py-induced cures in patients with limited stage disease (6-10).

For patients with disseminated diffuse histiocytic lymphoma, several drug combinations are available that assure high response rates. Table 1 of the paper by Laurence and associates in this issue (11) summarizes results of combination chemotherapy protocols in previously untreated patients with advanced diffuse histiocytic lymphoma. Since 1969 the frequency of complete remission has Increased from 40% to over 70% using various agents in combination chemotherapy protocols. Not only are 60% to 80% of patients achieving complete remissions, but 60% to 80% of those achieving complete remissions are disease-free for longer than 2 years (median survival) without maintenance therapy. *Also,* these newer drugs and new drug combinations have substantially reduced the incidence of central nervous system involvement seen in patients at high risk for such complications.

With the cure of diffuse histiocytic lymphoma becoming a reality in many patients, we must begin to address five residual issues. First, diffuse histiocytic lymphoma is a heterogeneous group of disorders as shown by Lukes and Collins (12) and others, and recognized in the recently proposed "Working Formulation for Clinical Usage" (13). Which histologic or immunologic subsets predict success or failure in response to current therapy programs (14-17)? Second, what are other characteristics of patients who do not respond to the current treatment programs? An analysis of this issue will require the identification of risk factors such as age, sex, location of primary lesion, bulky disease, stage IV, systemic symptoms, previous therapy, biochemical markers, and other factors (16, 18). Third, when should additional central nervous system prophylaxis be offered separately from the systemic treatment program? Fourth, is there any role for maintenance chemotherapy when a pathologically proven complete remission has been induced? And fifth, what new treatment strategies can be devised for persons with pathclogic, immunologic, and clinical risk factors that predict the failure of current treatment programs to induce complete remission?

Currently, 80% to 100% of patients with limited diffuse histiocytic lymphoma can be offered cure (with 5- and 10-year actuarial disease-free survival rates established in a number of series) using radiotherapy, chemotherapy, or a combination of the two therapies. The actuarial 2- and 5-year survival rate of over 60% of patients with disseminated diffuse histiocytic lymphoma is within reach. The challenge is to identify, early in the course of their disease, those patients who will fail current initial induction regimens and to devise treatment strategies and alternate programs to assure that these patients also will be cured. (JOHN E. ULTMANN, M.D.; *Department of Medicine and Cancer Research Center, University of Chicago; Chicago, Illinois*)

Grant support: in part by grant CA-14599. U.S. Public Health Service, the Joanne Heppes Fund, the Goldblatt Brothers Employees Nathan Goldblatt Cancer Research Fund, and the Jean Heiman Fund.

