Heterotransplantation of Spontaneous Leukemia of AKR Mice into Newborn Rats

WERNER H. KIRSTEN, DAVID G. ANDERSON, AND CHARLES E. PLATZ

(Department of Pathology, The University of Chicago, Chicago, Illinois)

SUMMARY

Spontaneous lymphoid leukemia of the inbred AKR strain was transplanted into newborn rats, not later than 24 hours after birth. Two intraperitoneal or intravenous injections, spaced 7–10 days apart, resulted in progressive, fatal growth. Single subcutaneous or intraperitoneal injections of leukemic cell suspensions did not establish permanent heterografts. Serial passage was successful in newborn, but not weanling or adult rats. During serial propagation the percentage of takes increased from 40 per cent to nearly 100 per cent, the necessary cell dose decreased sharply, and the time interval between inoculation and death was considerably reduced. The leukemia was converted into the ascitic form by serial intraperitoneal transplantation.

The use of the embryonal, newborn, or very young host is one of the oldest methods to exchange normal and tumor tissue between different species. This subject was critically reviewed by Toolan (23). The newborn recipient for tumor transplants has recently again been employed following the experimental demonstration of acquired immunological tolerance by Billingham, Brent, and Medawar (2). Many attempts were made to utilize this phenomenon in investigations other than skin homotransplantation. One of the early applications was Koprowski's demonstration that experimental tumors were transplantable into otherwise resistant homologous hosts (13–15). Exposure of the recipient to tumorous or normal donor cells during embryonic life rendered the host tolerant to the prospective tumor transplant. Successful grafts were also established with two heterologous tumors, but these were not serially transplantable in the adult, non-pretreated host. Other investigators extended these findings to heterologous tumor grafting, including human neoplasms (17, 20, 21, 24). Such attempts were met with partial success or failure.

The present study was undertaken to determine (a) the transplantability of a mouse leukemia to newborn rats, (b) the factors that govern success or rejection of leukemic heterografts, and (c) the serial propagation of mouse leukemia through generations of rats. Spontaneous, rather than isologously transplanted, lymphatic leukemia was employed as donor material. It was felt that some of the pitfalls inherent in the use of transplanted tumors could be avoided by the use of an original tumor (12).

MATERIALS AND METHODS

Animals.—Donors for the transplants were selected from a colony of male and female mice of the inbred AKR strain with spontaneous lymphoid leukemia. This stock, originally obtained from the R. B. Jackson Memorial Laboratory, Bar Harbor, Maine, was maintained by brother-sister matings for more than twenty generations. The incidence of spontaneous lymphoid leukemia in this strain ranged from 68 per cent for males to 79 per cent for females, after 6 months of life. Donor mice with spontaneous leukemia were randomly selected from this colony. Nonleukemic, young adult male and female AKR mice served as donors for the control series.

Male and female offspring of a randomly bred stock of Wistar rats procured from the Carworth Farms, New City, N.Y., were the recipients. Offspring of accidental brother-sister matings were excluded. All experimental and control litters were born and raised in this laboratory. The rats were weaned at 3–4 weeks and housed in stainless...
steel cages, six to eight per cage. Purina Laboratory Chow and water were fed ad libitum.

Preparation of cell suspensions.—Suspensions for experimental and control groups were prepared identically: spleen, liver, thymus, and lymph nodes were removed aseptically, snipped into small fragments, ground in a mortar, and homogenized in a glass homogenizer. Sterile instruments were used throughout. Two to 10 ml. of sterile Tyrode solution were added to adjust the suspension to a desired cell concentration. The suspension was passed through 6-ply gauze or a stainless-steel mesh to remove larger particles. The number of viable leukemic cells was counted in a Neubauer hemocytometer according to a method described by Schrek (18). Since cytoplasmic particles and tissue debris are toxic when injected intravenously into newborns (1), the filtered suspension was centrifuged at 500 × g for 5 minutes. The supernatant was discarded, and the sediment was resuspended in small amounts of Tyrode solution containing heparin, 10 i.u./ml. This final suspension was allowed to stand for 3–4 minutes before the supernatant was drawn off for use. Cell counts were obtained from the final supernatant.

Injections.—The orbital branch of the anterior facial vein was used for the intravenous route according to the technic described by Billingham et al. (1). Intraperitoneal injections were made by inserting the needle through the lower abdominal wall. Subcutaneous inocula were injected through the skin of the upper back. All injections were made through a 27- or 30-gauge needle attached to a tuberculin syringe. The total inoculum varied from 0.2 to 0.3 ml. for intraperitoneal and subcutaneous, and from 0.03 to 0.05 ml. for intravenous, injections.

