LEUKEMIA IN TWINS: ANTENATAL AND POSTNATAL FACTORS

LOUIS KEITH, ERIC R. BROWN, BRUCE AMES, MICHAEL STOTSKY, DONALD M. KEITH

Department of Obstetrics and Gynecology, and Department of Microbiology, The Chicago Medical School/ University of Health Sciences, Chicago, Illinois, USA

Two factors emerged from a search for obstetric phenomena that might explain concordance of leukemia in both members of a twin pair within days or months of each other: antenatal exposure to ionizing radiation; and antenatal cojoined intrauterine circulation. In addition, antenatal tumor metastasis and chromosomal changes, antenatal or postnatal, may be contributory. Continued observation of reports should be carried out.

Most clinical reports regarding leukemia in twins have been concerned with MZ twins in the perinatal-congenital period of life (Keith et al. 1970 and 1973, Keith and Brown 1971). Our prior communication have sought obstetric phenomena that might explain concordance of leukemia, especially during these early years. Two factors have emerged which may help explain the occurrence of this neoplastic disease in both members of a twin pair within days or months of each other: antenatal exposure to ionizing radiation; and antenatal cojoined intrauterine circulation. Two additional factors — antenatal direct materno-fetal metastasis, and antenatal or postnatal chromosomal changes — may be contributory.

MATERIAL

Between July 1, 1971, and September 1, 1974, a total of six clinical reports were published regarding 16 twin pairs with one or both members having leukemia. Table 1 lists these cases in the manner of our previous reports (Keith et al. 1970 and 1973, Keith and Brown 1971). All recent cases were of MZ twins. Only one twin pair was concordant; 15 of the 16 pairs were girls.

Table 2 summarizes certain features of the published clinical reports of leukemia in twins throughout the 46 years between 1928 and 1974. Data from our own prior publications and Table 1 are included. Unfortunantely, it has not been possible to obtain clinical information from some surveys of large numbers of leukemic patients published between 1960 and 1970 that include many members of twin pairs (Steinberg 1960, Jackson et al. 1969, Fraumeni et al. 1971). In these instances, the method of reporting was nonclinical and the cases could not be included here. It is our impression, however, that Table 1 and the tables published in 1970, 1971, and 1973 contain all the references to clinical reports in the generally available literature.

DISCUSSION

Exposure to Ionizing Radiation

The oncogenic potential of antenatal roentgenograms is not always appreciated by physicians (Lee 1972). Alice Stewart (1971, 1973) has emphasized the carcinogenic and leukemogenic effects of antenatal irradiation on the fetus. Her contention, supported by others (MacMahon 1962, Miller 1972, Kemp 1973) is that leukemia is more frequent than other childhood neoplasms among children whose mothers received antenatal irradiation. Stewart (1973, 1974) has postulated that the fetal reticulo-endothelial tissue is so exquisitely sensitive to irradiation that minute doses are sufficient to convert a mitotically competent cell into a cancer precursor (Stewart and Kneale 1971). Unfortunately, where fetuses *in utero* are concerned, available data on the possible sequelae of small doses of radiation do

CODEN: AGMGAK 25 336 (1976) — ISSN: 0001-5660
Acta Genet. Med. Gemellol. (Roma) 25: 336-341

Table 1. *Clinical reports of twins with leukemia* (July 1971-September 1974)

Author	Year	Sex	Zygosity	Concordance	Chromosomal abnormalities	Age of onset	Interval between diagnosis	Post-diagnosis survival	Type
Bohunicky et al.	1971	FF	MZ	C	None known	I 18 yrs II 19 yrs	17 mos 5 mos	Not stated	lymphogranulomatosis
Han and Wang	1972	MM	MZ	D	None known	I 26 mos II normal		I 2 yrs	Acute lymphoblastic
Levine et al.	1972	MM	MZ	D	None known	I 2 yrs II normal		Alive and in remission	ALL
Levine et al.	1972	FF	MZ	D	None known	I 3 yrs II normal		Alive and in remission	ALL
Levine et al.	1972	FF	MZ	D	None known	I 8 yrs II normal		Alive and in remission	ALL
Levine et al.	1972	MM	MZ	D	None known	I 2 yrs II normal		Alive and in remission	ALL
Levine et al.	1972	MM	MZ	D	None known	I 2 yrs II normal		Alive and in remission	ALL
Levine et al.	1972	FF	MZ	D	None known	I 5 yrs II normal		Alive and in remission	ALL
Levine et al.	1972	FF	MZ	D	None known	I 15 yrs II normal		Alive and in remission	AML
Levine et al.	1972	MM	MZ	D	None known	I 31 yrs II normal		Alive and in remission	ALL
Levine et al.	1972	MM	MZ	D	None known	I 13 yrs II normal		Alive and in remission	AML
Levine et al.	1972	MM	MZ	D	None known	I 3 yrs II normal		Alive and in remission	ALL
Rosenberg* et al.	1972	MM	MZ	D	None known	I 40 yrs II normal		Not stated	ALL
Baxt et al.	1973	MM	MZ	D	Abnormal nuclear DNA sequences	I 24 yrs II normal		Not stated	AML
Baxt et al.	1973	MM	MZ	D	None known	I 26 yrs II normal		Not stated	AML
Gatti et al.	1973	FF	MZ	D	Ph^1 chromosome	I 12 yrs II normal			CML

