PHAGOCYTOSIS OF ERYTHROCYTES IN THE BONE MARROW, WITH SPECIAL REFERENCE TO PERNICIOUS ANEMIA *

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The processes which bring about the destruction of red blood corpuscles have been studied intensively in man and in the lower animals by physiologists and pathologists, but our information regarding them still remains extraordinarily incomplete. The situation is presented clearly in the excellent review of the literature on the subject by Rous,[1] who discusses the various methods of blood destruction in different species and under normal and pathological conditions. Such a survey indicates the urgent need for more clinical observations and more animal experimentation directed towards the solution of the problem.

Among the processes which have been considered to account for the destruction of erythrocytes, that of phagocytosis by fixed tissue cells or by wandering cells has long been recognized, but, in spite of the fact that it has been frequently described as occurring under normal and pathological circumstances, it has not usually been regarded as a factor of particular significance in blood destruction in man. The recent publications of Aschoff [2] and Lepehne,[3] however, on the phagocytic cells of the so-called "reticulo-endothelial system" of the liver, spleen, lymph glands, hemolymph glands, and bone marrow, and their rôle in the pathogenesis of certain types of hemolytic jaundice, make it apparent that phagocytosis may, at least occasionally, become the predominant element in blood destruction. When one considers the relative bulk of the spleen and liver in comparison to that of the normal active bone marrow it is not surprising that the attention of investigators has been directed chiefly to these larger organs and that the bone marrow has received little consideration as a possible site of blood destruction. There are, however, pathological conditions in which the fatty marrow of the long bones becomes replaced by a cellular tissue and the bone marrow becomes an organ of material size. This happens, for instance, in

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pernicious anemia, and the fact that the hyperplastic bone marrow may be the seat of a striking amount of phagocytosis of red blood corpuscles has led us to a consideration of the part played by the bone marrow in blood destruction in this disease.

The occurrence of phagocytosis of red corpuscles in the bone marrow in pernicious anemia has been recognized ever since the earliest observations on the histology of the disease. Cohnheim [4] mentioned it in 1876, and in 1877 Osler and Gardner [5] described a case in which three or four cells, each containing five or six red corpuscles, were found in a single field of the vertebral bone marrow. Riess,[6] writing in 1881, was greatly impressed with the large numbers of phagocytic cells in the bone marrow in pernicious anemia, and raised the question of their relation to the pathogenesis of the disease. Dickson[7] says, "Pigment cells, and cells containing erythroblasts and red corpuscles are seen in very great numbers, for example, in pernicious anemia . . ." It is unnecessary to cite the extensive literature in which similar observations have been made, for the existence of phagocytosis in the bone marrow in pernicious anemia is commonly accepted. MacCallum [8] mentions it and illustrates it in his "Text Book of Pathology." With few exceptions, however, the writers have contented themselves with incidental references to the process and little attention has been paid to its possible relation to the pathogenesis of the disease. This aspect of the subject assumes some importance in the light of the current hypothesis, based largely on the abnormal increase of bilirubin in the blood serum and in the bile, that pernicious anemia is associated with an increased blood destruction. The failure to account for this excessive blood destruction satisfactorily in any other way raises the question as to whether the phagocytosis of erythrocytes, so frequently observed in the bone marrow, may be a factor in producing the destruction. The answer to this question depends in part, at least, on whether phagocytosis is more prominent in the bone marrow in pernicious anemia than in other diseases and on the constancy of its occurrence in pernicious anemia.

The phagocytic cells of the bone marrow arise either from the vascular endothelium or from the reticulum.[7] With the material and stains available it has not been considered possible to differentiate accurately between these two types of cell and no attempt has been made to do so. In all probability the majority of the phago-

cytes, and certainly those which are free, wandering cells, are to be classed as "endothelial leucocytes" in the nomenclature of Mallory [9] or as "clasmatocytes" in the nomenclature of Sabin.[10]

