c-Kit-Targeting Immunotherapy for Hereditary Melanoma in a Mouse Model

Masashi Kato,1,5 Kozue Takeda,1 Yoshiyuki Kawamoto,1 Toyonori Tsuzuki,2 Khaled Hossain,1 Akiko Tamakoshi,3 Takahiro Kunisada,4 Yasuhiro Kambayashi,5 Keiki Ogino,2 Haruhiko Suzuki,1 Masahide Takahashi,2 and Izumi Nakashima1

Abstract

The role of c-Kit in the development of melanoma was studied in line 304/B6 of RET-transgenic mice, in which melanoma spontaneously develops. In Wv/Wv-RET 304/B6-transgenic mice, in which c-Kit function was severely impaired, development of melanoma was strongly suppressed. Although 31 of the 44 original RET-transgenic mice died of rapidly growing melanoma within 12 months after birth, only 8 of the 44 Wv/Wv-RET-transgenic mice developed slowly growing melanocytic tumors with a greatly prolonged mean tumor-free period, 2 of which died of melanoma at a late stage. Even Wv/+ -RET-transgenic mice had a clearly prolonged tumor-free period and definitely reduced frequency (6 of 61) of tumor death within 12 months after birth. Melanin production in the skin of these mice was not strongly impaired, suggesting that c-Kit affects the development of melanomas in these mice with only minor effects in melanin production. c-Kit expression in skin soon after birth was promoted in RET-transgenic mice, and c-Kit was expressed at high levels at a benign but not malignant stage of the tumor. A single injection of the anti-c-Kit antibody (ACK2) into RET-transgenic mice soon after birth caused a surprisingly long-lasting suppression of development of melanoma, greatly prolonging the tumor-free period, and none of the 28 ACK2-treated RET-transgenic mice died from tumors 12 months of age. The c-Kit function needed for melanin production was also suppressed for an unusually long time in ACK2-treated, RET-transgenic mice. These results suggest that c-Kit can be a unique target molecule for melanoma treatment.

Introduction

Melanoma, one of the most aggressive human cancers, includes a relatively high percentage (6–14%) of hereditary cases (1, 2). Human congenital melanocytic nevus, which is present from birth, is linked to hereditary hypermelanocyte stimulation, a trait frequently giving rise to melanoma during aging. It has been reported that families of affected children had higher numbers of nevi and cafe-au-lait spots than did those of normal children, suggesting a possible hereditary component (3). Little progress has been made toward the establishment of effective therapy for melanoma with a hereditary load, despite recent progress in study on melanoma in general (4). We recently estimated an oncogene fused to the mouse RET-transgenic mouse line of a C57BL/6 background (304/B6) that develops hereditary melanoma (5). Skin melanosis (100% incidence before or just after birth; n = 50), benign melanocytic tumor (100% in mice >6 months old), and melanoma (65–70% in mice <18 months old) develop in a stepwise manner throughout the lifetime of this mouse line. The disease process in these mice closely resembles that of human congenital melanocytic nevus.

We have shown that receptor tyrosine kinase Ret/RET is physiologically expressed in melanocytes in the inner and outer sheaths of hair follicles and matrix of hair bulbs of the skin of normal C57BL/6 mice and humans in close association with both melanin production and hair growth of the anagen phase (6). These findings suggest that Ret/RET kinase is involved in the physiological mechanism of melanocyte activation and melanin production. On the other hand, it has been established that another protein tyrosine kinase, c-Kit/c-KIT, plays a crucial role in skin melanogenesis for both melanocyte entry into the epidermal layer at a restricted prenatal stage and for melanocyte activation during postnatal life (7–11). It has been reported that c-KIT is expressed in human normal melanocytes, benign nevi, some dysplastic nevi, and early stage of melanoma (12, 13). However, c-KIT expression is lost in the late stage of melanoma (12–14). This fact argues against the view that c-Kit plays a crucial role in the process of development of melanoma. Results of our earlier results suggested that c-Kit and RET collaborate in melanocyte activation and development of benign melanocytic tumors (15). However, the potential role of c-Kit/c-KIT in the development of melanoma is not known. Using a recently established new subline (line 304/B6) of RET-transgenic mice in which melanoma develops after development of benign melanocytic tumors (5), we found that, not closely linked to the known function for melanocyte activation, c-Kit plays a crucial role in the oncogene RET-dependent development of melanoma, and we describe here a novel immunotherapy-targeting c-Kit at the neonatal stage that strongly suppresses melanoma development.

