Important new observations about the origins of childhood cancer continue to be made at the bedside. These observations concern environmental factors or peculiarities of the host that carry high risk of certain neoplasms. (Tables 1 and 2.) It is therefore urgent to report such findings, because new impetus in cancer etiology often comes through the curiosity and perception of practicing physicians.

ENVIRONMENTAL FACTORS

Prenatal Exposure
The first transplacental chemical carcinogen in man, diethylstilbestrol (DES), was detected by alert clinicians who noted that adenocarcinoma of the vagina, a rare tumor early in life, was found in a cluster of adolescent girls and young women at the Massachusetts General Hospital during a four-year interval.\(^1\) Retrospective study of maternal histories revealed that DES had been administered during early pregnancy for threatened abortion. This neoplasm affects less than four per 1,000 daughters of women so treated.\(^2\)

Pediatricians should now be alert to the possibility that other known or suspected carcinogens in adults might induce cancer of the offspring exposed in utero, after a latent period that may be short or may last for decades. Among potential transplacental carcinogens are: immunosuppressants (reticulum cell sarcoma); vinyl chloride (angiosarcoma of the liver); benzene, chloramphenicol or alkylating agents (leukemia); oral contraceptives (benign hepatoma); and androgenic anabolic steroids (hepatoblastoma).\(^3\)\(^4\)

Lymphoma has been described in adult patients after prolonged use of hydantoin for epilepsy. In some instances, the neoplasm regressed if the drug was discontinued promptly.\(^4\) One would expect that lymphoma would also be found in children with the fetal hydantoin syndrome (underdevelopment of the mid-portion of the face and hypoplasia or absence of the fingernails and toenails) whose mothers were given hydantoin during pregnancy.\(^5\)\(^6\) It comes as a surprise, therefore, that instead of the expected lymphoma, two children with the syndrome have developed neuroblastoma.\(^7\)\(^8\) This may, of course, be due to chance, but the concurrence of both diseases in two patients within a short period of time suggests a causal relationship—especially since the mal-

Dr. Miller is Chief, Clinical Epidemiology Branch, National Cancer Institute, Bethesda, Maryland.
formation syndrome has been known for only two years. Should a few more such cases be reported, the association will be conclusively demonstrated.

**Childhood Exposure**

**Ionizing Radiation**

Studies of Japanese atomic bomb survivors have revealed that exposure of children to ionizing radiation increases the frequency of acute lymphocytic leukemia, acute or chronic myelogenous leukemia, thyroid tumors (benign or malignant) and perhaps a variety of adult cancers. Therapeutic radiation can induce osteosarcoma, fibrosarcoma and cancer of the skin or breast.

Under the assumption that the dose-response is linear and there is no threshold, it has been estimated that one or two cases of leukemia will be induced per million children, if each were exposed to one rad of radiation (e.g., one-two cases/10^6/year/ rad. The corresponding figure for thyroid cancer is two-three cases/10^6/year/ rad.10).

| Time of Exposure      | Known or Suspected Carcinogen | Type of Cancer Induced                                                                 |
|-----------------------|-------------------------------|----------------------------------------------------------------------------------------|
| Prenatal exposure     | Diethylstilbestrol            | Adenocarcinoma of the vagina                                                            |
| **Childhood exposure**| Ionizing radiation            | Acute lymphocytic leukemia, acute or chronic myelogenous leukemia, benign or malignant thyroid tumors |
|                       | Therapeutic radiation         | Osteosarcoma, fibrosarcoma, cancer of the skin or breast                                |
|                       | Radioisotopes (224 Ra)        | Osteosarcoma and benign bone tumors                                                     |
|                       | Androgenic anabolic steroids (oxymetholone) for aplastic anemia | Hepatocellular carcinoma                                                              |
|                       | Asbestos                      | Mesothelioma of the pleura; lung cancer (?)                                             |
|                       | Lead, copper, zinc            | Lung cancer (?)                                                                         |
|                       | Viruses (Epstein-Barr virus)  | Burkitt’s lymphoma (?)                                                                  |

**TABLE 1. ENVIRONMENTAL FACTORS IN THE ETIOLOGY OF CHILDHOOD CANCER**
Of the 19 children under 10 years of age exposed to the fallout from the Bikini thermonuclear test in 1954, 15 patients have developed thyroid nodules, including one with carcinoma. Two other children, who were less than one year old at the time of exposure, suffered ablation of the thyroid gland. Of four children exposed in utero, one developed a thyroid nodule at the age of 20 years.