* Nine sets of twins in this article are included in the listing for twins reproted by Levine.

Table 2. *Age distribution of clinical reports of leukemia* (1928-1974)

	MZ pairs		DZ pairs			
	Conc.	Disc.	Conc.	Disc.	ZU	Total
Perinatal-Congenital	14	1	1	1	2	19
Age 2-7	6	13	3	5	6	33
Age 7-12	1	8	—	1	2	12
Age 12 and over	5	14	0	3	1	23
Total	26	36	4	10	11	87

not permit extrapolation to the lowest potentially harmful dose or the construction of reliable dose: effect graphs (Marqulis 1973). According to Hutchinson (1972) and Miller (1972), preconceptual irradiation of either parent increases the incidence of malignancy in future offspring. If this is correct, its occurrence would complicate any potential carcinogenic or leukemogenic effect of intrauterine fetal irradiation.

Preliminary attempts have been made at establishing a safe threshold of irradiation for juvenile cancers. Ardran (1972) has calculated the doubling dose for childhood leukemia or neoplasia from fetal irradiation to be 1-4 rads. On the other hand, Lee (1972) considers as little as 0.3 rads during the first trimester could be correlated with a high tumor incidence.

In a further attempt to derive a dose:effect relation, Newcombe and McGregor (1971) reanalyzed Stewart's data, utilizing Woolf's Chi-square method. Their results at 0.2 rads to 0.25 rads conform closely to those of Stewart's and Kneale's (1970), making the existence of a safe radiation threshold unlikely. Whether the actual risk of subsequent neoplasm after intrauterine irradiation is increased by 50% as suggested by Ardran (1972) or 100% as postulated by Lee (1972) is not the crucial consideration, but rather what is crucial is whether irradiation is capable of influencing the subsequent development of leukemia and cancers in childhood.

The solution might be to dispense with any or all antenatal irradiation, but this is not realistic. The physician may not be aware that the patient is pregnant. In the presence of trauma or certain types of renal disease, the taking of roentgenograms may be mandatory. Short of the ability to do this without irradiation, the risk of irradiation will continue.

The single area of hope in reducing unnecessary irradiation is in lessening the use of roentgenograms for the diagnosis of uncomplicated multiple gestation. High quality ultrasonography can provide necessary diagnostic information without the potential of later adverse effects.

Cojoined Intrauterine Circulation

In the last few years, the importance of communicating vascular pathways on the surface of monochorionic placentas has received modest attention, primarily by pathologists who were concerned with its hemodynamic effects (Benirschke and Driscoll 1967, Altshuler and McAdams 1972, Scott and Ferguson-Smith 1973). These communicating vascular channels apparently facilitate the free passage of a variety of biologic elements. For example, MZ twins whose mothers took thalidomide have an almost universal concordance of deformities whereas this is not the case among DZ twins (Jorgensen et al. 1970). Similarly, Carvalho (1969) has described minor congenital abnormalities and dermatoglyphics possibly related to leukemia and probably shared by way of cojoined circulation.