Design and analysis of experiments.—Leukemic cell suspensions derived from one AKR mouse were injected intravenously, intraperitoneally, or subcutaneously at known times after birth, referred to as single injections. Alternate littermates received a second injection via the same route at various intervals thereafter, designated as double injections. Donors for the second injection also were spontaneously leukemic AKR mice of identical sex and approximately the same age as the initial donors. The experiments were terminated either by natural death of the recipients or by sacrifice when the animals were used for serial transplantation. All animals were observed for at least 3 months post-injection.

The criteria used to identify leukemia in donors and recipients were the gross appearance of the animals, white-cell counts of the peripheral blood, and histologic studies. Unless a generalized leukemic process was verified microscopically, the recipients were classified as negative, or the different process was specified. Tissues for microscopic examination were taken routinely from all experimental and control animals in the original transplantation from mouse to rat. In addition, samples of organs were taken from the recipients of serial transplants whenever desirable. Tissues were fixed in formalin or Zenker's formol, embedded in paraffin, and stained with hematoxylin-eosin, Giemsa stain, or Wilder's reticulum stain.

RESULTS

Preliminary experiments.—Weanling and adult Wistar rats of both sexes failed to maintain and grow leukemic heterografts administered once or twice intravenously, intraperitoneally, or subcutaneously. No leukemias developed up to 6 months in three groups of ten rats each, given single or double injections of up to 72 × 10⁸ cells subcutaneously or intraperitoneally and 5–8 × 10⁶ cells intravenously.

In contrast, the newborn rat was susceptible to mouse leukemic transplants made within 24 hours after birth. The interval of 4–6 weeks between preparatory and challenging doses as employed in experiments of skin homotransplantation by means of acquired immunological tolerance (2) proved ineffective in our system of heterotransplantation. The optimal interval was found to be 7–10 days, and it was used in all experiments to be described.

The success of transplants from leukemic mice to neonatal rats depended on three factors: number of injections, route of inoculation, and dosage of injected cells.

Efficacy of route and dose.—The results are summarized in Table 1. AKR leukemia was not transplantable by either single or double subcutaneous injections or a single intraperitoneal inoculation. In a few rats receiving double subcutaneous injections, an initial persistence of the second inoculum was noted at the site of the injection. Invariably, these temporary "takes" regressed by the fourth week post partum. White blood counts remained normal throughout, and microscopic examinations failed to reveal generalized leukemia or lymphosarcoma. Leukemic cell suspensions were transplanted to newborn rats by double intraperitoneal or intravenous injections. Between 39 and 48 per cent leukemic heterografts were accomplished by either procedure. Permanent lethal grafts were found only in three of 34 newborn rats given injections once intravenously. Leukemic manifestations were evident after 30 days post partum. Deaths occurred usually before the 50th day.
Exceptions to this rapid course were observed and are discussed under "Pathology."

The effects of various dosages were studied in litters of newborn rats that received double intraperitoneal injections (Table 2). Suspensions for reinjections were prepared from different individual donor mice, but the dose for the second inoculation was adjusted to approximately that of the initial, neonatal injection. The animals of a given litter received two intraperitoneal injections, each within the dose range indicated in Table 2. Under the conditions of this experiment $35 \times 10^6$ viable cells per rat represented the minimal requirement for permanent leukemic heterografts. Although the number of litters injected with the various dose ranges was not comparable, increased "takes" were obtained when $47-50 \times 10^6$ or $73-75 \times 10^6$ cells were given per rat. Only three newborn litters received $90 \times 10^6$ cells (in doses of 0.2 cc/rat). This resulted in the death of all recipients within a few hours or on the day following the rat required double intraperitoneal injections of at least $35 \times 10^6$ cells per rat. In serial transfers one neonatal intraperitoneal inoculation was sufficient to maintain vigorous growth of the graft. Almost all recipients accepted the foreign cells after a previous sojourn through a newborn of the same species. Moreover, the number of leukemic cells necessary for permanent takes decreased consistently with the number of transfers, particularly after the fifth generation. In fact, the inoculation of $35 \times 10^6$ cells per rat in the fifth serial passage resulted in high newborn mortality. This early death was characterized by massive abdominal hemorrhage without microscopic evidence of leukemia. In the ninth serial transfer the dose was further decreased to $3.8 \times 10^6$ cells to insure survival of the recipients. Enhanced potency of the serially transplanted leukemia was likewise reflected by a shortening of the time between inoculation and death from leukemia. While 30-50 days elapsed in the original transplantation