REFERENCES

1. DEVITA VT, JR. The consequences of the chemotherapy of Hodgkin's Disease the 10th David A. Karnofsky Memorial Lecture. *Cancer.* 1981;47:1-13.
2. CANTOR KP, FRAUMENI JF. Distribution of non-Hodgkin's lymphoma in the United States between 1950 and 1975. *Cancer Res.* 1980;40:2645-52.
3. SWEET DL, KINZIE J, GAEKE ME, GOLOMB HM, FERGUSON DL, ULTMANN JE. Survival of patients with localized diffuse histiocytic lymphoma. *Blood.* 1981;58:1218-23.
4. SWEET DL, GOLOMB HM, ULTMANN JE. et al. Cyclophosphamide, vincristine, methotrexate with leucovorin rescue. and cytarabine (COMLA) combination sequential chemotherapy for advanced diffuse histiocytic lymphoma. *Ann Intern Med.* 1980;92:785-90.
5. LEVITT SH, BLOOMFIELD CD, FRIZZERA G, LEE CKK. Curative radiotherapy for localized diffuse histiocytic lymphoma. *Cancer.* 1980;31(suppl II):237-41.
6. CABANILLAS F, BODY GP, FREIREICH EJ. Management with chemotherapy only of stage I & II malignant lymphoma of aggressive histologic types. *Cancer.* 1980;46:2356-9.
7. MILLER TP, JONES SE. Chemotherapy or chemotherapy with adjuvant radiotherapy for localized diffuse lymphoma. In: JONES SE, SALMON SE. eds. *Adjuvant Therapy of Cancer II.* New York: Grune & Stratton; 1979: 155.
8. BONADONNA G, LATTUADA A. MONFARDINI S, MILANI F, BANFI A. Combined radiotherapy-chemotherapy in localized non-Hodgkin's lymphomas: 5-year results of a randomized study. In: JONES SE, SALMON SE, eds. *Adjuvant Therapy* of *Cancer II.* New York: Grune & Stratton; 1979:145.
9. ROSENBERG SA. Current concepts in cancer: non-Hodgkin's lymphoma—selection of treatment on the basis of histologic type. *N Engl J Med.* 1979;301:924-8.
10. LESTER JN, FULLER LM. CONRAD FG, et al. The roles of staging laparotomy, chemotherapy, and radiotherapy in the management of localized diffuse large cell lymphoma: a study of 75 patients. *Cancer.* 1982;49:1746-53.
11. LAURENCE J, COLEMAN M, ALLEN SL, SILVER RT, PASMANTIER M. Combination chemotherapy of advanced diffuse histiocytic lymphoma with the six drug COP-BLAM regimen. *Ann Intern* Med. 1982;97:190-5.
12. LUKES RJ, COLLINS RD. Immunologic characteristics of human malignant lymphomas. *Cancer.* 1974;34:1488-503.
13. THE NON-HODGKIN'S LYMPHOMA PATHOLOGIC CLASSIFICATION PROJECT. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of working formulation for clinical usage. *Cancer.* 1982;49:2112-35.
14. STRAUCHEN JA. YOUNG RC, DEVITA VT, ANDERSON T, FANTORE JC. BERARD CW. Clinical relevance of the histopathological subclassification of diffuse "histiocytic" lymphoma. *N Engl J Med.* 1978;299:1382-6.
15. BLOOMFIELD CD, GAJL-PECZALSKA KJ, FRIZZERA G, KERSEY JH. GOLDMAN AI. Clinical utility of lymphocyte surface markers combined with the Lukes-Collins histologic classification in adult lymphoma. *N Engl J Med.* 1979;301:512-8.
16. KOZINER B, LITTLE C, PASSE S, et al. Treatment of advanced diffuse histiocytic lymphoma: an analysis of prognostic variables. *Cancer.* 1982;49:1571-9.
17. MILLER JB, VARIAKOJIS D. BITRAN JD, et al. Diffuse histiocytic lymphoma with sclerosis: a clinicopathologic entity frequently causing superior venacaval obstruction. *Cancer.* 1981;47:748-56.
18. FISHER RI. HUBBARD SM. DEVITA VT, et al. Factors predicting long-term survival in diffuse mixed, histiocytic, or undifferentiated lymphoma. *Blood.* 1981;58:45-51.

Leukemia and Benzene

ESTIMATES OF THE proportion of cancers attributable to occupational kxposures range from 1% to 38% (1). This quantification is hampered by many factors, including latency between past exposures and onset of disease, and difficulty in assigning the contribution of any single agent in the face of multifactorial causes. Knowledge of the true contribution of workplace exposures to overall rates has obvious importance given the inherently preventable nature of ohcupationally induced cancers.

While debates about cancer rates continue, workers continue to be exposed to known carcinogens. A specific instance is the *case* of benzene and leukemia as highlighted by a recent study published in the *American Journal of Industrial Medicine.* Rinsky and colleagues (2) report the findings of an epidemiologic investigation of workers exposed to benzene in the manufacture of rubber hydrochloride. This study is of unusual quality: The workers were exposed to only one agent that has been associated

with blood dyscrasias, benzene exposure data are uncommonly complete throughout the study period (1940 to 1975), and the authors ascertained the vital status (alive, dead, and cause of death) for 98% of the study population. There were seven deaths from leukemia (all myelocytic or monocytic) among the 748 workers; this rate is 5.6-fold greater than would be expected in a comparable population. For workers exposed 5 years or more there was a 21-fold increased risk of deaths from leukemia. This significantly increased risk for leukemias had been reported in a preliminary analysis published in 1977 when vital status of 75% of the population was ascertained (3). Some of the criticisms of this earlier report (4) should have been dismissed, because they were based on faulty reanalyses of the data. The ability of the findings to be generalized could have been fairly questioned, if the study population had had far greater exposures to benzene than present standards would allow; This latest report effectively addresses this concern: Rinsky and colleagues (2) provide extensive workplace-monitoring information indicating that the exposures of the workers were, for the most part, within limits permissible at the time. These limits are not greatly higher than the current legal standards.

