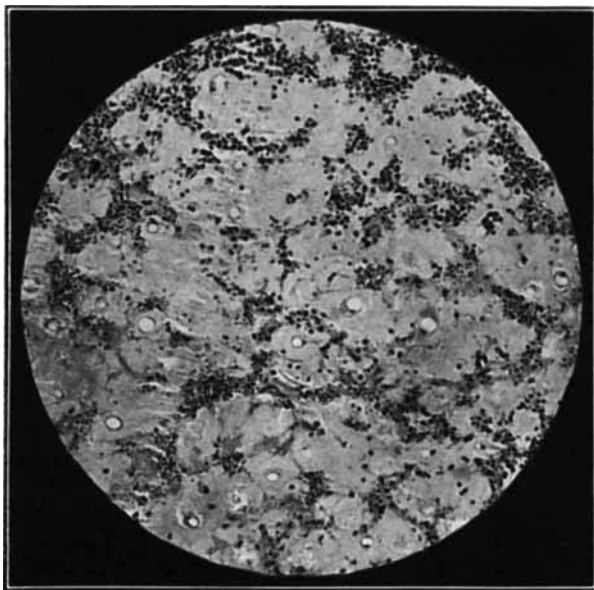


FIG. 179.—Case 4. This shows the appearance of advanced gelatinous degeneration of the marrow. It will be noted that in the degenerated areas there are no marrow cells, and a lack of evidence of marrow reaction in a case of this description is not surprising. ( $\times 100$ .)

tissue. Even if one cannot admit the existence of idiopathic cases of marrow aplasia in these malignant conditions, it is possible to conjecture as to the cause of the absence of the peculiar blood conditions. Fig. 179 shows a portion of bone-marrow from a case



of carcinosis of the marrow (*Case 4*) in which no blood changes other than those of simple anæmia were detected during life. The photograph shows a very advanced stage of 'gelatinous' degeneration of the marrow. It would be surprising if so degenerate a tissue could show much sign of reaction to any form of lesion. If metastases of cancer settled in the bone-marrow at an early stage of the life-history of the primary growth, one would not expect that blood changes would be very well marked, because of the absence of hyperplasia, due to lack of previous anæmia.

A third cause of the absence of pseudo-pernicious changes would be great extension of the cancerous process, and extreme destruction of the marrow tissue. G. R. Ward<sup>17</sup> made an interesting and important observation which bears a relation to this portion of my argument: in a case of aneurysm of the aorta, which was pressing upon and eroding the vertebræ, the blood was found to present no deviation from normal. It appears certain that the effect of deposits of cancer in the bone-marrow is specific, and there are apparently insuperable difficulties about any explanation of the blood changes if the conception of an intravascular trauma is not accepted.

In all the cases in which pseudo-pernicious blood changes have been recorded in the literature, there has been a remark on the extremely dense fibrous character of the primary growth, i.e., these have been cases in which the disease has been present for a sufficiently long time to permit hyperplasia of the marrow to have taken place.

#### VII. THE MODE OF SPREAD OF CARCINOMA INTO MARROW.

It is not the purpose of this paper to deal with those cancers of bone which are due to extension from a primary growth directly into the neighbouring bones; only such tumours as are ordinarily regarded as metastatic will be considered.

The old conception of a 'cancerous diathesis' is not discussed in detail: the only modes of spread which fall to be considered are dissemination by the blood-stream and permeation of the lymphatics. Before dealing with the literature of the subject, I will give a brief account of the cases which I have had an opportunity of examining.

*Case 1.*—This patient was a woman, age 55, who was admitted to hospital with an ulcerated and discharging nipple. She stated that the condition was of two years' duration.

On examination, the left nipple was found to have been destroyed by ulceration, and a few hard glands could be palpated in the left axilla. The left breast was amputated and the axilla was cleared. Two months later the patient, who appeared to be well, was sent to a convalescent home, where she died within a month. The autopsy was performed on May 25, 1920, about twenty-four hours after death, and an abstract of the notes is given here.

