Ultraviolet Radiation Perturbs Immune System, Makes Mice More Susceptible to Tumor Growth

By perturbing the immune system, ultraviolet (UV) radiation increases the susceptibility of mice to tumor growth. Experiments by Margaret L. Kripke, PhD, and her associates in the Department of Immunology have revealed some of the complex interactions between the immune system and UV radiation. These experiments have shown that UV irradiation produces specific and systematic changes in mice that weaken the immune system and help skin cancers to grow. These findings raise serious concern about the possible long-term effects of UV radiation on the human immune system.

UV Irradiation Effects in Mice

The first direct evidence for a relation between UV irradiation and the immune system came in experiments on tumor transplantation in mice. When mice were exposed to sufficient doses of UV radiation, they developed fatal skin cancers. But when these tumors were transplanted to syngeneic mice, few of them grew. This failure surprised Kripke and other investigators because most tumors induced in mice by chemical carcinogens are readily transplantable among members of the same inbred strain. In experiments she performed at the University of Utah, Kripke showed that the failure was a result of immunologic rejection—the tumors were highly antigenic.

"This high antigenicity in tumors with a long latent period contradicted a long-held immunologic dogma," Kripke said recently in an interview. "The belief was that the longer the latent period for a tumor, the less antigenic it was likely to be."

The highly antigenic nature of these tumors raised the question of why they had not been rejected in the primary host. Kripke attempted to answer this question in collaboration with Michael Fisher, PhD, then a student at the University of Utah Medical School. In these studies, mice exposed to UV radiation were unable to reject transplants of UV-induced tumors from syngeneic donors, even though they had been irradiated at a different body site (Fig. 1). Thus, exposing the animals to UV radiation produced a systemic effect: it interfered with the immunologic rejection of UV-induced tumors even at unirradiated sites. Furthermore, the time required to produce the systemic effect was shorter than that necessary to induce primary tumors.

Kripke and Fisher delineated the nature of the UV-irradiated mouse's failure to reject the tumors in a series of experiments on lethally X-irradiated mice. When spleen and lymph node cells from UV-treated donors were used to repopulate the lymphoid organs of these lethally irradiated syngeneic mice, the recipients were susceptible to tumor challenge. Lethally irradiated mice given lymphoid cells from unirradiated donors, however, rejected the tumor transplants. This experiment proved that the alteration was immunologic, because it could be transferred with cells of the immune system. In addition, when lymphoid cells from UV-irradiated and unirradiated mice were mixed and used to repopulate the lymphoid organs of the X-irradiated mice, the transplants were again not rejected, which suggested that a suppressor cell population was involved. Kripke and Fisher and other investigators then showed specifically that suppressor T lymphocytes, which are part of the immune regulatory system, were responsible for suppressing the immune response.

Role of Suppressor Cells

To study the role of suppressor cells in photocarcinogenesis, Kripke and Fisher again gave lethal doses of X-irradiation to mice and then repopulated the lymphoid organs with spleen and lymph node cells from syngeneic normal mice or from mice irradiated with sunlamps. Four weeks later pieces of dorsal skin from other syngeneic mice that had been exposed to UV irradiation for 16 weeks were grafted onto these mice. Few tumors developed in skin grafted to the mice that had received only normal lymphoid cells, but many tumors developed in skin grafted to mice that had received lymphoid cells from UV-irradiated donors or a mixture of cells from UV-irradiated donors and normal mice. This work supported the hypothesis that UV-induced suppressor T lymphocytes dictate whether visible tumors will develop in UV-irradiated skin.

In a companion experiment, mice were injected with T lymphocytes partially purified by separation on nylon wool columns, a process that increases the proportion of T lymphocytes and the suppressive activity of the preparation. The T lymphocytes had been obtained from normal or from UV-irradiated syngeneic...
mice. Both treated and control mice were then exposed to UV radiation. More mice that received T lymphocytes from UV-irradiated donors developed tumors than did uninjected mice or mice given normal T lymphocytes. In addition, skin cancers began to appear around week 20 in the mice injected with the cell population containing UV-induced suppressor T lymphocytes, but only after week 40 in the other two treatment groups.

