Chemically Induced Leukemia in Humans

by Richard H. Adamson* and Susan M. Seiber*

The human population may be exposed to potentially leukemogenic agents, either in the form of drugs and food additives or as environmental contaminants and pollutants. However, in spite of the large number and diversity of these chemicals, only a few have been implicated as human leukemogens. One such agent is benzene, a known bone marrow depressant. A number of case reports have associated chronic exposure to this agent with the development of acute leukemia, as have several epidemiologic surveys. Treatment with various antitumor agents, including procarbazine, melphalan, thio-TEPA, chlorambucil, and cyclophosphamide, has also been associated with the development of acute leukemia. In addition, chloramphenicol and phenylbutazone have been implicated as human leukemogens, but the association between exposure to these two agents and acute leukemia appears at present to be weaker than it is for benzene and antitumor agent exposure. Despite such associations between exposure to chemicals and acute leukemia, several important problems exist with regard to implicating specific agents in the development of this neoplasm in man, including the paucity of animal models for chemically induced leukemia, and the frequent necessity to rely on single case reports or clusters of cases in which chemical exposures are associated with acute leukemia. Future efforts should be directed at performing properly designed and well executed epidemiologic studies, and at developing new in vitro and in vivo models for the study of this neoplasm.

Introduction

The incidence of all types of leukemia in the general population is approximately 6/100,000 per year (1). Acute nonlymphocytic leukemia (ANLL) accounted for 36% of all leukemias diagnosed in the U.S. between 1954 and 1964, and for 44% of leukemias detected between 1965 and 1969 (2). The etiology of ANLL is largely unknown, although there is some evidence that chromosome breakage and/or aneuploidy may be a factor. For example, patients with Down's, Fanconi's, or Bloom's syndromes are known to suffer a higher incidence of acute myelogenous leukemia than occurs in the general population (3). A viral etiology for ANLL has also been proposed but is difficult to prove, and the causative role of viruses in this disease is impossible to assess at present (4).

It has been known since the early 1960's that ionizing radiation is a leukemogen in experimental animals and in humans (5-7). More recently the leukemogenic potential of chemical agents has been recognized, and a number of chemicals have been clearly shown to produce leukemia in experimental animals (8-12). However, chemically induced hematopoietic neoplasms in rodents, the experimental animals most frequently used in carcinogenesis testing, are primarily lymphomas and lymphoid leukemias; the only chemical which has been reported to induce a high incidence of nonlymphocytic leukemia in rats is N-butyl-N-nitrosourea (13). There is some evidence that certain chemicals may also be causative factors in human ANLL, but several important problems exist with regard to implicating specific agents with the development of this neoplasm in man. First, few satisfactory epidemiologic studies have been carried out in this area, and it is necessary to rely on single case reports or clusters of cases in which chemical exposures are associated with the development of ANLL. In addition, information as to the dose, the dose rate and the size of the population at risk is generally not available. And finally, few suitable animal
models for ANLL have as yet been developed. Nevertheless, based on information obtained from numerous case reports, several epidemiologic studies, and from studies in experimental animals, a number of chemicals have been implicated as etiologic agents in human leukemia.

Chemicals Implicated as Leukemogens in Humans

By far the largest proportion of agents implicated as human leukemogens are the alkylating agents employed in cancer chemotherapy (Table 1). During the past decade, approximately 150 case reports of ANLL developing after treatment with cancer chemotherapeutic agents have appeared in the literature (14). The great majority of these leukemias were morphologic variants of acute myelogenous or myelomonocytic leukemia, and developed after exposure to various alkylating agents either given as single agents or in combination with other drugs. In addition to the antitumor agents, benzene has been implicated as a causative factor in human leukemia, and there is also some evidence that chloramphenicol and phenylbutazone may be leukemogens. Exposure to a variety of other chemicals, including chloroquine (15), lysergic acid diethylamide (16–19), methoxypsoralen (20), griseofulvin (21), and ethylene oxide (22, 23), has been associated with the development of human leukemia, but for these chemicals the present evidence for risk appears to be tenuous at best. Therefore, this discussion will center around only those chemicals which are most strongly implicated as human leukemogens, namely benzene, cancer chemotherapeutic agents, chloramphenicol, and phenylbutazone.

Benzene

Benzene is a constituent of gasoline, occurs in the gaseous phase of cigarette smoke, and is in wide use in industrial and laboratory settings (24). In addition, benzene occurs naturally in the environ-

Table 1. Chemicals implicated as human leukemogens.

| Chemical     | Use            | Carcinogenicity in animals | Reference to human leukemogenesis |
|--------------|----------------|----------------------------|-----------------------------------|
| Benzene      | Industrial     | ±                          | (99-11)                           |
| Procarbazine | Antineoplastic | +                         | (14, 44-49)                       |
| Melphalan    | Antineoplastic | +                         | (50-66, 71)                       |
| Thio-TEPA    | Antineoplastic | +                         | (58, 62, 77-82)                   |
| Chlorambucil | Antineoplastic | +                         | (56, 58, 87-107)                  |
| Cyclophosphamide | Antineoplastic | +                         | (58, 71, 92, 108-115)            |
| Chloramphenicol | Antibiotic    | ±                          | (121-131)                         |
| Phenylbutazone | Anti-inflammatory | –                        | (135-144)                         |

Environmental Health Perspectives
acute myeloblastic leukemia, which was seen in 14 of the 26 cases. The duration of benzene exposure varied from 1-15 years with a mean of 9.7 years. The annual incidence was 13/100,000 compared to 6/100,000 in the general population (29).