The body was that of a stout woman showing early signs of wasting. There was a number of minute tumours on the pleuræ, but the lungs appeared to be free from invasion. The liver, which weighed 2700 grm., was extensively invaded by metastatic deposits which appeared to bear a close relationship to the

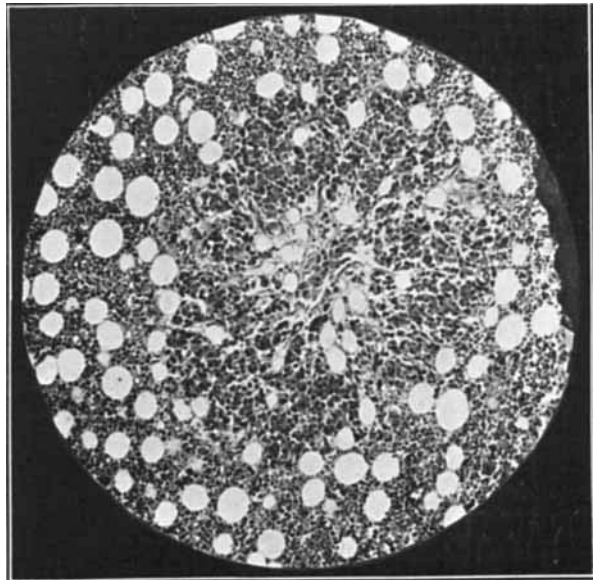


FIG. 180.—*Case 1.* This figure shows the appearance of one of the smaller masses of metastatic tumour in the marrow of the femur. The fungus-like mass of cells lies in the midst of hyperplastic cellular marrow, and, in the centre of the mass, the cells are seen to be arranged in a straight line. ( $\times 100$ .)

portal tracts. A few retroperitoneal glands showed signs

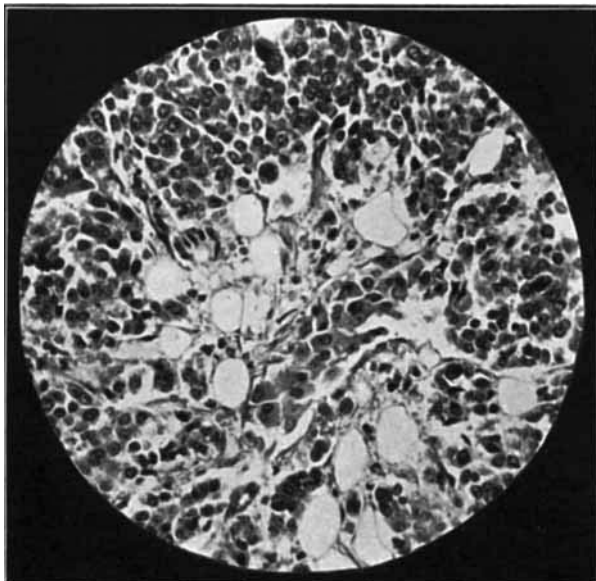


FIG. 181.—*Case 1.* This figure shows the central portion of the small tumour which is seen in the previous illustration. The row of cells in the centre is seen to be lying in a definite channel, which is lined by endothelium. It will be noted that in neither of these figures is there any appearance of blood channels other than the one containing the cancer cells. ( $\times 200$ .)

fungi in the surrounding hyperplastic marrow tissue (*Fig. 180*). With higher magnification it was possible to see quite clearly that the tumour cells in the centre of such a mass lay in a definite channel, which was lined by endothelium, and there was no reason for supposing that this was not a blood-vessel (*Fig. 181*).

I have to thank Mr. Seymour Barling for permission to refer to the above case, which was under his charge.

*Case 2.*—The patient was a man, age 46, who was diagnosed on clinical evidence as suffering from carcinoma of a bronchus with secondary deposits in the liver.

The autopsy revealed the presence of a white mass of tumour at the root of the left lung; this invaded the lung tissue and appeared to arise from a bronchus. There were many metastases in the liver, which weighed 2500 grm. Both suprarenal glands were invaded by nodular tumour growth. The sixth rib on the left side was invaded by tumour which had perforated the periosteum on the pleural aspect, but had not invaded the pleura. The right femur

of early invasion. The ribs were extensively invaded by nodules of tumour, which, in places, filled the whole medullary cavity, but did not penetrate the bone, and the periosteum was not affected. The vertebrae were extensively invaded, and the metastases had produced softening in the affected bones.

The right femur was cut longitudinally and the cut section appeared red almost down to the lower end, but in this red tissue there were about a dozen white areas; the largest of these white areas were in the upper third of the medullary cavity, while the smallest were in the lowest part of the red tissue. The upper epiphysis contained red tissue and also tumour nodules, but the lower epiphysis was mainly fatty and was free from tumours. The bony trabeculae were almost indetectable in the red tissue of the shaft.