By these experiments, Kripke and Fisher showed that immunologic surveillance occurs during UV carcinogenesis. Immunologic surveillance eliminates or controls nascent tumors arising early in the course of irradiation and is partly responsible for the long latent period for induction of these skin cancers. Earlier investigations had shown the immune surveillance system's effectiveness against tumor induction by oncogenic viruses; Kripke has demonstrated that a surveillance system also participates in nonviral carcinogenesis.

**Specificity of UV Radiation's Immune Effects**

The next question posed by the results was the specificity of the immune suppression: were mice immunosuppressed by UV irradiation able to respond to other antigenic challenges? Further research showed they were. Experiments showed that most immune responses were intact in UV-irradiated mice (with the exception of the contact hypersensitivity response to certain chemicals, a response that is also suppressed). In fact, the UV-irradiated mice could reject transplanted tumors from other strains of mice and even some syngeneic tumors induced by chemicals or viruses. Thus, generalized immune suppression did not seem to account for the failure of UV-irradiated mice to reject the highly antigenic tumor transplants.

Later experiments provided further evidence for the specificity of UV light's effects on the immune system. Kripke and her associates obtained tumor cell lines derived from cloned mouse fibroblasts transformed in vitro by UV radiation, 3-methylcholanthrene, or X-rays. The growth of these cell lines was compared in normal, UV-irradiated, and immunosuppressed mice. Only the tumor lines produced by transformation with UV radiation grew preferentially in UV-irradiated mice; the others grew equally well in all three groups of mice. UV-induced suppressor T lymphocytes accounted for this preferential growth.

Additional dramatic evidence for this specificity was produced by studies of skin cancer induced in mice by psoralen and UVA (UV light in the 320- to 400-nm range) (PUVA). This combined treatment produces many of the same biologic effects on skin that are produced by sunlamp irradiation, including the formation of skin cancers. Unlike UV-induced tumors, however, transplants of PUVA-induced tumors grew at the same rate and with the same incidence in normal and UV-irradiated mice.

Investigations by Kripke and Edward C. DeFabo, PhD, of George Washington University, of the dose-response relation between UV and these effects showed that susceptibility to tumor challenge was proportional to UV dose regardless of dose rate, number of exposures, and treatment duration. In fact, the effects in mice were cumulative over long periods. For example, 12 exposures given over four weeks produced the same effect as one exposure that was 12 times the single dose. Of potential relevance to natural UV exposure is that the UV wavelengths that were most effective in suppressing tumor rejection are present in sunlight. Indeed, Kripke and several associates have recently demonstrated that sun irradiation is capable of producing systemic immunologic changes in mice and guinea pigs.

**Implications for Human Beings**

The relevance of the UV light–skin cancer relationship in mice to that in human beings is not clear-cut. The latent period for photocarcinogenesis is very different in mice and people, the latent period in humans being far longer. But photocarcinogenesis at the molecular level is most likely the same, according to...
Bone Marrow Transplantation Makes High-Dose Cytoreductive Regimens, Remissions Possible

Karel A. Dicke, MD, PhD, Transplantation Center Chief, Department of Hematology

Megadoses of treatment to eliminate malignant cells, whether it consisted of combination chemotherapy and total body irradiation or combination chemotherapy alone, has induced long-term remissions and even "cures" in patients in whom conventional doses of cytoreductive therapy failed to maintain remission or to reinduce remission. Increasing the dosage, however, meant increasing toxicity, usually gastrointestinal reactions and bone marrow suppression.

Although physicians found no special therapeutic measures to neutralize severe gastrointestinal toxicity, they did discover that marrow transplantation could successfully restore hematopoiesis. Unfortunately, the proportion of patients who could benefit from transplantation was very small because of the scarcity of isogeneic and allogeneic donors. The proportion was narrowed further by age restrictions, because only about half of the patients who had suitable donors were considered young enough to withstand the cytoreductive regimen. Therefore, physicians began using autologous bone marrow transplantation (ABMT) as a protective measure against marrow suppression after high-dose cytoreductive therapy.