In this investigation a distinction has been made between the presence in a phagocyte of erythrocytes containing hemoglobin and the presence of granules of so-called "hemosiderin" in which the iron is in such a form as to give the Prussian blue reaction. This distinction seems to be justified because certain diseases, such as pernicious anemia, are characterized by a predominant phagocytosis of hemoglobin-containing cells, while others, such as hemochromatosis, are marked by the presence of large amounts of hemosiderin within the cells, and still others, such as cirrhosis of the liver, frequently show both features to a more or less similar degree. In many instances, special stains for iron have been made but the yellow-brown or yellow-green color of the latter pigment is so characteristic that they are not usually necessary. There can be no question that the hemosiderin is derived from hemoglobin but it is more difficult to determine whether this pigment has been formed within the phagocyte or whether it was already formed when taken up by the phagocyte. As far as it goes, the histological evidence indicates that in most cases certainly the bone marrow phagocyte ingests the red corpuscles and that the hemosiderin is formed from hemoglobin within the phagocyte. This is suggested by the presence of hemoglobin-containing cells and granules of hemosiderin in the same phagocyte and by the fact that phagocytes which contain erythrocytes of normal appearance may also contain masses, staining for iron, of the size and shape of a red corpuscle. These masses apparently represent the early phases in the transformation of hemoglobin into hemosiderin — perhaps before the complete dissolution of the stroma of the red corpuscle.

The relative extent to which hemosiderin granules or hemoglobin-containing red corpuscles are found in the phagocytes may merely indicate the capacity of the phagocytes for retaining or storing the ingested material, but it is also quite possible that it indicates the intensity or severity of the phagocytic process. The fact that the phagocytosis of hemoglobin-containing red cells is particularly prominent in certain diseases associated with anemia and jaundice would seem to make such an hypothesis quite plausible. If the pigment remains in the phagocyte for a certain length of time it is

probable that the change from hemoglobin to hemosiderin occurs. Rich [11] states that the splitting of hemoglobin into bile pigment and an iron-containing residue by phagocytic cells of mesodermal origin, in tissue cultures, can be watched under the microscope. Pearce,[12] reviewing his own work and that of Karsner, Amiral, and Bock,[13] on the production of phagocytosis of erythrocytes in the lymph nodes of splenectomized animals by the injection of hemolytic sera, says that the phagocytosis "reaches its height somewhere between twelve and twenty-four hours after injection, and then the destruction of corpuscles goes on, so that at forty-eight hours there is nothing left but pigment and corpuscular fragments. Furthermore, with the passage of time the individual phagocytes become more and more filled with erythrocytes until about twelve to twenty-four hours, at which time there is a disappearance of the erythrocytes with the substitution of the pigment granule." If this evidence can be accepted as throwing a general light on the situation in man, one is justified in assuming that phagocyted red corpuscles which contain unchanged hemoglobin have probably not been inside the phagocyte for more than twenty-four hours. Thus the association of a histological lesion showing extensive phagocytosis of hemoglobin-containing erythrocytes, together with an increase of the amount of bilirubin in the blood plasma would indicate an acute destructive process in which large numbers of erythrocytes have been ingested by phagocytes and have been again transferred, probably partially destroyed, into the blood stream before the change from hemoglobin to hemosiderin has had time to take place. On the other hand, the presence of a large amount of hemosiderin, with or without accompanying erythrocytes, in the phagocytic cells would suggest a much less acute phagocytic process, and the relative proportion of hemoglobin-containing erythrocytes to hemosiderin granules would give an indication of the rate of blood destruction and of pigment change.

Control Observations

In order to determine the frequency and extent to which phagocytosis of red blood corpuscles occurs in the bone marrow in conditions other than pernicious anemia, observations have been made on four specimens of normal vertebral bone marrow and on sections of bone marrow (mostly vertebral) from 130 autopsies of cases dying

in a general hospital. The latter were, with very few exceptions, unselected and represent the various types of disease which are usually seen in the Pathological Service of such an institution. The amount of material and the wide range of diagnosis is thus sufficient to give at least a general conception of the frequency and extent to which phagocytosis occurs in the bone marrow in man. Grohé,[14] in 1884, and Geelmuyden,[15] in 1886, reported similar studies on the bone marrow. Both of them observed phagocytosis in a variety of conditions, and neither felt that it was much more extensive in the few cases of pernicious anemia examined than in a number of other diseases.

All of the sections of the vertebral bone marrow from four normal adults, in whom death was the result of traumatism, showed the presence of intracellular hemosiderin granules. In two instances only occasional pigment granules were found; in the third there was a considerable number of phagocytes containing coarse pigment granules — an amount that under other circumstances might have been considered to be abnormally great. In only one specimen were any phagocyted erythrocytes seen, and in this instance they were extremely rare. They were apparently intact and contained unaltered hemoglobin. From these few observations one can merely conclude that phagocytosis of erythrocytes occurs normally in the human bone marrow, but that it occurs only to a very limited extent. In this connection it is worth noting that Van den Bergh [16] has found bilirubin to be present in the sera of many normal individuals and the suggestion may be made that the normal variations in bilirubin depend on the activity of the phagocytic cells of the bone marrow and of the other organs of the reticulo-endothelial system.

