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Definite progress has been made against cancer since the National Cancer Act was passed in 1971. Physicians are giving increased attention to cancer prevention. The exciting changes in molecular biology provide increased knowledge about basic mechanisms in tumor growth and metastases. Detailed discussions of two common solid cancers—breast and colorectal—attest to continuing advances in cancer diagnosis and treatment. All of these augur well for further progress in oncology. Continued research, basic and clinical, is mandatory.

The American Cancer Society states that there are over 6 million Americans alive today who have a history of cancer, among them 3 million who were diagnosed 5 or more years ago [*1*]. The Society estimates that 4 of 10 patients diagnosed with cancer in 1990 will be alive 5 years after diagnosis, compared with 1 in 5 in the 1930s, 1 in 4 in the 1940s, and 1 in 3 in the 1960s. The increase from 1 in 3 to 4 in 10 represents approximately 70,000 persons in 1990.

In 1990, it was predicted that slightly more than 1 million people in the United States would be diagnosed with cancer that year, and about half of them—500,000—would die of the disease. The 5-year survival rate is 50% for white Americans but only 38% for black Americans (**Figure 1**). The major cause of the progressive increase in the age-adjusted national death rate from cancer (143 deaths per 100,000 patients in 1930 to 173 per 100,000 in 1986) has been cancer of the lung. Except for this type of cancer, age-adjusted cancer death rates for major sites are reaching a plateau, and in some cases, declining (**Figures 2** and **3**).

Among the scientific advances since 1971 are those in the areas of (1) cancer genetics, (2) cellular communication, (3) biological response modifiers, and (4) molecular immunology. Dr. George Vande Woude, of the NCI—Frederick Cancer Research Facility in Frederick, Maryland, states, "In the past few years, five different cancer research areas—viruses, oncogenes, growth factors, growth regulation and chemical carcinogenesis—have all come together. Their common language is the genes that are the molecular basis of cancers." Oncogene research has revealed specific chromosomal abnormalities as the etiological factors in many malignant tumors [*2*].

The role of monoclonal antibodies in diagnosis and treatment of cancer is being studied intensively. Those agents with their specificities, when thoroughly studied and evaluated, may revolutionize cancer diagnosis and treatment as it is known today.

Of the more than 120 different types of cancer, only a few, so far, have been shown to be caused by abnormalities in gene regulation. A prime example is retinoblastoma, which can be either hereditary or spontaneous. Both forms are caused by a loss of function of a gene carried on chromosome 13. Analyses for chromosomal abnormalities were made possible in the 1970s by a new technique, chromosome banding, which in some cases became diagnostic, as in chronic myelogenous leukemia where appearance of the Philadelphia chromosome identifies the process.

Oncogenes, variants of normal cell genes, have the ability under certain conditions to change a normal cell into a cancer cell. Of the more than 50 known oncogenes, some play major roles in growth regulations. It has been noted that some children with neuroblastoma have excess copies of an oncogene called *n-myc* and that these pa-

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SITE	WHITE RELATIVE 5-YEAR SURVIVAL					BLACK RELATIVE 5-YEAR SURVIVAL				
	60-63[1]	1970-73[1]	1974-76[2]	1977-78[2]	1979-84[2]	1960-63[1]	1970-73[1]	1974-76[2]	1977-78[2]	1979-84[2]
All Sit	39%	43%	50%	50%	50%	27%	31%	38%	38%	37%
	45	43	54	53	54	–	–	35	35	31
›phagı	4	4	5	6	7	1	4	4	2	5
ımach	11	13	14	15	16*	8	13	15	16	17
lon	43	49	50	52	54*	34	37	45	44	49
	38	45	48	50	52*	27	30	40	40	34
	2	3	4	3	3	–	–	1	1	5
	1	2	3	2	3	1	2	2	3	5
Larynx	53	62	66	69	66	–	–	58	59	55
Lung & Bronchus	8	10	12	13	13*	5	7	11	10	11
Melanoma of Ski	60	68	78	81	80*	–	–	62##	–	61#
Breast (females)	63	68	74	75	75*	46	51	62	62	62
Cervix Uteri		64	69	69	67	47	61	61	63	59
Corpus Uteri		81	89	87	83*	31	44	61	58	52*
‘ary		36	36	37	37*	32	32	41	40	36
›stati										
Urinary Bladder										
Kidney & Renal P										
Brain & Nervous										
Thyroid Gland										
Hodgkin's Diseas										
Non-Hodgkin's L										
Mı										
Le										