The success of ABMT depends on (1) the cytoreductive regimen, (2) the quality of the graft, and (3) the time of transplantation. The cytoreductive regimen usually involves either high-dose chemotherapy or a combination of high-dose chemotherapy and total body irradiation. Because the acute leukemias have demonstrated the dose-response effect, most of the work with ABMT has been done in the acute leukemias and most of what follows is based on that work.

Cytoreductive Regimen

Basic to choosing a drug for dose escalation in a conditioning regimen is that its dose-limiting toxicity be myelosuppressive. In addition, the drug's nonhematological toxicity should not be cumulative and, of course, the increase in dose should lead to an increase in remission rate. Only a few drugs can be escalated fivefold or higher their usual maximum dose without producing intolerable extramedullary toxicity. Melphalan is the only drug investigated so far that can be escalated sixfold (from 30 mg/m² to 180 mg/m²) with the expected prolonged myelosuppression and acceptable extramedullary toxicity. Cyclophosphamide and etoposide have, even at a sixfold escalation, a rapidly reversible myelotoxicity, but their use is limited by extramedullary toxicities. Carmustine at an escalation of only fourfold and mitomycin at an escalation of two- to threefold produce multiple extramedullary toxicities. Amscarine, when escalated fourfold, produces severe gastrointestinal toxicity.

We in the Department of Hematology at UT MDAH are studying aziridinylbenzoquinone (AZQ), a drug that may have the same potential for escalation that melphalan has. A synthetic quinone compound, AZQ was designed for optimal central nervous system penetration because of its lipid solubility and low ionization potential. It has shown a broad spectrum of activity in animal tumors, including intracranially implanted ependymoblastoma, B16 melanoma, P388 leukemia, L1210 leukemia, and colon 26 cancer, and it has demonstrated antitumor activity in several human neoplasms, including brain tumors, lymphoma, and acute leukemias. At threefold the maximum dose, AZQ's hematopoietic toxicity is pronounced but nonhematological toxicity is minimal, and it is at that level—when the drug is escalated to 2.5 to 3 times the maximum dose—that responses occur.

We have found that the CBV regimen (6 mg/m² of cyclophosphamide, 300 mg/m² of carmustine [BCNU], and 750 mg/m² of etoposide [VP-16-213]) is an effective antileukemic regimen: two of five patients who underwent allogeneic bone marrow transplantation during their second complete remission are now long-term survivors. In one study of 21 patients who had acute myelogenous leukemia (AML) or acute lymphocytic leukemia (ALL) who underwent CBV therapy, 12 (57%) achieved complete remission after transplantation during relapse. In these patients the CBV regimen was salvage therapy, which was tried after other therapies had failed. In this same group, seven of 11 patients (63%) treated with CBV as a second salvage therapy achieved complete remission, a rate dramatically better than the 9% complete remission rate achieved with conventional regimens.

It remains to be seen whether chemotherapy by itself is as effective in eliminating leukemia as is the combination of irradiation and chemotherapy. Reports by European investigators are beginning to show that the results are better when total body irradiation is combined with the drug regimens. The value of high-dose therapy can only be assessed in randomized studies or by showing an increase in the success rate of salvage therapy with patients who have poor prognoses. Our group is designing cytoreductive protocols in which an approximate 75% remission rate can be achieved in patients treated during relapse, resulting in a small but meaningful fraction of long-term disease-free survivors. Such a protocol will then be used to treat patients who have less severe disease.

Quality of the Graft

One of the burning questions in treating a patient who has acute leukemia with high-dose cytoreductive therapy is whether autologous bone marrow can be used to restore hematopoiesis in the recipient. Physicians know the hazard of transplanting autologous marrow—the high chance that the marrow cell suspension used for transplantation contains leukemic cells, which may reinduce leukemia after transplantation.

The quality of the bone marrow depends on the quality of the patient's remission at the time of marrow collection, the efficacy...
UV Radiation . . .

