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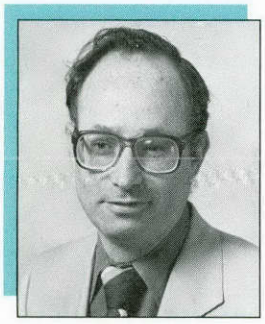
When in doubt, respect the family's wishes, but physicians should never ignore medical realities.

Decision making in critical illness: Who knows best?

By Michael S. Ewer, M.D., M.P.H.

Commentary



Michael S. Ewer is an associate professor of medicine in the Cardiopulmonary Section, Department of Medical Specialties

Ethicists, lawyers, and health-care professionals are currently debating a number of issues of great concern to the critically ill. Among the more emotional issues are those regarding the appropriate use of life-support systems and the balance between artificial extension of life and quality of life achieved through their use. When should the decision to end such use rest in the hands of the physician and when should it rest solely in the hands of the patient or his family? Here I would like to outline the issues underlying this question and present a paradigm that, I hope, may help physicians when confronting this decision.

Prolonging life or delaying death?

Most ethicists believe that life-support systems for critically ill patients should serve either to buy time for clinical improvement or to allow members of the health-care team to assess the likelihood of recovery. Most believe that the mechanical ventilator should not be employed merely to delay the moment of death or interrupt the process of dying. Ideally, mechanical support systems should be used in cases where such use results in patient recovery and should not be used for patients who cannot survive. Our inability to identify potential survivors and to predict outcomes creates a major problem for which we, as yet, have no solutions; our uncertainty may result in long-term support of patients who do not survive state-of-the-art treatment. Such measures are often painful, emotionally draining for family as well as patients, and expensive. Clearly we should not place all patients on life-support systems, for even if we, as a society, could afford to do so, we would be causing much needless suffering; we should not forget that life-support systems, when clearly futile, are undignified and most believe, wrong.

Ethical policies to ensure that life-support systems are used appropriately are evolving gradually. Patients are becoming increasingly vocal in expressing their desire not to have life-support systems used in cases when such use is considered unreasonable or futile. Many are requesting that directives to physicians (living wills) be drawn up in order to reduce the risk that undesired measures will be used. While such documents may be helpful in some settings, they often remain ambiguous; when a patient meets the criteria of "hopelessly ill" may depend on factors beyond physiological and pathological status to include the feelings, beliefs, or opinions of the physician. Some feel that the presence of life at any level implies hope, and "hopelessness" occurs only when death is final. Family members may withdraw directives when patients become incompetent, and occasionally patients with irreversible illness are placed on life-support at the insistence of family members over the objection of physicians.

Family should not be allowed to demand contraindicated treatment

Patients and family members *should* have input into decisions regarding the use of life-support systems, but not to the extent that clearly inappropriate decisions are made, or limited resources inappropriately expended in cases when such measures are obviously futile. One approach to decision making that attempts to balance the contribution of the health-care team with the desires of the patient or his family in a flexible manner involves a decision triangle illustrated in Figure 1. The base of the triangle (horizontal axis) represents the medical appropriateness index: strongly positive (appropriate or absolutely indicated) on the left extending to strongly negative (inappropriate or strongly contraindicated) on the right. The midpoint on the horizontal

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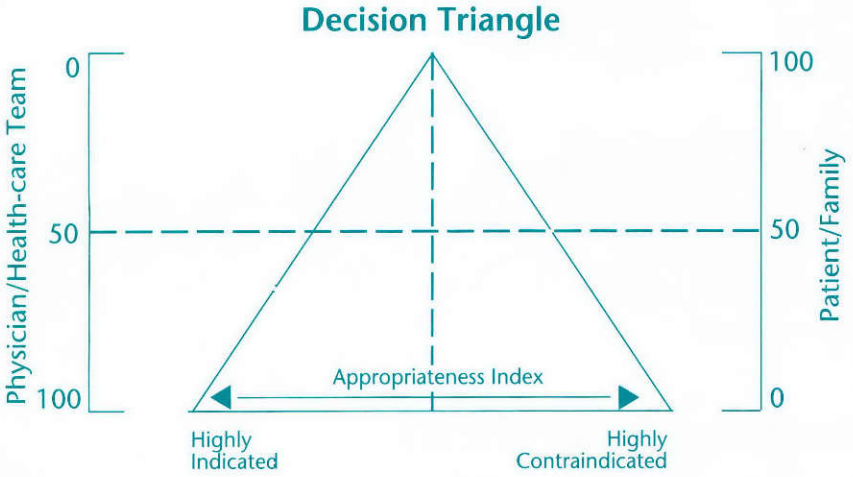

