Protooncogene Expression in Normal, Preleukemic, and Leukemic Murine Erythroid Cells and Its Relationship to Differentiation and Proliferation

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ABSTRACT

The expression of 18 protooncogenes was examined by Northern blot analysis in preleukemic and leukemic stages of murine erythroleukemias induced by Friend viruses. As controls, erythropoietically stimulated spleens from phenylhydrazine-treated mice were studied. Expression of 10 protooncogenes (c-erb-A, c-erb-B, c-ets, c-sis, c-mos, c-rel, c-src, c-fos, c-fms, N-ras) was not detectable in Friend erythroleukemias. One protooncogene (c-src) was found expressed in normal erythroid cells but not in erythroleukemias. Four protooncogenes (c-fos, c-abl, N-ras, and c-raf) were expressed at low levels in both steps of erythroleukemia. c-fos and c-abl RNAs were barely detectable in normal erythroid cells. High levels of four protooncogene transcripts (c-H-ras, c-K-ras, c-myc, and c-myb) were detected in preleukemic and leukemic tissues. While c-H-ras RNA was found at similar levels in normal and leukemic erythroid cells, c-myc, c-myb, and c-K-ras were not expressed in normal erythroid cells. To determine whether the elevated levels of c-myc, c-myb, and c-K-ras RNAs in erythroleukemic cells are related to the proliferative state or the undifferentiated state of the cells, the effect of dimethyl sulfoxide-induced differentiation on oncogene expression in two erythroleukemia cell lines was examined. Terminal differentiation was associated with lack of c-myc expression while c-myc and c-K-ras expression was essentially unaffected. These results suggest that the high levels of c-myc transcripts in erythroleukemias may reflect the undifferentiated state of the leukemic cells. In contrast, the elevated expression of c-myc and c-K-ras at both stages of the Friend disease is probably not related to the stage of differentiation but rather to the uncontrolled proliferation of the cells. Finally among 18 protooncogenes surveyed, only the accumulation of c-myc and c-K-ras RNAs appears to be associated with the Friend erythroleukemic process before the late leukemic phase develops.

INTRODUCTION

The replication defective SFFV and F-MuLV are retroviruses without recognized onc genes. In susceptible mice they induce multistep erythroleukemias characterized by an early preleukemic step followed by a late leukemic step (1-3). The preleukemic phase is characterized by a massive proliferation of nonmalignant erythroid precursor cells and the late leukemic phase by the emergence of tumorigenic proerythroblastic cells. The preleukemic cells are not transplantable, while the leukemic cells can be transplantable serially in vivo and established as permanent cell lines in vitro. Friend erythroleukemias appear to be a good animal model system for studying the multistage process of in vivo leukemogenesis.

Cellular oncogenes or protooncogenes have been implicated in the development and progression of human or animal tumors. In spontaneous cancers, one or more oncogenes appear to be involved in the transformation process as a result of chromosomal rearrangement, amplification, mutation, or other types of alterations (4-6). Changes in cellular oncogene expression have been reported in numerous neoplasms, particularly of the hematopoietic system (7-11). However, a direct relationship between protooncogene expression and tumor progression has not been established. Moreover most alterations of protooncogene expression have been detected in cultured cell lines established from tumors. For example, some protooncogenes were found to be expressed in Friend erythroleukemic cell lines and regulated during the in vitro differentiation process (12-13). In contrast, few studies have been reported on the expression of protooncogenes during the progression of erythroleukemia in animals.

In this study we investigated the expression of 18 protooncogenes in both preleukemic and leukemic stages of Friend erythroleukemia. For comparison, similar studies were performed on normal erythroid cells from spleens of phenylhydrazine treated mice. More than 90% of the phenylhydrazine-treated spleen cells are erythroid in nature with a majority of terminally differentiating cells (14). Since preleukemic and leukemic erythroid cells are less mature than those of phenylhydrazine-treated spleens, we also examined the expression of protooncogenes in erythroleukemic cells which were terminally differentiated by DMSO treatment.

MATERIALS AND METHODS

Normal and Leukemic Organs. Normal, preleukemic, and leukemic erythroid cells were obtained as described (15). Normal Erythroid Cells. Adult ICFW mice were given injections i.p. of phenylhydrazine (120 mg/kg). Spleens were taken 3 days after treatment.

Preleukemic Organs. Newborn ICFW mice were given injections i.p. of F-MuLV strain 15 and spleens were taken 2 months post-inoculation. When adult ICFW mice were given injections i.v. of Friend leukemia virus complex (SSFV Yoshikura strain), spleens were taken 10 days after virus inoculation.