In the study of the specimens of bone marrow from 130 patients dying in the hospital from various causes, an attempt has been made to estimate the extent to which erythrocytes and hemosiderin granules are present in the phagocytic cells. It is, of course, appreciated that this cannot be done with any high degree of accuracy because quantitative methods are not applicable, but it has been satisfactory to find that observations on the same specimen at widely separated intervals of time have been essentially in agreement. Specimens from different parts of the bone marrow in the same case may vary somewhat in histological picture but the differ-

ence is not sufficient to militate against the general value of observations on one or two sections. It is felt that the observations reported may be taken as rough representations of the amount of phagocytosis present. No further accuracy is claimed for them, and no further accuracy is necessary for the purpose in view.

In almost every case phagocytic cells containing either erythrocytes or pigment, or both, were found, and the impression was received that sufficiently extensive study would have revealed them in all. In seventy-seven out of the 130 cases the number of phagocytes containing either cells or pigment was not considered to be outside of what may be generally accepted as the normal limits. In twenty-one cases the phagocytosis was regarded as probably abnormal, and in thirty-two other cases the amount of phagocytosis undoubtedly exceeded the normal. In fourteen of the latter group pigment granules were present in the phagocytes to a relatively greater extent than were hemoglobin-containing erythrocytes. However, ingested red corpuscles were present in all specimens and usually in numbers greater than normal. The diagnoses in this group were — cirrhosis of the liver in three cases, hemachromatosis, adhesive pericarditis and perihepatitis, osteitis deformans and lobar pneumonia, lobar pneumonia and toxic jaundice, tuberculosis (two cases), carcinoma of esophagus, aplastic anemia and subdural hemorrhage, chronic myocarditis and chronic nephritis, actinomycosis, and Paget's disease. In twelve of the thirty-two cases there was a definitely excessive phagocytosis of erythrocytes, accompanied, in most instances, by a small or moderate number of hemosiderin granules. The diagnoses in this group were — bronchopneumonia or lobar pneumonia in six cases (with lung abscess and empyema in one case), typhoid fever, tuberculosis in two cases, mitral stenosis with thrombosis of left auricular appendage and multiple infarcts, and aplastic anemia and endometritis. One other case (24–112), which was studied incompletely in the clinic, as the patient died of a cerebral hemorrhage shortly after admission, is included here although the clinical record and the autopsy make it probable that he also had pernicious anemia. In the remaining six of the group of thirty-two cases both erythrocytes and pigment granules were present in the phagocytes to an abnormal extent. The diagnoses in these cases were — cirrhosis of the liver, chronic nephritis and healed perihepatitis, lobar pneumonia, bronchopneumonia and en-

cephalitis (?), gastric ulcer with perforation, and embolus of basilary artery. It is thus apparent that in a great variety of pathological conditions one may find a considerable number of erythrocytes and an abnormal amount of hemosiderin in the phagocytic cells of the bone marrow. It is impossible to classify these conditions, but the number of cases with liver lesions is rather striking. All five specimens of bone marrow from cases of cirrhosis of the liver showed red cells, pigment, or both, within the phagocytes. Beyond this one can only call attention to the incidence of increased phagocytosis in infections such as pneumonia, typhoid fever, and tuberculosis, in which the phagocytosis of cells is usually predominant. Similar findings have been described by Longcope [17] in typhoid fever and by Dickson [7] in pneumonia. While an excessive amount of phagocytosis was not observed in all of the cases of pneumonia or typhoid fever studied, it is of interest to call attention to the fact that certain cases of pneumonia and typhoid fever are associated clinically with slight degrees of jaundice, and Broun has found in some of these cases a "delayed" direct diazo reaction (Van den Bergh) which indicates that the jaundice is of hemolytic rather than of hepatic origin. It is quite probable that the hemolytic jaundice is the result of the phagocytosis. In cirrhosis of the liver Broun found the "prompt" direct diazo reaction, which is associated with jaundice of hepatic origin, but if the two types of jaundice, hepatic and hemolytic, were simultaneously present, the former would always mask the latter so that it would not be recognizable by this test.

An abnormal amount of phagocytosis is frequently observed in specimens of bone marrow which are hyperplastic, in the sense that there is an increase of cells at the expense of fat, but there is no definite relation between the degree of hyperplasia and the extent of the phagocytosis, and phagocytosis may be increased in specimens of bone marrow that are definitely not hyperplastic.

