Leukemia following phenylbutazone therapy has previously been reported in 29 cases as summarized in Table 7. Patients known to have received radiotherapy were not tabulated. As observed by Jensen and Roll [27] the diagnosis of leukemia was not well established in at least three patients (cases 3 and 5 of Bean [14] and that of Garrett [16]), and in certain other cases the brief "latent period" (time interval between phenylbutazone exposure and the diagnosis of leukemia) casts doubt on a causal relationship. Of the 26 patients with an apparently established diagnoisis of leukemia, 13 had time intervals of at least 18 months, the minimum latent period estimated for radiation-induced leukemia.[1] These patients consisted of seven men and six women, who ranged in age from 52 to 80 years, suffered from some form of chronic arthritis, and recived phenylbutazone from one month to eight years. One patient had chronic lymphocytic leukemia, but the remaining 12 had either chronic myelogenous leukemia or acute leukemia. Only one patient in this group (patient 1 of Woodliff and Dougan [21]) was noted to have bone marrow hypoplasia prior to the diagnosis of leukemia. It is of interest that two reports included retrospective leukemia surveys, in a search for prior exposure to phenylbutazone. At the leukemia registry of Western Australia, Dougan and Woodliff [24] found that five of 55 adult patients with acute leukemia had a history of phenylbutazone therapy, while only five of 417 patients with "chronic leukemia and allied disorders" had a similar history. Although no comparison group was given, Jensen and Roll [27] reported that among 50 patients admitted to a Danish hospital with actute leukemia, three were known to have received phenylbutazone at intervals of 12, 15, and 27 months prior to the diagnosis of leukemia.

COMMENT

This follow-up survey of patients registered with bone marrow depression showed that those with hematotoxic effects from chloramphenicol had a substantially less favorable outcome, with a greater mortality and lower recovery rate than those with phenydbutazone reactions. Deaths from chloramphenicol-induced marrow depression were attributed mainly to hemorrhage and infection. The hemorrhages were predominantly cerebral or gastrointestinal, and the infections were caused mostly by a variety of gram-negative organisms. Of additional interest in the chloramphenicol group was the occurrence of hemolytic anemia in four cases following the onset of bone marrow depression. Two of the patients were diagnosed as having paroxysmal nocturnal hemoglobinuria, recently recognized as a complication of aplastic anemia induced by drugs.[29] It is likely that some nonhematologic sequelae were actually present prior to onset of the blood dyscrasia, and may have contributed to the development of toxicity. Such disorders would include liver and kidney disease [30] and systemic lupus erythematosus.[31]

Wintrobe [32] has commented on certain features of registries on adverse drug reactions which would limit epidemiologic application of the data. Reports of adverse reactions come from different sources of varying reliability, represent only a small proportion of patients affected, provide no information on incidence of the reactions, and may not necessarily signify a causal relation to the drug which is implicated.[32] Use of these data for our follow-up survey of leukemia was further complicated by (1) the problem of clearly separating the drug exposure and adverse reaction from the outcome (leukemia); (2) the relative sparseness of the data (cases and person-years at risk), so that only very large increases in leukemia incidence could be detected; and (3) the possibility that physicians who did not respond observed different outcomes than those who did (the direction of this potential bias could not be assessed). Despite these limitations, recognized at the outset of the survey, we felt that some value should come from observations which could be made prospectively from the exceptional study group derived from the two registries. It is of interest that, whereas published case reports of leukemia following drug use have implicated phenylbutazone far more often than chloramphenicol, the latter drug was implicated in five of the six registered patients (Table 5), and three of the six unregistered patients (Table 6) in whom leukemia developed.

After excluding three cases in which the development of leukemia may have influenced reporting to the registry, in a total of 151 patients there were three cases of leukemia (2%). These cases were from the 124 patients in the chloramphenicol group, while leukemia did not occur among 24 patients in the phenylbutazone series or three patients registered with toxic effects following