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Kripke. The molecular lesions and effects produced in DNA by UV light are similar in mouse and human cells. Differences in repair capacity may explain the differences in the latent period: the ability to repair UV-induced lesions in DNA is much lower in mouse cells than in human cells. Patients with xeroderma pigmentosum show a similar diminished repair capacity, and they, too, quickly develop skin cancers when exposed to UV light.

It is not possible to demonstrate experimentally in humans the same three-way relationship of UV irradiation, the immune system, and photocarcinogenesis that has been demonstrated in mice. Nevertheless, there is evidence that in man a relationship exists between each of three possible pairs—the immune system and photocarcinogenesis, UV irradiation and photocarcinogenesis, and UV irradiation and the immune system.

For example, there are suggestions that immunologic factors participate in human photocarcinogenesis. That renal transplant patients have an increased risk of developing sunlight-associated skin cancers is the first of these. Long-term immunosuppressive therapy to suppress transplant rejection was believed to be a possible contributor to this increased risk. The second is the success of topical dinitrochlorobenzene (DNCB) treatment of patients with multiple skin cancers—immunologic reactivity against tumor tissue may play a role in the destructive process. Third, there are a few reports of lymphoid cell infiltrates at the site of human skin cancers, and in vitro assays of immunologic reactivity against tumor tissue have been positive.

According to Kripke, there is a direct and known relation between UV exposure and skin cancer in humans. "In fact," she says, "the term 'healthy tan' is an oxymoron. Although it is true that a darker skin will protect you from some of the sun's damaging effects, the tan itself is actually a response to damage."

In addition, Kripke explains that the relation between skin cancer and UV exposure from the sun is a direct dose-response relation: "Skin cancer is most related to total cumulative UV exposure and to genetic susceptibility. If you have a good tanning response, you are less likely to develop skin cancer, but with sufficient exposure to UV, even people who tan can develop skin cancers."

Evidence that UV exposure has an effect on the immune system of humans has been developed recently in Australia. According to Kripke, "The cult of sun worship is even stronger in Australia than in the United States. Ironically, the Australian population as a whole is even more genetically susceptible to photocarcinogenesis than Americans are."

Because sun exposure is such a problem in Australia, dermatologist Dr Peter Hersey and his colleagues in Australia studied the effects of salon tanning and sunbathing on the immune system. "Insofar as we can determine, the changes he found in human beings are similar to some that occur in mice exposed to UV radiation," Kripke said. In UV-exposed Australians, the response to contact allergens was reduced, a result that is analogous to the changes found in experiments performed on mice and guinea pigs. Following irradiation with UV light, these animals failed to demonstrate contact allergy to topically applied chemicals. In addition, the numbers of T and B lymphocytes were changed in the human subjects.

The University of Texas
M. D. Anderson Hospital and Tumor Institute
at Houston

Twenty-ninth Annual Clinical Conference

Diagnosis and Treatment Strategies
for Gynecologic Cancer

November 13–16, 1985
Shamrock Hilton Hotel, Houston

Chaired by Ralph S. Freedman, MD, PhD, David M. Gershenson, MD, and Felix N. Rutledge, MD, Department of Gynecology.

The conference will present current knowledge on diagnosis and treatment of gynecologic malignant diseases and highlight issues important to the practicing physician. In addition to the more common endometrial, cervical, and ovarian cancers, the conference speakers will deal with such topics as the use of tumor markers and therapy with biologic response modifiers.

Registration fees are $200 (in advance) and $250 (on site).

For registration information, contact Shirley Roy, Office of Conference Services, HMB Box 131, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030, 713/792-2222.

Therapeutic Potential

Because the immune system is pivotal in maintaining the body's integrity, protecting it from infectious microorganisms, toxic chemicals, and even some cancers, the disturbance of immune responses by environmental radiation may be a serious problem. On the other hand, it would often be highly desirable to redirect the immune system toward a pathway of specific unresponsiveness (e.g., in organ transplantation, contact allergies, and autoimmune reactions). Further advances by Kripke and others who are working in the new science of photoimmunology may lead to ways of exploiting the therapeutic potential of UV light and overcoming its deleterious effects.

