phenicol. Inconstant chromosomal changes have been observed in several series of cases of acute leukemia.[20,21] Similar changes have been found to follow radiation [4] and benzene [22] and to occur in hereditary states.[23] The chromosomal vacuolization seen after chloramphenicol may be a comparable lesion. Another possible explanation is that the leukemia is a secondary, perhaps reparative, response to aplastic anemia. A tendency to neoplasia of hypoplastic tissues has been recognized repeatedly in human pathology. Examples include atrophic gastritis and leukoplakia. Perhaps analogous to the potential of these disturbed tissues to transform into carcinoma is the eventual emergence of leukemia in the chronically aplastic bone marrow.

Finally, another explanation for the development of leukemia in these cases deserves consideration. Aplastic anemia and leukemia may both be thought of as growth disturbances of the bone marrow (myeloproliferative disorders). Thus they may occur either together or sequentially as phases of the same pathogenetic mechanism. Block et al.[24] had the unique opportunity to observe 12 patients for as long as twenty-seven months before the development of acute myelogenous or stem-cell leukemia. Most of the patients in this "preleukemic" phase displayed variable degrees of marrow hypoplasia as well as peripheral cytopenias. Blair and his associates [25] reported a similar experience in 16 cases of "atypical leukemia." Thus, it may be hypothesized that in some cases aplastic anemia and leukemia simply represent different expressions of the same fundamental disturbance. It is now reasonably clear that an "insult" to the bone marrow, as from chloramphenicol or another chemical, may either destroy totally or partially. Partial destruction of some cells may serve only to "knock out" one or two enzyme systems but not prevent cell reproduction. Under these circumstances, a new self-perpetuating cell line (clone) may develop—that is, leukemia, when white cells are concerned, or paroxysmal nocturnal hemoglobinuria with erythroblastic involvement. We have recently remarked upon the relation of paroxysmal nocturnal hemoglobinuria and aplastic anemia, particularly in association with chloramphenicol toxicity.[26]

The syndrome of aplastic anemia, regardless of cause, may lead to early death from hemorrhage or infection or may result in chronic bone-marrow malfunction. The development of leukemia and of paroxysmal nocturnal hemoglobinuria has been associated with the latter process. It is evident that chloramphenicol can result in this sequence of events. The continued widespread use of this drug, particularly in the less developed countries, and even among the highest-income groups of this affluent country, often for trivial reasons, may be a factor in the causation of some forms of leukemia, particularly of the relatively indolent, hypoplastic type.

SUMMARY AND CONCLUSIONS

The development of myeloblastic leukemia during the course of chloramphenicol-induced pancytopenia in 3 patients is described. Leukemia has been reported in a wide variety of clinical states commonly characterized by variable degrees of bone-marrow hypoplasia. Factors responsible for the development of aplastic anemia and drug-induced leukemia are considered. Chloramphenicol, by primary or secondary means, appears casually related to the blood dyscrasias in the cases presented. As stated so many times, indications for the routine or even common use of this drug in the treatment of infection must always be carefully scrutinized.

Senator NELSON. I am sorry to interrupt you.

Dr. DAMESHEK. Fine. I do not mind at all.

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