OF ALL the recent advances in medicine, the conquest of pernicious anemia is one that should make pathologists proud. Twenty-five years ago, Biermer's anemia was a pernicious anemia, often fatal and which could not be cured by any treatment. It is fair to acknowledge the brilliant work of Minot and Murphy, who conceived the idea of applying the liver treatment inaugurated by Whipple, to pernicious anemia. The results were such that since then, patients with pernicious anemia do not die of the disease any more. Simultaneously, hepatotherapy has provided a convincing argument in favor of the specificity of the disease. Confusion with other severe types of anemia has been avoided. In addition to hepatotherapy other arguments have supported the concept of pernicious anemia as an autonomous disease, entirely distinct from other types of anemia. Among these arguments, one of the most recent is based on the study of the myelogram in pernicious anemia.

The cytology of the bone marrow was already known before the use of sternal punctures. However, postmortem examinations are vitiated by the onset of cadaveric changes in the tissues. Therefore, the sternal biopsy is indispensable to an understanding of the bone marrow. This is why the technic of bone marrow biopsy, introduced in 1929 by Arinkin, provided a great impetus to the development of hematology. This applies particularly to the study of pernicious anemia.

Sternal puncture is a simple procedure carried out with a special needle containing a stilet, which penetrates easily through the anterior table of the sternum; local anesthesia is not necessary. The bone marrow is aspirated in very small quantities if one wants to have a rich myelogram. Reading of the myelogram is easy if the technic of preparation is adequate: spreading—compression between two slides of a very small quantity of tissue, preferably small fragments of bone marrow—double staining by May-Grunwald-Giemsa for one-half hour. The water used should have a neutral pH.

Naegeli first described the erythroblasts which characterize pernicious anemia. He called them megaloblasts and this term was responsible for much of the confusion that prevailed thereafter. This confusion arose from the fact that Ehrlich and also Jolly gave the name "megaloblast" to certain types of very young erythroblasts which are basophilic and are found in any normal marrow. These are not the megaloblasts which are found in pernicious anemia. These normal erythroblasts are also called pronormoblasts, basophil normoblasts or Naegeli's normoblasts.

The megaloblasts found in pernicious anemia represent a special lineage of erythroblasts, ultimately ending up in a special type of erythrocyte, the megalocytes, and having a characteristic morphology at each stage of the cytolologic development.
As seen in the bone marrow smear, the megaloblasts of pernicious anemia have a high optical density. The youngest forms arising from the reticulum are the promegagloblasts (called "erythrogones" by certain authors). They have a histioblastic appearance with a grayish blue protoplasm, more or less spread out, not sharply limited, with pseudopods and sometimes a protoplasmic connection with another promegagloblast. The nucleus is enormous and the chromatin shows a fine lacy structure with numerous bluish nucleoli.

Following the promegagloblasts come the basophilic megaloblasts which are frequently seen. These cells are large with a big round nucleus centrally placed. The chromatin has a fine skeinlike structure and is transparent. The protoplasm is very basophilic, has a variable thickness and is usually quite wide. In some cases, the basophilic megaloblast shows early eosinophilic granules.

As maturation progresses, the cellular anarchy becomes more manifest and the aspect of the megaloblast diverges more and more from that of the normoblast. The nucleus remains large, with a fine transparent chromatin, which in places condenses into pearl-like or blocklike structure. The peripheral protoplasm becomes lighter in an irregular fashion and its maturation may lag behind or, more often, precede that of the nucleus.

The fourth stage of the development is that of polychromatophilic megaloblast: the asynchronism between nucleus and protoplasm becomes manifest: a big nucleus may be found in conjunction with a small cytoplasm or a small nucleus in conjunction with a large cytoplasm. The cytoplasm shows vivid colors, purple or greenish with heterogeneous areas of variable shapes. The nucleus still has a partly reticulated structure and may undergo amitotic division or fragmentation which produces an aspect of a petalled flower. The nucleus is still young as shown by its transparent and pearl-like aspect. But the tendency toward the formation of fragments of the nucleus classifies the cell as an old type of cell. The nuclear fragments appearing early in the cell are the future Jolly's bodies.

The orthochromic megaloblasts have an orange color but may contain basophilic remnants in the form of basophilic areas or granules as in lead poisoning. The nucleus may be round and regular as the nucleus of the orthochromic normoblast, but more often it is reniform or dumbbell-shaped or has the shape of a clover leaf. The orthochromic megaloblasts vary in size and some may be rather small. When they lose their nucleus they become remnants, Cabot's rings, and Jolly's bodies. The megaloblasts in pernicious anemia often show atypical mitotic figures at all phases.

In summary, at all stages of the evolution, the megaloblast is an abnormal dystrophic erythroblast resulting in the creation of a large erythrocyte. This explains the anisocytosis, poikilocytosis and megalocytosis which are the expression of a cellular dystrophy and not of a cellular immaturity since most cells observed in the blood smear of a case of pernicious anemia are completely mature cells.

