

Epidemiologic Study of Leukemia in Twins (1928-1969)

Louis Keith, Eric Brown

SUMMARY

A review of 62 cases of leukemia in twins reveals most cases occurred in MZ twins, although diagnosis of zygosity was at times admittedly questionable. Concordance was clearly highest in MZ twins of the perinatal-congenital period. This tendency was not maintained at later stages of life.

The older concept of a human placental barrier has been greatly modified. Tracer substances have demonstrated that leukemic cells pass the placental barrier. Materno-fetal transmission of leukemia is well known; all forms of murine leukemia can be transmitted similarly from generation to generation. Certain requisites effect the transmission of neoplastic-hematopoietic disease during pregnancy. Rare cases are reported of pregnant women with leukemia who bear children in whom clinical leukemia subsequently develops. The maternal diagnosis was made at the time of, or shortly after, delivery, suggesting an evolution of the maternal disease late in pregnancy.

That both partners of a pair of twins, either MZ or DZ, can become ill with leukemia within days or months of each other, appears more than coincidental. Chromosomal defects, common environmental factors, and conjoined intrauterine circulations may be important in the transmission of leukemia from one twin to another, a theory supported by the frequent concordance during the first year of life.

Reports of leukemia among twins have appeared as single cases or as collections of cases for as long as 40 years (Siegel, 1928; Damashek et al, 1929; Pearson et al, 1963). Reviews of leukemia and textbooks of medicine and hematology mention this association only tangentially or not at all (Denolin-Rubens, 1957; Steinberg, 1957, 1960).

Recent advances have made the diagnosis of twin zygosity more reliable than formerly (Smith and Penrose, 1955; Cederlöf et al, 1961; Nichols and Bilbro, 1966; Jablon et al, 1967). Widespread application of chromosomal studies has opened new avenues of investigation to students of both gemellology and leukemia. The presence of abnormal chromosomes in patients with leukemia has been incorporated into reports of leukemia among twins (Nowell and Hungerford, 1960a, 1960b; Pearson et al, 1963; Kiossoglu et al, 1963, 1964; Goh and Swisher, 1965; Woodliff and Dougan, 1965; Woodliff et al, 1966; Dougan et al, 1966; Jacobs et al, 1966; Gunz et al, 1966; Sandberg et al, 1966; Goh et al, 1967; Tokuhata et al, 1968). These advances have incited interest in the occurrence of leukemia among twins (Nowell and Hungerford, 1960a, 1960b; Kiossoglu et al, 1963, 1964; MacMahon and Levy, 1964; Goh and Swisher, 1965; Woodliff and Dougan, 1965; Woodliff et al, 1966; Dougan et al, 1966; Jacobs et al, 1966; Gunz et al, 1966; Sandberg et al, 1966;

Iverson, 1966; Hewitt et al, 1966; Goh et al, 1967; Miller, 1967; Tokuhata et al, 1968). Data in early reports were often incomplete regarding zygosity (Cook, 1953), diagnosis (Siegel, 1928), therapy (Guasch, 1954), and survival (Guasch, 1954; Denolin-Rubens, 1957). This deficiency is being overcome.

Miller (1967) has shown MZ twins to be among five groups in whom the probability of development of leukemia within a short time is 1% or greater. Other groups are those with genetically transmitted diseases, such as Blum's syndrome and Fanconi's syndrome, previous or excessive exposure to ionizing radiation, and patients with Down's syndrome (Folley, et al, 1952; MacMahon, 1962; Miller, 1963, 1967; Fraumeni and Miller, 1967). Common to all these conditions is a distinctive genetic or cytogenetic characteristic.

MacMahon and Levy (1964) attempted to estimate the concordance rate of leukemia among twins. They concluded that the risk of leukemia among like-sexed cotwins of leukemia patients was 1 : 9.

Tabular Designations and Exclusions

We undertook an extensive review of world-wide reports of leukemia among twins. Our survey was a careful one; exclusions are inevitable, but if so, are inadvertent except for undocumented "personal communication" cases which have sometimes been included in large reviews of leukemia (Guasch, 1954) or leukemia among twins (Hitzig and Rampini, 1959). We have not included these and others in our tables about which information was too fragmentary for interpretation. Specific information regarding the cases of leukemia among twins was sometimes incomplete (Steinberg, 1957, 1960; Thomas et al, 1959; Thomas and Ferrebee, 1960; Boggs et al, 1962; Hewitt et al, 1966). In other instances, we adapted available information to our tables (Guasch, 1954; Iverson, 1966). Multiple references to the same occurrence of leukemia in a set of twins, or varying aspects of a given case of leukemia in a set of twins were sometimes reported in two or more communications; the specific case is listed only once in our table, but all references are cited in the table references.

Classification

MacMahon and Levy (1964) commented on the difficulty of establishing zygosity by retrospective analysis of records alone. Most reported series on leukemia among twins have used zygosity and concordance-discordance relations as major aspects of their classification of cases (Guasch, 1954; Hitzig and Rampini, 1959; Steinberg, 1960; Pearson et al, 1963; Iverson, 1966). This represents a source of inherent bias in most reviews, including the present one.