In another study, Vigliani and Saita (30) examined the incidence of leukemia in workers at shoe factories and in rotogravure plants where benzene was used as a solvent for glues and inks, respectively. The risk of leukemia was at least 20 times higher than in the general population and the majority of leukemias were myeloblastic, although one case of erythroleukemia also occurred.

Girard and Revol (31) carried out a retrospective study between 1966 and 1969 of 401 subjects with hemopathies and 124 controls with nonhematologic diseases in Lyon hospitals. They found that a significantly higher proportion of patients with aplastic anemia, acute leukemia or chronic lymphocytic leukemia had a history of exposure to benzene or toluene or to products containing benzene or toluene during the previous 10 years than did the controls. This was not true, however, for chronic myeloid leukemia or other blood disorders.

Despite this apparent association between benzene exposure and the development of leukemia, it is important to be aware of several points which tend to confuse the picture. First, in essentially all cases of leukemia attributed to benzene exposure, benzene itself was only one of several chemical agents to which the subject was exposed (24). Second, although there is no question that benzene is toxic in animals, it has not consistently produced hematologic or other malignancies despite extensive testing (32-34). And finally, Thorpe (35) carried out an epidemiologic study of 38,000 petroleum workers exposed to low levels of benzene for 10 years; he found no suggestion of a leukemogenic effect in this group, in which the incidence of leukemia resembled that of the general population. Although the Thorpe study has been criticized for some aspects of the methodology (36), nevertheless the results must be considered along with those from the other positive studies described above.

### Procarbazine

Procarbazine is an antineoplastic agent which is used chiefly as a component of the MOPP regimen. The MOPP regimen, which also includes nitrogen mustard (M), vincristine (O), and prednisone (P), is in wide use for treating Hodgkin's disease, a malignancy for which it appears curative (37). Direct evidence for the leukemogenic effects of procarbazine comes from animal studies in mice, rats and nonhuman primates. Procarbazine has been indirectly linked to human ANLL through numerous clinical case reports of Hodgkin's disease patients treated with the MOPP regimen who subsequently developed ANLL (14), and several surveys of large numbers of treated Hodgkin's disease patients in which the same phenomenon was noted.

The most persuasive experimental evidence that procarbazine is leukemogenic derives from a study of the long-term toxicity of this drug in nonhuman primates (38). A group of 50 rhesus and cynomolgus monkeys has received intraperitoneal or subcuta-

### Table 2. Acute leukemia induced in nonhuman primates by long-term treatment with procarbazine.

| Monkey No. | Species | Sex | Dosage schedule | Total dose, g | Latent period, mo | Histological diagnosis |
|------------|---------|-----|-----------------|--------------|------------------|-----------------------|
| 267D       | Rhesus  | F   | 50 mg/kg 1 time/wk SC for 15 mo., then 10 mg/kg 5 times/wk PO for 1 mo. | 2.64         | 16               | Acute myelogenous leukemia |
| 733I       | Cyno    | M   | 20 mg/kg 1 time/wk IP for 57 mo. | 7.29         | 57               | Acute undifferentiated leukemia |
| 726I       | Cyno    | M   | 20 mg/kg 1 time/wk IP for 68 mo. | 16.24        | 68               | Acute myelogenous leukemia |
| 313E       | Rhesus  | F   | 5-50 mg/kg 1 time/wk SC for 35 mo., then 10 mg/kg 5 times/wk PO for 33 mo. | 37.26        | 68               | Acute myelogenous leukemia |
| 567G       | Rhesus  | F   | 10-25 mg/kg 1 time/wk SC for 6 mo., then 10 mg/kg 5 times/wk PO for 71 mo. | 49.99        | 77               | Acute myelogenous leukemia |
| 13T        | Rhesus  | M   | 25-50 mg/kg 1 time/wk SC for 36 mo., then 10 mg/kg 5 times/wk PO for 73 mo. | 101.65       | 109              | Acute myelogenous leukemia |
| 336E       | Rhesus  | F   | 10-50 mg/kg 1 time/wk SC for 33 mo., then 10 mg/kg 5 times/wk PO for 110 mo. | 103.69       | 143              | Acute myeloblastic leukemia |

*Treatment with procarbazine began with 48 hr after birth for all monkeys except #13T, which received the first dose at 5 months of age.*

June 1981
neous and oral doses of procarbazine for periods up to 14 years. To date, 13 (26%) of the monkeys have developed malignant neoplasms, and 7 of the 13 malignancies were ANLL (Table 2). The leukemias were diagnosed in monkeys that had received an average cumulative procarbazine dose of 45.5 g (range 2.64-103.69 g); they developed after latent periods ranging from 16 to 143 months (average 77 months). The spontaneous tumor incidence in this monkeys colony is 2.8%, and no case of acute leukemia has been observed in control monkeys during the past 14 years.

Procarbazine is a potent carcinogen in rodents as well as in nonhuman primates; however, the tumors it induces in mice and rats are not ANLL, but instead are lung and mammary carcinomas and lymphocytic leukemia (12, 39, 40). As noted above, few experimental animals develop ANLL in response to carcinogen exposure. The exceptions are rats exposed to N-butyl-N-nitrosourea and nonhuman primates, suggesting that the latter species may be a particularly good model for evaluating the potential leukemogenicity of drugs and other chemicals.