On microscopical examination, the primary growth was found to be a scirrhous carcinoma, and the deposits in the liver were of a similar character, although many of the nodules showed marked necrotic change. The metastases in the bones were of a more cellular character than the primary growth, and, in the case of the smaller growths, resembled small radiating

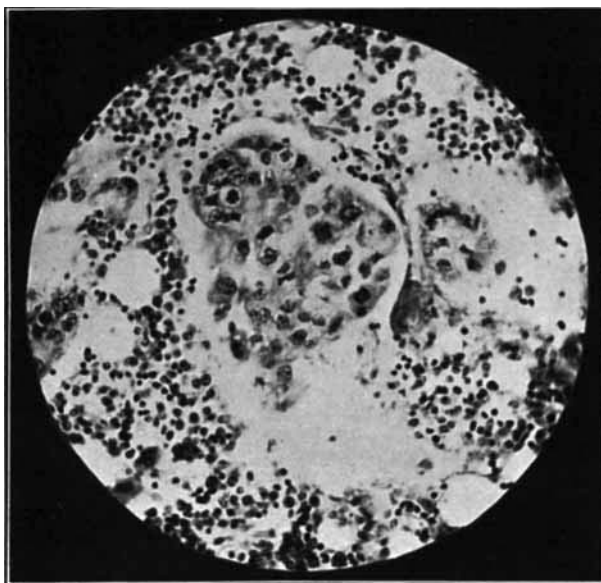


FIG. 182.—*Case 2.* This figure shows a single mass of metastatic tumour in the marrow of the humerus. The circumscribed mass is seen to lie in a definite channel, and no blood-vessels are seen in the neighbourhood. ( $\times 100$ .)

The right femur

showed a small mass of tumour tissue in the periosteum at the junction of the upper third with the lower two-thirds of the bone; a needle could be pushed into this nodule for a distance of about an inch. On cutting the bone longitudinally, this small mass in the periosteum was found to correspond to a large white area of metastatic deposit in the medullary cavity. The red marrow had extended about half-way down the medullary cavity, but no other metastases were found in it. The left humerus, on section, showed the presence of a white nodule at the junction of the upper third with the lower two-thirds of the bone, but no invasion of the periosteum could be found.

On microscopical examination, the bronchial tumour was found to be a cellular carcinoma of glandular type. The nodules in the bones were of similar structure, and it was easy to find plugs of tumour cells lying in channels, which were lined by endothelium. The periosteal mass at the upper end of the femur did not show any signs of intravascular arrangement and was continuous with the tumour in the medullary cavity through the eroded compact bone. The appearances of the metastatic deposits in the humerus can be seen in *Fig. 182*.

I have to thank Professor J. W. Russell for permission to refer to this case, which was under his charge.

*Case 3.*—The patient was a man, age 55, admitted to hospital with an acute abdominal catastrophe. At operation a perforation of a stercoral ulcer in the cæcum was found.

The autopsy showed that death was due to general peritonitis following perforation of a stercoral ulcer in the cæcum in a man suffering from carcinoma recti.

No metastases could be found in any of the organs, including the bones. The only long bone which was examined was the right femur, and in this the red marrow was found to occupy the upper third of the medullary cavity, the remainder of that space being filled with fat.

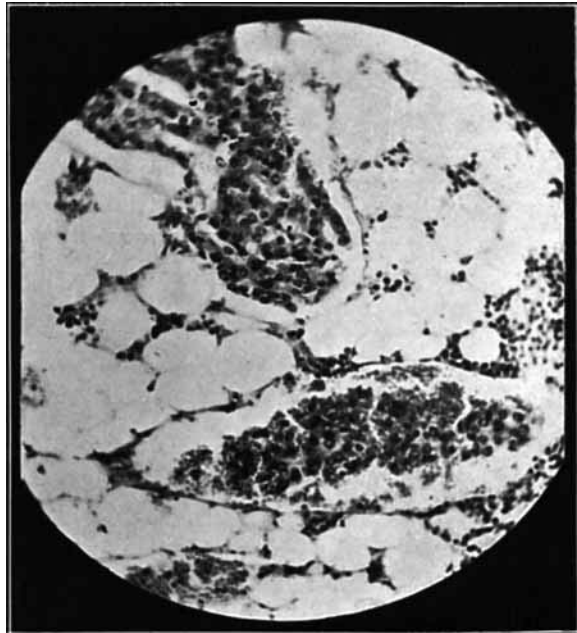
On microscopical examination, the primary tumour in the rectum was found to be an adenocarcinoma. Sections from the red marrow at the upper end of the right femur showed the presence of emboli consisting of tumour cells in the blood-vessels. The tumour cells lay in vessels which had a definite endothelial lining and contained red blood-corpuscles in a good state of preservation (*Figs. 183 and 184*).