›ource: Surveillance and Operations Research Branch, National Cancer Institute.

Rates are based on End Results Group data from a series of hospital registries a ›opulation-based re

Rates are from the SEER Program. They are based on data from population-base ‘ies in Connecticut, New Me
Seattle-Puget Sound and San Francisco-Oakland. Rates are based on follow-up ıts through 1985.

The difference in rates between 1974-76 and 1979-84 is statistically significant (p

standard error of the survival rate is between 5 and 10 percentage points.

: standard error of the survival rate is greater than 10 percentage points.

l survival rate could not be calculated.

Figure 1. Trends in survival by site of cancer, by race (from [*1*]).

tients have more progressive tumors requiring more intensive treatment. If these studies can be shown to exist in other common cancers, such as breast and colorectal, then appropriate adjuvant therapy can be given to these patients at higher risk. Scientists are using recombinant DNA techniques in yeast to duplicate the genes and develop a more precise genetic map of human genes and human chromosomes. Such genetic analysis aids greatly in understanding basic mechanisms in cancer [*2*].

Imaging studies for detection and diagnosis are also being used to determine stages of disease and to plan treatment regimens. Computed tomography and magnetic resonance imaging are well-known diagnostic tools. However, other promising methods of diagnosis include radiolabeled monoclonal antibodies and positron emission tomography (PET), which uses tracer doses of radioactive agents to reveal cellular metabolism in both normal and malignant tissues. Newer therapeutic measures that are undergoing further evaluation to determine their wider applicability include (1) proton beam therapy, especially for head and neck cancers; (2) photodynamic therapy using light beams to destroy tumor cells that have been made light-sensitive by treating them with a photosensitizer; and (3) hyperthermia in combination with radiotherapy and chemotherapy.

Biological response modifiers, produced by the body's immune and growth regulatory systems, represent an exciting group of agents that are proving to be of value against cancer. Among the most promising are the interferons, the lymphokines, growth factors, and monoclonal antibodies.

Three major types of interferons—interferon alfa, beta, and gamma—are being evaluated in different cancer treatments. Large amounts of interferon alfa became available through recombinant DNA techniques and have been found to be useful in lymphomas and leukemias. It is especially effective in the rare hairy cell leukemia, with some 90% of patients showing marked improvement.

Lymphokines, molecules secreted by lymphocytes, can mobilize and regulate the immune system. One form of interferon, gamma or immune interferon, is a lymphokine. One of the most exciting lymphokines is interleukin-2 (IL-2) which promotes rapid growth of T and B lymphocytes. Recombinant DNA techniques have made large amounts of IL-2 available for clinical study. Rosenberg and his associates [*3*] have championed the use of IL-2 for cancer. They incubated leucocytes of cancer patients with IL-2–generating lymphokine-activated killer cells (LAK cells) and returned these anti-cancer cells