Clarkson and Boyse (1971) suggest that many cases of concordant leukemia in MZ twins represent only one occurrence of leukemia, not two. They base their hypothesis on what is probably the inevitable result of these placental blood vessel anastomoses-hematopoietic chimerism (Owen 1945), in

which hematopoietic stem cells from each twin are exchanged with similar cells of the cotwin, causing permanent cross-colonization (Clarkson and Boyse 1971). Thus, the initial leukemic transformation of a single hematopoietic stem cell in one MZ twin would invariably affect the other, providing such transformation took place early in pregnancy. Such circumstances may explain the higher degrees of concordance observed during the perinatal-congenital period of life (Keith et al. 1970, 1973), but do not clarify the often prolonged delay in the appearance of concordant disease which occurs in later life (Clarkson and Boyse 1971). In point of fact, these delays are probably better explained by variations in the autonomy or growth potential of malignant cells. Since doubling times of leukemic cell populations *in vivo* are not known with certainty, the degree of concordance among MZ twins may be related to a scatter phenomenon in the length of latent periods.

Conceivably, a longer latent period might be observed if leukemic transformation does not take place until shortly before parturition. Compression of the fetus and its cord during passage of the first twin through the birth canal would not only account for hemodynamic changes suggestive of the twin transfusion syndrome (Klebe and Ingomar 1972) but also provide a protective effect in the longer interval between the onset of disease in concordant cotwins, or in the establishment of factors favoring discordance.

Direct Metastasis

Since the observation that the human placenta is not an absolute barrier, a number of biologic substances have been shown to pass from the mother to the child or from the child to the mother. Probably best known are passage of fetal red blood cells to the mother and maternal immunoglobulin to the fetus.

In the field of malignant diseases, passage of cellular material is theoretically increased during pregnancy, but in reality such occurrences are rare (Diamondopolous and Hertig 1963). In over 100 years, only 12 instances of metastasis of maternal tumors to the fetus have been reported (Stephenson et al. 1971). Stephenson and his coworkers (1971) postulate fetal rejection of circulating maternal or placental tumor cells, contending that those 12 cases represent instances of immunologic tolerance. With regard to leukemia, Rigby (1964) demonstrated the passage of leukemic cells across the placenta from mother to fetus, and Cramblett (1958) and Bernard et al. (1964) documented the transmission of maternal leukemia to the fetus *in utero*.

Chromosomal Changes

The most consistent chromosomal abnormality observed in patients with leukemia is the appearance of the Philadelphia (Ph^1) chromosome in association with chronic myelogenous leukemia (CM) (Baserga and Castoldi 1973). The exact relation between chromosomal aberrations and neoplasia is not presently clear (Bloom et al. 1970). We have evidence that: (1) somatic cells with altered karyotypes possess an increased sensitivity to the effects of oncogenic viruses, and (2) there is a greater likelihood of neoplastic diseases in populations having induced chromosomal aberrations (Wald et al. 1961, Holland et al. 1962, Lashof and Stewart 1965, Jackson et al. 1968, Bloom 1972).

It remains questionable whether the appearance of chromosomal changes in leukemia among twins is disease-related. Relatively few publications on leukemia among twins have included information regarding chromosomal abnormalities (Keith et al. 1973). This is unfortunate because adequate analysis of both members of the twin pair may be needed to fill gaps in our present knowledge.

It is conceivable that the relative frequency of chromosome abnormalities in preleukemic conditions can be used as a diagnostic tool.

While Nowell (1971) and Humbert et al. (1971) observed a greater risk of clinical leukemia among preleukemic patients having demonstrable chromosomal abnormalities, we have been unable to find such studies among twin pairs.

CONCLUSIONS

Each of the following, acting alone or in conjunction, may be contributory in the etiopathogenesis of leukemia in twins: exposure to ionizing radiation; cojoined intrauterine circulation; direct metastasis of maternal tumors to the fetus, and chromosomal abnormalities. Further study among leukemic twins and careful analyses of both members of the twin pair is needed to clarify the uncertainty presently recognized.

REFERENCES

Altshuler G., McAdams A.J. 1972. The role of the placenta in fetal and perinatal pathology. Am. J. Obstet. Gynecol., 113: 616-626.

Ardran G.M. 1972. Radiological and clinical implications of the cancer risk. Br. J. Radiol., 45: 796.

Baserga A., Castoldi G.L. 1973. The Philadelphia chromosome. Biomedicine, 18: 89-94.

Benirschke K., Driscoll S.G. 1967. The Pathology of the Human Placenta. Berlin, Heidelberg and New York: Springer-Verlag.

Bernard J., Jacquillat C., Chavelet F., et al. 1964. Leucemie aigue d'une infant de 5 mois née d'une mère atteinte de la leucemie aigue au moment de l'accouchement. Nouv. Rev. Fr. Hematol., 4: 140-146.