Materials and Methods

Mice. Line 304 of RET-transgenic mice, in which melanosis and benign melanocytic tumors develop in virtually all individuals, was originally obtained by introducing the human RFP-RET oncogene fused to the mouse metallothionine-I promoter enhancer (16), which encodes an activated form of RET (RFP-RET) kinase. The RFP-RET (hereafter called simply RET) was discriminated from mouse innate c-Ret by molecular size (6). We later established line 304/B6 of RET-transgenic mice by crossing the original line 304 with C57BL/6, in which melanoma developed frequently (5, 17). In this study, we crossed line 304/B6 RET-transgenic mice with c-Kit function-impaired Wv/+ (7, 8) C57BL/6 mice (Japan SLC, Inc., Hamamatsu, Japan) and obtained Wv/Wv and Wv/+ –RET (304/B6)-transgenic mice. By crossing line 304/B6 RET-transgenic mice with c-Kit ligand function-impaired Sld/+ (10) C57BL/6 mice, we obtained Sld/Sld and Sld/+ –RET (304/B6)-transgenic mice. We compared the levels of tumor growth in original line 304/B6 RET- and c-Kit (Wv/Wv or Wv/+ ) or c-Kit-ligand (Sld/Sld or Sld/+ ) function-impaired RET (304/B6)-transgenic mice. We also examined the effect of a single s.c. injection of 0.5 mg of monoclonal anti-c-Kit antibody (ACK2; Ref. 9) into line 304/B6 RET-transgenic and nontransgenic control mice within 3 days after birth on tumor growth and hair color. All mice were kept in a temperature- and humidity-controlled environment with a 12-h light-dark cycle in the Institute.
Western Blotting. Western blotting of c-Kit and RET was performed with skin lysates according to the method described previously (18). The lysates (30 µg/lane) were subjected to SDS-PAGE and transferred to polyvinylidene difluoride membranes (Nihon Millipore KK, Yonezawa, Japan). After the membranes had been reacted with anti-c-Kit or anti-Ret (Immuno-Biological Laboratories, Gunma, Japan) antibody, the reaction was examined using Western Blot Chemiluminescence Reagent (DuPont NEN, Boston, MA).

Histology and Immunohistochemistry. Skin sections were stained with H&E, and immunohistochemistry was performed with anti-c-Kit or -S100 protein antibody as described previously (17).

Statistical Analysis. Difference of tumor volumes in original RET (304/B6)-transgenic mice, Wv/+ -RET (304/B6)-transgenic mice, and Wv/Wv-RET (304/B6)-transgenic mice (Fig. 1D) or ACK2-treated and untreated RET (304/B6)-transgenic mice (Fig. 3A) in each month was statistically analyzed by the Mann-Whitney U test, as shown in the previous study (19). Tumor volumes in mice that died before the statistical comparison in each month were calculated as a continuation of the volume up to the month of comparison (Figs. 1D and 3A). Difference of life spans in original RET (304/B6)-transgenic, Wv/+ -RET (304/B6)-transgenic, and Wv/Wv-RET (304/B6)-transgenic mice (Fig. 1F) was statistically analyzed by Log-rank test. Difference of benign and malignant tumors incidence within 18 months after birth in original RET (304/B6)-transgenic, Wv/+ -RET (304/B6)-transgenic, and Wv/Wv-RET (304/B6)-transgenic mice (Fig. 1G) or in ACK2-treated and untreated RET (304/B6)-transgenic mice (Fig. 3C) was statistically analyzed by the χ² test.