SITES	SEX	1953-55	1983-85	PERCENT CHANGES	COMMENTS
ALL SITES	Male	175.7	203.1	+ 16	Steady increase mainly due to lung cancer.
	Female	145.1	138.2	- 5	Slight decrease.
BLADDER	Male	7.2	6.1	- 15	Slight decrease in recent years.
	Female	3.1	1.8	- 42	Some fluctuations; noticeable decrease.
BRAIN	Male	3.9	4.7	+ 21	Early increase in both sexes; later leveling off, reasons unknown.
	Female	2.6	3.2	+ 23	
BREAST	Male	0.3	0.2	*	Constant rate.
	Female	26.2	27.1	+ 3	Slight fluctuations; overall no change.
COLON & RECTUM	Male	25.8	24.7	*	Slight fluctuations; overall no change.
	Female	24.4	17.5	- 28	Slow, steady decrease.
COLON	Male	16.9	20.7	+ 22	Slow steady increase, leveling in recent years.
	Female	18.3	15.0	- 18	Slow, steady decrease.
RECTUM	Male	8.9	4.0	- 55	Slow steady decrease.
	Female	6.1	2.4	- 61	Slow steady decrease.
ESOPHAGUS	Male	4.7	5.6	+ 19	Some flucutations; small increase.
	Female	1.2	1.5	*	Slight fluctuations; overall no change.
KIDNEY	Male	3.6	4.9	+ 46	Steady slight increase.
	Female	2.2	2.3	*	Slight fluctuations; overall no change.
LARYNX	Male	2.6	2.7	*	Slight fluctuations; overall no change in both males and females.
	Female	0.2	0.5	*	
LEUKEMIA	Male	8.2	8.4	+ 2	Early increase, later leveling off and decrease.
	Female	5.5	5.0	- 9	Early slight increase; later leveling off and decrease.
LIVER**	Male	6.2	4.9	- 21	Decreasing rapidly early; later leveling off.
	Female	7.1	3.3	- 54	Some fluctuations; steady decrease.
LUNG	Male	28.0	73.1	+161	Steady increase in both sexes due to cigarette smoking.
	Female	5.1	25.3	+396	
LYMPHOMAS	Male	8.0	11.1	+39	Slow steady increase in both males and females.
	Female	5.1	7.5	+47	
ORAL	Male	6.0	5.2	*	Slight fluctuations; overall no change in both males and females.
	Female	1.5	1.8	*	
OVARY	Female	8.6	7.8	- 9	Steady increase; later leveling off and decrease.
PANCREAS	Male	9.1	10.2	+ 12	Steady increase in both sexes, then leveling off, reasons unknown.
	Female	5.7	7.2	+ 26	
PROSTATE	Male	21.3	23.2	+ 9	Fluctuations throughout; overall slight increase.
SKIN	Male	3.1	4.0	+ 29	Slight fluctuations; slight increase.
	Female	1.9	1.8	*	Slight fluctuations; overall no change.
STOMACH	Male	21.3	10.2	- 52	Steady decrease in both sexes; reasons unknown.
	Female	11.2	3.5	- 69	
UTERUS	Female	19.0	7.1	- 63	Steady decrease.

*Percent changes not listed because they are not meaningful.

**Primary and non-specified.

Figure 2. Thirty-year trends in age-adjusted cancer death rates (from [1]).