Leukemic Organs. Erythroid tumors were obtained by serial transplantation in vivo of erythroleukemic cells induced in ICFW mice by F-MuLV or by Friend leukemia virus complex. Myeloid tumors were obtained by serial transplantation in vivo of leukemic myeloid cells induced in DBA/2 mice by F-MuLV.

Cell Cultures. Friend erythroleukemia 745A cells were obtained from Dr. N. Mechtli (16) and grown in RPMI 1640 medium (Eurobio, Paris, France) supplemented with 10% fetal calf serum. TFP10 cells were a Friend tumor cell line derived from SFFV-induced erythroleukemia (17). They were grown in McCoy's 5A medium (Flow Laboratories) and supplemented with 10% fetal calf serum. DMSO treatment of 745A and TFP10 cells was added to the culture medium at a starting concentration of 1-2 x 10^-4 cells/ml. DMSO was added at a final concentration of 2% (v/v). The degree of differentiation was determined by the percentage of benzidine-positive cells. The proportion of benzidine-positive cells after DMSO treatment was 72 h, 28%; 96 h, 75%; 120 h, 92% for 745A cells and 72 h, 5%; 96 h, 16%; 120 h, 24% for TFP10 cells. PCC4 cells were undifferentiated murine teratocarcinoma cells grown in Dulbecco's modification of Eagle's medium supplemented with 10% fetal calf serum (18).

RNA Extraction and Analysis. Normal and leukemic organs were frozen and cytoplasmic RNA was prepared by the SDS-phenol proce-
dure as previously described (19). The poly(A)+ RNA was twice purified by chromatography on oligodeoxystymidylid acid cellulose. Five µg of poly(A)+-selected cDNA was denatured with glyoxal, fractionated by electrophoresis on 1% agarose horizontal gel, and blotted on nitrocellulose paper or on a Bio-dyne A nylon membrane (Pall). Northern blots were hybridized under stringent conditions with 32P-labeled probes as previously described (15). Probes were labeled by nick translation (specific activity, 106 cpm/µg) or by the multiprimmer DNA reaction (specific activity, 107 cpm/µg) with [α-32P]dCTP. The conditions of hybridization for avian probes (src, erbA, erbB, rel) were the same as described for murine probes (15) except that the blots were hybridized at 30°C instead of 42°C for murine and feline probes. Following hybridization, all the blots were washed in 2x SSC-0.1% SDS at room temperature (SSC, 0.15 M NaCl-0.015 M sodium citrate) and then in 0.1x SSC-0.1% SDS twice for 30 min at 50°C. Filters were exposed to X-ray film at −70°C using an intensifying screen.

Molecular Probes. The probes used in hybridization were actin, a 1.1-kb PstI fragment of mouse a-actin clone (20); GAPDH, 1.3-kb PstI fragment of cDNA of rat GAPDH (pR GAPDH 13) (21); erbA, a 0.5-kb PstI fragment of v-erbA from avian erythroblastosis virus (pAEV-11) (22); erbB, a 0.5-kb BamHI fragment of v-erbB from avian erythroblastosis virus (pAEV-11) (21); mos, a 0.4-kb PstI fragment of v-mos (23); ets, a 0.7-kb HindIII fragment of the human ets (obtained from Dr. D. Stehelin); sis, a 1-kb PstI-XbaI fragment derived from a subclone of the simian sarcoma virus (24); rel, a 4.3-kb EcoRI fragment of the v-rel from reticuloendothiosis virus (25); fms, a 1-kb PstI-BglII fragment of v-fms from cloned SM feline sarcoma virus (26); fes, a 0.5-kb PstI fragment of v-fes from ST feline sarcoma virus (27); N-myc, a 1-kb EcoRI-BamHI fragment of the human N-myc clone (28); src, a 0.8-kb PvuII fragment of v-src from the Rous sarcoma virus (29); fos, a 1-kb PstI fragment of v-fos from p-fos-1 (30); abl, a 3.5-kb BamHI-HindII fragment of v-abl clone from Abelson murine leukemia virus clone (31); raf, a 1.8-kb EcoRI fragment of human complementary DNA c-raf-1 (32); H-ras, a 2.3-kb EcoRI-XbaI fragment of rat c-H-ras1 clone (33); N-ras, a 1-kb PvuII fragment of human N-ras clone PT7.8 (34); myc, a 1.5-kb ScaI fragment of the human c-myc (35); myb, a 0.7-kb BamHI-XbaI fragment of the human c-myc (36); K-ras, a 2.0-kb EcoRI fragment of rat complementary DNA K-ras (obtained from P. Chardin).4