Leukemia appears to occur at four periods in the lives of twins: (1) the perinatal-congenital period; (2) early childhood; (3) late childhood, or (4) adulthood (Tables I-IV). The concept of perinatal leukemia was first proposed by Matallaer and Riley (1964) to include leukemia among premature, stillborn, and newborn infants. This opinion was later supported and enlarged on by Stransky (1967). Miller's "con-

Tab. 1. Leukemia in twins - 1. Perinatal-congenital period

Author and year	Zygoty	Sex	Concordance	Age at onset	Interval	Survival	Chromosomal abnormalities	Type
Gunz et al, 1966	DZ	♂♂	C	10mos. 30mos.	20mos.	I 3 days II 3 weeks	Probable	Acute lymphoblastic Acute lymphocytic
Iverson, 1966	?	♂♂	D	2mos.		I not stated II Normal		Acute
Sandberg et al, 1966	DZ?	♂♂	C	6mos. 7mos.	1mo.	I 1½mos. II 9mos.	Markers + In both	Acute myeloblastic
Macmahon & Levy, 1964	MZ	♀♀	C	11mos. 15mos.	4mos.	I 1mo. II 1mo.		Acute lymphatic
Rusescu et al, 1964	MZ	♀♀	C	6mos. 7mos.	1mo.	I 1mo. II 2mos.		Acute blastic
Wolman, 1964	MZ	♀♀	C	5½mos. 5½mos.	None	I 8mos. II 8mos.		Acute lymphocytic Acute lymphoblastic
Ioachim, 1962	MZ	♀♀	C	7mos. 8mos.	1mo.	I 3mos. II 2mos.		Acute with para-myeloblasts
Tiknomirow & Sirotin, 1959	MZ	♂♂	C	4mos. 4mos.	None	I 3mos. II 3mos.		Subacute Aleukemic lymphocytic
Hitzig & Rampini, 1959	MZ	♀♀	C	5mos. 5mos.	Almost none	I 12mos. II 10mos.		Paraleukoblastic
Hogg & Schmidt, 1958	DZ	♂*♀	D	Antenatal		I Stillborn II Normal		Myelogenous
Wegelius & Paaso, 1956	MZ	♀♀	C	10mos. 10mos.	Almost none	I 1mo. II 1mo.		Acute lymphatic
Hjelt & Wegelius, 1956	MZ	♀♀	D	Birth		I 3 weeks II Normal		Acute lymphocytic
Anderson & Herman, 1955	MZ	♀♀	C	9mos. 10mos.	4mos.	I 6 weeks II 5 weeks		Acute lymphatic
Guasch (Miller), 1954	MZ	♂♂	C	6mos. 18mos.	12mos.	I not stated II not stated		Acute
Jelke, 1939	MZ	♀♀	C	5mos. 5¼mos.	1 week	I 2 weeks II 6 weeks		Acute lymphatic

* Patient.

Tab. II. Leukemia in twins - 2. Early childhood

Author and year	Zygoty	Sex	Concordance	Age at onset	Interval	Survival	Chromosomal differences	Type
Lundmark et al, 1967	DZ	♂♂	C	3yrs. 11mos. 2yrs. 5mos.	18mos.	I 3mos. II 2mos.		Acute undiff. Blas.
Iverson, 1966	?	♂♂	D	4yrs.		I not stated II Normal		Acute
Iverson, 1966	?	♂♂	D	5yrs. 10mos.		I not stated II Normal		Acute
Iverson, 1966	DZ	♀*♂	D	3yrs. 7mos.		I not stated II Normal		Acute
Iverson, 1966	?	♂♂	D	3yrs. 7mos.		I not stated II Died at birth		Acute
Iverson, 1966	?	♀♀	D	4yrs. 8mos.		I not stated II Normal		Acute
Iverson, 1966	DZ	♂*♀	D	1yrs. 10mos.		I not stated II Normal		Acute
Iverson, 1966	?	♂♂	D	1yr. 11mos.		I not stated II Normal		Acute
Kiosoglou et al, 1964	DZ	♂*♀	D	4yrs.		I 3mos. II Normal	+ Affected - Normal	Acute granulocytic
Macmahon & Levy, 1964	MZ	♂♂	C	4yrs. 2mos. 4yrs. 2mos.	None	I 10mos. II not stated		Acute myeloid
Macmahon & Levy, 1964	MZ	♂♂	C	3yrs. 10mos. 4yrs. 10mos.	1yr.	I 15mos. II 1yr.		Acute lymphatic
Pearson et al, 1963	MZ	♂♂	C	3yrs. 6mos. 3yrs. 9mos.	5mos.	I 2yrs. 2mos. II 1yr. 4mos.	+ Affected + Affected	Acute lymphoblastic
Hitzig & Rampini, 1959	MZ	♂♂	D	5yrs.		I 1mo. II Normal		Acute paraneoplastic

* Patient.