Radioisotopes have also caused epidemics of cancer in adults following administration during childhood. Among 220 persons under 20 years of age experimentally given intravenous radium (\(^{224}\)Ra), primarily for tuberculosis of the bone, from 1944-1951, 36 developed osteosarcoma and 20 had benign bone tumors, 18 of which were osteochondromas. The latent period ranged from four to at least 21 years, and the lowest skeletal dose in a child who developed osteosarcoma was 270 rads.

### TABLE 2.
HOST FACTORS IN THE ETIOLOGY OF CHILDHOOD CANCER

| Type of Cancer          | Host Factor                                                                 |
|------------------------|-----------------------------------------------------------------------------|
| Leukemia               | Chromosomal abnormality, inborn or acquired                                  |
| Lymphoma               | Cell-mediated immunosuppression, inborn or acquired                          |
| Wilms' tumor           | Congenital hemihypertrophy; Beckwith-Wiedemann syndrome; congenital aniridia; renal dysplasia in the subcapsular area of the kidney |
| Neuroblastoma          | Aganglionic megacolon (?)                                                   |
| Retinoblastoma (bilateral, heritable form) | Chromosome abnormality, producing severe mental retardation and some multiple malformations; increased susceptibility to second primary cancers |
| Gonadoblastoma         | Gonadal dysgenesis and Y-chromosome cell line                               |

Chemicals
A series of case-reports indicates that
androgenic anabolic steroids (e.g., oxymetholone) used as treatment for aplastic anemia in childhood (idiopathic or Fanconi's) induces hepatocellular carcinoma, which may on occasion regress after the drug is discontinued.\textsuperscript{14,15}

Environmental exposure of children to asbestos from household contact with work-clothes induces mesothelioma of the pleura decades hence.\textsuperscript{16} These children might also be at increased risk of lung cancer, which shows a markedly elevated incidence in adult asbestos workers who smoke cigarettes.\textsuperscript{17}

Studies of migrants from one country to another have revealed that certain cancer rates of the old country persist among first generation inhabitants of the new country, even when migration occurred relatively early in life.\textsuperscript{18} These observations provide further evidence that the seeds of cancer in adults may be sown during childhood. In this connection, it has been reported that persons who live in areas of the United States that have smelters for lead, copper or zinc exhibit elevated mortality rates for cancer of the lung.\textsuperscript{19} This may be due to atmospheric arsenic, known to induce lung cancer in smelter workers. The appearance of lung cancer in exposed children would not be expected until the usual age of presentation for this neoplasm. However, the possibility of early onset should be kept in mind. Thus, when adult cancers are found in young patients, a history of environmental exposure may be especially important.

Viruses
Despite the hot pursuit of a viral etiology for childhood leukemia or Hodgkin's disease, there is as yet no persuasive epidemiologic evidence that these neoplasms are horizontally transmitted.\textsuperscript{20,21} However, such transmission may be so subtle that it is undetectable by present methods. The neoplasms with epidemiologic patterns most suggestive of an infectious mode of spread are Burkitt's lymphoma\textsuperscript{22} and, in adults, cancer of the uterine cervix.\textsuperscript{23}

\section*{HOST FACTORS}

\subsection*{Leukemia}
The high incidence of leukemia in children with Down's syndrome was first documented in the mid-1950s. The finding signified that, in these patients, leukemia is to some extent prezygotically determined and that chromosomal abnormalities may be important in the development of the neoplasm.\textsuperscript{24} Since then, it has been learned that most persons at high risk of leukemia have a chromosomal abnormality, whether inborn or acquired: aneuploidy in Down's syndrome, chromosomal fragility in Bloom's and Fanconi's syndromes, or long-lasting chromosome breaks after X-irradiation or exposure to benzene.\textsuperscript{25,26}