Figure 1. The decision triangle helps physicians evaluate the appropriateness (horizontal axis) of a proposed intervention. Where the argument for or against an intervention is clear (the extremes of the horizontal axis: highly indicated or highly contraindicated), physician input increases. In the absence of certainty (i.e., the absence of a medical community consensus), patient/family input increases (axis midpoint). For example, as certainty decreases (moving from the extremes to the midpoint of the axis), patient/family input approaches 100% (triangle apex).

Adapted with permission from *Critical Care Clinics* 5(3):685, 1989, courtesy of the W.B. Saunders Co.

axis (perpendicular to the dotted vertical line) depicts situations in which the risk-benefit ratio (i.e., between performing or not performing an intervention) is exactly equal. In such cases, for example, one half of physicians would prefer to offer a particular intervention, whereas the other half would not. The left vertical axis indicates the extent to which the responsibility of deciding for or against an intervention should be directed towards the health-care team, while the right vertical axis reflects the patient's or family's input into the decision. Decisions regarding options near the extremes of the horizontal scale (hightly indicated or highly contraindicated) should be confidently made by the health-care team and not offered as an option to patients or family members; options presented by physicians, even when coupled with advice that they not be followed, may be perceived by patients as realistic choices rather than as theoretical, i.e., futile, possibilities. Physicians must integrate all available data and make decisions as part of their commitment to their patients, and decisions regarding appropriateness of life-support systems are no exception.

Decisions near the midpoint of the horizontal axis cannot be appropriately made by the health-care team, and should be left to patient or family preference. While such a triangle cannot substitute for sensitive medical care, it can help physicians make better decisions. It can help them to place their decisions in a better perspective, and it can help to limit the offering of futile options to patients or their families. While patients have the right to refuse therapy they do not want, physicians have the responsibility to select the most appropriate therapies from those available for their patients. Physicians should not offer therapies where the risk-benefit ratio is clearly against the intervention or where the therapy represents only a futile effort; doing so offers little more than false hope, and often results in feelings of guilt and conflict among family members. The fine line between providing information regarding possible interventions and not offering false hope should be clear; options that a knowledgeable person would not consider need not be offered, while options that would be considered by a knowledgeable person can be presented.

When does a patient become "unsalvageable"?

Patients should let their next of kin know what their views are concerning decisions near the end of life, and their preferences regarding the use of life-support systems. The existence or absence of such directives or "living wills" should not be thought of as requests or demands for medical care that is futile, or a veto of appropriate and necessary measures, but rather as a guide to help with decisions that approach the midpoint on the horizontal axis of the decision triangle. Such decisions may need to be made by others if the patient is unable to make them on his own. It is not necessary to have a directive or living will in a physician's hands in order to justify not doing that which is pointless, not indicated, or futile.

Hospitalized patients usually do not become hopelessly ill suddenly; they deteriorate from a treatable and probably salvageable condition to a low likelihood of recovery condition over a period of time, and their prognosis must be continually reevaluated. The patient who is placed on a mechanical ventilator with a favorable prognosis may deteriorate and become hopelessly ill. Our inability to predict outcome for an individual patient should not restrict our use of life-support systems because of fear of having patients linger on ventilators without hope of recovery; part of our ongoing assessment of prognosis should be to determine when our efforts become futile. In those cases where life-support was appropriately initiated but has become futile during the course

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In recent years, the impact of genetics on medicine has become enormous, and it is highly likely that genetic applications will continue to become an integral part of both therapeutic and preventive medicine. This seems especially true in oncology as new information reveals more about genetic susceptibility and resistance to cancer and as we more clearly understand the relationship between mutagenic agents and cancer causation.