RESULTS

Expression of Protooncogenes in Normal Erythroid Cells and Preleukemic and Leukemic Stages of Friend Erythroleukemias. Northern blot analysis of cytoplasmic poly(A)+ RNAs obtained from spleens of mice infected by either SFFV or F-MuLV virus was performed. Preleukemic and leukemic stages of erythroleukemias were tested. We also examined normal erythroid spleen cells from phenylhydrazine-treated mice. Myeloid leukemia cells and a PCC4 teratocarcinoma cell line known to express a variety of oncogenes (18) were used as controls. Northern blots were routinely hybridized with actin or GAPDH to check for uniform loading in each lane. The expression of c-erbA, c-erbB, c-ets, c-sis, c-mos, or c-rel was not detectable in any of the cells examined in our study. However, each of these 6 oncogene probes hybridized as expected with fragments of EcoRI-digested leukemia or normal DNA (data not shown).

The patterns of protooncogene transcripts in the different cells examined are shown in Figs. 1 and 2. c-fes and c-fms were not expressed in normal and leukemic erythroid cells but were detected in leukemic myeloid cells suggesting tissue specificity expression of these genes (Fig. 1). No N-myc expression was obvious in any of the erythroid cells tested; however, N-myc RNA was observed in teratocarcinoma cells as previously described (37) (Fig. 1). c-src was not transcribed in the erythroleukemias examined but c-src-related transcripts (4.0 and 4.8 kb) were detected in normal erythroid cells (Fig. 1). The biological significance of this observation is obscure.

Four protooncogenes (c-abl, c-fos, N-ras, and c-raf) were expressed at low levels in all of the preleukemic and leukemic erythroid cells examined (Fig. 1). The sizes of these protooncogene transcripts were similar to those described elsewhere and their levels of expression were substantially lower in erythroleukemias than in teratocarcinoma cells. c-fos and c-raf transcripts were barely detectable while c-N-ras and c-raf transcripts were completely undetectable in normal erythroid cells.

In erythroleukemias 4 protooncogenes (c-H-ras, c-K-ras, c-myc, and c-myb) were expressed at high levels (Fig. 2). Similar RNA levels of these protooncogenes were observed among preleukemic and leukemic stages. c-H-ras RNA was expressed at the same level in normal and leukemic erythroid cells, whereas c-K-ras, c-myc, and c-myb expression was not detectable in normal erythroid cells. Using a viral probe from a Kirsten murine sarcoma virus clone, we had previously failed to detect any c-K-ras RNA in erythroleukemias (15). However, two 5.4 and 2.2-kb c-K-ras transcripts were detected with a cellular K-ras probe in preleukemic and leukemic cells. As already described (15) c-myc RNA was highly expressed in erythroleukemia but not in normal erythroid cells. Elevated amounts of c-myb RNA were also detected in preleukemic and leukemic erythroid cells but not in normal cells. The 3.8-kb size of c-myb transcripts was similar to that reported in other hematopoietic murine cells.

Thus, our screening of protooncogene expression in Friend erythroleukemia shows that only 3 oncogenes (c-myc, c-myb, and c-K-ras) are found to accumulate in leukemic cells relative to their normal counterparts. Furthermore, both preleukemic and leukemic stages exhibit similar high levels of these 3 oncogenes suggesting that c-myc, c-myb, and c-K-ras oncogenes...
may be implicated or required in the early proliferative stage of Friend diseases.

Structure of c-myc, c-myb, and c-K-ras DNA in Erythroleukemias. Southern blot analysis of various restriction endonuclease DNA digests from preleukemic and leukemic cells revealed neither amplification nor rearrangement of c-myc, c-myb, and c-K-ras genes (data not shown). However, such a study does not exclude subtle genomic lesions.

Expression of c-myc, c-myb, and c-K-ras RNAs in Terminally Differentiated Erythroleukemic Cells. The spleens from phenylhydrazine-treated mice contain a majority of terminally differentiated erythroid cells (14) while Friend erythroleukemic cells are immature proerythroblastic cells blocked in an early stage of differentiation (1, 2). The high levels of c-myc, c-myb, and c-K-ras transcripts in erythroleukemic cells compared to normal cells may reflect their undifferentiated state. To investigate this possibility we examined the expression of these protooncogenes during the terminal differentiation of a Friend leukemia cell line (745A) treated with DMSO. We also examined the expression of the same protooncogenes in another Friend cell line (TFP10) resistant to DMSO differentiation.

