EXPERIMENTAL STUDIES ON THE RELATION OF PREGNANCY TO LEUKEMIA

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There are on record many cases of human leukemia complicated by pregnancy. Leukemia, both myeloid and lymphoid, has been discovered in the course of pregnancy, but no instance is known in which a pregnant woman has transmitted the disease to her child. Since several viruses readily pass the placental barrier, experiments were undertaken to ascertain whether under carefully controlled conditions the disease would pass from a leukemic mother to her offspring.

That mouse leukemia is readily transmitted by the inoculation of leukemic cells has been shown by Korteweg (1), Richter and MacDowell (2), Furth and Strumia (3), and others. Most workers consider this the only means of transmission, but Engelbreth-Holm and Frederiksen (5) believe that the disease can also be transmitted by cell-free material.

Reports on human leukemia associated with pregnancy have been reviewed by Ohlsson (6), Brandstrup (7), Mehta (8, 9), and Forkner (10). Of the 70 reported cases, 47 are regarded by Forkner as authentic. In 22 of this group pregnancy occurred during leukemia, and in 25 leukemia made its appearance in the course of pregnancy. Of the former group of patients 21 had chronic myeloid leukemia and 1 chronic lymphoid leukemia; of the latter group 10 had acute myeloid, 8 acute lymphoid, 6 chronic myeloid, and 1 "hemocytoblastic leukemia." Altogether, 20 living children born to leukemic mothers, including one set of twins, have been reported. In the case of Russell (11) the child showed a blood picture simulating leukemia at six months of age, but was healthy at one year (12). Evidently this was an instance of leukemoid reaction. Ohlsson (6) found normal blood cells in the chorionic villi of the placenta of a leukemic woman and leukemic cells in the intervillous spaces. Furth (4), examining a leukemic woman dying at the fifth month of pregnancy, found leukemic infiltration of maternal organs, but normal blood in the fetal placenta and normal blood formation in the organs of the fetus.

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Several cases of congenital leukemia have been reported. Stransky (13) described leukemic infiltrations of the skin at the time of birth in an infant dying at three weeks of age. Autopsy showed conspicuous leukemic infiltration of spleen, liver, and lymph nodes. The mother of this baby, however, was not leukemic. Büngeler (14) reported congenital leukemia in a seven-months-old still-born fetus with advanced myeloid infiltration of all organs. The mother of this fetus likewise was not leukemic, and her previous child was healthy at the age of two years. Büngeler also mentions a report of congenital leukemia by Koch. A survey of the literature fails to reveal any substantiated case of leukemia coexisting in mother and fetus.

Lymphomatosis is common among cattle, and in pregnant cows suffering from this disease leukemic infiltration has been observed in the fetus and interpreted by Dobberstein and Seifrid (15) as an extension of the leukemic infiltration from the maternal uterus.
Two strains of transmitted mouse leukemia, one acute lymphoid (Akf 5) and the other chronic myeloid leukemia (Akh 106), were used in this study, and three cases of spontaneous leukemia were also examined. Pregnant mice were injected intravenously with 0.1 c.c. of a cell suspension from the spleen of a leukemic mouse, and were then placed in individual cages and watched carefully for leukemia. Eighteen of the female mice studied died of the disease; they had a total of 114 young. Seven mice died with fetus in utero (Group I); 6 died post partum and also lost their young (Group II); the young of 5 others which died post partum were successfully raised by foster mothers (Group III). The organs of all mothers and offspring dying during the experiment were studied microscopically for evidence of leukemia. In order to ascertain if young born to leukemic mothers are susceptible to leukemia, a group of such mice were inoculated on the thirteenth day of life with leukemic cells (Group IV). Transmitted acute lymphoid leukemia, strain Akf 5, was used in all experiments unless it is otherwise stated.

*Group I. Observations on Mice Which Died with Fetus in Utero:* Autopsy of the 4 female mice that were injected intravenously with a suspension of leukemic spleen and died before delivery showed advanced leukemia with conspicuous infiltration of liver, spleen, and lymph nodes. Microscopic examination of the 25 fetuses showed normal liver and spleen with normal fetal blood formation. Leukemic infiltration was found in none of the fetuses examined. Sections of the maternal uterus showed massive leukemic infiltration (Figs. 1 and 2) with occasional infiltration of the maternal side of the placenta. Although the maternal blood showed large numbers of leukemic cells (Fig. 3), the chorionic villi were filled with normal fetal blood containing many nucleated red cells (Figs. 1, 2, 3).
Three female mice which died of spontaneous leukemia with fetus in utero were studied. Although the uterus and ovaries were extensively infiltrated (Fig. 4), no leukemic infiltration was found in the fetuses examined.