(Physicians who desire additional information should write Margaret L. Kripke, PhD, Department of Immunology, MDAH Box 178, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030—ED.)

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of eliminating residual leukemic cells from the marrow suspension, and the storage procedure.

The speed of myeloid hematopoietic recovery in humans after transplantation has been shown to be directly proportional to the number of granulocyte-macrophage colony-forming cells (GM-CFCs) infused. Studies comparing the marrow of patients with leukemia in remission with that of hematologically normal individuals have shown that the GM-CFC concentration in marrow from the patients is 50% that in marrow from normal individuals. Because 0.5 x 10^6 cells/kg of body weight from hematologically normal individuals are needed for optimum engraftment, twice that, or 1 x 10^6, are needed when marrow from patients in remission is used.

At remission, the number of leukemic cells in the marrow may vary from 10^2 to 10^10. We consider 10^6 cells a realistic estimate, though of course the actual number depends on the quality of the patient's remission. If we assume a homogeneous distribution of leukemic cells in the marrow, the number of leukemic cells in the marrow cell suspension to be transplanted is 10^6, inasmuch as 1% of the entire bone marrow reserve is aspirated during marrow harvest. Currently, no satisfactory assay exists for reliably predicting hemoimmunologic reconstitution, and because we cannot yet identify the number of clonogenic leukemic cells, every leukemic cell must be removed.

To purge leukemic cells from marrow, researchers have used monoclonal antibodies and complement, immunotoxins linked to monoclonal antibodies, magnetic microspheres bound to monoclonal antibodies, rat monoclonal antibody cytotoxic "cocktails," and colloidal immunomagnetic fluids. None of the methods, though, could demonstrate in a clinical setting more than a 2-log reduction of tumor cells, and a 6-log kill is believed necessary. Furthermore, although some of the chemicals employed did destroy leukemic cells, they also reduced the GM-CFC population. In our studies we are evaluating such drugs as L-asparaginase, vincristine, bleomycin, and possibly spirogermanium, which can be used at relatively high concentrations in vitro without compromising the hematopoietic restoration potential.

To ensure the viability of the hematopoietic stem cell population afterwards, we monitor the following four factors in storing marrow for transplantation: (1) composition of the cells to be stored, (2) freezing procedure, (3) temperature at which the cells are stored, and (4) manipulation of the cells after storage. Granulocytes and platelets in the cell suspension decrease stem cell viability after storage, but they can be removed effectively before freezing by Haemonetics centrifugation or by the use of Ficoll-Hypaque or Percoll gradients. Generally, the cells are frozen at a rate of 1°C/minute from 4°C to -40°C and stored in liquid nitrogen at -156°C. When the time for transplantation arrives, the cells are rapidly thawed in a 50°C water bath and infused immediately without being diluted.

Time of Transplantation

The best time for transplantation, we think, is when the patient's disease is minimal. The best time for studying the effectiveness of transplantation is when the disease has reached a phase at which conventional doses of chemotherapy no longer induce a long-term remission, yet when the tumor still responds to high-dose cytoreductive therapy in conjunction with infusion of marrow free of leukemic cells (e.g., from isogenic—identical twin—donors). When such treatment induces long-term disease-free survival in a substantial proportion of patients (30%-50%), it indicates that high-dose cytoreduction is still effectively eradicating residual leukemic cells. (The long-term survival rate of relapsed patients treated only 10 years ago with conventional therapy was close to zero.) We believe that patients in a second remission from AML and second and subsequent remissions from ALL fulfill these criteria.

In our experience, performing transplantation during relapse does not offer the best opportunity to assess the role of purging bone marrow of leukemic cells, because the remission after transplantation is short. If reports from several teams are compiled, we see that of 95 patients who had relapsed with acute leukemia and undergone autologous bone marrow transplantation, 60 achieved complete remissions. Unfortunately, complete remissions lasted for a median of only six months (range, 1+ to 38 months), and only four patients, fewer than 5% of the entire population undergoing transplantation during relapse, remained in continuous complete remission for two years. Relapse after high-dose treatment is predominantly because of residual disease.