The leukemogenic activity of procarbazine has also been inferred from human observations. Several relatively large surveys of Hodgkin's disease patients have been published which specify the total number of patients observed, the length of time during which the observations were made, and the number of patients who developed ANLL. From this information it was possible to estimate the incidence of ANLL and compare it with that in the general population of the U.S. (2.2/100,000 per year). The incidence of ANLL, expressed as cases/100,000 per year, in nine groups of Hodgkin's disease patients was calculated from published reports, and is shown graphically in Figure 1.

In two surveys of Hodgkin's disease patients, encompassing over 3,000 cases observed from 1944 to 1953 (41) and from 1949 to 1962 (42), no cases of ANLL were noted. In most of the other surveys (43-47), however, the incidence of ANLL has ranged between 15 and 26/100,000 per year, representing a 5-10-fold increase over the incidence of ANLL in the general population. An incidence of 156 was calculated for a group of patients described by Weiden (48), and an even higher incidence (406) derived from a report by Bonadonna et al. (49). Although these two values represent 50-100 fold increases over the incidence of ANLL in the general population, it should be noted that they came from small groups of Hodgkin's disease patients which have been treated relatively recently.

Thus it appears that successfully treated Hodgkin's disease patients are at increased risk of developing ANLL. The role that the therapy they received played in the etiology of the leukemias is not completely clear. For example, it is possible that Hodgkin's disease patients are predisposed to develop multiple neoplasms, and that the therapy employed served to extend their survival sufficiently long to allow for the development of the second tumor (ANLL). In addition, many (but not all) of the patients developing ANLL following successful treatment for Hodgkin's disease received ionizing radiation, a known human leukemogen (6, 7). Nevertheless, there does seem to be a clear association between the MOPP regimen and ANLL; on the basis of the available experimental evidence, the component of the MOPP regimen most likely to be leukemogenic is procarbazine.

**Melphalan**

Melphalan is an antineoplastic agent active against a variety of human neoplasms, and is employed as prophylactic chemotherapy following surgery for ovarian and mammary carcinoma as well. Its widest use, however, is in the treatment of multiple myeloma and other plasma cell dyscrasias. It is now apparent that patients receiving prolonged treatment with melphalan are at increased risk of developing ANLL. The association between melphalan treatment and ANLL comes from numerous case reports of patients developing leukemia after melphalan treatment for malignant disease (50-62), including at least 21 patients with multiple myeloma (50-56, 61), 14 women with ovarian carcinoma (57-61), and one patient with
mammary carcinoma (62). Several patients with nonmalignant disease who received therapy with melphalan have also developed ANLL (63-66), and a number of large surveys of multiple myeloma patients have indicated that this population may indeed be at increased risk for ANLL.

The incidence of ANLL in multiple myeloma patients was calculated for seven groups of patients in which the appropriate information as to sample size, observation period, and number of patients developing this complication was specified (Fig. 2). In one survey (67), no cases of multiple myeloma terminating as ANLL were found among 57 patients observed between 1930 and 1956. In six other surveys of myeloma patients (68-73), the incidence of ANLL ranged between 20 to more than 5000. This latter value, representing an approximately 2000-fold increase over the incidence in the general population, came from a report by Anderson and Videbaek (71) on a small group of patients observed over a relatively short and recent time period. As with the Hodgkin's disease patients developing ANLL, the leukemia emerging as a terminal event in multiple myeloma patients may be related to the therapy employed. Again, however, the picture is complicated by the fact that a proportion of the myeloma patients developing ANLL were also irradiated.

A few studies have been carried out on the carcinogenicity of melphalan in experimental animals, and have produced positive results. For example, Shimkin et al. (74) reported that melphalan increases the incidence of pulmonary tumors in strain A mice, and the drug was also found to increase the number of lung tumor nodules per mouse from a control level of 0.5 to 4.5 (75). Melphalan treatment also resulted in a significant increase in the incidence of peritoneal sarcomas in the CD rat (40).

The issue of the potential leukemogenicity of melphalan is an important one because of its wide clinical use, and the animal data are still rather scanty and difficult to extrapolate to man. Therefore, a study of the leukemogenic effects of melphalan in nonhuman primates was initiated in this laboratory several years ago. A total of 20 monkeys is currently being treated with melphalan at a dose (1.2 mg/m²) comparable to that used clinically; they receive the drug orally, 5 days every week. To date (Table 3), one group of 10 monkeys has received an average cumulative melphalan dose of 59.5 g/m² over an average of 64 months. The second group began receiving melphalan 10 months after treatment of the first group had been initiated, and thus far has ingested an average cumulative dose of 52.6 g/m². In order to put these cumulative melphalan doses into perspective, women receiving prophylactic melphalan therapy for ovarian carcinoma would receive in the prescribed 18 month dosing period a total dose of 660 mg/m² (76), a dose some 100-fold lower than that already ingested by these monkeys. Moreover, the cumulative melphalan dose administered to patients who subsequently developed ANLL ranged between 0.19 g/m² (57) and 5.1 g/m² (73), with latent periods ranging from 2 to 105 months. None of the monkeys on the study have died and all appear to be in good health. Thus, it seems that if melphalan is a carcinogen in monkeys, the latent period required for its carcinogenic effects to become manifest is in excess of 5 years.