For the past 15 years, it has been known that 90 percent of patients with chronic myelogenous leukemia have a consistent chromosomal abnormality. Originally this aberration was thought to be a deletion of the long arm of chromosome 21. Now, with new chromosome banding techniques, the defect has been identified not as a deletion but as a translocation from chromosome 22 usually to chromosome 9.\textsuperscript{27-28} Banding techniques have also revealed previously unknown chromosomal abnormalities in patients with acute myelogenous leukemia.\textsuperscript{29}

Acute lymphocytic leukemia (ALL) has been subdivided according to immunologic markers, as B, T or "null" cell in type. The B-cell type is rare; the T-cell type usually affects older children who present with a thymic mass and high white blood cell count. These
children respond less well to therapy than those with the more prevalent null-cell type of ALL.\(^3\)\(^\circ\)

**Lymphoma**

Cytogenetic abnormality does not typify persons at high risk of lymphoma, who have instead cell-mediated immunosuppression, either inborn (as in ataxia-telangiectasia, Wiskott-Aldrich syndrome or combined variable immunodeficiency diseases) or acquired (as in renal transplant patients given immunosuppressive therapy).\(^3\)\(^1\),\(^3\)\(^2\) The type of lymphoma varies with the form of immunosuppression, an observation of potential etiologic importance. Renal transplant patients given immunosuppressive therapy and those with the Wiskott-Aldrich syndrome show a predilection for reticulum cell sarcoma, often of the brain. By contrast, patients with ataxia-telangiectasia and combined variable immunodeficiency states are prone particularly to lymphosarcoma.

**Wilms' Tumor**

In an entirely different orbit are Wilms' tumor, as well as adrenocortical neoplasia and primary liver cancer, which are all associated with several congenital growth excesses. Each of these three neoplasms has a frequency in children with congenital hemihypertrophy; both the cancer and the hemihypertrophy are frequently associated with large, pigmented or vascular nevi—among other hamartomas—and with the visceral cytomegaly (Beckwith-Wiedemann) syndrome.\(^3\)\(^3\) The syndrome is characterized by omphalocle, macroglossia and cytomegaly of visceral organs, including the three in which neoplasia have been observed in association with hemihypertrophy.\(^3\)\(^4\)

Wilms' tumor also occurs excessively with congenital aniridia. This ocular defect, bilateral absence of the iris of the eyes, is usually extremely rare. However, in children with Wilms' tumor, it occurs at about 1,000 times the normal rate.\(^3\)\(^5\) Aniridia in the general population is caused by an autosomal dominant gene, and two-thirds of the patients have a familial history of the defect. With one exception, aniridia with Wilms' tumor has been non-familial,\(^3\)\(^6\) an indication that the eye defect and the tumor were caused by a new genetic mutation or an environmental agent that mimicked the action of a gene.

It has recently been reported that in patients with bilateral (i.e., multifocal) Wilms' tumor, renal dysplasia was regularly found, distinct from the cancer, in the subcapsular area of the kidney.\(^3\)\(^7\) According to the two-step oncogenic process proposed by Knudson for Wilms' tumor and other childhood cancers, if the tumor is multifocal, there is a prezygotic determinant plus a second step that is postzygotic.\(^3\)\(^8\) The renal dysplasia observed in children with bilateral Wilms' tumor may represent the first (prezygotic) step, which later undergoes malignant transformation. In the non-hereditary form of Wilms' tumor, Knudson has proposed that both steps occur postzygotically and affect a particular renal cell by chance.

**Neuroblastoma**

The vast majority of neuroblastomas are diagnosed in children under five years of age.\(^3\)\(^9\) A study of 504 hospital charts for children with this tumor revealed no excessive occurrence of specific congenital anomalies.\(^3\)\(^9\) Knudson's hypothesis has also been applied to neuroblastoma,\(^4\)\(^0\) possibly with aganglionic megacolon as a manifestation of the germinal mutation.\(^4\)\(^1\)

**Retinoblastoma**

Retinoblastoma falls into two genetic
categories, according to Knudson’s hypothesis. In the heritable form, about 45 percent of offspring are affected—usually bilaterally. In the non-heritable form, comprising the majority of retinoblastomas, the tumors are unilateral and non-familial.42