It is especially appropriate to introduce our Golden Jubilee series with Dr. T. C. Hsu, a world leader in cytogenetics. Pioneer, protagonist, and prophet in genetics research, Dr. Hsu has spent the past four decades elucidating the relationships between chromosomal structural changes and their consequences. Recently, he has significantly contributed to our ability to relate chromosome damage to cancer risk and causation. This work holds great promise for establishing a basis for a personal assessment of cancer risk in asymptomatic populations. "Chromosomes and Cancer" traces some of the key developments in this important area, providing for us a window to the future.

—James M. Bowen, Ph.D., Professor
of Virology, Vice President
for Academic Affairs

Chromosomes and Cancer

By T. C. Hsu, Ph.D.

Special Series

Golden Jubilee
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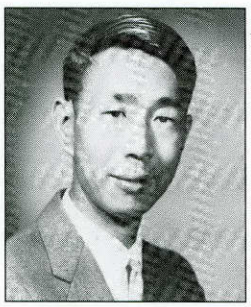
In the past four decades, human and mammalian cytogenetics, an important component of the golden era of biology, has made long strides, especially in genome analyses and cancer. Here I would like to describe these advances and their impact on the study of carcinogenesis.

Cytogenetics, a biological discipline studying the relationship between chromosomes and heredity, developed early in this century, using mainly insect and plant materials; but the available techniques were not suitable for observations of human and mammalian chromosomes. Thus, this particular branch of cytogenetics remained dormant until the 1950s.



T. C. Hsu, professor emeritus, Department of Cell Biology

Perhaps the first technical breakthrough on studies on human chromosomes was accidently made by me in 1952 when I was a postdoctoral fellow in the laboratory of Professor C. M. Pomerat at The University of Texas Medical Branch at Galveston. A technician mistakenly prepared a bottle of saline with less salt than prescribed. When I used this hypotonic solution to wash cells in tissue culture, I found the chromosomes were beautifully spread apart. However, I could not repeat my initial success. Desperately, I attempted to modify every step of the procedure, but to no avail—until I tried to change the tonicity of the washing solution. When the tonicity of the saline solution was lowered, the miracle reappeared. This procedure has been standard ever since.

The correct number of diploid human chromosomes, 46, was finally determined by J. H. Tjio and Albert Levan (Lund, Sweden) in 1956. (Previous reports varied from 6 to 60, and at one point the correct number had been "established" as 48.) Within a couple of years, the correct number was confirmed by many laboratories. It was nice to know how many chromosomes we have, but what other information could we acquire that might be useful for the basic and medical sciences? Could this signal the beginning of a golden age of medical genetics or the end of a passing interest?

In the late 1950s and early 1960s, two major discoveries had great impact on our understanding of human diseases. The first was made by Jerome Lejeune (Paris) in 1959 on Down's syndrome. Lejeune found that children with Down's syndrome had 47, instead of 46, chromosomes, with chromosome 21 appearing in three copies instead of the usual two. This discovery suggested that many baffling congenital syndromes might also be caused by chromosome disturbances. Subsequent investigations by cytogeneticists indicated that several specific syndromes were indeed caused by specific chromosomal alterations. Lejeune's initial discovery blossomed into not only a branch of pediatrics but also a blooming business with no end in sight. I remember I went to Minneapolis for the Golden Anniversary celebration of a hospital and met an obstetrician. He told me he had never learned cytogenetics. I said to him, "Doctor, one of these days you will have to learn it." I proved to be a prophet, because amniocentesis had not come into existence then.

The second major contribution was made by Peter Nowell and David Hungerford (Philadelphia), who discovered that in chronic myelogenous leukemia (CML) cells one chromosome was distinctly shorter than it should be. Various laboratories later confirmed that this unique chromosome, now known as the Philadelphia chromosome, is etiologically associated with this type of malignancy.