Pernicious Anemia

Eleven cases of pernicious anemia which have received careful clinical study form the basis of this report. Eight of them were patients at the Boston City Hospital and three at the Peter Bent Brigham Hospital. For the clinical records of the latter we are indebted to Dr. H. A. Christian, and for the pathological records and material to Dr. S. B. Wolbach. Ten of these cases may be said

to have died in an acute stage of the disease, although one of them (Case 2) also had a terminal pneumonia. The red corpuscle counts taken shortly before death varied between 500,000 and 1,000,000 per c.mm., and the hemoglobin variations were between 10 and 24 per cent in nine of the patients. In one case (Case 7) the hemoglobin was 55 per cent and the erythrocyte count was 1,200,000

TABLE 1

Cases of Pernicious Anemia

Case No.	Age	Per Cent Hemoglobin	Red Cells Million	Transfusions		Phagocytosis in Bone Marrow		Remarks
				Total Number	Last before Death	Hemosiderin	Erythrocytes	
1	64	19	1.0	2	14 days	+	+++++	
2	64	10	0.5	2	7 months	+	++++	
3	45	17	0.8	9	4 days	+	++++	Lobar pneumonia (terminal)
4	39	20	1.0	4	17 days	+	+++	
5	58	16	0.5	2	1 month	+	++++	
6	63	24	0.8	4	1 day	+	+++±	
7	55	55	1.2	0	.....	+	+++±	Last hemoglobin determination was 13 days before death
8	65	10	0.8	1	5 weeks	+	+++±	
9	52	16	1.0	0	.....	+	+++	
10	67	14	0.6	4	3 months	+±	+++±	
11	37	50	2.0	0	.....	±	+	Lobar pneumonia

thirteen days before death. On the day before death the erythrocyte count was 1,080,000 per c.mm. The bilirubin in the blood plasma was between 1.3 and 4.0 mgm. per 100 c.c. of blood in four of the cases just before death, and was 0.8 and 2.0 mgm. in Cases 1 and 6 just after death. The eleventh case is considered separately from those dying in an acute stage of the disease because death was due to lobar pneumonia contracted during a remission of the pernicious anemia, at a time when the red cell count was 2,000,000 per c.mm. and the hemoglobin was 50 per cent. As will be seen, the histological findings in the bone marrow in this case were quite different from those in the cases dying in an acute stage of pernicious anemia.

Two important features characterize the phagocytic process in

the bone marrow in the first ten cases. These are the extraordinarily great amount of phagocytosis of erythrocytes and the relatively slight amount of hemosiderin present in the cells. The iron-staining pigment is not at all prominent and often scarcely exceeds the quantity that may be present in normal bone marrow. A part of it is deposited in very fine granules in the endothelium lining the vascular sinuses and a few small masses may be extracellular. The rest is in phagocytic cells, and is usually interspersed between the ingested red corpuscles. The extent to which erythrocytes have been phagocyted, on the other hand, is, as far as can be roughly estimated in eight cases, greater than in any of the control cases, and in two cases about equal in degree to the half dozen control cases which showed the largest amount of phagocytosis of cells. With one exception, however, (24–112, probable pernicious anemia) all of these control cases showed much more pigment than did the cases of pernicious anemia.

The phagocytosis of erythrocytes usually takes place in free, round or oval cells (endothelial leucocytes; clasmatocytes) with large vesicular nuclei which become compressed, often curved, and displaced toward the periphery of the cell when many red corpuscles have been ingested. If a single erythrocyte has been ingested it often lies within the concavity of the nucleus. Phagocytosis may also occur in cells with slightly eosinophilic cytoplasm and delicate cytoplasmic processes. The number of phagocytic cells varies in different parts of the same section but there are often as many as three to six in a single high-power field. The number of erythrocytes ingested by a single phagocyte is also very variable and runs from one to three up to twenty or more. When one takes into consideration the fact that in pernicious anemia the cellular, hyperplastic bone marrow is a wide-spread, extensive tissue which fills the long bones as well as the short bones and which even brings about an enlargement of the marrow cavities within the long bones, it is apparent that the number of erythrocytes which are being phagocyted is enormous. The extent of the phagocytosis is indicated by Figures 1 to 4, each of which is from a drawing of the cells in a single oil-immersion field.