Performing transplantation during a patient's first complete remission may also present difficulties in evaluating the effectiveness of transplantation, because the prognosis of a patient after bone marrow transplantation is based on the length of the complete remission before transplantation. Of patients whose first complete remission lasts six months, 25% can expect to have long-term disease-free survival, whereas more than 75% of the patients who remain in first complete remission for more than two years achieve long-term disease-free survival with conventional chemotherapy (Fig. 1). Careful analysis of the timing of transplantation is necessary, therefore, to assess the contribution of transplantation to long-term survival.

ABMT and Acute Leukemia

Although the low number and diversity of the patients studied prevent conclusions from being drawn about the role of ABMT in acute leukemia, some promising early data come from physicians using purged marrow. At Johns Hopkins Oncology Center, researchers studying ABMT in patients in second and subsequent remission from AML have treated 15 patients with purged marrow. Five are in continuous complete remission more than one year after treatment.

Reports of patients treated with unpurged marrow are less promising. In one study, 10 AML patients treated with nonpurged marrow, only one is alive more than three years after transplantation. Preliminary data from our two-part study of a group that was treated during second or third complete remission with CBV and nonpurged marrow show that only one patient of 11 had a transplantation remission longer than the remission before transplantation. We found also that on rare occasions this phenomenon can be achieved with chemotherapy in conven-
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tional doses, as it was in one patient in this group. This patient's first complete remission lasted 24 months and the second complete remission lasted 93 months. In the 11 patients undergoing transplantation, median duration of the transplantation remission was 7.5 months, whereas the median duration of the preceding remission was 14 months.

Of 29 patients with ALL in second and subsequent remissions treated at Johns Hopkins with purged marrow, only three have achieved two-year disease-free survival. In a study at Duke University Medical Center, of 24 patients with ALL in second complete remission, nine are still in remission, five of these longer than one year. In two of these patients, the duration of the transplantation remission exceeds the preceding remission, which is seldom the case in patients treated with conventional chemotherapeutic protocols.

ABMT and Hodgkin's Disease

Our group's results in treating Hodgkin's disease with high-dose CBV chemotherapy and ABMT are also promising. Of 16 adult patients with progressive or relapsed Hodgkin's disease, 12 had progressive disease at the time of transplantation. Thirteen patients had undergone three or more previous salvage chemotherapies, and the same number had also had radiotherapy. Of the 16 patients treated, six achieved complete remission and six a partial response. Only four did not respond. Responders survived a median of 15 months. Three of the 16 are alive and disease free at more than 44, 16, and 14 months after transplantation.

ABMT and Small Cell Bronchogenic Carcinoma

Work done by our group and others indicates that the natural history of small cell bronchogenic carcinoma in patients who have extensive disease but achieve a complete remission cannot yet be influenced by high-dose cytoreductive protocols. These regimens do produce favorable results, however, in patients whose disease is limited and who are able to achieve complete remission after three initial courses of normal chemotherapy. Five of 13 patients who underwent transplantation at UT MDAH have achieved long-term (more than two years) disease-free remissions. There appears to be no difference in the percentage of patients who achieve disease-free survival between patients who achieve complete remission early in conventional treatment and those who achieve complete remission after additional courses of induction chemotherapy at conventional doses (in both groups, about 10% achieve disease-free survival). Though the numbers in our study are small, it is encouraging that five of 13 patients (38%) are potential long-term disease-free survivors, particularly since only nine of these 13 underwent the total two courses of intensified therapy, including high-dose chemotherapy and chest irradiation.

We have introduced multiple transplants (administering more than one course of high-dose chemotherapy and following with ABMT) in treating this tumor. By doing this we can increase the normal dose of Cytoxan (cyclophosphamide) and etoposide sixfold with acceptable nonhematopoietic toxicity. Furthermore, because solid tumors respond best after more than one course of conventional cytoreductive therapy, sequential administration of high-dose cytoreductive therapy is logical.

