EDITORIAL

Pernicious Anemia, Megaloblastosis and the Di Guglielmo Syndrome

PERNICIOUS ANEMIA, at least in the temperate zones, is almost always due to a "conditioned" deficiency in vitamin B₁₂ due to lack of gastric intrinsic factor. This results in a distinctive (megaloblastic) type of erythropoiesis and thus in macrocytic anemia. Much evidence indicates that the greatly reduced content of vitamin B₁₂ in the blood leads to a disturbance in nucleic acid metabolism of the developing nucleated red cells in the bone marrow, and thus, presumably, to megaloblastosis.¹ The type of erythroblastic proliferation seen in pernicious anemia is distinctly abnormal; in fact, first inspection of the intensely megaloblastic marrow, particularly from sections, might lead one to consider a neoplastic type of proliferation. Perhaps, as Osgood has stated,² this is neoplastic, with such characteristic features of neoplasia present as nuclear immaturity, numerous mitoses, polyploidy, asynchronism between the cytoplasm and the nucleus, presence of increased numbers of primitive erythroblasts, etc. In addition—and it is now rather difficult to remember—prior to 1926, the megaloblastic anemia of pernicious anemia eventually became irreversible and almost invariably resulted in death.

In a recent article, Reisner³ has presented evidence from tissue culture studies for the hypothesis that megaloblasts are red cell precursors with a prolonged resting phase between mitoses. Mitosis goes on very slowly, apparently because the requisite amount of deoxyribonucleic acid (DNA) is greatly reduced. Thus, the marrow becomes crowded with cells, often of a highly primitive type, waiting to divide. RNA persists in the cytoplasm of the megaloblast during this phase of slowed maturation, and the combination of these two defects is thought to lead to the megaloblastosis (and macrocytosis) of the disease. It is worthy of note that according to Berenblum,⁴ such features as delayed maturation, accumulation of "pockets" or colonies of primitive cells are characteristic of malignancy. Nevertheless, there can be no question that the megaloblastosis of pernicious anemia is due to a "deficiency" of vitamin B₁₂ in the plasma and that this can be quickly reverted to normal by therapy with vitamin B₁₂.

Megaloblastosis is not always so readily reversible. There are some cases of progressive anemia with striking erythroblastic hyperplasia of the bone marrow of the megaloblastic type in which even massive doses of vitamin B₁₂ and folic acid are without effect and the patient goes on to die with or without developing a terminal leukemic status. These cases, which are generally known as "erythremic myelosis," and which we have called the Di Guglielmo Syndrome,⁵ may be regarded as acute or highly malignant examples of the myeloproliferative syndrome.⁶ During the early stages of the disease, the preponderant proliferation is erythroblastic, and megaloblastosis with polyploidy, primitivity and many mitoses are seen. The serum vitamin B₁₂ concentration, in contrast with that of pernicious anemia, is unusually high.⁷
Is it possible that the megaloblastosis of “erythremic myelosis” is indicative of an intrinsic defect of the developing red cell due perhaps to a missing enzyme concerned either with the uptake of B$_{12}$ from the plasma or its actual utilization by the developing erythroblast for proper nucleic acid formation?

The theory that at least some types of neoplasia—including leukemia—develop because of deletion of a specific gene or enzyme is gaining in favor, with Haddow as its principal exponent. The evidence for this viewpoint is marshalled in a recent, very impressive issue (May, 1958) of the British Medical Bulletin devoted to “Causation of Cancer.” It rests upon the assumption that certain chemicals (carcinogens) and other factors may inhibit “certain fundamental processes of genetical or enzyme synthesis.” This may then be “followed by the generation of new self-duplicating fibre or template, chemically modified, hence genetically so.” With the elimination of certain key proteins or enzyme proteins essential to the regulation of normal growth, there may thus be liberated “more primitive synthetic reactions upon which the process of cell division depends, and from the uncontrolled impetus of which it then proceeds more or less continuously.” Such enzyme deletion may conceivably result in a slightly different but highly abnormal type of metabolism within a group of cells—e.g., erythroblasts, myeloblasts, etc.—and thus in the various features of what we call neoplasia. These include a new, bizarre, apparently lawless type of growth pattern, often with nuclear immaturity, polyploidy, asynchronism between cytoplasm and nucleus, etc.

In leukemia, this may represent a new “race” of white cells. In the Di Guglielmo Syndrome, one may speculate that initially, at least, a new megaloblastic “race” of erythroblasts develops, and that this is self-perpetuating because the defect, once acquired, becomes genetically determined.

One may conceive of megaloblastosis, if well-defined, as a “marker” for either B$_{12}$ or folic acid deficiency, which may develop in various ways. Thus, it is found in the fetus, in certain deficiency states, whether directly induced or “conditioned,” and in occasional cases of drug poisoning. In fetal hematopoiesis, there may be a lack of enough vitamin, or possibly a lack of development of certain specific cellular enzymes. In pernicious anemia, there is quite clearly a lack of the essential vitamin B$_{12}$, which is thought to act as a co-enzyme for other specific enzymatic materials within the developing red cells. In the megaloblastosis of dilantin toxicity, it is possible that a specific enzyme may have been “poisoned” by the chemical or that the drug may be in “competition” with an essential cellular metabolite. This is perhaps similar to the effects noted in some cases of leukemia treated with the folic acid antagonists. In the Di Guglielmo Syndrome, it is conceivable that “deletion” of a similar if not identical enzyme may have been induced by a carcinogenic agent—whether chemical, viral or physical—with the result that although the cell continues to grow, its growth pattern is now highly abnormal. This would lead to a neoplastic type of red cell development, i.e., a self-replicating and thus far irreversible megaloblastosis.

Well-defined megaloblastosis has previously been thought to be due to an “extrinsic” defect (i.e., a lack of B$_{12}$ or folic acid in the blood), but in view
of the findings in dilantin toxicity, and in prolonged therapy with the folic acid antagonists as well as in the Di Guglielmo Syndrome, one must consider the possibility that an "intrinsic" metabolic defect of the nucleated red cells may be acquired during life.

The hypothesis that at least some neoplasia are on the basis of an acquired self-perpetuating metabolic defect due to enzyme deletion, whether brought about by chemical, radiation or viral means, is made the more attractive because it offers the possibility that such abnormal proliferations may ultimately be converted into normal channels of growth, rather than destroyed as we must now attempt to do. In the neoplastic megaloblastosis of erythremic myelosis, the possibility is present that ultimately the abnormal megaloblastic proliferation can be circumvented by administering an appropriate metabolite. It is therefore conceivable that in this disturbance, which has features resembling pernicious anemia, there may lie the key unlocking not only its own destructive mystery but others as well. Thus the Di Guglielmo Syndrome, only recently a morphologic curiosity of uncertain type, may well emerge into the present-day chemical limelight surrounding leukemia and other neoplasia. If so, its possible relationships to that extraordinarily well-studied disease, pernicious anemia, will bear intensive scrutiny.

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REFERENCES


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