"When the tonicity of the saline solution was lowered, the miracle reappeared"

Prior to the monumental discovery of Nowell and Hungerford, many cytogeneticists had examined the chromosomes of various neoplasms but only found frustration. Most cancer cells had highly abnormal chromosome constitutions, both in terms of number and morphology. One often wondered whether such inconsistent abnormalities were the cause or the consequences of abnormal growth. The CML cells, having a minimal amount of cytogenetic change, gave the first indication that cancers may be the result of specific genetic alterations.

Nevertheless, cancer cytogenetics did not advance rapidly. Many pairs of human chromosomes were indistinguishable, thus making determinations of specific chromosome changes in specific cancers not feasible. I must admit that I was also frustrated in this endeavor, so I decided to work on more basic problems, such as chromosome physiology, mitotic mechanics, and chromosome responses to chemicals that cause DNA damage. My collaborators (B. R. Brinkley and T. Elton Stubblefield) and I were the first to describe the ultrastructure of the kinetochore, a structure of each chromosome that attaches itself to the spindle apparatus. But as far as cancer cytogenetics was concerned, investigators had to wait until the late 1960s and early 1970s, when several methods were invented to longitudinally differentiate each chromosome into characteristic zones or bands. There were four major banding techniques developed within a short, two-year span.

With new banding techniques, chromosomes and their subdivisions could be routinely identified. In cancer research, the first significant finding was made by Janet Rowley (University of Chicago), who demonstrated that the chromosome segment missing from the Philadelphia chromosome (now known as chromosome 22) was not really lost, but moved, to chromosome 9, a process known as translocation. When two chromosomes exchange segments, both must be broken before an exchange; and the breaks may sever two genes, one on each chromosome. The exchange may cause both genes to malfunction, resulting in abnormal growth or malignancy. A specific translocation between chromosomes 8 and 14 was the dominant characteristic of Burkitt's lymphoma (first described by Lore Zech, Stockholm), and a specific translocation between chromosomes 8 and 21 was found to associate with acute nonlymphocytic leukemia (Jose Trujillo, M. D. Anderson).

In the early 1970s, an important concept was advanced by Alfred G. Knudson, then dean of the University of Texas Graduate School of Biomedical Sciences at Houston and chief of the Office of Education at M. D. Anderson. Knudson proposed a two-mutation hypothesis of carcinogenesis. In essence, the hypothesis considers that to turn a normal tissue cell into a neoplastic cell, a particular gene must mutate or be missing. Since each gene is represented by two copies, one from each parent, one mutation does not affect the normal behavior of that cell because the homologous gene still functions. When both genes mutate, then the cell may become neoplastic.

Two-mutation hypothesis stimulates search for chromosome markers

Knudson had studied two forms of retinoblastoma and found that hereditary retinoblastoma has an earlier onset and usually results in bilateral lesions, whereas the sporadic type has a late manifestation and is expressed as a single lesion. These phenomena suggested that hereditary retinoblastoma has one pre-existing mutation. Therefore, just one an additional mutation at the same locus in the homologous chromosome would be sufficient to trigger a malignant conversion. In the sporadic variety, both genes must mutate postnatally, thus delaying the onset. (Collaborating with Louise Strong, Knudson found similar phenomena in hereditary and sporadic Wilms' tumor.)

Knudson's paper stimulated cytogeneticists to examine retinoblastoma cells for specific chromosome markers. Indeed, in some cases, one of the two chromosome 13s was distinctly shorter than

normal, and the missing segment was in the middle of its long arm. (In Wilms' tumor, a deletion in the short arm of chromosome 11 was also found by Victor Riccardi [Baylor College of Medicine].) A chromosome deletion thus leaves the individual with only one set of normal genes in the corresponding segment of the homologous chromosome. Functionally, a gene deletion and a gene mutation are equivalent, since, technically, in either case the original gene is absent. Although deletion is not a prerequisite for retinoblastoma, the presence of a deletion in the same chromosome from different patients strongly supported Knudson's two-mutation hypothesis of cancer etiology and allowed molecular geneticists to focus their attention on a smaller cluster of genes instead of the entire genome. Indeed, whenever cytogenetic analyses reveal a chromosome aberration in a particular neoplasm, the task of elucidating its etiology is advanced.