The prezygotic event may sometimes involve chromosomal deletion, specifically of the D-chromosome, producing the 13q-syndrome in which there is a high risk of bilateral retinoblastoma.43 Children with the syndrome usually have severe mental retardation and multiple malformations. However, several children with retinoblastoma and no abnormality except mental retardation have had small deletions of chromosome 13, a finding that helps to identify the locus of the retinoblastoma gene.44 Needless to say, when a child is seen with retinoblastoma and mental retardation, it is important to obtain cytogenetic studies, because identification of the chromosomal deletion is of value both in research and in genetic counselling.

Children with bilateral retinoblastoma may also have an increased risk of second primary cancers of dissimilar type, especially osteosarcoma of the femur.44,45 The second primaries are not attributable to therapy. These new primaries may occur individually among close relatives.46 Laboratory studies, particularly of DNA repair, may be important in identifying the pathobiology involved in the genesis of these neoplasms.

Gonadoblastoma
At present, gonadoblastoma is the only tumor for which a congenital defect is known to be a prerequisite. This tumor develops only if the patient has gonadal dysgenesis and, apparently, only if there is a Y-chromosome cell line. The probability that such patients will develop gonadoblastoma is so great (about 25 percent) that prophylactic removal of the gonadal streak is indicated.47

FAMILIAL CANCER

Apart from the known genetically determined cancers, certain other neoplasms seem to aggregate excessively in families. These cancers may be of a single histologic type, as in a Boston family where seven, and possibly 10, members had ovarian carcinoma.48 Or, the cancers may be of dissimilar cell types, the rarity of which makes their occurrence in several unrelated families seem unlikely to be caused by chance. Soft-tissue tumors in siblings during childhood have been found in several families in whom other cancers, especially of the breast in young females, affect close relatives.49,50 In addition to the combination of retinoblastoma and osteosarcoma, several other dissimilar histologic types of cancer have been observed in first-degree relatives in several families, for example, glioma, adrenal cortical carcinoma, and either rhabdomyosarcoma or osteosarcoma.51 The same cancers that occur as double primaries may also be distributed individually among family members.

Similarly, the syndromes involving cancer and non-cancerous disease may also be found throughout the family rather than concentrated on one individual. For example, in one family the mother had congenital hemihypertrophy, three of her children had Wilms’ tumor and a fourth child had duplication of the left renal collecting system.52

When cancers aggregate excessively in families, with or without other disorders, there is an opportunity for extensive laboratory investigation to determine if common subclinical features that portend high risk can be found in affected members as well as those who
are phenotypically normal. The results will be helpful in understanding the pathogenesis of the neoplasm, and ultimately its prevention and early detection.