Tab. II - Continued

Author and year	Zygoty	Sex	Concordance	Age at onset	Interval	Survival	Chromosomal differences	Type
Hitzig & Rampini, 1959	MZ	♂♂	D	4yrs.		I 2mos. II Normal		Acute paramyeloblastic
Hitzig & Rampini, 1959	MZ	♀♀	D	2yrs. 3mos.		I L & W 1yr. II Normal		Aleukemic para-leukoblastic
Atkinson et al, 1959	MZ	♀♀	D	1yr. 6mos.		I 8mos. II Normal		Acute lymphoblastic
Denolin-Rubens, 1957	DZ	not stated	C	2yrs. 5mos. 2yrs. 6mos.	1mo.	I not stated II not stated		Acute micromyeloblastic
Guasch, 1954	MZ	♂♂	D	3yrs.		I not stated II L & W at 2yrs.		Acute
Guasch, 1954	MZ	♂♂	D	3yrs. 6mos.		I not stated II not stated		Acute
Guasch (Piney), 1954	MZ	♂♂	C	4yrs. 6mos. 5yrs. 3mos.	9mos.	I not stated II not stated		Acute
Guasch, 1954	DZ	♀♂	D	2yrs. 6mos.		I not stated II L & W at 3yrs.		Acute
Cook, 1953	DZ ?	♂♂	C	1yr. 5mos. 1yr. 11mos.	6mos.	I 1mo. II 1mo.		Acute lymphatic Acute lymphoblastic
Riel, 1948	MZ	♂♂	C	3yrs. 3mos. 3yrs. 6mos.	3mos.	I 1/2mo. II 1 week		Acute lymphatic
Videback, 1947	DZ	♀♀	D	2yrs.		I 5yrs. II not followed		Acute lymphatic
Hofmeyer, 1938	MZ	♀♀	C	2yrs. 6mos 4yrs.		I not stated II not stated		Acute
Siegel, 1928	DZ	♀♀	C	2yrs. 6mos. 2yrs. 6mos.		I Normal II Normal		Acute myeloid

Tab. III. Leukemia in twins - 3. Late childhood

Author and year	Zygoty	Sex	Concordance	Age at onset	Interval	Survival	Type
Iverson, 1966	DZ	♂♀*	D	12yrs. 1mo.		I not stated II and twin (male died at 4mos.	Acute
Iverson, 1966	?	♂♂	D	12yrs. 9mos.		I not stated II L & W	Acute
Iverson, 1966	?	♂♂	D	8yrs. 8mos.		I not stated II L & W	Acute
Mac Mahon & Levy, 1964	MZ	♀♀	C	7yrs. 9mos. 9yrs. 6mos.	21mos.	I 4mos. II 10mos.	Acute stem cell
Depaillat, 1961	MZ	♂♂	D	12yrs.		I 7yrs. II L & W at 19yrs.	Chronic myeloid
Hjelt and Wegelius, 1960	MZ	♀♀	D	9yrs.		I 2mos. II Normal	Acute myeloid
Anderson & Herman, 1955	MZ	♀♀	D	7yrs.		I 12 weeks II Normal	Subacute lymphatic
Guash, 1954	MZ	♀♀	D	10yrs.		I not stated II L & W at 2yrs.	Acute
Guash, 1954	MZ	♂♂	D	9yrs.		I not stated II L & W at 1yr.	Acute

* Patient.

Tab. IV. Leukemia in twins - 4. Adulthood

Author and year	Zygoty	Sex	Concordance	Age at onset	Interval	Survival	Type	Chromosomal differences
Tokuhata et al, 1968	MZ	♂♂	C	64yrs. 64yrs.	3mos.	I 6mos. II 2yrs. 7mos.	Chronic myelocytic	+ +
Goh et al, 1967	MZ	♂♂	D	16yrs.		I L & W at 9mos. II Normal	Chronic myelocytic	+ Affected - Normal
Jacobs et al, 1966	MZ	♂♂	D	31yrs.		I L & W at 6mos. II Normal	Chronic myelocytic	+ Affected - Normal
Dougan et al, 1966	MZ	♂♂	D	35yrs.		I L & W at 3yrs. II Normal	Chronic granulocytic	+ Affected - Normal
Goh & Swisher, 1965	MZ	♂♂	D	23yrs.		I 3yrs. II Normal	Chronic myelocytic	+ Affected - Normal
Aleksandrowicz & Blicharski, 1960	MZ	♀♀	C	45yrs. 50yrs.	5yrs.	I 5yrs. II 4 weeks	Chronic granulocytic Acute myeloblastic	
Guash, 1954	MZ	♀♀	D	23yrs.		I not stated II L & W at 2yrs.	Chronic myeloid	
Stobbe & Taeschner, 1952	MZ	♂♂	C	71yrs. 56yrs.	15yrs.	I 8mos. II 4yrs.	Chronic lymphatic	
Videbaek, 1947	DZ	♂♂	D	65yrs.		I 1yr. II L & W at 4yrs.	Chronic lymphogenous	
Videbaek, 1947	DZ	♂*♀	D	19yrs.		I 11 days II L & W at 4yrs.	Acute lymphogenous	
Kellett, 1937	MZ	♀♀	D	14yrs. 6mos.		I 2 weeks II Normal	Acute myeloid	
Darnashek et al, 1929	MZ	♂♂	C	56yrs. 56yrs.		I 10mos. II 1 week	Chronic lymphatic	

* Patient.

genital leukemia" (1954-1955) included perinatal cases and those occurring in the first year of life. We have combined those cases occurring in the first year under the title: Perinatal-Congenital. We have compiled 62 cases of leukemia among twins from reports over the world publications¹ in the following categories: Perinatal-Congenital, 15; Early Childhood, 26; Late Childhood, 9; Adulthood, 12.