Bloom A.D. 1972. Induced chromosomal aberrations: biological and clinical significance. J. Pediatr., 81: 1-8.

Bloom A.D., Nakagome Y., Awa A.A., Neriishi S. 1970. Chromosomal aberrations and malignant disease among A-bomb survivors. Am. J. Public Health, 60: 641-644.

Carvalho R.I. 1969. Minor congenital abnormalities, dermatoglyphics and childhood leukemia. Rev. Bras. Pesqui. Med. Biol., 2: 51-61.

Clarkson B.D., Boyse E.A. 1971. Possible explanation of the high concordance for acute leukemia in monozygotic twins. Lancet, 1: 699-701.

Cramblett H.G. 1958. Leukemia in an infant born of a mother with leukemia. N. Engl. J. Med., 259: 727-729.

Diamondopolous G., Hertig A. 1963. Transmission of leukemia and allied diseases from mother to fetus. Obstet. Gynecol., 21: 150-154.

Fraumeni J.F., Manning M.D., Mitus W.J. 1971. Acute childhood leukemia. Epidemiologic study by cell type of 1,263 cases at the Children's Cancer Research Foundation, Boston, *1947-1965*. J. Natl. Cancer Inst., 46: 461-470.

Holland W.W., Doll R., Carter C.O. 1962. The mortality from leukemia and other cancers among patients with Down's syndrome (mongols) and among their parents. Br. J. Cancer, 16: 177-186.

Humbert J.R., Hathaway W.E., Robinson A., Peakman D.C., Githens J.H. 1971. Pre-leukaemia in children with a missing bone marrow C chromosome and a myeloproliferative disorder. Br. J. Haematol., 21: 705-716.

Hutchinson G.B. 1972. Late neoplastic changes following medical irradiation. Radiology, 105: 645-652.

Jackson E.W., Norris F.D., Klauber M.R. 1969. Childhood leukemia in California born twins. Cancer, 23: 913-919.

Jackson E.W., Turner J.H., Klauber M.R., et al. 1968. Down's syndrome: variation of leukemia occurrence in institutionalized populations. J. Chronic Dis., 21: 247-253.

Jorgensen G., Lenz W., Pfeiffer R.A., Schaafhausen Ch. 1970. Thalidomide-embryopathy in twins. Acta Genet. Med. Gemellol. (Roma), 19: 205-210.

Keith L., Brown E. 1971. Epidemiologic study of leukemia in twins (1928-1969). Acta Genet. Med. Gemellol. (Roma), 20: 9-22.

Keith L., Brown E., Fields C. 1970. A review: perinatal-congenital leukemia in twins. Chicago Med. Sch. Quart., 29: 1-8.

Keith L., Brown E.R., Fields C., Stepto R. 1973. Age group differences of twins with leukemia. In: R.M. Dutcher and L. Chieco-Bianchi (eds.): Unifying Concepts of Leukemia. Bibl. Haemat., No. 39 [pp. 1125-1135]. Basel: Karger.

Kemp F.H. 1973. Irradiation of the fetus. Br. Med. J., 3: 497.

Klebe J.G., Ingomar C.J. 1972. The fetoplacental circulation during parturition illustrated by the interfetal transfusion syndrome. Pediatrics, 49: 112-115.

Lashof J.C., Stewart A. 1965. Oxford survey of childhood cancers. Progress report 3. Leukaemia and Down's syndrome. Monthly Bull. Minist. Hlth. (London), 24: 136-143.

Lee H.F. 1972. How to shoot a patient without really trying. Clin. Pediatr. (Phila.), 11: 284-287.

MacMahon B. 1962. Prenatal X-ray exposure and childhood cancer. J. Natl. Cancer Inst., 28: *1173-1191*.

Margulis A.R. 1973. The lessons of radiobiology for diagnostic radiology. Am. J. Roentgenol. Radium Ther. Nucl. Med., 117: 741-756.

Miller R.W. 1972. Radiation-induced cancer. J. Natl. Cancer Inst., 49: 1221-1227.

Newcombe H.B. McGregor J.F. 1971. Childhood cancer following obstetric radiography. Lancet, 1: 1151-1152.

Nowell P.C. 1971. Marrow chromosome studies in "preleukemia". Cancer, 29: 513-518.