References

1. Herbst, A.L.; Ulfelder, H., and Poskanzer, D.C.: Adenocarcinoma of the vagina. N. Engl. J. Med. 284:878-881, 1971.
2. Herbst, A. et al.: Age-incidence and risk of diethylstilbestrol-related adenocarcinoma of the vagina and cervix. Am. J. Obstet. Gynecol. 128:43-50, 1977.
3. Cole, P., and Goldman, M.B.: Occupation. In: Fraumeni, J.F., Jr. (ed.): Persons at High Risk of Cancer: An Approach to Cancer Etiology and Control. New York: Academic Press, 1975. Pp. 167-183.
4. Hoover, R., and Fraumeni, J.F., Jr.: Drugs. In: Fraumeni, J.F., Jr. (ed.): Persons at High Risk of Cancer: An Approach to Cancer Etiology and Control. New York: Academic Press, 1975. Pp. 185-198.
5. Hanson, J.W., and Smith, D.W.: The fetal hydantoin syndrome. J. Pediatr. 87:285-290, 1975.
6. Hanson, J.W.; Myrianthopoulos, N.C.; Harvey, M.A., and Smith, D.W.: Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. J. Pediatr. 89:662-668, 1976.
7. Pendergrass, T.W., and Hanson, J.W.: Fetal hydantoin syndrome and neuroblastoma. Lancet 2:150, 1976.
8. Sherman, S., and Roizen, N.: Fetal hydantoin syndrome and neuroblastoma. Lancet 2:517, 1976.
9. Miller, R.W.: Late radiation effects: status and needs of epidemiologic research. Environ. Res. 8:221-233, 1974.
10. Advisory Committee on the Biological Effects of Ionizing Radiations: The effects on populations of exposure to low levels of ionizing radiation. Natl. Acad. Sci.-Natl. Res. Council, Washington, D.C., 1972.
11. Conard, R.A. et al.: A 20-year review of medical findings in a Marshallese population accidentally exposed to radioactive fallout. Springfield, Virginia: National Technical Information Service, U.S. Department of Commerce, September 1975.
12. Spiess, H., and Mays, C.W.: Bone cancers induced by 226 Ra (ThX) in children and adults. Health Phys. 19:713-729, 1970.
13. Spiess, H., and Mays, C.W.: Addendum. Health Phys. 20:543-545, 1971.
14. Johnson, F.L., et al.: Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. Lancet 2:1273-1276, 1972.
15. Meadows, A.T.; Naiman, J.L., and Valdes-Dapena, M.: Hepatoma associated with androgen therapy for aplastic anemia. J. Pediatr. 84:109-110, 1974.
16. Anderson, H. et al.: Household-contact asbestos neoplastic risk. Ann. N.Y. Acad. Sci. 271:311-323, 1976.
17. Selikoff, I.J., and Hammond, E.C.: Multiple risk factors in environmental cancer. In: Fraumeni, J.F., Jr. (ed.): Persons at High Risk of Cancer: An Approach to Cancer Etiology and Control. New York: Academic Press, 1975. Pp. 467-483.
18. Haenszel, W.: Migrant studies. In: Fraumeni, J.F., Jr. (ed.): Persons at High Risk of Cancer: An Approach to Cancer Etiology and Control. New York: Academic Press, 1975. Pp. 361-371.
19. Blot, W.J., and Fraumeni, J.F., Jr.: Arsenical air pollution and lung cancer. Lancet 2:142-146, 1975.
20. Miller, R.W.: Radiation, chromosomes and viruses in the etiology of leukemia. Evidence from epidemiologic research. N. Engl. J. Med. 271:30-36, 1964.
21. Smith, P.G.; Pike, M.C.; Till, M.M., and Hardisty, R.M.: Epidemiology of childhood leukemia in Greater London: A search for evidence of transmission assuming a possibly long latent period. Br. J. Cancer 33:1-8, 1976.
22. Pike, M.C.; Williams, E.H., and Wright, B.: Burkitt's tumour in the West Nile district of Uganda, 1961-1965. Brit. Med. J. 2:395-399, 1967.
23. Kessler, I.I.: Human cervical cancer as a venereal disease. Cancer Res. 36:783-791, 1976.
24. Miller, R.W.: Neoplasia and Down's syndrome. Ann. N.Y. Acad. Sci. 171:637-644, 1970.
25. Miller, R.W.: Persons at exceptionally high risk of leukemia. Cancer Res. 27:2420-2423, 1967.
26. German, J.: Genes which increase chromosomal instability in somatic cells and predispose to cancer. In: Steinberg, A.G., and Bearn, A.G. (eds.): Progress in Medical Genetics. Vol. VIII. Grune and Stratton, Inc. Pp. 61-101.