Benzene's myelotoxic properties, including its ability to cause aplastic anemia, have been long accepted (5, 6). Clinical reports of benzene-induced leukemia have been accumulating since the first case report in 1928 and in the past 2 decades reports of acute or subacute leukemia have exceeded those of fatal pancytopenias (7). However, acceptance of the leukemogenic properties of benzene has been slow. This reluctance was due in part to the unusual difficulty in producing an animal model of benzene's carcinogenicity; only in the last few years have investigators shown benzene to systematically induce malignancies in rats (8). Numerous studies have shown chromosomal damage in benzene-exposed workers, including increased damage in workers exposed to levels of benzene that are permissible by today's standards (6). Epidemiologic studies in the mid-1970s, even before the preliminary report of the study by Infante and colleagues (3). implicated benzene as leukemogenic to such an extent that in 1977 the National Institute for Occupational Safety and Health recommended that benzene be considered carcinogenic in humans and allowable occupational exposure to benzene be reduced (9). The Occupational Safety and Health Administration responded promptly to this recommendation by promulgating an emergency standard that was significantly more stringent than the 1971 consensus standard then in effect. The 1971 standard still stands, however, because in 1980 the Supreme Court overturned implementation of the more stringent standard (6).

Thus, the standard in effect today is one that was issued without concern for the carcinogenic risk from benzene. The standard violates the principle of reducing exposure to carcinogens to the lowest possible level. Achievement of exposure levels far below the current standard is technologically feasible by enclosing production processes, prohibiting the occupational use of benzene in open-type operations, and substituting safer products where possible (9). The significance of continued exposure to benzene is best understood in the context of benzene use today; it is a major raw material in the chemical industry, a solvent in common use. a gasoline additive, and an intermediate in the synthesis of (and, thus, a contaminant in) numerous chemicals. In 1979 over 12 billion pounds of benzene were produced in the United States (8) and it has been estimated that 2 million American workers are exposed to benzene either in its production or through contact with substances containing benzene (5). It is possible to extrapolate from data presented by Rinsky and colleagues (2) that 8.4% of leukemias in America, workers are secondary to benzene exposure. Because of benzene's ubiquitous nature nonoccupational exposures may be significant, with an estimated 75% of the population having been exposed (8).

Calkins and associates (10) have proposed a two-stage model for the control of potential human carcinogens. At stage I the identification and characterization of the risk of a carcinogen is made, based on scientific activity and judgment. In stage II, choices are made among regulatory options for control of the recognized hazard, based on social and political judgment. In the case of benzene, the stage I risk has been well established and characterized since at least 1977. Litigation by manufacturers has blocked implementation of the stage II regulatory response to the scientific evidence. Although it is important to continue to define the risk of benzene (stage I), unfortunately we are doing so while a significant number of workers continue to be exposed to unnecessarily high levels of a known carcinogen. (LINDA ROSENSTOCK, M.D., M.P.H.; *The Robert Wood Johnson Clinical Scholars Program, and The University of Washington; Seattle, Washington)*

REFERENCES

1. PETO R, SCHNEIDERMAN M. eds. *Banbury Report 9: Quantification of Occupational Cancer.* Cold Spring Harbor, New York: Cold Spring Harbor Laboratory; 1981.
2. RINSKY RA. YOUNG RJ, SMITH AB. Leukemia in benzene workers. *Am J Ind Med.* 1981;2:217-45.
3. INFANTE PF, RINSKY RA, WAGNONER JK, YOUNG RJ. Leukemia in benzene workers. *Lancet.* 1977;2:76-8.
4. TABERSHAW IR. LAMM SH. Benzene and leukemia [Letter]. *Lancet.* 1977;2:867-8.
5. NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. *Criteria for a Recommended Standard: Occupational Exposure to Benzene.* U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control; 1974:20-56. (HEW Publication No. (NIOSH) 74-137).
6. WHITE MC. INFANTE PF. WALKER B. Occupational exposure to benzene: a review of carcinogenic and related health effects following the U.S. Supreme Court decision. *Am J Ind Med.* 1980;1:233-43.
7. VIGLIANI EC. Leukemia associated with benzene exposure. *Ann NY Acad Sci.* 1976;271:143-51.
8. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *Second Annual Report on Carinogens.* Washington. D.C.: U.S. Department of Health and Human Services; 1981:47-9. (NTP 81-43).
9. NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. *NIOSH Revised Recommendation for an Occupational Exposure Standard for Benzene.* U.S. Department of Health. Education and Welfare. Public Health Service, Center for Disease Control; 1977. (G.P.O. 757-009/8).
10. CALKINS DR, DIXON RL, GERBER CR, ZARIN D, OMENN GS. Identification, characterization and control of potential human carcinogens: a framework for federal decision-making. *J Natl Canc Inst.* 1980;64:169-76.

"From Other Pages": A New Feature

THE EDITORS of this journal are as aware as the clinicians who read it that those who practice medicine have little time to scan the many clinical journals relevant to