Conclusion

Rescue by autologous bone marrow transplantation is still in its infancy. Work continues, not only in leukemia, lymphomas and Hodgkin's disease, and small cell bronchogenic carcinoma, but also in breast cancer, neuroblastoma, primary tumors of the central nervous system, melanoma, and testicular and ovarian cancers. The intent is to develop curative treatment. We believe that developing assays, purging methods, and new cytoreductive regimens are difficult tasks but that striking results await us and others working in this field. These will come when, after ABMT produces an approximate 75% remission rate and a resulting proportion of long-term disease-free survivors of advanced disease, it can be used to treat disease at an early stage.

(Physicians who desire additional information should write Karel A. Dicke, MD, PhD, Transplantation Center Chief, Department of Hematology, MDAH Box 55, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030.—ED.)
Psychological and Social Cures Next for Children Who Recover from Cancer

In the 1990s, only a few years hence, cancer in children will be accepted as a normal illness of childhood. This celebrates the fact that "the care and cure of cancer in children is decades ahead of the care and cure of cancer in adults," Jan van Eys, PhD, MD, said at UT MDAH's Tenth Annual Mental Health Conference. But it requires clinicians involved in children's biologic cancer treatment to be concerned now with the children's psychological and social cures—their return to ordinary living in family, school, and community.

In his summary of the conference, Childhood Cancer Survival: Living Beyond Cure, held April 11-12 in Houston, van Eys, Mosbacher Professor of Pediatrics and head, Division of Pediatrics, recalled that a decade ago the first of these meetings introduced the concept of the "truly cured child," a child "developmentally and educationally on par with peers in spite of the experience with cancer."

The challenge today, he said, is "the acceptance of cancer as another normal illness of childhood." This goal is achievable because psychological adjustment and social acceptance follow, though not without effort, when an illness comes to be seen as curable.

Referring to the sequential stages in care (Table 1) and control (Fig. 1), van Eys said they are circular, one depending on and following the other. He compared the socialization problems of children with cancer with the racial integration struggles of the sixties.

"Whenever a profound social change occurs," he said, "there are usually two driving forces. The first, and rarely the primary cause, is a significant and fundamental rethinking of basic principles. A second force is economic. The redistribution of health care costs is going on whether we like it or not. Cancer and its treatment are simply too expensive for society to maintain as a unique approach. Financially, cancer will become just another disease, and that perception will be generally seen within the next decade. Cancer patients will be just another group of people."

But cure has its consequences, he said. "There are physical defects to overcome, psychological handicaps, social barriers, and genetic uncertainties. Those are the burdens of the cured child."

As long as these children were considered as special persons, he said, "'rescued from the dead,' strangers in a strange land, they were received with open arms and yet, because of special status, excluded from society. As society begins to accept them as just another patient, they have to shed their self-image of strangeness. They have to feel integrated."

Biologic cure still carries a high cost to patient and society, he said, and psychological cure faces great obstacles because of that cost. Social cure is handicapped by the threat of later recurrence of the illness.

"The patient still has to adapt," he said, "to having had cancer. All the reasons why a truly cured child is a necessary and realistic goal of cancer care apply, but now the normally sick child must also be a necessary and realistic goal for the care-giving community and the patient."

Van Eys predicted a clamor for simplification of therapy and a "strong push" away from large clinical trials. "The next challenge in our care for cancer is to work on the end point of the circle," he said. "We need to simplify our care, and understand that care is not effective unless and until it can be made part of everyday life."