I have to thank Mr. J. B. Leather for permission to refer to this case, which was under his charge.

*Case 4.*—The patient was a woman, age 23, who had enjoyed good health until about six weeks before her death, when she noticed pain in the lower part of the back and the development of lumps in the neck. The blood was only examined on one occasion about four days before death and no marked deviation from the normal condition could be detected other than a slight decrease in the number of red corpuscles, which were calculated at 4,000,000 per cubic millimetre.

The post-mortem examination showed the presence of a tumour in the right lung. The upper lobe of this lung was white in colour and firm in consistence, being completely converted into tumour, which invaded a bronchus. The lower lobes contained only a few discrete masses of tumour. Metastases were found in the bronchial glands, left suprarenal gland, and left ovary. There were thread-like lymphatics all over the surface of the heart, and these were found to be filled with tumour cells.

The bones were examined as far as was possible and extensive invasion was found. All the segments of the vertebral column were invaded in varying degrees, as were also most of the ribs. The sixth rib on the right side was almost fractured by growth, but, on the inner aspect, the



*FIG. 183.*—*Case 3.* Shows the intravascular arrangement of the cancer cells in the marrow. In the vessel in the lower part of the field there are epithelial cells in the middle of the lumen, while the periphery is occupied by red blood-corpuscles. It will be noticed that there is practically no appearance of reaction on the part of the marrow tissue, and this is compatible with the fact that these metastases were of extremely early date in the history of this case. ( $\times 100$ .)

compact bone still remained and separated the growth from the pleural periosteum. The tumour in this rib lay about one inch behind the costochondral junction.

The left clavicle showed a condition of almost complete fracture, but the posterior lamella of compact bone was not completely eroded. There were tumours in both humeri: in each case these were situated at the junction of the upper third with the lower two-thirds of the bone—the position of the red marrow normally present at this place in the adult. The red marrow in this case occupied an area which was no larger than that normal in persons of this age. The compact bone surrounding the medullary cavity was not eroded. In the head of the right humerus there was a nodule of tumour lying in the cancellous bone.

On transverse section of a bone at a point corresponding to a metastasis, it could be seen that the tumour mass lay completely in the marrow and did not invade the compact bone, although it lay in contact with it at the inner side of the cavity. The right femur was examined and showed a tumour lying in the red marrow at the upper part of the medullary cavity. No tumours could be found in the medullary cavity or epiphyses of the right tibia, which contained fatty tissue and no appreciable amount of cellular marrow. A nodule of cancer was present in the substance of the musculus tibialis anticus, and this was in contact with the tibia.

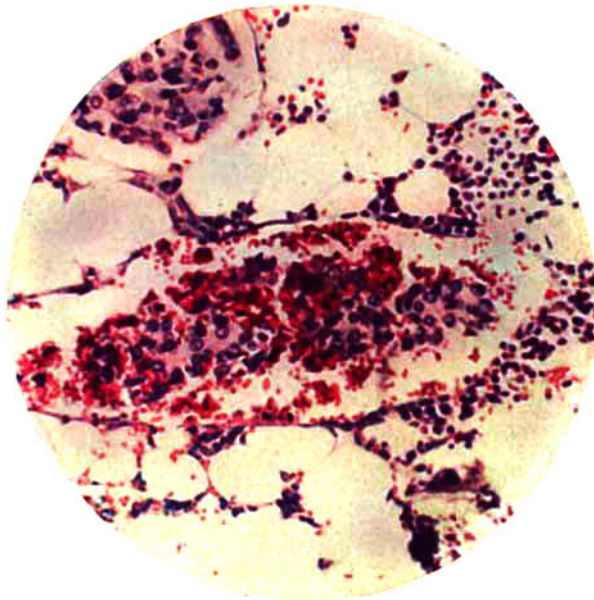


FIG. 181.—Case 3.

On microscopical examination, the primary tumour in the lung was found to be a carcinoma, apparently derived from the epithelium of the alveoli, and the metastases in other organs showed very great similarity in structure; this similarity was most marked in the case of deposits in the vertebral column (*Fig. 185*). The metastases in the long bones showed an alveolar arrangement, but this was not quite so similar to the primary tumour as were the deposits in the vertebral column. The nodules in this case were more advanced than those in the previous cases, and it was not easy to find a plug of cells lying in a vessel; but ultimately a mass of cells was found lying in a definite channel, which was lined by endothelium (*Figs. 186 and 187*).