In our tables, early childhood extends from about 2 to 7 years (MacMahon and Levy's cut-off for high risk, 1964), and late childhood from 7 through 12 years. All other cases have been considered within Adulthood. Two cases occurring in teenagers have been placed in this group, in accordance with clinical practice. The cases are listed in each table in reverse chronological order.

Except for those instances about which writers admitted that the diagnosis of zygosity was in question (Cook, 1953; Sandberg et al, 1966; Iverson, 1966), most cases occurred in MZ twins. There were 39 cases of leukemia in MZ twins, 13 cases in DZ twins and 10 cases in whom zygosity was in doubt. Tab. V lists the number of concordant and discordant cases in the MZ and DZ groups.

Among 39 sets of twins with a reasonably assured diagnosis of monozygosity, there were 21 instances of concordance for leukemia and 18 instances of discordance. When grouped according to the stages of life, concordance-discordance ratios were 10:1 in the perinatal-congenital period and 6:6 in early childhood. Discordance became more prevalent in the late childhood where the ratio was 1:5; this pattern was continued in adulthood with a concordance-discordance ratio of 4:6. When DZ twins were examined, the ratios were 1:1 in the perinatal-congenital period, 3:5 in early childhood, and 0:1 and 0:2 in late childhood and adulthood respectively.

Of the twin pairs, 32 were male, 22 female, and 7 male-female; in 1 case the sex was not stated.

We hesitate to draw conclusions from these compilations. Cases of concordance of any neoplasm in twins are reported more frequently than are discordant cases. Because unreported cases may exist, a source of error becomes constant.

The Problem of Lymphoma among Twins

Although the simultaneous occurrence of leukemia and pregnancy has been noted frequently, the possibility that maternal leukemic cells could cross the placenta and affect the fetus had long been denied (Erf, 1947). The older concept of a human placental barrier has been modified greatly. Investigations of erythroblastosis fetalis have shown clearly that fetal cells pass the placenta into the mother's circulation

¹ ADDENDUM: Since the completion of this manuscript two additional instances of leukemia in twins were reported. In the case reported by Bauke (*Cancer*, 24: 643, 1969) MZ adult male twins were described. The affected twin had chronic myelocytic leukemia with typical Philadelphia chromosome abnormality. His normal cotwin was free of disease and chromosomal abnormalities 8½ years later. Kosenow and Pfeiffer (*Deutsch. Med. Wschr.*, 94: 1170, 1969) described 7-year-old discordant MZ female twins one of whom had chronic myeloid leukemia and also exhibited the Philadelphia chromosome in the bone marrow. Her identical cotwin was free of disease or chromosomal abnormalities.

Tab. V

Stage of life	No. of cases	MZ ^a		DZ ^a		Sex ratio (M : F) ^b
		C	D	C	D	
Perinatal-Congenital	15	10	1	1	1	5 : 9; 1 set MF
Early Childhood	26	6	6	3	5	15 : 6; 1 set not stated; 4 sets MF
Late Childhood	9	1	5	—	1	4 : 4; 1 set MF
Adulthood	12	4	6	—	2	8 : 3; 1 set MF

^a 10 cases of doubtful zygosity excluded.

^b Include all cases.

(Chown, 1954; Bromberg et al, 1956; Creger and Steele, 1957; Zipursky et al, 1959). Desai and Creger (1963) and others (Cohen and Zuelzer, 1964; Cohen, 1965) have shown that maternal erythrocytes may pass the placenta into the fetal circulation. This observation opened the possibility of consideration that leukemia cells from a pregnant patient may enter the bloodstream of her fetus. By the use of tracer substances, Rigby et al (1964) demonstrated that leukemic cells also passed the placental barrier. Leukemic cells had previously been observed at autopsy by Bierman et al (1956) to have infiltrated the myometrium and lymphatics in the uterus of a pregnant leukemic patient. The maternal side of the previously delivered placenta in the same case was likewise affected.

The materno-fetal transmission of leukemia in lower animals is well known. Bittner (1936) was the first to show that breast cancer could be transmitted to offspring by way of the milk of the affected mother; later, Gross (1951) demonstrated that cell-free extracts given to mice in the suckling stage were capable of transmitting lymphocytic leukemia to all offspring of an affected mother. Brown and associates (Brown, 1961; Schwartz et al, 1963; Brown and Schwartz, 1966; Brown et al, 1967) subsequently showed that all forms of murine leukemia can be transmitted similarly from generation to generation.

Diamondopolos and Hertig (1963) stated four requisites for the successful transmission of neoplastic-hematopoietic diseases during pregnancy: (1) the hereditary pattern for transmission as excellent as is generally available in man and second only to that shared by identical twins; (2) immune intolerance during intrauterine and early extrauterine life; (3) the ability of maternal cells that reach the fetus to remain intact with a better chance of survival; (4) a relatively long period of exposure to the oncogenic agent (assuming that one exists) during the nine months of gestation.