The ingested erythrocytes are for the most part strikingly normal in their appearance, both as regards size and shape. Small, abnormal, irregular forms and poikilocytes are often seen but they are,

on the whole, less common than normal red corpuscles. The hemoglobin usually stains exactly as does the hemoglobin in the red cells in the vascular spaces. Erythrocytes in which the pigment has been altered so that it has the appearance of hemosiderin or gives an iron stain are distinctly rare. Nucleated erythrocytes are very frequently found within phagocytes and occasionally leucocytes have been ingested.

The phagocytic cells described above are seen best in well-stained thin sections of bone marrow. They are, however, often somewhat difficult to distinguish in the densely cellular tissue and may be more easily recognized along the edge of the sections where the cells have been mechanically separated. In spite of being present in large numbers, they may well be overlooked in a routine study of the bone marrow unless attention is directed to this particular feature. The phagocytic cells are also readily found in fresh smears or in smears made from fresh emulsions of marrow in salt solution. They are quickly destroyed in smears dried in the air before fixation, but excellent preparations may be obtained by fixing the smears while still wet in Zenker's solution and then staining. Dickson[7] recommends this method of examination. Very satisfactory preparations may also be made by fixing in Zenker's solution the sediment of an emulsion of bone marrow in salt solution. These "wet fixed" smears may be stained with eosin and methylene blue or with one of the Romanowsky stains. The phagocytic cells are also easily seen in fresh, unstained emulsions of bone marrow in normal salt solution, and Dr. C. A. Doan has recently made a beautiful preparation of living bone marrow cells stained with neutral red and Janus green in which the phagocytic cells were particularly prominent.

Case 11, who, as mentioned above, died of pneumonia during a remission in the pernicious anemia, and in whom the relative inactivity of the process causing the anemia is indicated by a red corpuscle count of 2,000,000 per c.mm., and a blood bilirubin content of only 0.8 milligrams per 100 c.c., showed a histological picture in the bone marrow which was quite different from that described in the ten cases just referred to. There was very little phagocytosis either of erythrocytes or of pigment. The degree of phagocytosis in a single section could hardly be considered beyond the normal limits, although, of course, the process was going on throughout a tissue that is somewhat more extensive than the normal bone mar-

row. In this connection another point in the histology may be mentioned. Eight of the ten cases dying in an acute stage of pernicious anemia were almost without fat in the bone marrow, while two others (Cases 4 and 10) had only a slight amount of fat in the marrow. Case 11, on the other hand, had a very considerable amount of fat in the femoral bone marrow. This is unquestionably another indication that the pernicious anemia was undergoing a remission, for Zadek [18] has shown by examination of the marrow during life that during remissions in the disease the bone marrow tends to become more yellowish and less red in color.

Discussion

The observations on the bone marrow which have just been described indicate that phagocytosis of erythrocytes occurs to a very limited extent in normal marrow; that it may be considerably increased in a variety of pathological conditions; that in the active stages of pernicious anemia it occurs to a degree which, with rare exceptions, is not met with in other diseases, and that during a remission in the course of pernicious anemia it may cease to be a prominent factor in the bone marrow.

The first point for discussion with regard to the phagocytosis of erythrocytes in pernicious anemia is as to the character of the ingested cells. Are they foreign cells which have recently been introduced by transfusion? That they are not transfused cells is evident for a number of reasons: extensive phagocytosis of erythrocytes was frequently described long before transfusion became a common procedure; many of the ingested erythrocytes are young cells that still retain their nuclei; Case 2 of this series, with an enormous amount of phagocytosis, had not been transfused for nearly seven months; and Cases 7 and 9 had never been transfused. It is also of interest in this connection that in one of Dr. Channing Frothingham's patients who had received thirty-two transfusions, the bone marrow showed no phagocytosis of erythrocytes, but contained a very large amount of intracellular hemosiderin. The second question with regard to the character of the ingested erythrocytes is less easy to answer. Are they abnormal or inadequate cells? Is the phagocytosis merely a mechanism for ridding the circulation of worthless cells? The fact that the ingested cells look like entirely normal erythrocytes is,

of course, no evidence as to their functional efficiency. The occurrence, however, of so many nucleated red corpuscles among the phagocyted cells indicates that if these cells are indeed inadequate, they must become so very early. This is opposed to the observation of Wearn, Ames, and Warren [19] that the cells of a patient with pernicious anemia, transfused into another subject, continue to remain in the circulation as long as transfused normal cells. Such evidence certainly does not suggest that the erythrocytes in pernicious anemia are, as a whole, in any degree inadequate, but whether or not some of the red cells are rendered more liable than normal to phagocytosis in the patient with pernicious anemia is not known. The phagocytosis of erythrocytes in pernicious anemia must depend either on an alteration in the red cells which makes them more readily phagocyted or on a stimulus to the phagocytic cells which increases their avidity for erythrocytes. No convincing proof of either process can, however, be brought forward at the present time.