Results and Discussion

**c-Kit Is Needed for Melanoma Development.** Original Wv/Wv-mice, which have white hairs as shown in the left end of Fig. 1A, were characterized by anemia, sterilization, and disturbance of mast cell, B-cell, and melanocyte development (7–11, 20, 21). There was basi-
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...no difference in the characteristics regarding sterilization and disturbance of B-cell development in bone marrow between the Wv/Wv mice and newly produced Wv/Wv-RET (304/B6)-transgenic mice in our preliminary results. However, the Wv/Wv-RET (304/B6)-transgenic mice had a mosaic of white and black hairs/skin (the area of black hairs/skin occupying 5–70% of the total skin area of an individual mouse; Fig. 1A) and excess melanogenesis in and around hair bulbs in the area of black hairs/skin (Fig. 1B), apparently not less extensively than did original line 304/B6 RET-transgenic mice (6). Interestingly, the area of black hairs but not that of white hairs clearly expressed RET protein (Fig. 1A, A and C). It is known that c-KIT function is required for both melanocyte entry into the epidermal layer during midgestation and for melanocyte activation linked to the hair growth cycle during the postnatal phase (9, 22). The c-KIT Wv protein is indistinguishable from normal c-KIT protein with regard to size and cell surface expression, but its in vitro kinase activity is ~10–20% of that in +/+ cells (8). It was thought from the data on hair/skin color of Wv/Wv-RET (304/B6)-transgenic mice that severe impairment of c-kit function partially blocked the entry of melanocytes into the epidermis in the presence of activated RET but did not greatly reduce the RET-mediated excess melanin production in melanocytes that entered epidermis. We compared the long-term (30 months) profiles of the time-dependent development of melanoma in line 304/B6 RET- and Wv/Wv-RET (304/B6)-transgenic mice (Fig. 1, D and E). Unexpectedly, from the rather small effect of severe impairment of c-KIT function on RET-mediated excess melanin production, even benign melanocytic tumors failed to develop in 38 (86.3%) of the 44 Wv/Wv-RET (304/B6)-transgenic mice throughout their lifetime (Fig. 1G). At 12 months after birth, none of the Wv/Wv-RET-transgenic mouse had died of melanoma growth, whereas 28 (70%) of the 40 parental line 304/B6 RET/transgenic mice had died from rapidly growing melanoma. Melanocytic tumors that had developed in only 8 of the 44 Wv/Wv-RET (304/B6)-transgenic mice grew very slowly except in 2 mice, which died of tumor growth at a late time (at 16.5 and 23.1 months old). The tumor-free period of the Wv/Wv-RET (304/B6)-transgenic mice (mean ± SD: 13.8 ± 4.6 months) was much longer (P < 0.0001) than that of line 304/B6 RET-transgenic mice (3.7 ± 1.3 months). The life span of the former (15.8 ± 5.9 months; n = 25) was significantly longer (P < 0.0001; n = 50) than that of the latter (9.7 ± 3 months; n = 50; Fig. 1F). Even the Wv/+ RET (304/B6)-transgenic mice (13.2 ± 4.8 months; n = 50) had a significantly (P < 0.0001) prolonged life span, compared with that of original RET (304/B6)-transgenic mice (Fig. 1F). The mean life span of the Wv/Wv-RET (304/B6)-transgenic mouse was not significantly shorter than the mean life span of parental Wv/Wv mice (15.7 ± 4.9 months; n = 10), which was much shorter than that of conventional C57BL/6 mice (>24 months), probably because of impairment of c-KIT-dependent hematopoietic stem cell activity (7). These results demonstrated that severe impairment of c-KIT function rescued the majority (42 of 44 mice) of RET (304/B6)-transgenic mice from otherwise destined death caused by hereditary melanoma (P < 0.0001).

Prolongation of the tumor-free period (11.9 ± 4.9 months) and life span (13.2 ± 4.8 months) to lesser degrees and reduction of overall tumor growth to a lesser degree (Fig. 1D) were also observed in Wv/+ RET (304/B6)-transgenic mice (n = 61), in which c-KIT function was thought to be impaired in >50% of the mice. Melanin was produced in skin/hair of these mice almost as extensively as that in skin/hairs of original line 304/B6 RET-transgenic mice (data not shown). Nevertheless, no detectable tumors developed in 19 (31.1%) of the 61 Wv/+ RET (304/B6)-transgenic mice throughout their lifetime, and only 6 (9.8%) and 25 (40.9%) of the mice died of growing melanoma within 12 and 18 months after birth, respectively. c-KIT ligand function-impaired Sld/Sld- and Sld/+–RET (304/B6)-transgenic mice also displayed basically the same phenotype as did Wv/Wv- and Wv/+–RET (304/B6)-transgenic mice (data not shown). These results indicated that c-KIT function is essential for oncogene RET-dependent melanoma development and that this c-KIT function, unlike the c-KIT function needed for melanin production, is not able to be compensated by RET. It was noted that life-threatening melanoma barely or rarely developed in Wv/Wv- and Wv/+–RET (304/B6)-transgenic mice even in areas with excess melanin production, in which RET was clearly expressed (Fig. 1C) and compensated the impaired c-KIT function for excess melanin production by melanocytes localized in skin (Fig. 1B). These results argued against the view that c-KIT function is required for melanoma development simply through its actions to localize RET-expressing melanocytes in the skin and activate them for melanin production. It seems that the threshold of the requirement of c-KIT for melanoma development is higher than that for skin localization and melanin production by melanocytes, possibly because some c-KIT function other than that needed for the physiological dynamics of melanocytes is required for the signaling to melanocytes for oncogenesis.