On rare occasions, pregnant women with leukemia bear children in whom clinical leukemia subsequently develops. Guasch (1954) suggested that this happened

in his cases attributed to Pincy and Debré and their coworkers; but details were not given. Cramblett et al reported the first well documented instance in 1958. The infant was nine months old at the time that acute lymphatic leukemia developed. Although the maternal diagnosis was not made until the eighth postpartum day, signs and symptoms of acute leukemia were exhibited during the seventh month of pregnancy.

Bernard et al (1964) reported the occurrence of acute lymphoblastic leukemia in an infant five months of age whose mother had the same condition at the time of birth. They pointed out the remarkable similarities between their case and that of Cramblett et al (1958). In both instances, the maternal diagnosis was made at the time of, or shortly after the delivery, suggesting an evolution of the maternal disease late in pregnancy. They did not think that such occurrences were coincidental, but postulated one of the following mechanisms: (1) similar genetic anomaly between the mother and infant; (2) transplacental passage of a viral factor; (3) contamination of the infant at the time of birth; or (4) possible graft of maternal leukemia cells to the infant. The unusual nature of these two cases is in line with Boronow's review (1964) attesting to the paucity of published cases concerning maternal neoplastic disease in the placenta or the fetus.

That both partners of a pair of twins, either MZ or DZ, can become ill with leukemia within days or months of each other, appears more than coincidental. With the exception of the extremely rare instances in which the mother had leukemia, it is difficult to ascertain exactly when the leukemia process became active in twins or when they were first exposed to any leukemogenic factor.

Wolman (1962) has reiterated that vessel-to-vessel anastomoses in the placentas of MZ twins allow for intrauterine blood exchanges between the fetuses. He postulated a free exchange of any leukemogenic agent or abnormal leukocytes between the infants. To our knowledge, Wolman (1962) and MacMahon and Levy (1964) were the first to suggest that in addition to the possibility of chromosomal defects and common environmental factors, conjoined intrauterine circulations may be important in the transmission of the disease from one twin to another. We believe that this line of thinking is reasonable and probably should be pursued further. It may explain the overwhelming concordance noted in the perinatal-congenital period.

References

- ALEKSANDROWICZ J., Blicharski J. (1960). Leucémie chez deux sœurs jumelles (monozygotes). Essai de traitement par la transfusion de la moelle osseuse. *Sang*, **31**: 49.
- ANDERSON R. C., HERMAN H. W. (1955). Leukemia in twin children. *J.A.M.A.*, **158**: 652.
- ATKINSON J. B., MAHONEY F. J., SCHWARTZ I. R., HESCH J. A. (1959). Therapy of acute leukemia by whole body irradiation and bone marrow transplantation from an identical normal twin. *Blood*, **14**: 228.
- BERNARD J., JACQUILLAT C., CHAVELET F., BOIRON M., STOITCHKOV Y., TANZER J. (1964). Leucémie aiguë d'une enfant de 5 mois née d'une mère atteinte de la leucémie aiguë au moment de l'accouchement. *Nouv. Rev. Franc. Hemat.*, **4**: 140.