As reported by others (12, 13) Fig. 3 shows that in DMSO-treated 745A cells, c-myc RNA levels declined rapidly (2 h) and returned to a level comparable to that of untreated cells by 20 h. When the cells were completely differentiated (5 days) the c-myc RNA remained expressed. The level of c-myb transcript which was more abundant than the larger one was restrained. In contrast, at day 5 when the cells were completely differentiated no c-myc expression was detected while c-myb RNA was still observed at day 5 in untreated 745A cells. In treated TFP10 cells we observed an early decrease of c-myb RNA more severe than in treated 745A cells. A rebound of transcript level occurred at 20 h in TFP10 cells and persisted at 5 days of treatment when the cells were not differentiated. Two sizes of 3.8- and 4.2-kb c-myb RNA were observed in untreated 745A and TFP10 cell lines while only a 3.8-kb transcript was observed in preleukemic and leukemic organs. Multiple c-myb transcripts have been also reported in different murine cells of hematopoietic origin corresponding to selective utilization of different initiation cap sites (38).

The larger (5.4-kb) c-K-ras transcript showed a biphasic response to DMSO treatment in both the 745A and TFP10 cells which was analogous to the change observed with the c-myc probe. In contrast the level of the smaller (2.2-kb) c-K-ras transcript which was more abundant than the larger one was essentially unaffected by DMSO treatment in 745A and TFP10 cells. When 745A cells were terminally differentiated at 5 days the levels of both c-K-ras transcripts were very high and similar to the untreated cells grown for 5 days.

In conclusion, our studies of protooncogene accumulation during erythroleukemia cell differentiation show the persistent expression of c-myc and c-K-ras at elevated levels and the complete disappearance of c-myb RNA when the erythroleukemic cells become irreversibly differentiated.

DISCUSSION

In this study we have screened 2 stages of Friend murine erythroleukemias induced by Friend retroviruses for the expression of 18 cellular protooncogenes. Evidence for expression of 8 protooncogenes (c-fos, c-abl, c-raf, N-ras, c-H-ras, c-K-ras, c-
myc, and c-myb) was found in both Friend erythroleukemias tested with a wide range of transcript level. No significant differences were detected when comparing the transcript levels of these 8 protooncogenes in the preleukemic versus the leukemic stage of the disease. These results suggest that the expression of some of these genes play a role in murine erythroleukemia, they are implicated in the early proliferative phase of the disease. The preleukemic stage of murine erythroleukemia is characterized by an uncontrolled proliferation of erythroid precursor cells which leads to the leukemic phase of the disease (1–3). In contrast the proliferation of precursor erythroid cells induced by phenylhydrazine in normal mice and characterized by an increase of spleen weight and cell number (×10) remains restricted (14, 15). c-fos, c-abl, c-H-ras were expressed in normal proliferative erythroid cells. The quantitative expression of these genes is not critically affected in erythroleukemia suggesting that they are not implicated in the leukemic process. Concerning N-ras and c-raf expressed at low levels in erythroleukemia but not in normal erythroid cells, it is possible that they are involved in the proliferative stage of the disease. However, very few examples of amplified expression of N-ras and c-raf have been reported in leukemias or other cancers. In contrast activated N-ras by point mutation has been implicated in some human leukemias and carcinogen-induced murine lymphomas (39, 40). It would be interesting to test if any mutation of N-ras can be detected in murine erythroleukemia. Activated forms of c-raf have also been reported in some human tumors but not in leukemias (41).

c-myb was expressed at high levels in both stages of erythroleukemia but not in normal erythroid cells. When erythroleukemic 745A cells are treated by DMSO and terminally differentiate at 5 days, c-myb transcripts disappear. This disappearance of c-myb transcription in terminally differentiated erythroid cells was not due to DMSO treatment since c-myb transcripts were found at high levels in erythroleukemic TFP10 cells not terminally differentiated 5 days after DMSO treatment. Our results suggest that c-myb expression observed in erythroleukemic cells may be related to their undifferentiated state and not to their proliferation. Other studies using cultures of erythroleukemic cells treated with hexamethylenedisilazamide have suggested that the persistent suppression of c-myb transcripts may be critical in permitting the cells to proceed to commitment to terminal differentiation (13). c-myb was transcribed specifically in hematopoietic cells and was down regulated in all hematopoietic lineages during maturation (42–45). It has been suggested that c-myb may be involved in the control of cell proliferation at a specific stage of hematopoietic maturation (46, 47). It is also possible that c-myb may play a role in the balance of self renewal versus maturation during normal hematopoiesis and that its alteration may disrupt this balance resulting in leukemic cells (48, 49).