**Table 3. Summary of melphalan study in nonhuman primates.**

| No. of monkeys | Months dosed | Avg. total dose, g | Avg. total dose, g/m² |
|----------------|--------------|--------------------|-----------------------|
| 10             | 64           | 4.96               | 59.5                  |
| 10             | 54           | 4.38               | 52.6                  |

*Monkeys are receiving oral doses of melphalan (1.2 mg/m²) daily, 5 days every week.*

**Figure 2.** Incidence of ANLL in various groups of multiple myeloma patients, expressed as cases/100,000/year. Arrow indicates approximate time melphalan introduced into clinical use for treating this neoplasm.

June 1981
Chlorambucil

Chlorambucil is an alkylating agent which has clinical activity against a variety of tumors and which has also been found useful for treating collagen vascular and other presumably autoimmune disorders. A number of case reports have linked prolonged treatment with this drug with the development of ANLL in patients with nonmalignant disease (87-95), including 20 with arthritis (89, 90, 92, 94), two with Wegener's granulomatosis (91), four with glomerulonephritis (93-95), and individuals with malignant exophthalmia (87) and scleroderma (88). In addition ANLL has been diagnosed in at least 24 patients after they had received chlorambucil for other malignancies (56, 58, 96-107); these cases included nine patients with Hodgkin's disease (96, 97, 105) or non-Hodgkin's lymphoma (56, 98, 99, 104), one patient with Waldenstrom's macroglobulinemia (100), four patients with chronic lymphocytic leukemia (101, 102, 105), three patients with breast cancer (107), and seven women with ovarian or Fallopian tube carcinomas (58, 103, 106). Many of these reports have come from France, where chlorambucil is particularly popular. Chlorambucil has carcinogenic activity in rodents, inducing lymphosarcomas and pulmonary and ovarian tumors in mice (40, 74, 75) and lymphomas in rats (40). In view of the numerous case reports in which prolonged chlorambucil treatment has been associated with the development of ANLL and the positive results with this drug in the rodent carcinogenesis bioassay, it is highly likely that chlorambucil is a human leukemogen.

Cyclophosphamide

Cyclophosphamide is a widely employed alkylating agent useful as a single agent and as a component of combination chemotherapy regimens. As with chlorambucil, it is in increasing use for the treatment of various nonmalignant conditions including chronic glomerulonephritis, rheumatoid arthritis, and other collagen-vascular disorders. As its use in both malignant and nonmalignant disease has increased, so has the number of reports linking treatment with this drug to the development of ANLL. Individuals developing ANLL after cyclophosphamide treatment for nonmalignant disease include six arthritis patients (89, 90, 92, 108), three patients with chronic renal disease (109), and one patient each with fibromatosis (110), Sjogren's syndrome (111), Wegener's granulomatosis (112), and macroglobulinemia (113). Moreover, ANLL has been reported to be the terminal event in five patients with multiple myeloma (71, 72, 113, 114), two ovarian carcinoma patients (58), and four women with breast cancer (115). Cyclophosphamide has well-demonstrated carcinogenicity in rodents (40, 74, 75, 116), and a study of its leukemogenic potential in nonhuman primates was recently initiated in this laboratory.
a number of case reports in which ANLL was associated with chloramphenicol treatment (121-131). Fraumeni's review (128) of clinical and epidemiologic information related to the outcome of patients with chloramphenicol-induced bone marrow depression failed to implicate the drug as clearly leukemogenic. Unfortunately animal studies of chloramphenicol carcinogenesis have not been informative. German and Loc (132) reported that spleen homogenates from chloramphenicol-treated mice produced tumors when inoculated into recipient mice; however, other studies in rats have shown that chloramphenicol treatment exerts a protective effect against liver tumor induction by fluorenylacetamide (133) and diethylnitrosamine (134).

Phenylbutazone
Phenylbutazone is an anti-inflammatory agent used in the treatment of rheumatic disorders and for the therapy of acute gout. It is known to produce bone marrow toxicity in some patients, and late in the 1950's reports began appearing in the literature linking treatment with this drug to ANLL (135-138). Bean (139) reported six cases of leukemia in patients who had received phenylbutazone, and Woodliff and Dougan (140) described five cases of acute leukemia developing in patients treated with phenylbutazone out of a total of 55 cases of acute leukemia diagnosed between 1959-1963 in Australia. Similarly, of 50 cases of acute leukemia recorded in Scandinavia between 1959-1964, three were diagnosed in individuals receiving phenylbutazone (141). Nevertheless, phenylbutazone does not seem to be mutagenic (142, 143) or to induce chromosomal damage in bone marrow cells of rats (144) or hamsters (145), and a study of its carcinogenic activity in rats produced negative results (146). Moreover, Fraumeni (128) failed to find an association between phenylbutazone-induced myelosuppression in 24 treated patients and the subsequent development of ANLL.

Conclusions and Recommendations
The human population may be exposed, either intentionally in the form of drugs and food additives or unintentionally as is the case with environmental contaminants and pollutants, to potentially leukemogenic agents. Despite the large number and the diversity of these chemicals, only relatively few have been implicated as human leukemogens, namely benzene, several alkylating antitumor agents, chloramphenicol, and phenylbutazone. The association between human ANLL and exposure to benzene and the antitumor agents appears at present to be stronger than it is for chloramphenicol and phenylbutazone. It is possible that a given proportion of individuals who develop bone marrow depression as a consequence of chemical exposure may ultimately develop ANLL regardless of which agent produced the marrow toxicity, and indeed all of the chemicals which have been implicated as leukemogens can be myelosuppressive. Nevertheless, there are also chemicals which are potent depressants of bone marrow function but that have not been associated with human ANLL, and these agents include methotrexate, cytosine arabinoside, and the vinca alkaloids. Thus the relationship between chemically induced bone marrow suppression and ANLL is not entirely clear.