27. O'Riordan, M.L.; Robinson, J.A.; Buckton, K.E., and Evans, H.J.: Distinguishing between the chromosomes involved in Down's syndrome (trisomy 21) and chronic myeloid leukemia (Ph+) by fluorescence. Nature 230:167-168, 1971.
28. Rowley, J.D.: Do human tumors show a chromosome pattern specific for each etiologic agent? J. Natl. Cancer Inst. 52:315-320, 1974.
29. Mitelman, F.; Nilsson, P.G.; Levah, G., and Brandt, L.: Non-random chromosome changes in acute myeloid leukemia. Chromosome banding examination of 30 cases at diagnosis. Int. J. Cancer 18:31-38, 1976.
30. Tsukimoto, I.; Hong, K.Y., and Lamkin, B.C.: Surface markers and prognostic factors in acute lymphoblastic leukemia. N. Engl. J. Med. 294:245-248, 1976.
31. Kersey, J.; Spector, B.D., and Good, R.A.: Primary immunodeficiency diseases and cancer: the Immunodeficiency Cancer Registry. Int. J. Cancer 12:333-347, 1973.
32. Hoover, R., and Fraumeni, J.F., Jr.: Risk of...
cancer in renal-transplant recipients. Lancet 2:55-57, 1973.
33. Miller, R.W.: Relation between cancer and congenital defects. An epidemiologic evaluation. J. Natl. Cancer Inst. 40:1079-1085, 1968.
34. Sotelo-Avila, C., and Gooch, W.M.: Neoplasms associated with the Beckwith-Wiedemann syndrome. Perspect. Pediatr. Pathol. 3:255-272, 1976.
35. Miller, R.W.; Fraumeni, J.F., Jr., and Manning, M.D.: Association of Wilms' tumor with aniridia, hemihypertrophy and other congenital malformations. N. Engl. J. Med. 270:922-927, 1964.
36. Fraumeni, J.F., Jr., and Glass, A.G.: Wilms' tumor and congenital aniridia. JAMA 206:825-828, 1968.
37. Bove, K.E., and McAdams, A.J.: The nephroblastomatosis complex and its relationship to Wilms' tumor: a clinicopathological treatise. Perspect. Pediatr. Pathol. 3:185-223, 1976.
38. Knudson, A.G., Jr.: Mutation and human cancer. Adv. Cancer Res. 17:317-352, 1973.
39. Miller, R.W.; Fraumeni, J.F., Jr., and Hill, J.A.: Neuroblastoma: epidemiologic approach to its origins. Amer. J. Dis. Child. 115:253-261, 1968.
40. Knudson, A.G., Jr., and Strong, L.C.: Mutation and cancer: neuroblastoma and phaeochromocytoma. Am. J. Hum. Genet. 24:514-532, 1972.
41. Knudson, A.G., Jr., and Meadows, A.T.: Developmental genetics of neuroblastoma. J. Natl. Cancer Inst. 57:675-682, 1976.
42. Knudson, A.G., Jr.; Hethcote, H.W., and Brown, B.W.: Mutation and childhood cancer: a probabilistic model for the incidence of retinoblastoma. Proc. Natl. Acad. Sci. 72:5116-5120, 1975.
43. Knudson, A.G., Jr.; Meadows, A.T.; Nichols, W.W., and Hill, R.: Chromosomal deletion and retinoblastoma. N. Engl. J. Med. 295:1120-1123, 1976.
44. Jensen, R.D., and Miller, R.W.: Retinoblastoma: epidemiologic characteristics. N. Engl. J. Med. 285:307-311, 1971.
45. Kitchin, F.D., and Ellsworth, R.M.: Pleiotropic effects of the gene for retinoblastoma. J. Med. Genet. 11:244-246, 1974.
46. Gordon, H.: Family studies in retinoblastoma. Birth defects: Original Article Series X(10):185-190, 1974.
47. Mulvihill, J.J.; Wade, W.A., and Miller, R.W.: Gonadalblastoma in dysgenetic gonads with a Y chromosome. Lancet 308:863, 1975.
48. Li, F.P.; Rapoport, A.H.; Fraumeni, J.F., Jr., and Jensen, R.D.: Familial ovarian carcinoma. JAMA 214:1559-1561, 1970.
49. Li, F.P., and Fraumeni, J.F., Jr.: Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann. Intern. Med. 71:747-752, 1969.
50. Li, F.P., and Fraumeni, J.F., Jr.: Familial breast cancer, soft-tissue sarcomas, and other neoplasms. Ann. Intern. Med. 83:833-834, 1975.
51. Miller, R.W.: Deaths from childhood leukemia and solid tumors among twins and other sibs in the United States, 1960-1967. J. Natl. Cancer Inst. 46:203-209, 1971.
52. Meadows, A.T.; Lichtenfeld, J.L., and Koop, C.E.: Wilms' tumor in three children of a woman with congenital hemihypertrophy. N. Engl. J. Med. 291:23-24, 1974.