The true reason why melanoma would not develop in the Wv/Wv-RET (304/B6)-transgenic mice is still unknown. Host–tumor interactions often play an important role in tumor control and elimination. In fact, the establishment of tumor immunity for RET oncogene product is crucially involved in the mechanism to suppress the tumor development in line 242 of RET-transgenic mice (17, 23). The Wv/Wv-RET (304/B6)-transgenic mice, in which c-KIT protein with a mutation expresses, may cause the mutant c-KIT-specific immune responses, which lead to the suppression of development. Anyhow, further study is required to clarify the mechanism of c-KIT mutation-linked suppression of melanoma development in the Wv/Wv-RET (304/B6)-transgenic mice.

**c-KIT Expression Is Promoted by RET Soon after Birth.** We showed previously that both innate c-Ret and RET in RET-transgenic mice are transiently expressed at high levels soon after birth in association with primary hair growth (6, 17). c-KIT was also reported to be expressed in melanocytes in skin soon after birth (22). We compared the levels of c-KIT expression in skin of RET-transgenic and littermate nontransgenic mice soon after birth. As shown in Fig. 2, A and B, c-KIT expression levels in RET-transgenic mice, which were determined by either immunohistochemistry (A) or Western blotting (B), were elevated compared with those in nontransgenic mice, suggesting that RET promoted expression of c-KIT in the skin. Together with our results that impairing the c-KIT function would inhibit tumor growth in the RET (304/B6)-transgenic mice (Fig. 1D), these results suggest that c-KIT works in the downstream of RET-mediated signal transduction for the development of melanoma. As shown in Fig. 2C, benign melanocytic tumors expressed high levels of RET, which decreased when the tumors became melanoma, in agreement with our findings reported previously (23). Benign melanocytic tumors, in which RET was expressed at high levels, expressed as a high level of c-KIT, as did the skin obtained from RET-transgenic mice soon after birth, which decreased in melanoma. These results suggest that protein expression levels of c-KIT and RET bidirectionally control melanoma development. The down-regulation of c-KIT protein expression level at the late stage of melanoma development may permit melanoma cells to avoid stem cell factor/c-KIT-mediated apoptosis, hence contributing to tumor growth. To further evaluate the potentially bidirectional roles of c-KIT during the melanoma development and study the relationship between the roles of RET gene and c-KIT gene, establishment of tumor cell lines derived from RET (304/B6)-

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* M. Kato et al., unpublished observations.
transgenic mice and Wt/Wv-RET (304/B6)-transgenic mice would be useful.

**c-Kit-Targeting Immunotherapy of Hereditary Melanoma.** On the basis of the above-described observation that c-Kit, of which the expression is enhanced by RET soon after birth, basically assists RET to develop melanoma, we examined the therapeutic effect of injection of a monoclonal ACK2 (9, 22) into line 304/B6 RET-transgenic mice soon after birth on melanoma development. It was unexpectedly found that melanoma development was long lastingly suppressed in RET-transgenic mice that received a single postnatal ACK2 injection within 12 months after the ACK2 injection (Fig. 3, A and B), although tumors developed in some mice at a later stage (Fig. 3A). In 13 of the 28 ACK2-treated mice, even benign melanocytic tumors did not develop within 18 months after birth (Fig. 3C). The tumor-free period of the treated mice (11.1 ± 1.7 months) was much longer (P < 0.0001) than that of the untreated control mice (3.7 ± 1.3 months). At 12 months after birth, >70% of the control RET-transgenic mice (n = 46) had died of tumors, but none of the 28 ACK2-treated transgenic mice had died from rapidly growing melanoma. At 18 months after birth, only 9 (32.1%) of the 28 ACK2-treated mice had died from melanoma (Fig. 3C). The life span of the treated mice (14.2 ± 3.2 months) was 46% longer (P < 0.0001) than that of the control mice. Injection of ACK2 at an early time after birth seems to be critical because the number of deaths from tumors in RET-transgenic mice that had been given an injection of ACK2 within 24 h after birth (4 of 18, 22.2%) was fewer than that in mice that had been given an injection 3 days after birth (4 of 9, 44.4%).