Epidemiologic studies can give important and meaningful clues to the leukemogenic potential of drugs and chemicals in our environment, but only if they are properly designed, properly controlled and well executed. Unfortunately, many such studies in the past have been flawed, their conclusions subject to debate. Epidemiologic studies also have the drawback of being expensive and time-consuming; in addition, although they are usually able to define specific populations at risk, they rarely are capable of identifying single agents as causative factors. More importantly, however, they are useful in identifying a hazardous substance after exposure has taken place, but obviously are not able to prevent its introduction into the environment or into clinical use.

One of the problems in avoiding human exposure to potentially leukemogenic chemicals is the paucity of animal models for evaluating such substances. Although rodents are commonly used in carcinogen bioassays, the only chemical which produces a high yield of ANLL in rodents is N-butyl-N-nitrosourea, and it appears that this malignancy is produced only in rats. Besides man, the only species of animal which develops ANLL in response to chemical exposures is the Old World monkey. As with epidemiologic surveys, however, studies of potential leukemogens in monkeys are costly and time-consuming. This lack of suitable animal models represents a major obstacle to identifying chemicals as potential human leukemogens, and it would be prudent during the next few years to direct greater research effort toward developing new models both in vitro and in animals, and more effective utilization of existing animal models for this neoplasm. The development and utilization of in vitro and in vivo test systems will serve to prevent potential leukemogens from entering the

June 1981
human environment; future well designed and
trolled epidemiologic surveys will allow for the
identification of leukemogens already present. It is
only through these efforts that human leukemogens
can be detected and our exposure to them minimized.