### Table 1

<table>
<thead>
<tr>
<th>No. injections</th>
<th>Route</th>
<th>No. litters injected</th>
<th>No. newborns injected</th>
<th>No. cells injected $\times 10^6$</th>
<th>Leukemias: ratio*</th>
<th>Leukemic deaths†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single‡</td>
<td>S.C.</td>
<td>10</td>
<td>61</td>
<td>30-50</td>
<td>0/38</td>
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<tr>
<td>Double§</td>
<td>S.C.</td>
<td>10</td>
<td>55</td>
<td>30-50</td>
<td>0/51</td>
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<tr>
<td>Single</td>
<td>I.P.</td>
<td>7</td>
<td>67</td>
<td>30-50</td>
<td>0/36</td>
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<td>Double</td>
<td>I.P.</td>
<td>22</td>
<td>180</td>
<td>30-50</td>
<td>56/145 (39%)</td>
<td>30-50</td>
</tr>
<tr>
<td>Single</td>
<td>I.V.</td>
<td>7</td>
<td>58</td>
<td>3-10</td>
<td>5/34 (9%)</td>
<td>40-60</td>
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<tr>
<td>Double</td>
<td>I.V.</td>
<td>5</td>
<td>33</td>
<td>3-10</td>
<td>10/21 (48%)</td>
<td>35-55</td>
</tr>
</tbody>
</table>

* Ratio = leukemic rats/number of rats surviving neonatal injection.
† Leukemic deaths = in days after birth.
‡ Single = rats received one injection, at birth.
§ Double = rats received one injection at birth, and reinjection 8 days later.
S.C. = subcutaneous.
I.P. = intraperitoneal.
I.V. = intravenous.

### Table 2

<table>
<thead>
<tr>
<th>No. cells given per injection $\times 10^6$</th>
<th>No. litters injected</th>
<th>No. newborns injected</th>
<th>No. leukemias: ratio*</th>
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<tr>
<td>12-20</td>
<td>9</td>
<td>60</td>
<td>0/55</td>
</tr>
<tr>
<td>35-37</td>
<td>7</td>
<td>51</td>
<td>11/47 (25%)</td>
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<tr>
<td>47-50</td>
<td>7</td>
<td>46</td>
<td>28/45 (62%)</td>
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<tr>
<td>73-75</td>
<td>2</td>
<td>9</td>
<td>8/9 (89%)</td>
</tr>
<tr>
<td>90</td>
<td>3</td>
<td>21</td>
<td>0/0</td>
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</table>

* Ratio = leukemic rats/number of rats surviving neonatal injection.
series (cf. Table 1), the average survival time diminished to 12 days during the serial propagation.

Transplantation assays.—Back-transplantation of leukemic cell suspensions into AKR mice was attempted from randomly selected rats of the original transplant generation and from each serial transfer. The leukemic cell suspensions were prepared as described previously. In each back-transplant, three to five AKR mice, less than 20 weeks old, received single intraperitoneal injections of $10 \times 10^6$ to $45 \times 10^6$ cells. Of the 243 AKR mice so treated, 231 died of abdominal intravenous, intraperitoneal or subcutaneous injections. In analogy to the experimental groups, varying cell concentrations (from 10 to $90 \times 10^6$ cells) were given. After 6 months no leukemias were detectable. In one control experiment of eleven newborn rats receiving single intravenous injections of $13 \times 10^6$ normal AKR cells, seven animals died between 16 and 23 days after birth. Retarded growth, sparse hair, a characteristic hunched posture, and diarrhea in the absence of detectable natural infections identified these rats before death. Histologically, these animals were reminiscent of “immunological runts.”

