use of both drugs. Although the frequency of leukemia among persons with chloramphenicol-attributed marrow depression appeared to exceed expectation—3/124 in our series as compared with the US age-adjusted leukemia mortality of 6/100,000/yr—an association observed between drug exposure and leukemia may have one or more of the following interpretations: (1) A causal relationship exists between drug exposure and the development of leukemia. (2) Patients undergoing drug therapy for disorders such as immunologic deficiency and collagen disease may be at high risk of leukemia. (3) The ailment being treated is a manifestation or a complication of leukemia in its early phase (eg, rheumatic complaint, fever, infection). (4) Another therapeutic modality is leukemogenic (eg, radiotherapy). (5) The sequence of drug intake and leukemia is a chance occurrence.

The possibility of a causal relationship between drug use and leukemia would be supported by the following case characteristics: relatively high dose of the administered drug; no evidence of leukemia at the time of drug use; and absence of diseases or other agents know or suspected to be leukemogenic. Furthermore, if the relationship is comparable to radiation-induced leukemia (1), the cytologic type should be chronic myelogenous or acute leukemia, and the interval between start of drug exposure and development of leukemia should exceed approximately 18 months. Among the three leukemia patients observed in the survey, only one had all the characteristics which would suggest a causal relationship between chloramphenicol exposure and leukemia. The significance of one case is, of course, unclear. Because of the small study group and relatively brief period of follow-up, the risk of leukemia would have to be very high for additional cases to have occurred. If exposure to marrow-depressing drugs does confer a later increased risk of leukemia, one might anticipate the risk to be greatest among persons in whom signs of marrow depression actually develop, as those in the present study. From a single case of leukemia following toxic effects from chloramphenicol, however, it is not possible to conclude that chloramphenicol is, or that phenylbutazone is not, leukemogenic. Since radiation-induced leukemia has a peak occurrence three to eight years after exposure, a more realistic opportunity for evaluating leukemia risk awaits a larger sample size and longer period of observation following the drug reaction.

Finally, an evaluation between drug exposure or toxic effects and leukemia should benefit from cytogenetic studies of individuals treated with drugs that affect bone marrow function. Chromosomal abnormalities of blood cells have been described in the following situations where marrow depression may predispose to leukemia: (1) persons exposed to marrow depressants which are definitely or probably leukemogenic-radiation [33] and benzene [34]; (2) children born with Fanconi's familial aplastic anemia, who appear to carry an excess risk of leukemia [35]; and (3) certain forms of refractory anemia which later progress to leukemia.[36, 37] Indeed, cytogentic aberrations have been observed in virtually all groups of individuals who are, or seem to be, at high risk of leukemia.[38] Demonstration of a consistent chromosomal abnormality in patients who receive a particular drug or in whom toxic effects develop would enhance the possibility that an observed sequence of drug exposure and leukemia may have a cause-and-effect relationship.

GENERIC AND TRADE NAMES OF DRUGS

Chloramphenicol—*Chloromycetin.*
Phenylbutazone—*Butazolidin, Butadion, Artrizin, Pyrabutol.*
Amphetamine sulfate—*Benzedrine, Linampheta, Amitrene, Amphedrine, Amphoid-S.*
Prednisone—*Deltasone, Deltra, Meticorten, Paracort, Cotone, Lisacort, Metasone.*
Aminopyrine—*Pyramidon, Kalmine.*
Oxyphenbutazone—*Tandearil.*

REFERENCES

[1] Brill, A.B.; Tomonaga, M.; and Heyssel, R.M.; Leukemia in Man Following Exposure to Ionizing Radiation, *Ann Intern Med* 56: 590–609 (April) 1962.
[2] Miller, R.W.: Radiation, Chromosomes and Viruses in the Etiology of Leukemia: Evidence From Epidemiologic Research, *New Eng J Med* 271: 30–36 (July 2) 1964.
[3] Court-Brown, W.M., and Doll, R.: Mortality From Cancer and Other Causes After Radiotherapy for Ankylosing Spondylitis, *Brit Med J* 2: 1327–1332 (Dec 4) 1965.
[4] Bizzozero, O.J., Jr.; Johnson, K.G.; and Ciocco, A.; Radiation-Related Leukemia in Hiroshima and Nagasaki, 1946–1964; I. Distribution, Incidence and Appearance Time, *New Eng J Med* 274: 1095–1101 (May 19) 1966.
[5] Vigliani, E.C., and Saita, G.; Benzene and Leukemia, *New Eng J Med* 271: 872–876 (Oct 22) 1964.