The marrow tissue in this case was scarcely hyperplastic, but there was definite 'gelatinous degeneration' visible in some places (*Fig. 179*). This case illustrates the point that metastases in bone lie in the red cellular marrow and do not extend into the fat. There is no evidence in this case that the metastases had extended into the medullary cavity from the periosteum. The nodule which lay in the musculus tibialis anticus was only adherent to the tibial periosteum, and no sign of invasion of the periosteal lymphatics could be found on microscopical examination. The tumour in the sixth rib shows the preference of metastatic deposits for the place at which fatty marrow passes over into the red cellular marrow.

I have to thank Professor J. W. Russell for permission to refer to this case, which was under his charge.

These four cases are quite illustrative of the morbid anatomical features of carcinosis of the bone-marrow. The main points worthy of attention are :—

1. The position of the cancer cells in channels which are lined by endothelium.

2. The escape of the distal bones of the limbs.

3. The absence of evidence of permeation of fascial lymphatics in the neighbourhood of the invaded bones.

4. The position of the metastases, which is always in the red cellular marrow.

5. The points of emergence of the tumour on the surface of the bones correspond to the places of exit of the veins.

#### LITERATURE AND DISCUSSION.

F. von Recklinghausen<sup>26</sup> was the great exponent of the theory of the spread of metastases by the blood-stream into the marrow. His main contentions in favour of this conception were as follows :—

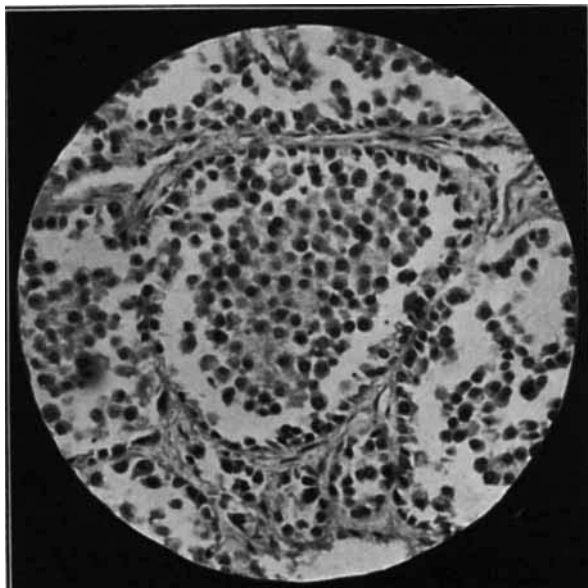


FIG. 185.—Case 4. Shows a portion of one of the many metastases in the vertebral column. The close resemblance of this secondary deposit to lung tissue is well seen. The masses in the vertebræ were so advanced as to make it impossible to discover any arrangement in vessels. ( $\times 100$ .)

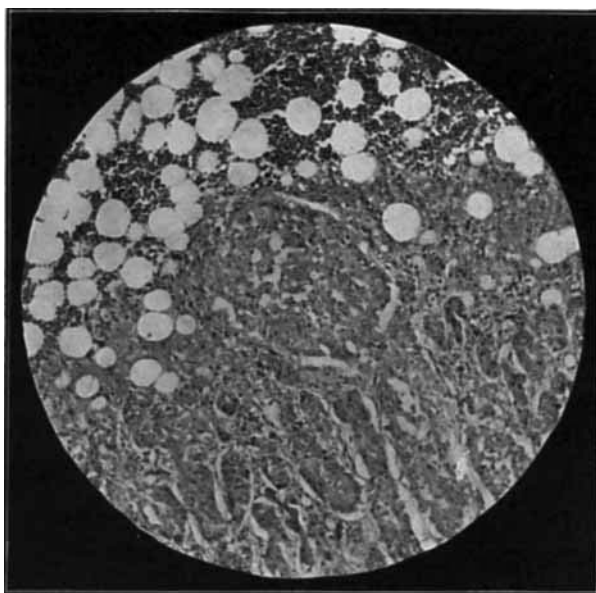


FIG. 186.—Case 4. The upper portion of the figure shows rather hyperplastic marrow tissue, while the lower two-thirds shows invasion by cancer. It will be noted that a mass of epithelial cells lies in a definite channel at the junction of the marrow tissue with the tumour mass. ( $\times 100$ .)

1. Metastases in bones occur in the interior of the medullary cavity, and only reach the periosteum by extension from this place.

2. The masses in the subperiosteal tissue are always in the region of the large foramina which serve for the outward passage of the veins.