<table>
<thead>
<tr>
<th>Transpl. generat.</th>
<th>No. donors</th>
<th>No. litters injected</th>
<th>No. newborns injected</th>
<th>No. cells injected $\times 10^6$</th>
<th>Leukemias: ratio*</th>
<th>Leukemic deaths†</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>2</td>
<td>4</td>
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<td>35</td>
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<td>11–20</td>
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<td>3</td>
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<td>25</td>
<td>70</td>
<td>17/23 (74%)</td>
<td>11–15</td>
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<tr>
<td>2</td>
<td>2</td>
<td>3</td>
<td>29</td>
<td>35</td>
<td>15/30 (48%)</td>
<td>13–18</td>
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<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>70</td>
<td>7/7</td>
<td>12–18</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3</td>
<td>29</td>
<td>35</td>
<td>14/20 (70%)</td>
<td>13–25</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>16</td>
<td>30</td>
<td>15/13</td>
<td>6–12</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>4</td>
<td>19</td>
<td>25</td>
<td>18/18</td>
<td>10–17</td>
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<td></td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>50</td>
<td>2/2</td>
<td>7–8</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>3</td>
<td>14</td>
<td>30</td>
<td>14/14</td>
<td>6–19</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>2</td>
<td>11</td>
<td>3.4</td>
<td>9/10</td>
<td>9–13</td>
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<tr>
<td>7</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5.0</td>
<td>5/5</td>
<td>8–10</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>5.0</td>
<td>6/6</td>
<td>9–11</td>
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<td>9</td>
<td>2</td>
<td>3</td>
<td>11</td>
<td>3.8</td>
<td>9/9</td>
<td>10–13</td>
</tr>
</tbody>
</table>

* Ratio = leukemic rats/number of rats surviving neonatal injection.
† Leukemic deaths = in days after birth.

lymphosarcoma with lymphoid leukemia. The time of death after injection ranged from 8 to 31 days. These data indicate that AKR leukemia transplanted into newborn rats retained the immunogenetic identity of the donor.

Preliminary data with regard to heterograft survival in rats older than 24 hours after birth suggest that 2- to 3-day-old rats may be rendered susceptible to serially passed leukemic cells. Complete failure to establish growth of leukemic cells in either weanling or in adult noninbred Wistar rats was found even after the ninth serial passage.

Control series.—These comprised twelve experiments with eight to fifteen newborn rats each. Pooled cell suspensions of weanling, nonleukemic AKR mice were administered by single or double disease was recently described in rats as a consequence of neonatal exposure to immunologically competent homologous cells (3, 6, 25). Severe atrophy of lymphoid tissues in spleen, lymph nodes, and thymus was observed regularly. Proliferation of reticulum cells and histiocytes accounted for the moderate enlargement of spleen and lymph nodes. A notable exception in these seven rats was absence of the exfoliative dermal lesions described by Billingham et al. (3).

Pathology.—Lymphoid leukemia in the context of these experiments is defined as a systemic, infiltrative process of primitive cells resembling those of the lymphoid series and invariably leading to death of the host. Spontaneous lymphoid leukemia of the AKR strain involves the thymus,
liver, spleen, lymph nodes, bone marrow, and many other organs commonly not classified as hemopoietic or belonging to the reticuloendothelial system. The leukemic type of white cell counts accompanies this widespread, tissue infiltrative process.

Heterologously transplanted leukemia exhibits distribution and cytological features similar to those of the spontaneous disease. Differences between donor and recipient leukemia are mainly those of the site of origin. Early AKR mouse leukemia is manifest as thymic lymphosarcoma. When initially transplanted into the heterologous host by intravenous or intraperitoneal administration, the growth pattern is that of a generalized leukemic process. High white cell counts in the peripheral blood are caused by the presence of primitive, lymphoblastic cells ranging up to 130,000 cells/cu mm. Serial transplantation by the intraperitoneal route results in a vigorously growing abdominal lymphosarcoma with infiltration of the viscera and a moderate ascites. Spread to distant organs and leukemic blood counts occur terminally in some of these animals. In others the cellular multiplication in the abdominal cavity is often so rapid as to kill the animal before generalization has occurred. Thus, serially, intraperitoneally transplanted leukemia in the rat may be converted into the ascites type.

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Two distinctly different features of the transplanted leukemia were noted in the course of these experiments. One relates to the appearance of late leukemias, the other to the occurrence of tumors other than leukemia in the treated rats. Animals not accepting leukemic grafts in 10–50 days after intraperitoneal inoculation (cf. Tables 1–3) were apparently healthy, but they were observed for more than 3 months. Approximately 10 per cent of such initially negative recipients developed "late leukemias," i.e., between 3 and 5 months after injection. Macroscopically, the "late leukemias" were seen as a greatly enlarged thymus, liver, spleen, and mesenteric lymph nodes. Conversion of the abdominal and perirenal fat into large leukemic masses, so characteristic of the serially transplanted disease, was absent. Thymomegaly occasionally led to respiratory death prior to the involvement of distant organs. Histologically, these tumors were thymic lymphosarcomas, invading adjacent structures. Leukemic infiltrates in the liver, spleen, and lymph nodes occurred somewhat later and coincided with a large number of primitive blast cells in the peripheral blood. (Rats with late leukemias were omitted from Tables 1–3.)