Sense amid chaos

As alluded to earlier, the chromosome constitutions of most solid tumors are so complex that they practically defy analysis. Undoubtedly, many chromosome aberrations found in these cells are incidental and are therefore inconsequential because they rarely occur twice. But among all the aberrations, there may be hidden one or more that are responsible for cancer initiation, others for cancer progression, and still others for metastasis. In order to find some sense amid chaos, several groups of cytogeneticists, including Sen Pathak, Ph.D., and his collaborators (M. D. Anderson), compared the chromosome patterns (karyotypes) of tumors of the same pathology, hoping to see whether some aberrations were shared by all samples. Using this approach, cytogeneticists have found consistent chromosome rearrangements in breast cancer, renal cell carcinomas, and small cell lung cancer and chromsome segment deletion in colorectal carcinomas. Could there be genes in these chromosomes that are vital to normalcy of these particular tissue cells? Whatever the fundamental reasons for malignant transformation, it is entirely possible that in the future cytogenetics will be an indispensable tool for diagnosis of solid tumors.

Despite the enormous contributions of cytogenetics to understanding the etiology of cancer, its valuable clinical applications, and its anticipated future refinements, cytogenetics alone cannot answer the most fundamental question: to what extent have the genes been changed and why do such changes alter gene function? The hope lies in future advances in molecular genetics.

In the past two decades, two exciting new disciplines, gene mapping and molecular genetics, have proved very promising, and many hope they can be used to solve the fundamental problems of human genetics. Gene mapping was developed under the leadership of Frank H. Ruddle (Yale University). At present the chromosome locations of hundreds of human genes, including oncogenes, have been documented. Molecular geneticists already have the vision that sooner or later the entire human genome can be deciphered. Currently many of them are analyzing gene contents of many chromosome segments and are detecting deletions (suggested by a loss of heterozygosity) that are too small for detection by cytogenetic (microscopic) techniques. Eventually, molecular geneticists should be able to tell us the precise changes in the crucial gene or genes for each malignancy. However, within this endeavor, cytogeneticists can make their task much easier—by showing them where to start. ■

Physicans who desire additional information may write T. C. Hsu, Ph.D., Department of Cell Biology, Box 181, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, or call (713) 792-2582.

Who Knows Best?

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of therapy, the support systems should be thought of as other therapies—they should be used when indicated, and when the indication no longer exists, they should be stopped. Only then can we avoid inappropriately allocating our limited resources because of our inability to predict those who cannot survive despite the highly technical environment of the intensive care unit.

The question of who knows best in medical decision making is complex. When some degree of certainty of outcome is clear, physicians are more appropriate decision makers; patients should have the prerogative to accept or refuse a recommended intervention, but not to demand treatment that is medically contraindicated. For decisions with increasing uncertainty, patients should make increasing contributions to the decision. ■

Physicians who desire additional information may write Michael S. Ewer, M.D., M.P.H., Department of Medical Specialties, Box 70, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, or call (713) 792-6239.

Hodgkin's Disease

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The 1960s saw the introduction of MOPP chemotherapy (mechlorethamine, vincristine [Oncovin], prednisone, and procarbazine), a major step forward that led to long-term disease-free survival in slightly more than half of patients with advanced Hodgkin's disease. Soon it was recognized that 90% of men who received more than six cycles developed long-term azoospermia. Likewise, half of women receiving six or more cycles of MOPP developed prolonged amenorrhea, which was strongly dependent on age at treatment: only 20% of women younger than 25 years developed amenorrhea, whereas 90% of women older than 25 did so. The consequence of gonadal failure in men with Hodgkin's disease is mainly infertility, with little or no effect on testosterone levels and sexual function. The medical consequences of ovarian failure in women are more far reaching than infertility, however, since the associated hypoestrogenemia, if untreated, may lead to menopausal symptoms, osteoporosis, and a higher risk of coronary artery disease.

Approaches to prevention and treatment of gonadal dysfunction

When a potentially sterilizing treatment is chosen (such as MOPP or pelvic radiation), there are several options to be considered for prevention or treatment of infertility. For men, sperm banking prior to therapy should be done if children are desired. Although sperm counts in men with Hodgkin's disease are often lower than normal, even ejaculates with low sperm numbers should be stored because of the possibility of future in vitro fertilization.