The early down regulation of c-myc transcripts 2 h after DMSO treatment is found as well in 745A and TFP10 cells suggesting that this initial event is not sufficient for the terminal differentiation of erythroleukemic cells. The return to normal levels after the first 24 h of DMSO treatment and the persistence of elevated levels of c-myc when the cells are terminally differentiated have also been reported when hexamethylenedisilazamide, another differentiation inducer was used (13). The same down regulation, with a return to the normal level was observed during the erythroid differentiation of human K562 cell line (50). In contrast c-myc is permanently down regulated during the differentiation of murine and human myeloid cell lines (44, 51). However, one report showed increased c-myc RNA levels associated with the precommitment state during HL60 myeloid differentiation and only a decrease of c-myc in advanced cultures with growth arrest after terminal differentiation (52). After 5 days of DMSO treatment the erythroleukemic cells stop growing, but we cannot exclude the possibility that they retain some proliferative capacity and with it the ability to express myc. Nevertheless our results suggest that the c-myc expression found in erythroleukemias is related to the unrestricted proliferative state of the cells rather than to their state of differentiation.

In contrast to both c-myc and c-myb genes, no severe early down regulation of the major 2.2-kb c-K-ras transcript was observed after 2–4 h of DMSO treatment of 745A and TFP10 cells. Conversely, the minor 5.4-kb c-K-ras transcript was down regulated as c-myc and c-myb 2 h after DMSO treatment. As the larger 5.4-kb transcript has long 3' untranslated regions which play a role in the stability of the transcript (53), it is possible that it is less stable than the smaller 2.2-kb transcript. Since DMSO-differentiated erythroleukemic cells express both c-K-ras transcripts at elevated levels, it seems unlikely that the absence of c-K-ras expression in normal erythroid cells can be explained by their mature state.

In conclusion among 18 oncogenes listed only c-myc and c-K-ras genes were found expressed at high levels in Friend erythroleukemic cells and seemed to be implicated in the initial phase of the disease. It is not known at present if the constitutive expression of these 2 genes in preleukemic cells is the cause or the consequence of the unrestricted proliferation of the cells. No amplification or rearrangement of c-myc and c-K-ras genes was observed in both stages of the disease indicating no visible modification of these genes in erythroleukemias. Although the role of the Friend retroviruses in the early proliferative stage of the disease is unclear, it is possible that the Friend viruses induce a constitutive expression of c-myc and c-K-ras in infected erythroid precursor cells. The hypothesis that viruses may be involved directly or indirectly in the increase of c-myc transcription during viral infection has been recently suggested for the Epstein-Barr (54) and bovine leukemia (55) viruses. Determination of the mechanism by which c-myc and c-K-ras expression is increased in preleukemic cells should provide additional insight into the regulation of these protooncogenes.

ACKNOWLEDGMENTS

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REFERENCES

PROTOONCOGENES IN NORMAL AND LEUKEMIC ERYTHROID CELLS


COLLECTED PERSPECTIVES IN CANCER RESEARCH

Oncogenes, natural killer cells, breast cancer treatment modalities, colon cancer, and retroviruses, including their relationship to AIDS, are among the topics of current interest featured in the recently published *Collected Perspectives in Cancer Research: 1986–1987*. Containing the twenty-two articles published as "Perspectives in Cancer Research" in the last two volumes of the journal *Cancer Research*, the compilation presents the insights and interpretations of recognized authorities in the study of cancer. Each article explores contemporary and sometimes controversial areas of investigation, analyzing recent progress in cancer research and offering ideas on where such research should be heading. This collection of incisive and stimulating viewpoints will serve as a valuable resource and teaching tool for the cancer research community. Copies of this publication may be ordered from the Subscription Fulfillment Department, Waverly Press, Inc., P.O. Box 64473, Baltimore, Maryland 21264-0473, at a price of $9.00 per copy. Orders outside the U.S. add $2.00/copy to offset postage costs.

INTERNATIONAL UNION AGAINST CANCER: FELLOWSHIPS AND PERSONNEL EXCHANGES

The International Union Against Cancer (U.I.C.C.) offers long-, medium-, and short-term fellowships and personnel exchanges to appropriately qualified investigators in the field of Cancer Research worldwide. The following grants and awards are now available.