**Group II. Observations on Mice Which Died Post Partum Whose Young Also Died:**

(a) **Acute Lymphoid Leukemia:** Three female mice inoculated with leukemia during pregnancy gave birth to 22 living young. The mothers died with leukemia from six to ten days post partum. Their offspring died from the fourth to the sixth day, presumably of malnutrition. The mother’s generally debilitated condition was the probable cause of her inability to feed her offspring. Sections of the breasts showed either slight or no leukemic infiltration, and in no instance was this enough to be considered the cause of the failing milk supply. Sections of the liver and spleen of the young mice showed no signs of leukemic involvement.

(b) **Chronic Myeloid Leukemia:** Three female mice which became pregnant during the course of a transmitted chronic myeloid leukemia (Strain Akh 106) were studied. In one of these, dying six days post partum, a typical blood picture of chronic leukemia was manifest at the time of delivery, but in the other two mothers the disease was latent at parturition and was not fatal until the thirtieth and forty-second day post partum. At autopsy all three mothers showed conspicuous infiltration of liver and spleen, but sections of the uterus were not taken. The young of these mothers died together as litters on the first, eleventh, and sixteenth day of life, no attempt having been made to have them raised by foster mothers. Microscopic examination of these 20 young showed no leukemic infiltration.

**Group III. Observations on Mice Which Died Post Partum but Whose**
Young Were Raised by Foster Mothers: Five pregnant females that were inoculated with leukemic cells gave birth to 27 offspring. The mothers in this group were inoculated during the late stage of pregnancy and were able to care for their offspring during the first few days of life before a foster mother could be obtained. Fourteen of the young were raised and were found to be healthy at the age of three months. The other 13 were living and well at two weeks of age. The mothers died of leukemia from four to ten days post partum.

Group IV. Test of Susceptibility to Leukemia of Young Mice Born to Leukemic Mothers: In a study of the possible resistance to leukemia of offspring of leukemic mothers two female mice of a stock known to be highly susceptible to leukemia were impregnated. They were then injected intravenously with a leukemic cell suspension on the estimated fifteenth day of pregnancy. The young were fostered as soon as possible after birth. At the age of approximately two weeks 13 living healthy young from these two mothers were inoculated subcutaneously with a leukemic cell suspension and all died of the disease from two to three weeks after inoculation.

Discussion

In a series of 18 female mice in which pregnancy and leukemia were associated we were unable to demonstrate transmission of the disease from mother to any of the 114 offspring. Since in the acute type of leukemia the usual duration of life between inoculation with leukemic cells and death is only from eight to fifteen days, the offspring of these mice should have had enough time to develop leukemia. Engelbreth-Holm and Frederiksen (5) found an increased incubation period in leukemia transmitted by cell-free material. If leukemia is produced by a virus, as suggested by these authors, it is conceivable that some of the young which died of malnutrition in the first few days of life might, with proper nourishment, have lived on and developed leukemia at a later date.

The question whether leukemia of mice is associated with a filtrable agent is still debatable. Some workers believe that transmission of leukemia by cell-free material is difficult because the hypothetical virus requires living cells for its protection. Engelbreth-Holm and Frederiksen (5) postulate the presence of an agent capable of existence outside the cells, whose action is inhibited by oxidation unless special precautions are observed. They have reported the transmission of lymphoid leukemia in mice by means of cell-free material guarded against oxidation by a cobalt-cysteine reducing system.

Although no intermingling of fetal and maternal blood cells is thought to occur during pregnancy (16, 17) many virus diseases readily penetrate the placental barrier in human subjects, and babies have been born with chickenpox, measles, and smallpox (18). Herrmann (19) has successfully recovered the virus of rabies from the brain tissue of fetuses whose mothers had died of rabies, and Lanfranchi and Lenzi (20) have made similar observations in dogs and in rabbits. Leukemia of the fetus resulting from direct extension of uterine infiltration has been described in cattle but in no other species.

One possible cause of the apparent failure to transmit the disease trans-
placentally cannot be completely ruled out by any of the observations hitherto available. This is the possible resistance of the fetus in utero to leukemia in general. Tumors can be grafted readily on the chorioallantoic membrane of chick embryos, and Jarmai (21) has successfully injected chick embryos with the virus of chicken leukemia, but whether the mouse embryo is resistant to leukemia or tumors is not known.

**Summary**

Attempts to transmit leukemia of mice to the fetus by injecting pregnant females with leukemic cells have been unsuccessful.

Offspring of leukemic mothers, in utero, in the neonatal period, or at the age of three months were found to be free from leukemia in spite of the advanced leukemic infiltration of the uterus of the mother before, at, or shortly after parturition.

Offspring of leukemic mothers when tested by direct inoculation showed no immunity to leukemia.

A review of the literature on human leukemia likewise gives no authentic case of transmission of the disease from mother to fetus.

Since many virus diseases are known to cross the placental barrier, these studies support the view that leukemia of mice is not transmitted by virus.

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**Bibliography**