Owen R.D. 1945. Immunogenetic consequences of vascular anastomoses between bovine twins. Science, 102: 400.
Rigby P.G. 1964. Passage of leukemic cells across the placenta. N. Engl. J. Med., 271: 124-127.
Scott J.M., Ferguson-Smith M.A. 1973. Heteromonster. J. Obstet. Gynecol. Br. Commonw., 80: 52-59.
Steinberg A.G. 1960. The genetics of acute leukemia in twins. Cancer, 13: 985-999.
Stephenson H.E., Terry C.W., Lukens J.N., Shively J.A., Busby W.E., Stoeckle H.E., Esterly J.A. 1971. Immunologic factors in human melanoma " metastatic " to products of gestation (with exchange transfusion of infant to mother). Surgery, 69: 515-522.
Stewart A. 1971. Low dose radiation cancers in man. Adv. Cancer Res., 14: 359-390.
Stewart A. 1973. The carcinogenic effects of low level radiation. A re-apparaisal of epidemiologists methods and observations. Health Phys., 24: 223-240.
Stewart A. 1974. Factors affecting recognition of infant leukemias and lymphomas. Br. Med. J., 2: 611-612.
Stewart A., Kneale G.W. 1970. Radiation dose effects in relation to obstetric X-rays and childhood cancers. Lancet, 1: 1185-1188.
Stewart A., Kneale G.W. 1971. Prenatal radiation exposure and childhood cancer. Lancet, 1: 42.
Wald N., Borges W.H., Li C.C., et al. 1961. Leukemia associated with mongolism. Lancet, 1: 1228.

ADDENDUM

Gedda and Brenci (1973) have added a new dimension to the study of C/D with their work on chronogenetics. Simply put, they state that the appearance of genetically determined events is time related, and that the inheritance of the time of occurrence of an event is genetically related. As stated previously (Keith et al. 1973), concordance of leukemia among MZ twins appears to be due to some process other than mere concidence alone. Gedda and Brenci (1973) note that isochronic concordance of disease is practically nonexistent in random individuals, while such temporal simultaneity represents the rule with MZ twins. They contend it would be inconsistent to explain qualitative concordance but not the chronological concordance as a result of sharing a common heredity, i.e., the twin genome contains the information determining biological time, which in turn totally characterizes the individual, being the single endogenous factor mixing with cosmic time responsible for any function or disease of an organism (Gedda and Brenci 1973).

Chronogenetics defines the age of onset of disease as the time when a potentially disease-producing gene ceases to supply normal information. Such loss of gene stability is concordant in MZ twins (Gedda and Brenci 1971). The construction of a time table of the effects, e.g., on parents and child, of biological time and the occurrence of various pathological processes, e.g., the onset of childhood leukemias, would obviously be a giant achievement for preventive medicine.

Two of our fundamental concepts have gained support in a recent article by Gross (1974): the now widely accepted cause and effect relationship between ionizing radiation and leukemia, and direct metastases of leukemogenic structures from mother to fetus. Gross (1974) contends the transmitting structures are viruses. As a result of his experiments with mice, he could explain the familial incidence of cancer as a consequence of " verticle transmission " from mother to embryo of oncogenic viruses (Gross 1974). While this has never been proven in humans, it is not unreasonable to ask if a similar process does not exist. It this were the case, the viruses and their host, whose total existence was governed by hereditary biological time (Gedda and Brenci 1973), would coexist symbiotically until a particular chronogenetic event altered this balanced state and allowed, in this example, for leukemogenesis. Since MZ twins have identical hereditary biological time tables, and hypothetically, assuming both could harbor latent carcinogenic viruses via their shared intrauterine circulations, the statistically significant C/D ratios of MZ twins and the relative degree of simultaneity in disease evolution is clarified. Thus, in a characteristically tedious fashion, information concerning ante and postnatal factors affecting leukemia in twins is accumulating. Our broad concepts (Keith et al. 1973) are generally being supported, expanded and refined.

REFERENCES

Gedda L., Brenci G. 1971. Chronology of the gene. Acta Genet. Med. Gemellol. (Roma), 20: 323-349.
Gedda L. and Brenci G. 1973. Chronogenetics: its foundations, scope, and impact. Acta Genet. Med. Gemellol. (Roma), 22: 3-17.
Gross L. 1974. The role of viruses in the etiology of cancer and leukemia. JAMA, 230: 1029-1032.

Dr. Louis Keith, 333 East Superior St., Chicago, Illinois 60611, USA.