Corresponding to the unexpectedly long lasting effect of ACK2 injection for melanoma suppression, the treatment caused an unusually long lasing change in hair color of the transgenic mice. As shown in Fig. 4, hair color of nontransgenic control mice (No. 1 and No. 2 mice in Fig. 4, A–D) had changed from black (No. 1) to gray/white (No. 2) at 4 days after ACK2 injection (Fig. 4B), and the change was most evident at 12 days after ACK2 injection (Fig. 4C). This change in color, which agrees with a finding reported previously (22), was reversed almost to the native color (black) within a few months (Fig. 4D). Interestingly, the hair color of RET-transgenic mice (No. 3 and No. 4 mice) had changed from deep black (No. 3) to gray (No. 4) at 4 days after ACK2 treatment (Fig. 4B) and at 12 days after the treatment (Fig. 4C) and, more importantly, had not returned to black

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**Fig. 2.** Expression levels of c-Kit and RET in the skin and tumors. A, c-Kit protein expression levels in the skin of a 1-day-old line 304/B6 RET-transgenic mouse (A-1) and control littermate nontransgenic mouse (A-2) determined by immunohistochemistry. Scale bar: 80 μm. B, c-Kit protein expression levels in the skin of RET-transgenic and control littermate nontransgenic mice of indicated ages determined by immunoblot analysis with anti-c-Kit antibody (top), RET (top, REP RET) and c-Kit (middle) protein expression levels in skin from 6-day-old control nontransgenic (Lane 1) and RET-transgenic (Lane 2) mice and benign melanocytic tumors (Lanes 3 and 4) and melanoma (Lane 5). The protein level for each lane was checked by staining the membrane with anti-β-actin antibody (bottom for B and C).

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**Fig. 3.** Anti-c-Kit antibody (ACK2)-mediated suppression of melanoma development. A, tumor volumes (mean ± SE) in line 304/B6 RET-transgenic mice that had received s.c. injection of 0.5 mg of ACK2 within 3 days after birth (●, n = 28) and in control line 304/B6 RET-transgenic mice (○, n = 42). *, †, §, significantly different (*, P < 0.0001; †, §, P < 0.005) from the control. B, macroscopic appearances of a representative 8-month-old, ACK2-treated line 304/B6 RET-transgenic mouse (top) and control age-matched untreated RET-transgenic mouse (bottom). Arrowheads, tumors. C, incidence of benign and malignant tumors within 18 months after birth in line 304/B6 RET-transgenic mice that had received s.c. injection of 0.5 mg of ACK2 within 3 days after birth (n = 28) and control line 304/B6 RET-transgenic mice (n = 46). *, †, significantly different (*, P < 0.0001; †, P < 0.005) from the control (top panel).

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**Fig. 4.** Hair color of nontransgenic control mice (No. 1 and No. 2 mice in Fig. 4, A–D) had changed from black (No. 1) to gray/white (No. 2) at 4 days after ACK2 injection (Fig. 4B), and the change was most evident at 12 days after ACK2 injection (Fig. 4C). This change in color, which agrees with a finding reported previously (22), was reversed almost to the native color (black) within a few months (Fig. 4D). Interestingly, the hair color of RET-transgenic mice (No. 3 and No. 4 mice) had changed from deep black (No. 3) to gray (No. 4) at 4 days after ACK2 treatment (Fig. 4B) and at 12 days after the treatment (Fig. 4C) and, more importantly, had not returned to black
mate mice (genic mice (J–G)) and H&E (80/H9262 E, G, (and H) within 24 h after birth. In 3
E from ACK2-treated (and F, H, (and I) littermate 12-month-old RET
number of S100-containing melanocytes and amount of melanin pig-
ment in the skin of 12-month-old
RET mice (Fig. 4, I) which were much larger than those in littermate nontransgenic
I)
at 3 months after (Fig. 4D) or even at 8 months (Fig. 3B, top) to 18
months (data not shown) after the injection. Correspondingly, the
number of S100-containing melanocytes and amount of melanin pig-
mament in the skin of 12-month-old RET-transgenic mice (Fig. 4, G and I), which were much larger than those in littermate nontransgenic
mice (Fig. 4E), were reduced by injection of ACK2 soon after birth, and
these changes were not reversed at 12 months after the injection
(Fig. 4, H and J). In contrast, the effect of the injection of ACK2
almost disappeared in nontransgenic control mice in a few months
(Fig. 4, E and F). These observations demonstrated that overall c-Kit
function was decreased more by the ACK2 treatment than by Wv
mutation, resulting in reduction of not only melanoma development
but also melanocyte activation in the presence of RET and that this
change was maintained for an unusually long time in ACK2-treated
RET-transgenic mice.