Clinician's Index

- 90% of patients with early-stage Hodgkin's disease survive.
- Sterility may result from MOPP chemotherapy or irradiation.
- The sequelae of treatment-induced sterility pose a significant health threat to women. The hypoestrogenemia caused by ovarian failure may result in menopausal symptoms, osteoporosis, and an increased risk of coronary heart disease.
- In men, sterility induced by pelvic irradiation can be avoided by careful shielding techniques.
- Preliminary results suggest NOVP chemotherapy cures disease

Pelvic shielding more difficult in women

For men receiving pelvic radiation, meticulous *testicular shielding* is important to prevent permanent azoospermia. For women receiving pelvic radiation, direct shielding is not as easily done, since this would also shield the lymphatic area where treatment is intended. To circumvent this problem, a surgical procedure called *oophoropexy* moves the ovaries to the midline, where they are attached to the uterus and then shielded externally from radiation. An alternative procedure, *lateral ovarian transposition*, moves the ovaries to the pelvic crests where the radiation dose is calculated to be even lower. Although initial success was reported for oophoropexy in preserving fertility, later reports were less encouraging. With the increased use of combination chemotherapy, single-modality radiation therapy, which includes the pelvis, is much less common than 10 to 20 years ago. As a result, oophoropexy is rarely done

Germ cell suppression is an investigational approach that has been used to attempt prevention of chemotherapy-induced sterility. Theoretically if one could inhibit proliferation of cells in the testes or ovaries, the effects of chemotherapy on these organs could be ameliorated. Animal studies have been promising, but when oral contraceptives in women, testosterone in men, or gonadotropin-releasing hormone analogues in both women and men with Hodgkin's disease have been used, infertility was not prevented.

Alternative treatments

Treatment options for Hodgkin's disease involve a weighing of benefits and risks, sterility being just one of those risks. Controversy surrounds treatment decisions for all stages of Hodgkin's disease and relates to clinical versus laparotomy staging, extent of radiation, and type of chemotherapy. Mantle radiation alone in the patient with laparotomy-staged supradiaphragmatic, non-bulky mediastinal Hodgkin's disease results in high failure-free survival (~90%) and yet preserves fertility. Recently ABVD (doxorubicin [Adriamycin]), bleomycin, vinblastine, dacarbazine) has demonstrated an advantage over MOPP in failure-free survival in two prospective, randomized studies. Additionally, ABVD has little long-term gonadal toxicity and therefore provides an effective alternative to MOPP. At Stanford University another regimen, VBM (vinblastine, bleomycin, methotrexate) has been used with involved-field radiation in patients with early-stage Hodgkin's disease. This combi-

"The next decade holds the promise of effective but relatively nontoxic combination chemotherapy programs"

nation has also been effective and has lacked gonadal toxicity in preliminary studies.

Since 1980, The University of Texas M. D. Anderson Cancer Center has taken the approach of reducing the duration of MOPP therapy to two cycles (together with radiation therapy) to reduce sterility and also treatment-related leukemia, both presumably due to the two drugs mechlorethamine and procarbazine. Results have supported this approach in patients with bulky mediastinal disease and stage III Hodgkin's disease except for patients with stage III_3B disease (pelvic nodal involvement), for which more intensive therapy is necessary. Sterility is reduced to 30% in men after 2-MOPP, and infertility also appears reduced for women treated with this regimen.

NOVP: a new M. D. Anderson combination chemotherapy regimen

Available combination chemotherapy regimens all have disadvantages: MOPP has a significant risk of sterility and treatment-related leukemia; ABVD avoids these risks but can result in pulmonary or cardiac dysfunction. In hopes of avoiding these complications, we at M. D. Anderson have developed NOVP (mitoxantrone [Novantrone], vincristine [Oncovin], vinblastine, prednisone). This program is used in patients who have stage I or II Hodgkin's disease and associated adverse factors of bulky mediastinal disease, hilar adenopathy, or B symptoms. NOVP is used in patients with stage III disease except when both B symptoms and pelvic disease are present (stage III_3B). Following three cycles of NOVP, radiation therapy is given to the mantle and upper abdomen in clinical stage I or II patients and in both clinical and pathological stage III patients. For stage III_2A and B patients, an abdominal spade field is also irradiated. Patients with stage III_3A also receive radiation to an additional full pelvic field.