Many litters of newborn rats receiving intraperitoneal or intravenous injections of either AKR mouse suspensions or cells from leukemic rats showed a combination of renal sarcomas, osteosarcomas, chondrosarcomas, subcutaneous sarcomas, and multifocal hemangiomas with or without leukemia following neonatal injections. These tumors were probably due to the polyoma virus known to be present in AKR leukemic tissues (10, 19). None of the litters with tumors other than leukemia were included in the tabulated results. Further studies on the polyoma tumors are now in progress.

**DISCUSSION**

Leukemia in rats as a consequence of single or double neonatal injections with leukemic cells from AKR mice is here described. The occurrence of such leukemias can be explained as either cellular transplantation or induction by a filterable virus known to be present in AKR tissues (9) or acceleration of an inherent rat leukemia. Although the available data are not sufficient to exclude the latter mechanisms several findings favor the former explanation.

Two forms of leukemia were observed in these experiments—"early" and "late" leukemias. Early leukemias cause death within 30–50 days *post partum*; the late leukemias occur 3–5 months after birth. The short interval between injection and death of the recipients seen in the early forms strongly suggests survival and multiplication of the injected leukemic AKR cells. When bioassayed, early leukemias are antigenically of the donor type, and they retain their lethal effects on the original mouse host after ten serial cellular transfers. Failure to adapt leukemic cells to normal adult rats even after serial propagation is not unexpected in the noninbred Wistar rat. Other techniques of heterotransplantation require that the natural host defense be modified or abolished when the adult recipient is used. For example, permanently transplantable human tumors are maintained only in conditioned heterologous hosts (22). Similarly, continual growth and propagation of AKR leukemia require the favorable environment of the newborn recipient.

Murine leukemias, including spontaneous lymphoid leukemia of the AKR strain, are known for their rigid host requirements when tested in homologous and heterologous tumor-host combinations (8, 11, 16). Acceptance of heterologous leukemic grafts by newborn rats may be mediated by acquired immunological tolerance. If indeed
tolerance to heterologous tumor cells exists, its demonstration would require additional data, e.g., specific suppression of the immune response by tumor cells, abrogation of the tolerant state by adoptive immunization, and the production of a second-set response (2, 7). Detailed studies by Bollag (4) indicate that tolerance to the Crocker sarcoma 180 can be conferred upon newborn rats only partially, ultimate regression of the transplant being the rule. Green and Lorincz failed to demonstrate specific immunological suppression in chick embryos when Krebs ascites tumor was injected intravenously 10 or 11 days before hatching (7). Death of the tumor cells followed the appearance of natural antibodies in the chick embryo. At the present time it is reasonable to assume that the transplanted leukemia reaches irreversibly size before a normal or weak host response is mobilized. A second administration of leukemic AKR cells given 7-10 days after the initial injection provides an additional overwhelming dose of viable leukemic cells. Their continuous multiplication results in "takes" as observed in the experiments utilizing double, intraperitoneal, or intravenous injections.

During the initial transfer of AKR leukemic cells into newborn rats a certain percentage fail to die of leukemia within 50-50 days post partum. Some of these "negative" animals develop thymic lymphosarcomas with generalized lymphoid leukemia and are designated "late" leukemias. Late leukemias are readily transplantable by one subcutaneous, intraperitoneal, or intravenous injection into newborn and weanling rats but fail to grow in AKR mice. The inability of late leukemias to be transplanted into the original AKR donor strain is additional evidence to consider late leukemias as viral neoplasms rather than the result of delayed cellular multiplication. Experiments are now in progress to elucidate the etiology and pathogenesis of these late leukemias.

REFERENCES

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Fig. 1.—Gross appearance of rat with intraperitoneally transplanted AKR leukemia. Note hepatosplenomegaly and mesenteric tumor.

Fig. 2.—Photomicrograph of leukemic cell infiltration in the liver of the rat demonstrated in Fig. 1. Hematoxylin and eosin. X150.

Fig. 3.—Infiltration of rat liver by leukemic cells with accumulation around a portal vein branch and in the sinusoids. X500.

Fig. 4.—Mesenteric lymph node of rat with transplanted leukemia. The lymph node is replaced by leukemic cells, and the mesenteric fat is infiltrated by leukemic cells. X120.

Fig. 5.—Diffuse infiltration of rat kidney with leukemic cells. AKR leukemia was transplanted 35 days prior to death. X120.

Fig. 6.—Thoracic muscle infiltrated with cells from adjacent thymic lymphosarcoma (see text). X365.
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