3. The cancer cells in the marrow lie in definite channels which are arranged in a manner similar to that of the veins normally present in the marrow. He believed that these canals were blood channels for two reasons : (a) Because no lymphatics were known to exist in the marrow, and (b) because no other blood channels than the invaded ones could be found in the affected areas. He admits that he was unable to discover any place in which such a channel contained both cancer cells and red blood-corpuscles.

In the marrow of one of his cases Assmann<sup>27</sup> was able to find a capillary which was blocked by cancer cells, while another branch of the same vessel was quite free from invasion and only contained red blood-corpuscles.

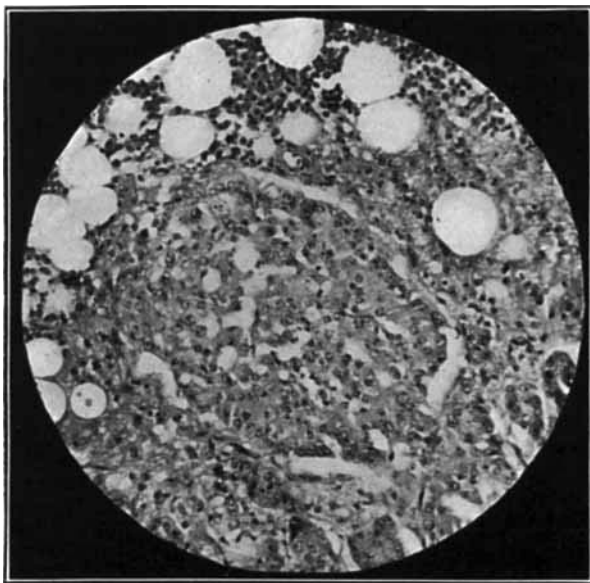


FIG. 187.—Case 4. Shows the arrangement inside the channel which is seen in the previous photograph. An appearance of degeneration can be seen in the marrow tissue at the edge of the tumour mass. ( $\times 200$ .)

Erbslöh<sup>28</sup> was able to observe masses of epithelial cells in vessels, which still contained red corpuscles, in a case of carcinosis of the marrow secondary to carcinoma of the bile passages.

Goetsch<sup>29</sup> was inclined to believe that the subperiosteal nodules which occurred in some of his cases were earlier than those in the medullary cavity; but microscopical examination showed that the tumour in the marrow had undergone a greater degree of degeneration than had that in the periosteum, and was, therefore, probably the older. He was also able to observe that the cancer cells in the marrow lay in channels which occasionally were seen to contain red corpuscles.

It will be seen that the conception of dissemination by the blood-stream has appeared to

many observers to be the almost certain explanation of the metastases in the bone-marrow; nevertheless, there is a school which holds that the invasion of bones is by means of lymphatic permeation. Sampson Handley, to whom the science of morbid anatomy owes its revival, is the great champion of the conception of lymphatic permeation as applied to the metastases in bones. His classical work on 'Cancer of the Breast'<sup>30</sup> has been the source from which I have obtained the details of the theory, which has done so much to advance the art of surgery in relation to the mammary gland; but, as far as it is applied to the invasion of bones, I am unable to accept it.

Many of Handley's statements are based on the most careful observation and are, therefore, quite immune from criticism; but the interpretations are liable to alteration. As far as I can gather the arguments from his work, they are as follows:—

1. The freedom of the distal bones of the limbs from invasion by secondary cancer is regarded as incompatible with the conception of embolic spread, because these bones would be quite as liable to embolism as any others.

2. The liability of a bone to cancerous metastasis is said to increase with its proximity to the primary growth.

3. The femur is said to be invaded at the base of the great trochanter, but fracture usually occurs somewhat lower down on account of the thinner compact bone; invasion and fracture of the humerus are said to occur about the middle of the bone.

4. He disposes of the argument that deposits bear a close relation to the direction of the nutrient artery by pointing out that, in the humerus, the deposits are above the point of entrance of the nutrient vessel, which is directed distally.

5. If the bones are invaded from the lymphatic plexus of the deep fascia, the point of attack should be the part of the bone which lies nearest to the cutaneous surface, and this, he says, is the case.

6. The escape of the distal bones is simply due to the fact that the patient usually

dies before the process of lymphatic permeation has proceeded sufficiently far to invade the deep fascia of the distal parts of the limbs.

7. As additional evidence of the conclusion that bone metastases are associated with lymphatic permeation, he points out that the areas liable to cutaneous nodules and to bone metastases are similar in extent. He has demonstrated that cutaneous nodules are certainly due to permeation of fascial lymphatics.

In a footnote he says, "I do not deny that in rare cases bone deposits may be the result of arterial or capillary embolism".