REFERENCES
1. Waterhouse, J. A. H. Cancer Handbook of Epidemiology
   and Prognosis. Churchill Livingstone, Edinburgh and
   London, 1974, p. 80.
2. End Results in Cancer, Report No. 4, End Results Section,
   Biometry Branch, National Cancer Institute, DHEW Pub-
   lication No. (NIH) 73-272, U. S. Department of Health,
   Education and Welfare, Public Health Service, National
   Institutes of Health, National Cancer Institute, Bethesda,
   Md. 20014, 1972, p. 193.
3. Ellison, R. R. Acute myelocytic leukemia. In: Cancer
   Medicine. J. F. Holland and E. Frei, Eds., Lea and
   Febiger, Philadelphia, 1973, pp. 1199-1234.
4. Rauscher, F. J., Jr. Background and current status of the
   search for etiological agents in leukemia and lymphoma in
   man. In: Neoplasia in Childhood. (12th Annual Clinical
   Conference on Cancer, M. D. Anderson Hospital and
   Tumor Institute, Houston, Texas), Year Book Medical
   Publishers, Chicago, 1969, p. 25.
5. Kaplan, H. S. Leukemia and lymphoma in experimental
   and domestic animals. Ser. Haematol. 7: 94 (1974).
6. Pochin, E. E. Leukemia following radioidine treatment of
   thryotoxicosis. Brit. Med. J. 2: 1545 (1960).
7. Smith, P. G., and Doll, R. Late effects of x-irradiation in
   patients treated for metropathia haemorrhagica. Brit. J.
   Radiol. 49: 224 (1976).
8. Huggins, C. B., and Sugiyama, T. Induction of leukemia in
   rats by pulse doses of 7,12-dimethylbenz(a)anthracene.
   Proc. Natl. Acad. Sci. (U.S.) 55: 74 (1966).
9. Hartman, H. A., Miller, E. C., Miller, J. A., and Morris,
   F. K. The leukemogenic action of 2-acetylaminophenanthrene.
   Cancer Res. 19: 210 (1959).
10. Morris, H. P., Wagner, B. P., Ray, F. E., Snell, K. C., and
    Stewart, H. L. Comparative studies of cancer and other
    lesions of rats fed N,N-2,7-fluorenylenebisacetamide or
    N-2-fluorenylacetamide. Natl. Cancer Inst. Monograph 5: 1
    (1961).  
11. Kelly, M. G., O'Gara, R. W., Yancey, S. T., and Botkin, C.
    Carcinogenicity of 1-methyl-1-nitrosourea in newborn mice
    and rats. J. Natl. Cancer Inst. 41: 619 (1968).
12. Kelly, M. G., O'Gara, R. W., Gadekar, K., Yancey, S. T.,
    and Oliviero, V. T. Carcinogenic activity of a new antitumor
    agent, N-isopropyl-a-(2-methylhydrazine)-p-toluamide,
    hydrochloride (NSC-77213). Cancer Chemother. Rep. 39:
    77 (1964).
13. Odashima, S. Leukemogenic effects of N-nitroso-N-
    nitrosoamides in rats. Gann Monograph Cancer Res. 12:
    283 (1972).
14. Sieber, S. M., and Adamson, R. H. Toxicity of antitumor
    agents in man: chromosomal aberrations, antifertility ef-
    fects, congenital malformations and carcinogenic potential.
    Adv. Cancer Res. 22: 57 (1975).
15. Nagaratnam, N., Chetiyawardana, A. D., and Rajiyah, S.
    Aplasia and leukemia following chloroquine therapy.
    Postgrad. Med. J. 54: 108 (1978).
16. Goh, K., and Bauman, A. W. Lysergic acid diethylamide
    and acute leukemia. J. Am. Med. Wom. Assoc. 33: 419
    (1978).
17. Sohn, K., and Boggs, D. R. Klinefelter's syndrome, LSD
    usage and acute lymphoblastic leukemia. Clin. Genet. 6: 20
    (1974).
18. Garson, O. M., and Robson, M. K. Studies in a patient with
    acute leukemia after lysergide treatment. Brit. Med. J. 2:
    800 (1969).
19. Grossbard, L., Rosen, D., McGilvray, E., de Cappa, A.,
    Miller, O., and Bank, A. Acute leukemia with Ph-like
    chromosome in an LSD user. J. Am. Med. Assoc. 205: 791
    (1968).
20. Hanson, N. E. Development of acute myeloid leukemia in a
    patient with psoriasis treated with oral 8-methoxypsoralen
    and long-wave ultraviolet light. Scand. J. Haematol. 22: 57
    (1979).
21. König, E., Berthold, K., Hienz, H. A., and Brittinger, G.
    Griseofulvin and chronic granulocytic leukemia. Helv.
    Med. Acta 35: 103 (1969/1970).
22. Hogstedt, C., Malmqvist, N., and Wadman, B. Leukemia
    in workers exposed to ethylene oxide. J. Am. Med. Assoc.
    241: 1132 (1975).
23. Hogstedt, C., Röhlen, O., Berndtsson, B. S., Axelson, O.,
    and Ehrenberg, L. A cohort study of mortality and cancer
    incidence in ethylene oxide production workers. Brit. J.
    Ind. Med. 36: 276 (1979).
24. Health Effects of Benzene: A Review Committee on
    Toxicology, Academy of Life Sciences, National Research
    Council, National Academy of Sciences, Washington, D.
    C., 1976.
25. Tabershaw, I. R. Protection from adverse effects of
    benzene. Texas Rep. Biol. Med. 37: 162 (1978).
26. Saita, G. Benzene induced hypoplastic anemia and
    leukemia. In: Blood Disorders Due to Drugs and Other
    Agents, R. H. Girdwood, Ed., Exerpta Medica, Amsterdam,
    1975, pp. 127-146.
27. Gunz, F., and Baikie, A. G. Leukemia, 3rd Ed. Grune and
    Stratton, New York, 1974, p. 110.
28. Cronkite, E. P. Evidence for radiation and chemicals as
    leukemogenic agents. Arch. Environ. Health 3: 297 (1961).
29. Aksoy, M. Erdem, S., and Dincol, G. Leukemia in shoe
    workers exposed chronically to benzene. Blood 44: 837
    (1974).
30. Vigliani, E. C. and Saita, G. Benzene and leukemia. New
    Engl. J. Med. 271: 872 (1964).
31. Girard, R. and Revol. L. La Fréquence d'une exposition
    benzénique au cours des hémostopathies graves. Nouv. Rev.
    Fr. Hematol. 10: 477 (1970).
32. Laerum, O. D. Reticulum cell neoplasms in normal and
    benzene treated hairless mice. Acta Pathol. Microbil. Scand.
    A81: 57 (1973).
33. Ward, J. M., Weisburger, J. H., Yamamoto, R. S.,
    Benjamin, T., Brown, C. A., and Weisburger, E. K.
    Long-term effect of benzene in C3HBL/6N mice. Arch.
    Environ. Health 30: 22 (1975).
34. Maltoni, C., and Scarnato, C. First experimental demon-
    stration of the carcinogenic effects of benzene. Med.
    Lav. 70: 362 (1979).
35. Thorpe, J. J. Epidemiologic survey of leukemia in persons
    potentially exposed to benzene. J. Occup. Med. 16: 375
    (1974).
36. Brown, S. M. Leukemia and potential benzene exposure. J.
    Occup. Med. 17: 5 (1975).
37. Berard, C. W., Gallo, R. C., Jaffe, E. S., Green, I., and
    DeVita, V. T. Current concepts of leukemia and lympho-ma:
    etiology, pathogenesis and therapy. Ann. Intern. Med. 85:
    351 (1976).
38. Sieber, S. M., Correa, P., Dalgard, D. W., and Adamson,
    R. H. Carcinogenic and other adverse effects of procarbazine
    in nonhuman primates. Cancer Res. 38: 2125 (1978).