From the point of view of pernicious anemia the problem of immediate interest is whether this phagocytic process is an incidental matter, as it has generally been regarded, or whether it is a significant phase of the pathology of the disease. If the phagocytic process does have an essential relation to the pathology of the disease, this relation is, of course, limited to the hematological manifestations of the disease, namely, the anemia and the hemolytic jaundice. No other explanation of the cause of the anemia has been presented which is in any degree convincing and there are, on the other hand, certain facts which indicate that the phagocytosis may play a part in its production. The most striking of these is that in certain cases of pernicious anemia there is an easily demonstrated phagocytosis of erythrocytes in the bone marrow which is rarely equaled in degree in other pathological conditions. There can be no doubt that the phagocyted cells are ultimately destroyed and the amount of phagocytosis throughout the greatly increased bone marrow must account for the destruction of a very large number of erythrocytes. The histological picture of the bone marrow, with extensive phagocytosis of hemoglobin-containing erythrocytes, and with very little retention of hemosiderin in the phagocytes suggests an active hemolytic process. The hemoglobin or its decomposition products immediately after their formation probably pass quickly from the phagocyte into the blood stream. This would account for the finding

of hemoglobin and hematin, as well as bilirubin, in the plasma in acute stages of pernicious anemia, as reported by Broun, Ames, Warren, and Peabody.[20] Unfortunately the group of cases thus far studied satisfactorily, both clinically and pathologically, is extremely small but it is significant that the cases dying during an acute phase of the disease showed the greatest amount of phagocytosis of erythrocytes, while the case dying of pneumonia during a remission of the anemia showed by far the least amount of phagocytosis.

In this paper attention has been directed entirely to the phagocytosis of erythrocytes in the bone marrow. The bone marrow has been considered to be of particular interest because it is so large an organ in pernicious anemia, and also because phagocytosis is, at least as demonstrated histologically, a less considerable feature in the liver and spleen in this disease. The failure to cure pernicious anemia by splenectomy also indicates that the spleen plays, at most, a subordinate rôle in the production of the anemia. The bone marrow is not the only tissue, however, in which extensive destruction of red corpuscles takes place in pernicious anemia. In 1902 Warthin[21] published a paper on "The Pathology of Pernicious Anemia with Special Reference to Changes Occurring in the Hemolymph Nodes," and described extensive phagocytosis of erythrocytes in eight cases. One of his conclusions may well be quoted verbatim as it summarizes his point of view as to the hemolytic process in pernicious anemia. "The poison of pernicious anemia stimulates the phagocytes of the spleen, lymph and hemolymph glands, and bone marrow to increased hemolysis (cellular hemolysis). Either the phagocytes are directly stimulated to increased destruction of red cells, or the latter are so changed by the poison that they themselves stimulate the phagocytes. The hemolysis of pernicious anemia differs only in degree, not in kind, from normal hemolysis or the pathological increase occurring in sepsis, typhoid, etc."

Our own observations on the lymph nodes in pernicious anemia have, as yet, been limited in number but they are in entire agreement with those reported by Warthin. The studies on the bone marrow, described in this paper, taken in conjunction with the observations of Warthin, lend considerable support to his explanation of blood destruction in pernicious anemia by cellular hemolysis. Whether or not this method of blood destruction is the only factor in the production of the anemia, of course, remains an unsettled

question. It is quite possible that the hemolytic jaundice of pernicious anemia is the result of phagocytic action but that other factors take part in the causation of the anemia.

Conclusions

1. Phagocytosis of erythrocytes occurs in the normal bone marrow and to a much greater extent in a variety of pathological conditions. Among the latter the most notable are certain cases of cirrhosis of the liver, and of infectious diseases such as pneumonia, typhoid fever, and tuberculosis.

2. Phagocytosis of erythrocytes occurs in the bone marrow of patients dying in an acute stage of pernicious anemia in a degree rarely met with in other conditions. In a single case of pernicious anemia dying in a remission of the disease, phagocytosis of red blood corpuscles was not a striking phenomenon.