It has seemed to me that the most satisfactory mode of criticism would be the consideration of each of these headings separately, so that a final summary of the evidence in favour of the theory of cancerous embolism as an efficient cause of carcinosis of bones might be appended to this paper.

1. The apparent immunity of the distal bones of the limbs is explicable on definite anatomical grounds. It will be recalled that, in the section of this paper which deals with the anatomy of the adult bone-marrow, it has been pointed out that the red marrow persists only in the upper ends of the shafts of the proximal bones of the limbs. It was also pointed out that the blood-supply of this cellular marrow was extremely complicated, inasmuch as the definite channels in the fatty tissue break up into a vascular system which is not unlike an angioma in arrangement. It is obvious that this widening of the stream-bed must be associated with a very considerable decrease in the rate of the blood flow. Decrease of the rate of blood flow is always associated with 'pavementing' of the leucocytes, which are the solid bodies of the normal circulation. There appears to be no adequate reason for supposing that cancer cells would not be cast out to the periphery of the stream in a similar manner. In normal circumstances there is no evidence that leucocytes divide in the course of their journey in the main circulation, but in the red marrow they can often be seen lying in the periphery of the blood channels and showing evidence of division. These facts indicate that the stream at the periphery of the marrow vessels is slow, and that the development of cells in this situation would not be interfered with in a marked manner.

The process of embolism demands both the presence of insoluble particles in the circulation and also the possession of a suitable site of lodgement for such particles. The slowness of the circulation and the complication of the course of the marrow vessels appear quite adequate to supply the second factor.

All these points are a portion of the explanation of the fact that metastases in the bone-marrow invariably lie in the cellular marrow and never in the fatty tissue.

2. If there is a greater liability to invasion on the part of the bones nearest to the primary growth, it may be due to direct invasion of the arterial system in the region, but my own observations and my investigations of the literature have not shown that there is any such predisposition.

3. Handley states that the femur is invaded at the base of the great trochanter but that spontaneous fractures occur rather lower down on account of the thinner layer of compact bone. The site of invasion corresponds to the area of red marrow in the normal adult femur. He states that the humerus is invaded about the middle of the shaft and also breaks in this position: he gives no reason for ignoring the possibility of invasion rather higher up, with subsequent spread in the distal direction. My cases show that the first invasion is at the upper end of the diaphysis and that dissemination can occur both upwards and downwards. Metastases in the medullary cavity are always situated in the red marrow, and growth along the cavity is associated with an increase in amount of the red marrow which always precedes the deposition of the metastases.

4. The arguments of Handley efficiently dispose of the idea that the direction of the nutrient artery is of any importance in this connection.

5. The position of metastases at the periphery of the medullary cavity is explicable on the basis of the embolic theory, because of the lower level to which the cellular marrow reaches at the periphery: this is described in some detail in the section which deals with the anatomy of the organ.



6. The discussion of this contention was dealt with in paragraph 1 above.

7. The resemblance in extent between the areas liable to cutaneous nodules and those liable to metastases in the bones is surely a very weak support for Handley's contention. Many cases with cutaneous nodules in an advanced state of development show no signs of invasion of the bones, and most certainly not all cases of carcinosis of the bones are accompanied by cutaneous nodules.

There are several other points which merit attention. Thus, there may be difficulty in the explanation of the spread of cancer cells in the circulation from the venous side to the arterial side without involvement of the lungs. M. B. Schmidt<sup>31</sup> showed that small thrombi containing cancer cells were common in the capillaries of the lungs even in cases where there was no tumour in these organs on ordinary examination. Many of the epithelial cells in such thrombi appear to be destroyed; but he was able to observe that they might, on occasion, grow through the thrombus material; in this way cells may easily pass through the lesser circulation and be set free in the greater circulation and so pass to the bones.

If bones were invaded by permeation of lymphatic channels, it would be reasonable to suppose that examination of the periosteum would show evidence of invasion before the medulla contained any epithelial cells. In *Case 2*, where the periosteum of the femur was invaded, there was no evidence that the cells lay in any channels in this tissue, and in addition the periosteal tumour was in direct continuity with the cancerous mass in the medullary cavity. This bone is obviously one from which it is impossible to draw any definite conclusions, but the other bones in this case were found to contain tumour in the medullary cavity and not in the periosteum, and in their case it seemed impossible to conceive that invasion was from the periosteal lymphatics. In *Case 4*, the nodule which affected the periosteum of the tibia was a direct extension from the mass in the musculus tibialis anticus, and the lymphatic channels in the adjacent periosteum were unaffected.