American Cancer Society—Eleanor Roosevelt International Cancer Fellowships (funded by the American Cancer Society)

15 to 20 grants are available annually to recognized senior investigators who have been actively engaged in cancer research for at least five years. The grants contribute to the travel and cost of living expenses of the Fellow and a maximum of three dependents for a period of six to twelve months. The average total grant value is $27,000. Application deadline is October 1 for selection in March the following year.

Yamagiwa-Yoshida Memorial International Cancer Study Grants (funded by the Japanese National Committee for the U.I.C.C. and the Olympus Optical Company in Tokyo)

10 to 15 grants are available annually for bilateral research projects, including advanced training in experimental methods or special techniques. Grants are generally awarded for periods of one to three months and contribute to the awardee's travel and cost of living expenses. The average grant value is $5,000. Application deadlines are June 30 and December 31, and awardees are notified in September and March of the following year, respectively.

International Cancer Research Technology Transfer Project (ICRETT) [funded jointly by the National Cancer Institute (USA), the Imperial Cancer Research Fund (UK), the Cancer Research Campaign (UK), the National Cancer Institute (Canada), Deutsche Krebshilfe (FRG), the Nordic Cancer Union (Denmark, Finland, Iceland, Norway, Sweden), the Swedish Cancer Society, and the Israel Cancer Association]

Around 150 awards are available annually to scientifically or medically qualified investigators in the early stages of their career to spend 14 to 28 days in an appropriate host institute abroad for the development, exchange, and compilation of research data and techniques in the basic, clinical, or behavioral areas of cancer research. The maximum award value of 2,400 is a contribution towards the awardee's travel and cost of living expenses. Selections are made on an ongoing basis, and awardees are usually notified within two months of the receipt of a complete application.

Applications: Suitably qualified candidates are invited to contact the Fellowships Department, U.I.C.C., 3 rue Conseil-Général, 1205 Geneva, Switzerland for application forms.

RECENT DEATHS

We regret to report the deaths of the following members of the American Association for Cancer Research: Dr. Hans Brockmann of the Institute of Organic Chemistry, University of Göttingen, Göttingen, West Germany; and Dr. Harold P. Rusch of the McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI. Dr. Brockmann was a Corresponding Member of the American Association for Cancer Research. Dr. Rusch was an Honorary Member as well as a former Director (1951–1954) and President (1953–1954) of the Association. He also served as Editor of *Cancer Research* from 1950 to 1964.

CALENDAR OF EVENTS

Course entitled “AIDS and the Oncologist,” September 16–17, 1988, Hotel Nikko, San Francisco, CA. Contact: Extended Programs in Medical Education, Room 569-U, University of California School of Medicine, San Francisco, CA 94143-0742. Telephone: (415) 476-4251.

Second Gordon Research Conference on Mammalian DNA Repair, January 23–27, 1989, Casa Sirena Marina Hotel, Oxnard, CA. Contact: Dr. Anthony E. Pegg, Dept. of Physiology, The Milton S. Hershey Medical Center, The Pennsylvania State University, College of Medicine, P.O. Box 850, Hershey, PA 17033. Telephone: (717) 531-8152; or Dr. Richard Setlow, Biology Dept., Brookhaven National Laboratories, Upton, NY 11973. Telephone: (516) 282-3391.


Second Meeting of the International Association for Vitamin and Nutritional Oncology (IAVNO), June 26–29, 1989, Charleston, SC. Contact: IAVNO Coordinator, Box A031, University of Colorado Health Sciences Center, 4200 E. 9th Ave., Denver, CO 80262. Telephone: (303) 394-7830.

Errata

The article “Protooncogene Expression in Normal, Preleukemic, and Leukemic Murine Erythroid Cells and Its Relationship to Differentiation and Proliferation” by J. Robert-Lézénès et al., which appears on pp. 3972–3976 of the July 15, 1988, issue, contains an error on p. 3972. In the sixth line of the Abstract, the tenth protooncogene referred to in parentheses should be N-myc, not N-ras.

The article “Comparison of CA15-3 and Carcinoembryonic Antigen in monitoring the Clinical Course of Patients with Metastatic Breast Cancer” by C. Tondini et al., which appears on pp. 4107–4112 of the July 15, 1988, issue, contains an error on p. 4108. At the bottom of the left column, the formula should read:

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\text{No. of patients with PD and with serial Ag levels which increase over 25\%}
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\text{No. of patients with PD}
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