Environmental Health Perspectives
39. Kelly, M. G., O’Gara, R. W., Yancey, S. T., and Botkin, C. Induction of tumors in rats with procaine hydrochloride. J. Natl. Cancer Inst. 40: 1027 (1968).
40. Weisburger, J. H., Grieswold, J. P., Prejean, J. D., Casey, A. E., Wood, H. B., and Weisburger, E. K. The carcinogenic properties of some of the principal drugs used in clinical cancer chemotherapy. Recent Results Cancer Res. 32: 1 (1975).
41. Moertel, C. G., and Hagedorn, A. B. Leukemia or lymphoma and coexistent primary malignant lesions: a review of the literature and study of 120 cases. Blood 12: 788 (1957).
42. Berg, J. W. The incidence of multiple primary cancers. I. Development of further cancers in patients with lymphomas, leukemias and myeloma. J. Natl. Cancer Inst. 38: 741 (1967).
43. Peters, V. M., and Middlemiss, K. C. H. A study of Hodgkin's disease treated by irradiation. Am. J. Roent. Rad. Ther. Nuclear Med. 79: 114 (1968).
44. Ezdinli, E. Z., Sokal, J. E., Aungst, C. W., Kim, U., and Sandberg, A. A. Myeloid leukemia in Hodgkin's disease: chromosomal abnormalities. Ann. Intern. Med. 71: 1097 (1969).
45. Newman, D. R., Maldonado, J. E., Harrison, E. G., Kiely, J. M., and Linman, J. W. Myelomonoctytic leukemia in Hodgkin's disease. Cancer 25: 128 (1970).
46. Sahakian, G. J., Al-Mondhiry, H., Lacher, M. J., and Connolly, C. E. Acute leukemia in Hodgkin's disease. Cancer 33: 1369 (1974).
47. Canellis, G. P., DeVita, V. T., Arseneau, J. C., Whang-Peng, J., and Johnson, R. E. C. Second malignancies complicating Hodgkin's disease in remission. Lancet i: 947 (1975).
48. Weiden, P. L., Lerner, K. G., Gerdes, A., Heywood, J. D., Fefer, A., and Thomas, E. D. Pancretopenia and leukemia in Hodgkin's disease: report of three cases. Blood 42: 571 (1973).
49. Bonadonna, G., DeLena, M., Banfi, A., and Lattuada, A. Secondary neoplasms in malignant lymphomas after intensive therapy. New Engl. J. Med. 288: 1242 (1973).
50. Holt, J. M., Robb-Smith, A. H. T., Callender, S. T., and Spriggs, A. I. Multiple myeloma—development of alternative malignancy following successful chemotherapy. Brit. J. Haematol 22: 633 (1972).
51. Marcovic, N., Hansson, B.-G., and Hallen, J.: Myelomatosis and acute monocytic leukemia. Scand. J. Haematol. 12: 32 (1974).
52. Marsan, C., Henon, P., Quillard, A., Grimaldi, A., Cywiner-Golenzer, C., Adotti, F., Dryll, A., and Roujeau, J. Myeloma et leucose myelo-monocytare. Role du melphalan. Nouv. Presse Med. 2: 2585 (1973).
53. Law, I. P., Plovinik, H. S., and Beddow, D. G. Multiple myeloma, sideroblastic anemia and acute leukemia. New Engl. J. Med. 294: 164 (1976).
54. Gonzalez, F., Trujillo, J. M., and Alexanian, R. Acute leukemia in multiple myeloma. Ann. Intern. Med. 86: 440 (1977).
55. Dubrovsksy, D., and Jacob, P. Acute leukaemia and myeloma. Lancet i: 1113 (1974).
56. Clément, F. Les hémosthapes malignes induites. Schweiz. Med. Wschr. 109: 544 (1979).
57. Shetty, M. R. and Freid, R. Therapy-linked leukemia: A case report. Gyn. Oncol. 7: 264 (1979).
58. Reimer, R. R., Hoover, R., Fraumeni, J. F., and Young, R. C. Acute leukemia after alkylating agent therapy of ovarian cancer. New Engl. J. Med. 287: 177 (1977).
59. Foucar, K., McKenna, R. W., Bloomfield, C. D., Bowers, T. K., and Brunning, R. D. Therapy-related leukemia. Cancer 43: 1265 (1979).
60. Einhorn, N. Acute leukemia after chemotherapy (melphalan). Cancer 41: 444 (1978).
61. Freisler, H. D., and Lyman, G. H. Acute myelogenous leukemia subsequent to therapy for a different neoplasm: clinical features and response to therapy. Am. J. Hematol. 3: 209 (1977).
62. Rosner, F., Carey, R. W., and Zarrabi, M. H. Breast cancer and acute leukemia: report of 24 cases and review of the literature. Am. J. Hematol. 4: 151 (1978).
63. De Bock, R. F. K., and Peetermans, M. E. Leukemia after prolonged use of melphalan for non-malignant disease. Lancet i: 1208 (1977).
64. Grünwald, H. W., and Rosner, F. Acute leukemia and immunosuppressive drug use. Arch. Intern. Med. 139: 461 (1979).
65. Kyle, R. A., Pierre, R. V., and Bayrd, E. D. Primary amyloidosis and acute leukemia associated with melphalan therapy. Blood 44: 333 (1974).
66. Stavem, P., and Harboe, M. Acute erythroleukemia in a patient treated with melphalan for the cold agglutinin syndrome. Scand. J. Haematol. 8: 375 (1971).
67. Weitzel, R. A. Carcinoma coexistent with malignant disorders of plasma cells. Cancer 11: 546 (1958).
68. Nordenson, N. G. Myelomatosis: a clinical review of 310 cases. Acta Med. Scand. (Suppl.) 446: 178 (1966).
69. Edwards, G. A., and Zawadzki, Z. A. Extraosseous lesions in plasma cell myeloma. Am. J. Med. 43: 194 (1947).
70. Kyle, R. A., Pierre, R. V., and Bayrd, E. D. Multiple myeloma and acute myelocytic leukemia. New Engl. J. Med. 283: 1121 (1970).
71. Andersen, E., and Videbaek, A. Stem cell leukemia in myelomatosis. Scand. J. Haematol. 7: 201 (1970).
72. Karchmer, R. K., Amare, M., Larsen, W. E., Mallouk, A. G., and Caldwell, G. G. Alkylating agents as leukemogens in multiple myeloma. Cancer 33: 1108 (1974).
73. Khaleel, M., Keane, W. M., and Lee, G. R. Sideroblastic anemia in multiple myeloma: a preleukemic change. Blood 41: 17 (1974).
74. Shimkin, M. B., Weisburger, J. H., Weisburger, E. K., Guibareff, N., and Suntzeff, V. Bioassay of 29 alkylating chemicals by the pulmonary-tumor response in strain A mice. J. Natl. Cancer Inst. 36: 915 (1966).
75. Weisburger, E. K. Carcinogenicity of alkylating agents. Publ. Health Rep. 81: 772 (1966).
76. DeVita, V. T., Wasserman, T. H., Young, R. C., and Carter, S. K. Perspectives on research in gynecologic oncology. Treatment protocols. Cancer 38: 509 (1976).
77. Garfield, D. H. Acute erythromegakaryocytic leukemia after treatment with cytostatic agents. Lancet ii: 1037 (1970).
78. Perlman, M. and Walker, R. Acute leukemia following cytotoxic chemotherapy. J. Am. Med. Assoc. 224: 250 (1973).
79. Allan, W. S. A. Acute myeloid leukemia after treatment with cytostatic agents. Lancet ii: 775 (1970).
80. Solomon, R. B. and Firat, D. Acute leukemia. N. Y. State J. Med. 71: 2422 (1971).
81. Carey, R. W., and Long, J. C. Presentation of case 28-1977. New Engl. J. Med. 297: 102 (1977).
82. Kapadia, S. B., and Krause, J. R. Ovarian carcinoma terminating in acute non-lymphocytic leukemia following alkylating agent therapy. Cancer 41: 1676 (1978).
83. Smith, C. G., S., and Meyler, L. Acute myelogenous leukemia after treatment with cytostatic agents. Lancet ii: 671 (1970).
Environmental Health Perspectives
chloramphenicol or phenylbutazone: leukemia and other sequelae. J. Am. Med. Assoc. 201: 828 (1967).