In addition to the cases which I have had the opportunity of examining, there are many published cases which bear out my contention that the site of first settlement of metastases in bones is in the medullary cavity: in fact I have been unable to find any published cases, other than those of Sampson Handley, in which careful examination had led the author to any other conclusion.

#### VIII. THE EVIDENCES OF THE EMBOLIC ORIGIN OF METASTASES IN THE MARROW.

1. The absence of any histological or experimental evidence of the presence of lymphatic channels in the bone-marrow is an important argument in favour of the contention that carcinomatous metastases reach the bones by means of the blood-stream. It is admitted that the proof of a negative proposition of this kind is always an extremely uncertain basis of argument, but in the present case there are so many even more important evidences of the embolic theory that this one need not be unduly stressed.

2. The demonstration of plugs of epithelial cells in channels lined by endothelial cells and surrounded by red corpuscles in *Case 3* is evidence in favour of the embolic theory which is very difficult to confute. In other cases it has not been possible to demonstrate the intravascular position of the cancer cells with the same degree of certainty, but the presence of epithelial cells in passages lined by endothelium is regarded as weighty evidence that the position of the cancer cells is intravascular, although it has not been possible to show definitely that the passages are blood channels.

3. The objection to the embolic theory, which is based on the fact that the distal bones of the limbs are extremely rarely affected by secondary carcinoma, is dependent upon a deficient appreciation of the anatomy of the bone-marrow. The embolic theory demands, not only that the carcinoma cells should have access to the blood-stream, but that they should settle in a tissue and proliferate there. The settlement of an embolus demands the presence of certain anatomical factors, such as slowing of the blood-stream



and a complication in the course of the vessels. These desiderata are found in the red bone-marrow, although they are not present in the fatty marrow. The red bone-marrow is a place in which the stream-bed of the blood widens, the course of the vessels becomes more complicated, and the conditions for the lodgement of an embolus become correspondingly more favourable. Red marrow with its wide blood channels is absent from the distal bones of the limbs and also from the distal parts of the proximal bones, and therefore these places are unfit for the settlement of emboli.

4. The site of the earliest metastatic tumours of bones is in the medullary cavity, at the lower edge of the red marrow in the proximal bones of the limbs. Fracture does not occur until tumour tissue has spread along the shaft of the bone to a place where the compact bone is fairly thin. The spread of tumour tissue is preceded by a spread of red marrow. If there is hyperplasia of the red marrow in the bones, owing to previous anæmia, the first deposition of metastases will not necessarily be at the upper end of the medullary cavity, but may be at the lower part of the hyperplastic red marrow.

5. The slowing of the blood-stream in the red marrow operates in a very definite manner: it results in the solid elements of the blood being sent to the periphery of the stream. This is seen frequently enough in the phenomenon of 'pavementing' of the leucocytes in the process of inflammation. Epithelial cells are certainly solid elements when compared with red corpuscles, and would, therefore, pass to the periphery of the blood-vessels of the marrow and proliferate there, where there would be little interference with their further development.

6. The grave changes in the composition of the blood picture are only explicable on the basis of an intravascular trauma to the marrow, as extravascular injury would result in changes in the distribution of the white cells of the blood: this latter type of change is well seen in cases of lymphadenoma affecting the bone-marrow.

7. The route by which emboli reach the arterial stream is not certain in all cases, but the work of M. B. Schmidt has demonstrated the frequency with which the vessels of the lung contain thrombi consisting, in part, of epithelial cells derived from a primary carcinomatous growth. These cells may be destroyed in the vessels of the lungs, but some of them may grow through the thrombus material and so give rise to emboli which are capable of colonizing elsewhere. This process would perhaps account for recurrences of carcinoma many years after removal of the primary growth. This explanation of the occurrence of late metastases is at least as plausible as the theory of uninterrupted permeation of lymphatic channels for a period of years.

8. The lack of observations on the involvement of the deep fascia in some of the cases of metastatic involvement of bones is another piece of evidence against the theory of lymphatic permeation.

9. The points at which carcinomatous metastases reach the surface of an affected bone correspond to the foramina through which the veins emerge.

## IX. CONCLUSIONS.

The present investigation has led the writer to the conclusion that metastatic deposits in bones are due to arterial or capillary embolism. The main evidence which is brought forward is the detection of cancer cells in vascular channels in the bone-marrow. The vascular nature of these channels is demonstrated by the fact that they contain red corpuscles in addition to the epithelial cells. Evidence is also brought forward to show that the bone-marrow contains no lymphatic channels.

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