3. It is suggested that phagocytosis of erythrocytes may be a factor in the production of the hemolytic jaundice and of the anemia in pernicious anemia.

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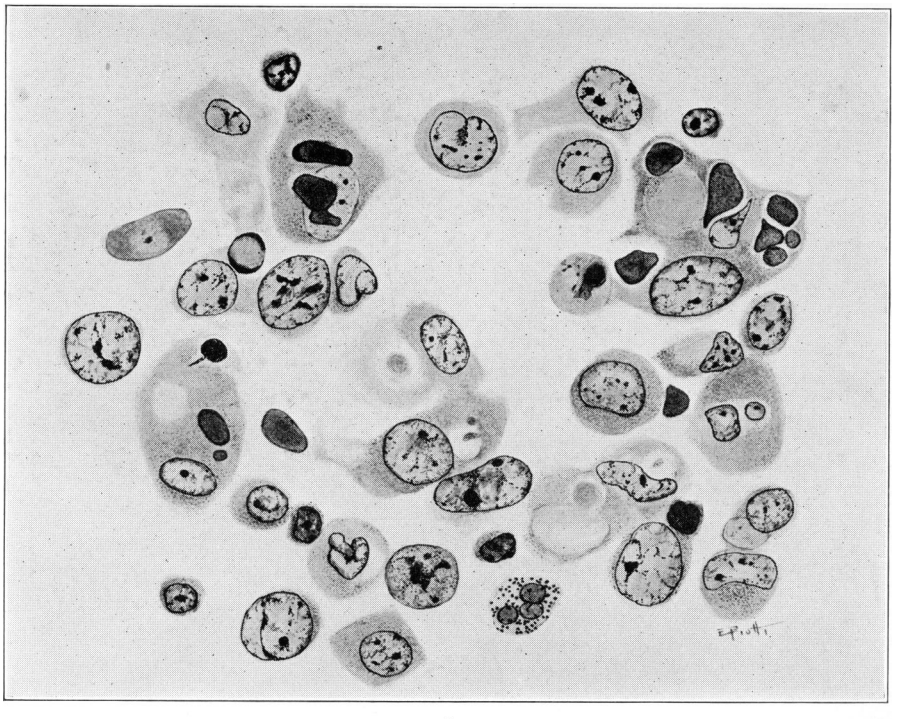
DESCRIPTION OF PLATES XXIX AND XXX

The illustrations are photographs, from drawings by Miss E. Piotti, of cells found in a single oil-immersion field.

Figures 1 and 2 are from smears of femoral bone marrow, and Figures 3 and 4 are from sections of femoral bone marrow.



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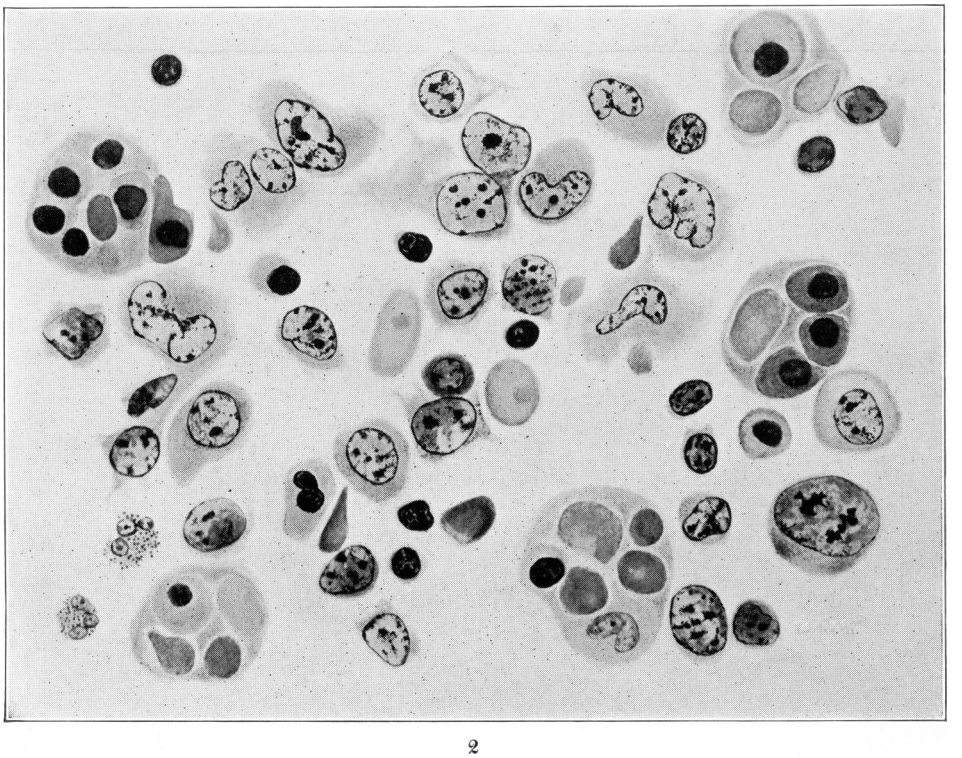