When Frederick Hagemeister, M.D., Department of Hematology, analyzed the first 41 patients entered, he found a 90% failure-free survival at 22 months. Also encouraging are the sperm counts recorded by Marvin Meistrich, Ph.D., Department of Experimental Radiotherapy, in the first 14 men to undergo this treatment. Although 13 of the men developed azoospermia or oligospermia at 2 to 3 months from the start of chemotherapy, rapid recovery ensued. By 2 to 3 months following the end of chemotherapy, 7 of 10 men analyzed were normospermic and the other 3 were oligospermic. All five men followed for at least 10 months from the end of therapy are now normospermic.

Reducing curative treatment's toxicity will be a continual goal for the next decade

Curative treatment of Hodgkin's disease need not necessarily result in morbidity, and the next decade holds the promise of effective but relatively nontoxic combination chemotherapy programs. Reproductive status is of great concern to many young men and women with Hodgkin's disease, but there is increasing optimism that fertility can be preserved in the vast majority. Another cause for optimism is the finding that where fertility is preserved, there is no increase in congenital defects in the progeny. Treatment choice in Hodgkin's disease continues to involve a balance between effectiveness and toxicity, but the future promises an enhanced therapeutic index.■

Dr. Redman recently accepted a position as medical director at Theradex Systems, CN-5257, Princeton, NJ 08543. Physicians who desire additional information may write the author at that address or write Fredrick Hagemeister, M.D., Department of Hematology, Box 68, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, or call (713) 792-2860.

A further discussion of late complications of treatment may be obtained in *Hodgkin's Disease: The Consequences of Survival*, edited by Mortimer Lacher, M.D., and John R. Redman, M.D., Lea and Febiger, Philadelphia, 1990.

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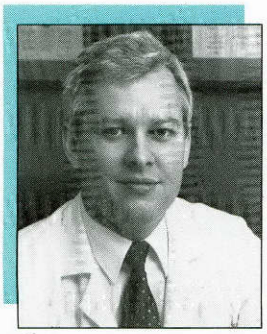
Successful Hodgkin's disease treatment can also preserve reproductive function

By John R. Redman, M.D., F.A.C.P.

Treatment Update



John Redman, recently an assistant professor of medicine in the Department of Hematology, is currently medical director at Theradex Systems

The treatment of Hodgkin's disease is one of the successes of contemporary medicine. This disease was almost uniformly fatal until three decades ago, but continuous advances in radiation therapy and chemotherapy have led to long-term survival in the vast majority of patients, nearly 90% in those with early-stage disease. Concomitant with this success, however, have come late complications, including sterility, secondary malignancies, cardiac and pulmonary dysfunction, hypothyroidism, immune deficits, and osteonecrosis. The possibility of sterility has been a prominent concern because Hodgkin's disease (1) frequently occurs during the reproductive years (median patient age 32 years), (2) it is highly curable, and (3) many patients receive frequent exposure to pelvic radiation, chemotherapy, or both. Reducing the risk of sterility is an obvious objective, and to this end several preventive measures and alternative chemotherapeutic protocols have been or are being developed. With these past and current developments, a significant number of patients can be treated for Hodgkin's disease and still preserve their reproductive capacity.

Ovarian failure caused by pelvic irradiation

Radiation therapy has played a key role in the curative treatment of Hodgkin's disease. Prior to the advent of effective chemotherapy, this more frequently involved total nodal irradiation with inclusion of the gonads in a pelvic field. In early studies men who received pelvic radiation had a low chance of sperm recovery, but more recently, with greater attention to testicular shielding, close to 90% may have recovery by two years after treatment. Therapeutic pelvic radiation in women does not have the easily applicable advantage of shielding, and therefore the doses typically used (30 to 45 Gy) result in ovarian failure in 90% of patients.

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