- BIERMAN H. R., AGGELER P. M., THELANDER H., KELLY K. H., CORDES F. (1956). Leukemia and pregnancy. A problem of transmission in man. *J.A.M.A.*, **161**: 220.
- BITTNER J. J. (1936). Some possible effect of nursing on the mammary gland tumor incidence in mice. *Science*, **84**: 162.
- BOGGS D. R., WINTROBE M. M., CARTWRIGHT G. E. (1962). Acute leukemias. *Medicine (Balt.)*, **41**: 163.
- BORONOW R. (1964). Extra pelvic malignancy and pregnancy. *Obstet. Gynec. Survey*, **19**: 1.
- BROMBERG Y. M., SALZBERGER M., ABRAHAMOV A. (1956). Transplacental transmission of fetal erythrocytes with demonstration of fetal hemoglobin in maternal circulation. *Obstet. Gynec.*, **7**: 672.
- BROWN E. R. (1961). Factors in immunology of cancer as related to dissemination. In W. H. Cole: *Dissemination of Cancer: Prevention and Therapy*. Appleton-Century Crafts, New York.
- BROWN E. R., SCHWARTZ S. O. (1966). Immunofluorescent antibody studies of murine leukemia virus: comparison of human, bovine and murine systems. *Experientia*, **22**: 686.
- BROWN E. R., BUINAUSKAS P., SCHWARTZ S. O. (1967). Certain physical and chemical properties of two murine leukemia viruses. *Canad. J. Microbiol.*, **13**: 957.
- CEDERLÖF R., FRIBERG L., JONSSON E., KAIJ L. (1961). Studies on similarity diagnosis in twins with the aid of mailed questionnaires. *Acta Genet. (Basel)*, **11**: 338.
- CHOWN B. (1954). Anemia from bleeding of the fetus with the mother's circulation. *Lancet*, **1**: 1213.
- COHEN F., ZUELZER W. W. (1964). Identification of blood group antigens by immunofluorescence and its application to the selection of the transplacental passage of erythrocytes in mother and child. *Vox Sang.*, **9**: 75.
- COHEN F. (1965). Transplacental passage of maternal erythrocytes into fetus. *Amer. J. Obstet. Gynec.*, **93**: 566.
- COOK J. V. (1953). Acute leukemia in twins. *J.A.M.A.*, **152**: 1028.
- CRAMBLETT H. G., FRIEDMAN J. L., NAJJAR S. (1958). Leukemia in an infant born of a mother with leukemia. *New Eng. J. Med.*, **259**: 727.
- CREGER W. P., STEELE M. R. (1957). Human fetomaternal passage of erythrocytes. *New Eng. J. Med.*, **256**: 158.
- DAMASHEK W., SAVITZ H. A., ARBOR B. (1929). Chronic lymphatic leukemia in twin brothers aged 56. *J.A.M.A.*, **92**: 1348.
- DENOLIN-RUBENS R. (1957). Le diagnostic de la leucémie aiguë: ses difficultés et ses limites. *Acta Clin. Belg.*, **12**: 451.
- DEPAILLAT A. (1961). A propos d'un cas de leucémie affectant un jumeau monozygote. *Arch. Franc. Pediat.*, **18**: 1054.
- DESAI R. G., CREGER W. P. (1963). Materno-fetal passage of leukocytes and platelets in man. *Blood*, **21**: 665.
- DIAMONDOPOLOS G., HERTIG A. (1963). Transmission of leukemia and allied diseases from mother to fetus. *Obstet. Gynec.*, **21**: 150.
- DOUGAN L., SCOTT I. D., WOODLIFF H. J. (1966). A pair of twins, one of whom has chronic granulocytic leukemia. *J. Med. Genet.*, **3**: 217.
- ERF L. A. (1947). Leukemia (summary of 100 cases) and lymphosarcoma complicated by pregnancy. *Amer. J. Clin. Path.*, **17**: 268.
- FOLLEY J. H., BORGES W., YAMAWAKI T. (1952). Incidence of leukemia in survivors of the atom bomb in Hiroshima and Nagasaki, Japan. *Amer. J. Med.*, **13**: 311.
- FRAUMENI J. F., MILLER R. W. (1967). Epidemiology of human leukemia: recent observations. *J. Nat. Cancer Inst.*, **38**: 593.
- GOH K., SWISHER S. (1965). Identical twins and chronic myelocytic leukemia. Patient with chronic myelocytic leukemia and his normal identical twin. *Arch. Intern. Med. (Chicago)*, **115**: 475.
- GOH K., SWISHER S., HERMAN E. C. (1967). Chronic myelocytic leukemia in twins. *Arch. Intern. Med. (Chicago)*, **120**: 214.
- GROSS L. (1951). "Spontaneous" leukemia developing in C₃H mice following inoculation in infancy with AK leukemia extracts, or AK embryos. *Proc. Soc. Exp. Biol. Med.*, **76**: 27.
- GUASCH J. (1954). Hérité des leucémies. *Sang*, **25**: 384.
-