After a long period of discussion, hematologists agree among themselves that the megaloblastosis belongs specifically to pernicious anemia. I, personally, do not think that megaloblasts are observed in any anemia except pernicious anemia, provided one adheres to the definition of the megaloblast as I have given it, and one does not consider the megaloblast as a very young nucleated basophilic erythrocyte.
Every time I have been invited to see so called megaloblasts in the myelograms from patients having blood disease but no pernicious anemia, I have recognized that these were not megaloblasts. While the megaloblast is specific for pernicious anemia, there are also normoblasts and their proportion to the number of megaloblasts is variable. They are seen in early cases of pernicious anemia. Also they completely and rapidly replace the megaloblasts as soon as hepatotherapy is instituted. This fact permits one to conclude that the megaloblastosis is conditioned by a deficiency of the hemopoietic factor of maturation of red cells which is provided by the liver.

The generally accepted opinion, proposed by Naegeli, by Ferrata, and most hematologists is that the megaloblast represents a revival of the embryonic erythrocyte of the first generation. There is a certain morphologic analogy between the megaloblast and the nucleated erythrocyte of the fetus. One arrives therefore at the conception, as already advanced by Dameshek and Wilkinson and Israels, that there are two types of hemopoiesis: the normoblastic or adult type and the megaloblastic or embryonic type. Their appearance or disappearance depends on the factor of Whipple: if the maturation factor is deficient, the fetal type of erythroblasts appears in the bone marrow but if the factor is administered, the normal type of erythroblasts replaces the megaloblasts.

My interpretation is a little different from what precedes. The megaloblast does not appear as the result of a substitution of two erythroblastic lineages, because such a substitution is never observed. Rather than a substitution, a real transformation occurs which changes the normal erythroblast into a megaloblast: this morphologic transformation is caused by a deficiency of the maturation factor. In other words the megaloblast is a normoblast suffering from a nutritional deficiency.

This interpretation explains several particularities of the disease: first of all, the megaloblast may exhibit morphologic monstrosities in a varying degree according to the degree of the deficiency. This is analogous to what is seen in dystrophies caused by endocrine or vitamin deficiencies. In very advanced cases of pernicious anemia, the megaloblasts are typical and numerous. In incipient cases, the erythroblasts are not very much different from normoblasts and there are intermediary forms between normoblasts and megaloblasts. Finally when the treatment by liver injections is instituted, there is a rapid transformation of the megaloblasts into normoblasts.

The metaplasia from normoblast to megaloblast, or vice versa, always affects the young forms of the series: proerythroblasts and basophilic erythroblasts. This is why in cases of pernicious anemia in relapse the young basophilic cells are megaloblastic while the older cells are normoblastic. As soon as the liver treatment is instituted, the myelogram shows a normoblastic transformation of the basophilic erythroblasts without change in the polychromatophilic and orthochromic megaloblasts.

Another proof of the existence of a nutritional dystrophy in pernicious anemia is provided by the aspect of the granulocytes and megakaryocytes of the bone marrow.

The granulocytes show morphologic changes: the myelocytes are very large and
pale looking with enormous nuclei. The metamyelocytes have a ribbon-shaped nucleus with pseudopods. The polymorphonuclears have a polyelegmented nucleus (up to 15 segments) giving the appearance of a knotted chord.

The megakaryocytes also have a polyelemented nucleus: all the cells formed in the bone marrow are affected in pernicious anemia. Biermer's disease is a dystrophic myelosis, affecting the bone marrow as a whole, and producing anemia, neutropenia and thrombocytopenia. The morphologic changes resulting from the dystrophy are specific and constitute the basis for the diagnosis.

From a scientific point of view, the myelogram in pernicious anemia is very interesting because it constitutes an instance of a cytologic dystrophy which can be reversed by the administration of liver, of Castle's factor, of folic acid.

One cannot help being struck by the analogy between the cytologic dystrophy of pernicious anemia and certain cellular alterations of malignant neoplastic tissues. In both cases there is the same excessive proliferation, the same cellular monstrosity, the same cytoplasmic-nuclear asynchronism, the same young aspect of the nucleus, same abnormal mitotic or amitotic cellular division.

On the other hand, hepatotherapy or folic acid treatment are very similar to vitamin therapy.

At the present time, therefore, one can say without exaggerating too much that pernicious anemia is a nutritional deficiency and a disease rather akin to cancer, in which the abnormal cellular proliferation is corrected by a chemically defined organic substance.
THE STUDY OF THE MYELOGRAM (BONE MARROW PUNCTURE) IN PERNICIOUS ANEMIA AND THE PROBLEM OF THE MEGALOBLAST

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