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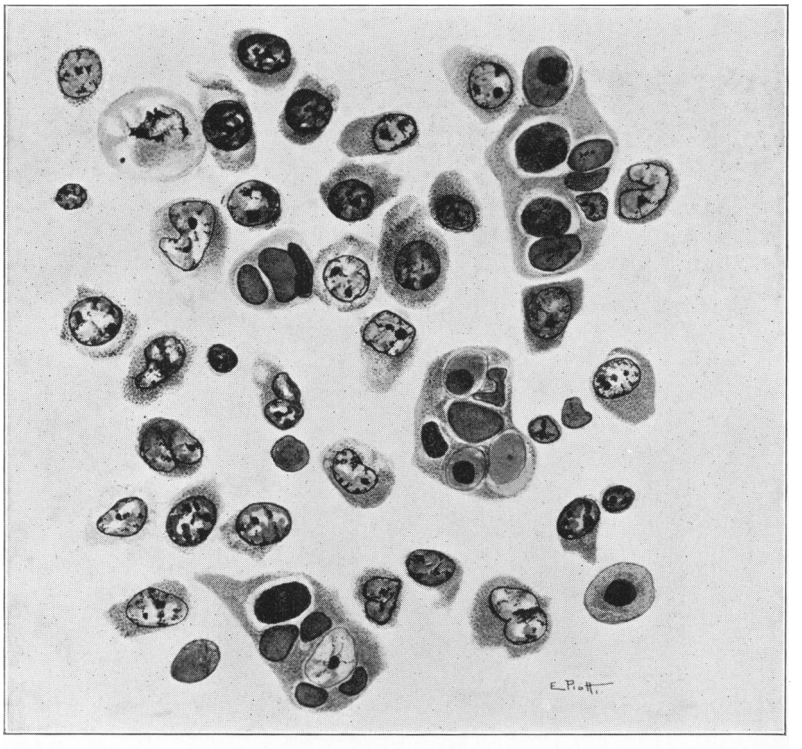

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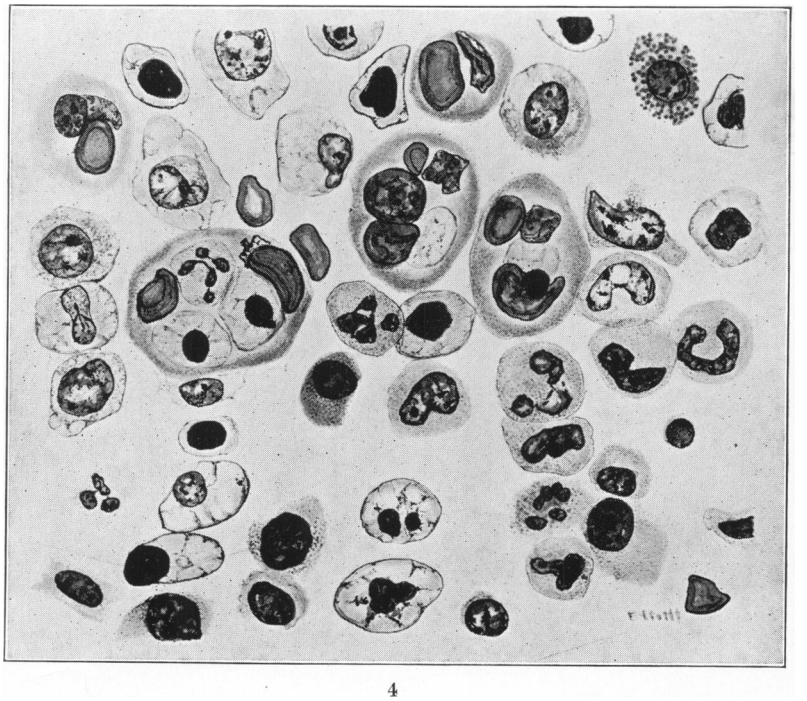

4