Table 1. Stages in Cancer Care

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<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>1945</td>
<td>Recognition of childhood cancers as treatable—development of chemotherapy.</td>
</tr>
<tr>
<td>1960</td>
<td>Recognition of the psychosocial struggle for the patient—death and dying movement.</td>
</tr>
<tr>
<td>1975</td>
<td>Recognition of cure as the expected outcome—the truly cured child.</td>
</tr>
<tr>
<td>1990</td>
<td>Acceptance of cancer as another normal illness of childhood—the normally sick child.</td>
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Fig. 1. Evolution of the control of childhood cancer.
Patients with Liver Cancer in Drug Infusion Trial

Programmable, implantable infusion devices now make it possible to provide more accurate arterial hepatic chemotherapy for patients who have primary and secondary liver neoplasms.

Studies with the Infusaid percutaneously implantable pump and a new combination of drugs, cisplatin and fluorouracil (FUDR), have been done during the last two years at UT MDAH by Yehuda Z. Patt, MD, associate professor of medicine and chief of the Regional Therapy Service of the Division of Medicine, and Arthur W. Boddie, Jr, MD, associate professor of surgery, with patients whose colon cancer metastasized to the liver.

A newer type of infusion device is the Medtronic pump. Like the Infusaid pump developed earlier, it is implanted directly and completely under the abdominal skin. The ability to program the Medtronic pump with an external wand, Patt explained, gives physicians more versatility than was possible before in changing chemotherapy regimens and altering treatment intervals.

The procedure involves intravenous hydration of the patient with 150 ml/hour of normal saline for 36 hours, both before and after two-hour arterial infusion of 100 mg/m² of cisplatin. During cisplatin administration with the arterial pump, 300 ml of 3% saline and mannitol are infused intravenously. This is followed by arterial infusion of 100 mg/m²/day of FUDR for five days. At the end of this period, the treatment team evacuates the pump and refills it with 20 ml of heparinized saline (500 units/ml).

The pump is then programmed to deliver 0.6 to 0.72 ml of the saline solution per day, at a "keep open" rate that gives the patient a 26- to 32-day interval at home until the next arterial infusion treatment and reprogramming session.

Patt's recent phase II trial with this chemotherapeutic regimen included 29 patients and involved infusion with the Medtronic pump, the Infusaid pump, and percutaneously placed arterial catheters.

Four patients achieved a complete remission and 11 a partial remission—a response rate of 52%. Median survival for the total group was 12 months, despite some patients' extrahepatic disease and a few patients' extensive liver disease. In those who responded to treatment, Patt said, the extent of liver disease did not affect survival. Among the nonresponding patients, he explained, those who had less severe disease survived twice as long as did those whose cancer was more advanced.

"Our patients have to be very faithful, of course, in having their pumps checked," he said. "But they are happy with them—they are at home and working, and some are playing tennis, swimming, running, jogging, or playing racquetball."

To determine the role of cisplatin in the drug combination, Patt and his team are now conducting a larger randomized trial of FUDR alone and FUDR and cisplatin in a study in which they hope to include more than 100 patients.

"The advent of implantable infusion devices," Patt said, "has made large-scale hepatic arterial studies feasible. Most attractive for patients is the convenience of not having to stay in the hospital during the entire treatment and being able to continue their normal activities between intensive treatment sessions."

Arterial infusion is still costly, he said, both because of the pump's initial price and the cost of the surgical procedure to implant it. "But the pump has made long-term treatment more economical," he said, "because pump implantation is much less expensive than the repeated and longer hospital admissions required for drug infusion through catheters."

He cautioned that hepatic arterial chemotherapy for liver metastasis is still experimental and can only be done in a research center. Optimal drug regimens remain to be discovered, and FUDR has been reported to cause hepatitis and biliary sclerosis in some patients.

"Modern technology has brought us some excellent infusion devices," Patt said, "but our drug development has lagged. We must find new and better combinations."

His group's initial results with FUDR and cisplatin suggest that the combination is a good one, Patt said, but a confirmatory trial is essential.

"The versatility of the Medtronic infusion device will allow us, we hope, to complete a large trial and go on to next-generation studies," he said, referring to expected technological improvements in the implantable devices and more effective drug combinations.

(Physicians who desire additional information should write Yehuda Z. Patt, MD, Regional Therapy Service, Division of Medicine, MDAH Box 41, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030—ED.)