129. Brauer, N. J., and Dameshek, W. Hypoplastic anemia and myeloblastic leukemia following chloramphenicol therapy. N. Engl. J. Med. 277: 1003 (1967).

130. Gadnon, H., Gethmann, U., Jessenberger, K., and Riehm, H. Akute leukämie nach Chloramphenicol-Exposition? Mschr. Kinderheilk. 121: 590 (1973).

131. Awwaad, S., Khalifa, A. S., and Kamel, K. Acute leukemia after Chloramphenicol exposure? Mschr. Kinderheilk. 121: 590 (1973).

132. German, A., and Loc, T. B. Induction of a transplantable tumor in Swiss mice by injections of chloramphenicol. Ann. Pharm. France 20: 116 (1962).

133. Puron, R., and Firminger, H. I. Protection against induced cirrhosis and hepatocellular carcinoma in rats by chloramphenicol. J. Natl. Cancer Inst. 35: 29 (1965).

134. Alonso, A., and Herranz, G. Der Einfluss von Chloramphenicol auf die Leber-Cancerisierung durch Diathylnitro- samin. Naturwissenschaften 57: 247 (1970).

135. Hamer, J. W., and Gunz, F. W. Multiple aetiological factors in a case of acute leukemia. New Zeal. Med. J. 71: 141 (1970).

136. Chatterjea, J. B. Leukemia and phenylbutazone. Brit. Med. J. 4: 875 (1964).

137. Chalmers, T. M., and McCarthy, D. D. Phenylbutazone therapy associated with leukemia. Brit. Med. J. 1: 747 (1964).

138. Hart, G. D. Leukaemia and phenylbutazone. Brit. Med. J. 2: 569 (1964).

139. Bean, R. H. D. Phenylbutazone and leukemia. A possible association. Brit. Med. J. 4: 1552 (1960).

140. Woodliff, H. J., and Dougan, L. Acute leukemia associated with phenylbutazone treatment. Brit. Med. J. 1: 744 (1964).

141. Jensen, M. K., and Roll, K. Phenylbutazone and leukemia. Acta Med. Scand. 178: 585 (1965).

142. McCann, J., Choi, E., Yamasaki, E., and Ames, B. N. Detection of carcinogens as mutagens in the Salmonella/microsome test: assay of 300 chemicals. Proc. Natl. Acad. Sci. (U.S.) 72: 5135 (1975).

143. Machemer, L., and Hess, R. Induced dominant lethals in female mice: effects of triaziquone and phenylbutazone. Experientia 29: 190 (1973).

144. Gebhart, E., and Wissmüller, H. F. Investigations on the effect of phenylbutazone on chromosomes and mitosis in the bone marrow of rats. Mutat. Res. 17: 282 (1973).

145. Müller, D., and Strasser, F. F. Comparative studies on the Chinese hamster bone marrow after treatment with phenylbutazone and cyclophosphamide. Mutat. Res. 13: 377 (1971).

146. Breuer, H., Knupper, R., and Schmähl, D. Fehlen einer carcinogenen Wirkung bei einem körpereigenen Steroidepoxyd. Z. Krebsforsch. 66: 549 (1965).