This woman of sixty-one, always in good health except for head colds, took 60 capsules of chloramphenicol during fourteen months as a prophylactic measure against further colds. This was successful, but pancytopenia and the indications in the bone marrow of hypoplasia and of primitive cell (myeloblast) leukemia developed. Chloramphenicol was discontinued. The patient was well for about six months, and then the various clinical manifestations of acute leukemia developed and she died fourteen months after the diagnosis had been made.

DISCUSSION

Hypoplastic anemia has been defined in various ways by various observers. We prefer to reserve this term for cases showing pancytopenia of the blood and well defined hypoplasia of the bone marrow. Those with increased cellularity of the marrow and blood pancytopenia may indicate other conditions ranging from maturation arrest to the DiGuglielmo syndrome or leukemia. In the aplastic anemia that follows the administration of chloramphenicol, 2 main forms may be discriminated. In the first the onset is acute, seemingly dose related and frequently associated with a normocellular bone marrow, which exhibits vacuolization of erythroblasts and granulocytic precursors. Moderate anemia, reticulocytopenia, increased plasma iron and delayed plasma iron clearance have been observed in this setting.[9] Unless the dosage of drug has been inordinately high, this type is usually reversible when the drug is discontinued. Work in mammalian cell-free systems suggests that prolonged exposure to chloramphenicol and high blood levels of unbound drug are both important factors in inhibiting protein synthesis through interaction with messenger RNA. This may help to explain the bone-marrow hypofunction.[11]

The second form, or "late-onset type," may not be dose related. It is characterized morphologically by hypoplasia or severe aplasia of the bone marrow. In most patients manifestations of marrow depression develop after the drug has been stopped, often weeks or months later. In such cases, indications of marrow injury remain long after the last trace of the drug have disappeared. Conceivably, injury to a large number of stem cells might explain such an effect. An interval would then be required before the stem-cell pool became depleted and cytopenia was manifest. That some patients, because of a metabolic abnormality or deficiency, may be more susceptible than others to the action of chloramphenicol or its degradation products, is an attractive but unproved possibility. In fact, there is no ready explanation at present for the apparent susceptibility of some persons to the development of serious disorders of the marrow after chloramphenicol or other agents.

The development of leukemia in the course of aplastic anemia is of considerable interest. Although most large series of acquired aplastic anemia [12-14] contain no such reports, examples may be found with benzene toxicity,[1,2] after radiation,[3,4] after administration of phenylbutazone,[15,16] during the hypoplastic phase of paroxysmal nocturnal hemiglobinuria [17] and in hereditary hypoplastic syndromes.[5,6] The development of paroxysmal nocturnal hemoglobinuria during aplastic anemia [18] is of additional interest. This may be but another example of the development of abnormal cell lines in a previously injured bone marrow.

The induction of leukemia by chemicals (including drugs) may be mediated through chromosomal injury. In line with this is the recent observation by Castoldi and Mitus [19] of chromosomal vacuolization in patients receiving chloram-

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