- GUNZ F., DAMASHEK W. (1957). Chronic lymphocytic leukemia in a family including twin brothers and a son. *J.A.M.A.*, **164**: 1323.
- GUNZ F., FITZGERALD P. H., CROSSEN P. E., MACKENZIE I. S., POWLES C. P., JENSEN G. R. (1966). Multiple cases of leukemia in a sibship. *Blood*, **27**: 482.
- HEWITT D., LASHOF J. C., STEWART A. M. (1966). Childhood cancer in twins. *Cancer*, **19**: 157.
- HITZIG W. H., RAMPINI S. (1959). Leukämie bei Zwillingen. *Helv. Paediat. Acta*, **14**: 67.
- HJELT L., WEGELIUS R. (1956). Congenital leukemia. *Ann. Paediat. Fenn.*, **2**: 206.
- HJELT L., WEGELIUS R. (1960). Discordant leukemia in twins. A report of two cases, including one of congenital leukemia. *Ann. Paediat. Fenn.*, **6**: 227.
- HOFMEYER K. (1938). Die Bedeutung der Erbanlagen für die Kinderheilkunde. *Arch. Kinderheilk.*, **14**: 1.
- HOGG G. R., SCHMIDT O. A. (1958). Myelogenous leukemia in a stillborn infant. *Canad. Med. Ass. J.*, **78**: 421.
- IOACHIM H. (1962). Acute leukemia in uniovular twins. *Cancer*, **15**: 539.
- IVERSON T. (1966). Leukemia in infancy and childhood. *Acta Paediat. Scand.*, Suppl. 167.
- JABLON S., NEEL J. V., GERSHOWITZ H., ATKINSON G. F. (1967). NAS-NRC twin panel: methods of construction of panel, zygosity diagnosis and proposed use. *Amer. J. Hum. Genet.*, **19**: 133.
- JACOBS E. M. et al (1966). Chromosome abnormalities in human cancer. Report of a patient with chronic myelocytic leukemia and his non-leukemic monozygotic twin. *Cancer*, **19**: 869.
- JELKE H. (1939). Akute Lymphatischer Leukämie bei eineiigen Zwillingen. *Acta Paediat.*, **27**: 87.
- KELLETT C. E. (1937). Acute myeloid leukemia in one of identical twins. *Arch. Dis. Child.*, **12**: 239.
- KIOSOGLU K. A. et al (1963). Multiple chromosome aberrations in Down's syndrome associated with twinning and acute granulocytic leukemia. *Lancet*, **2**: 944.
- KIOSOGLU K. A., ROSENBAUM E. H., MITUS W. J., DAMASHEK W. (1964). Multiple chromosomal aberrations in a patient with acute granulocytic leukemia associated with Down's syndrome and twinning. *Blood*, **24**: 134.
- LUNDMARK K. M., THILÉN A., VAHLQUIST B. (1967). Familial leukemia; three cases of acute leukemia in four siblings. *Acta Paediat. Scand.* (Suppl.), **172**: 200.
- MACMAHON B. (1962). Prenatal X-ray exposure and childhood cancer. *J. Nat. Cancer Inst.*, **28**: 1173.
- MACMAHON B., LEVY M. (1964). Prenatal origin of childhood leukemia. *New Eng. J. Med.*, **270**: 1082.
- MATALLAER P. M., RILEY D. Jr. (1964). Leukemia in the perinatal period. *Ann. Paediat. (Basel)*, **203**: 14.
- MILLER F. (1954-1955). Angeborene Leukämie. *Virchow Arch. (Path. Anat.)*, **326**: 73.
- MILLER R. W. (1963). Down's syndrome (mongolism), other congenital malformations and cancer among the sibs of leukemic children. *New Eng. J. Med.*, **268**: 393.
- MILLER R. W. (1967). Persons with exceptionally high risk of leukemia. *Cancer Res.*, **27**: 2420.
- NICHOLS R. C., BILBRO W. C. (1966). Diagnosis of twin zygosity. *Acta Genet. (Basel)*, **16**: 265.
- NOWELL P. C., HUNGERFORD D. A. (1960a). Chromosome studies on normal and leukemic human leukocytes. *J. Nat. Cancer Inst.*, **25**: 85.
- NOWELL P. C., HUNGERFORD D. A. (1960b). A minute chromosome in human chronic granulocytic leukemia. *Science*, **132**: 1497.
- PEARSON H. A., GRELO F. W., CONE T. E. (1963). Leukemia in identical twins. *New Eng. J. Med.*, **268**: 1151.
- RIEL L. (1948). Akute lymphatische Leukämie bei (eineiigen) Zwillingen. *Kinderärzt. Prax.*, **16**: 148.
- RIGBY P. G., HANSON T. A., SMITH R. S. (1964). Passage of leukemic cells across the placenta. *New Eng. J. Med.*, **271**: 124.
- RUSESCU A., BALAN A., ANCA I. (1964). Leukoza acuta la gemeni univitelini. *Pediatrics (Bucur.)*, **13**: 245.
- SANDBERG A. A., CORTNER J., TAKAGI N., MOGHADAM M. A., CROSSWHITE L. H. (1966). Differences in chromosomal constitution of twins with acute leukemia. *New Eng. J. Med.*, **275**: 809.
- SCHWARTZ S. O., GREENSPAN I., BROWN E. R. (1963). Leukemia cluster in Niles, Illinois: immunologic data. *J.A.M.A.*, **186**: 106.
- SIEGEL A. E. (1928). Lymphocytic leukemia occurring in twins. *Atlantic Med. J.*, **31**: 748.
- SMITH S. M., PENROSE L. S. (1955). Monozygotic and dizygotic twins diagnosis. *Ann. Hum. Genet.*, **19**: 273.

- STEINBERG A. G. (1957). A genetic and statistical study of acute leukemia in children. Proc. 3rd Nat. Cancer Conf., 353.
- STEINBERG A. G. (1960). Genetics of acute leukemia in children. Cancer, **13**: 985.
- STOBBE H., TAESCHNER H. (1952). Konkordantes Auftreten lymphatischer Leukämie bei eineiigen Zwillingen. Z. Ges. Inn. Med., **7**: 736.
- STRANSKY E. (1967). Perinatal leukemia. Acta Paediat. Acad. Sci. Hung., **8**: 121.
- THOMAS E. D., LOCHTE H. L., CANNON J. H., SAHLER O. D., FERREBEE J. W. (1959). Supralethal whole body irradiation and isologous marrow transplantation in man. J. Clin. Invest., **38**: 1709.
- THOMAS E. D., FERREBEE J. W. (1960). Irradiation and marrow transplantation studies in Cooperstown. Lancet, **1**: 1289.
- TIKHOMIROV A. S., SIROTIN B. Z. (1959). Case of leukemia in two uniovular twins. Prob. Hemat. Blood Trans., **4**: 75.
- TOKUHATA G. K. et al (1968). Chronic myelocytic leukemia in twins. Blood, **31**: 216.
- VIDBAEK A. (1947). Heredity in Human Leukemia. H. K. Lewis and Co. Ltd., London, and Nyt. Nordisk Forlage, Arnold Busck, Copenhagen.
- WEGELIUS R., PAASO E. J. (1956). Identical twins simultaneously dying of leukemia. Ann. Paediat. Fenn., **2**: 137.
- WOLMAN I. J. (1962). Parallel responses to chemotherapy in identical infants with concordant leukemia. J. Pediat., **60**: 91.
- WOODLIFF H., DOUGAN L. (1965). Studies on identical twins, one of whom has chronic granulocytic leukemia. Med. Res., **1**: 149.
- WOODLIFF H., DOUGAN L., ONESTI P. (1966). Cytogenetic studies in twins, one with granulocytic leukemia. Nature (London), **211**: 533.
- ZIPURSKY A., HULL A., WHITE F. D., ISRAELS L. G. (1959). Foetal erythrocytes in maternal circulation. Lancet, **1**: 451.