The exact mechanism of the long lasting suppression of c-Kit
function in RET-transgenic mice after a single injection of ACK2 soon
after birth remains unknown. It has been reported that melanocytes in
newborn mice are c-Kit dependent and undergo apoptosis when c-Kit
receptors are blocked by ACK2 early after birth (22). RET possibly
forces the majority of melanocyte lineage cells to express c-Kit in a
synchronized manner soon after birth, and these cells thereby become
sensitive to ACK2 antibody for apoptosis induction. Reduction in the
number of melanocytes in the skin through this mechanism may not,
however, be the sole reason for the strong suppression of melanoma
development after the ACK2 injection, because some c-Kit function
other than that needed for melanocyte physiology was shown to be
required for the process of development of melanoma from skin-
localized, melanin-producing melanocytes in a study using RET-
transgenic mice bearing c-Kit with Wv mutation in which the function
of c-Kit was partially impaired (Fig. 1).

These results might encourage us to use a c-KIT-specific antibody
in the future to treat some cases of human hereditary melanoma, such
as congenital melanocytic nevus in which c-KIT expression in mel-
anocyte lineage cells and their precursors may be promoted in a
synchronized manner by RET-equivalent oncogenes. c-KIT could also
be a target molecule for prevention and treatment of melanoma in
general, although a preliminary trial of application of ACK2 injection
to already established melanoma-bearing RET-transgenic mice was
not successful. 7 In addition, the results of our study suggest a new
principle for use of monoclonal antibodies in treating congenital
diseases through eliminating “sick” cells that may express targeting
antigens for immunotherapy in a synchronized manner.

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assistance.

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7 M. Kato et al., unpublished data.


Announcements

MEETING OF THE RADIATION RESEARCH SOCIETY

The annual meeting of the Radiation Research Society will be held at the State University of Iowa, Iowa City, on June 22–24, 1953. The Society will be the guest of the University, and all meetings will be held on the campus. The program will consist of: (1) Two symposia, one on "The Effects of Radiation on Aqueous Solutions," which includes the following speakers: E. S. G. Barron, Edwin J. Hart, Warren Garrison, J. L. Magee, and A. O. Allen. The second is "Physical Measurements for Radiobiology" and companion talks by Ugo Fano, Burton J. Moyer, G. Failla, L. D. Marinelli, and Payne S. Harris. (2) On Monday night, June 22, a lecture by Dr. L. W. Alvarez on meson physics has been tentatively scheduled. On Tuesday night, June 23, Dr. L. H. Gray of the Hammersmith Hospital, London, will speak on a topic to be announced. Dr. Gray's lecture is sponsored by the Iowa Branch of the American Cancer Society. Those desiring to report original research in radiation effects, or interested in attending or desiring additional information, please contact the Secretary of the Society, Dr. A. Edelmann, Biology Department, Brookhaven National Laboratory, Upton, L.I., New York.

ERRATUM

The following correction should be made in the article by Beck and Valentine, "The Aerobic Carbohydrate Metabolism of Leukocytes in Health and Leukemia. I. Glycolysis and Respiration," November, 1952, page 891; substitute for the last paragraph:

The data in Table 8 permit several interesting calculations. If one compares the amount of glucose actually disappearing with the sum of the amount equivalent to lactate acid produced plus that equivalent to O2 consumption, it is seen that the amount of glucose "cleavage products" exceeds the amount of glucose utilized by 12 per cent in N and 27 per cent in CML and is exceeded by the glucose utilized by 16 per cent in CLL. If the assumption is made that, in this respect, the myeloid and lymphoid cells of leukemia are similar to those of normal blood, it may be that the computed normal figure represents a summation of the myeloid (M) and lymphoid (L) cells that make up the normal leukocyte population. Thus, if M = +0.27 and L = −0.16 and the normal differential is 65 per cent M and 35 per cent L, then

\[ 0.65 (+0.27) + 0.35 (-0.16) = +0.12 \]

a figure identical to the observed +0.12 for normal leukocytes.
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