RIASSUNTO

Una rassegna di 62 casi di leucemia in gemelli rivela che i MZ sono quelli più colpiti (per quanto la diagnosi di zigotismo sia a volte incerta) e che la concordanza è più elevata nel periodo congenito-perinatale, per poi ridursi successivamente.

Il vecchio concetto di una barriera umana placentare è stato ampiamente modificato; mediante sostanze marcate si è infatti dimostrato che le cellule leucemiche attraversano la barriera placentare. La trasmissione materno-fetale della leucemia è ben nota: tutte le forme leucemiche nel topo possono essere trasmesse analogamente, di generazione in generazione. Alcune condizioni favoriscono la trasmissione della malattia neoplastico-emopoietica durante la gravidanza. Sono noti alcuni rari casi di donne leucemiche incinte, il cui figlio ha successivamente manifestato leucemia clinica. La diagnosi della madre è stata fatta all'epoca del parto, o subito dopo, il che suggerisce un'evoluzione della malattia materna in fase avanzata di gravidanza.

Che due cogemelli, sia MZ che DZ, possano ammalarsi di leucemia nel giro di giorni o mesi l'uno dall'altro, non sembrerebbe una pura coincidenza. Difetti cromosomici, fattori ambientali comuni, e una circolazione intrauterina congiunta possono avere un ruolo nella trasmissione della leucemia da un gemello all'altro, teoria suffragata dalla frequente concordanza nel corso del primo anno di vita.

RÉSUMÉ

Une revue de 62 cas de leucémie chez les jumeaux révèle que les plus atteints sont les MZ (quoique le diagnostic de zygotisme soit parfois incertain) et que la concordance est plus élevée dans la période congénitale-périnatale, pour se réduire ensuite.

La vieille conception d'une barrière humaine placentaire a été largement modifiée; par des substances marquées il a été en effet démontré que les cellules leucémiques passent la barrière placentaire. La transmission

materno-fœtale de la leucémie est bien connue: toutes les formes leucémiques chez la souris peuvent être transmises analogiquement, d'une génération à l'autre. Certaines conditions facilitent la transmission de la maladie néoplastique-hémopoïétique au cours de la grossesse. On connaît de rares cas de femmes leucémiques enceintes dont le fils a successivement manifesté la leucémie clinique. Le diagnostic chez la mère a été fait à l'époque de l'accouchement, ou tout de suite après, ce qui suggère une évolution de la maladie maternelle dans un stage avancé de la grossesse.

Le fait que des jumeaux, MZ ou DZ, puissent manifester une leucémie concordante avec une différence de quelques jours ou quelques mois, ne semble pas être seulement une coïncidence. Des défauts chromosomiques, des facteurs ambiants communs, ainsi qu'une circulation endoutérine conjointe peuvent jouer un rôle dans la transmission de la leucémie d'un jumeau à l'autre — une théorie qui est confirmée par la fréquente concordance au cours de la première année de vie.

ZUSAMMENFASSUNG

Ein Überblick über 62 Leukämiefälle bei Zwillingen zeigt, dass EZ mehr betroffen werden als ZZ (wenn auch die Eizkeitsdiagnose manchmal ungewiss erscheint) und dass die Konkordanz in der Zeit vor und während der Geburt am höchsten ist, um dann allmählich abzufallen.

Das alte Konzept von der menschlichen Plazentaschranke wurde weitgehendst abgeändert; mit Hilfe von markierten Substanzen konnte man nämlich beweisen, dass die Leukämiezellen die Plazentaschranke überschreiten. Dass die Leukämie von der Mutter auf den Foetus übertragen wird, ist wohlbekannt: alle Formen der Leukämie bei der Ratte lassen sich ähnlich von einer Generation auf die nächste übertragen. Einige Umstände begünstigen die Übertragung dieser neoplastisch-hämopoietischen Erkrankung während der Schwangerschaft. Einige seltene Fälle von schwangeren Frauen mit Leukämie sind bekannt, bei denen dann auch das Kind eine klinisch nachweisbare Leukämie aufwies. Bei der Mutter wurde die Diagnose zur Zeit der Geburt oder sofort darauf gestellt, was vermuten lässt, dass sich die Krankheit bei der Mutter erst in der letzten Schwangerschaftszeit entwickelt habe.

Dass zwei EZ- oder auch ZZ-Paarlinge im Abstand von Monaten oder Tagen nacheinander erkranken können, erscheint nicht als reiner Zufall. Aus der häufigen Konkordanz der Zwillinge im ersten Lebensjahr lässt sich vermuten, dass bei der Übertragung der Leukämie von einem Paarling zum anderen Chromosomendefekte, gemeinsame Umweltfaktoren und der zusammenhängende intrauterine Kreislauf eine Rolle spielen.

LOUIS KEIGH, M.D., The Chicago Medical School, 2020 West Ogden Avenue, Chicago, Illinois 60612, USA.