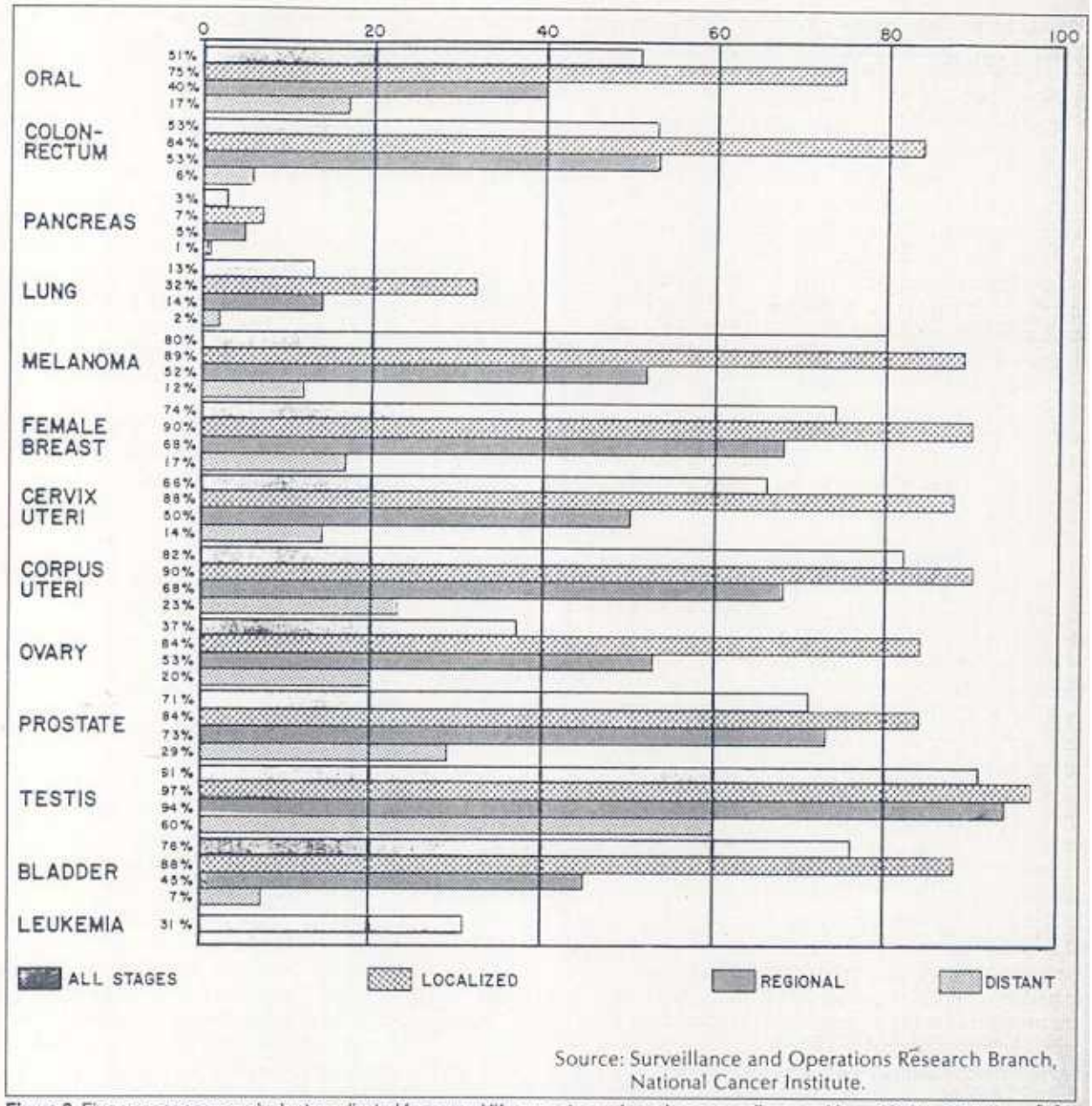

Figure 3. Five-year cancer survival rates adjusted for normal life expectancy, based on cases diagnosed from 1979 to 1984 (from [1]).

to the patient with additional doses of IL-2. All of these patients had advanced cancers that were unresponsive to traditional therapy. Encouraging results were noted in patients with melanoma and renal cell carcinoma.

Growth factors, especially colony-stimulating factors (CSF), help regulate the production of granulocytes and macrophages in the bone marrow. The administration of growth factors to patients receiving chemotherapy may ameliorate some of the toxic effects secondary to leukopenia. Clinicians have observed that patients receiving granulocyte colony-stimulating factors have higher granulocyte counts than patients not receiving such agents.

Monoclonal antibodies are used for diagnosis and treatment. However, much more study is needed before general clinical applicability can be recommended. For example, since cancer cells evolve as the disease progresses, a different monoclonal may be needed later to maintain effectiveness of therapy. Further, most monoclonals in use today came from mouse cells, and these are likely to be rejected by the body's immune system before they can deliver their anti-cancer therapy to the targeted tissue. Efforts are underway to perfect mouse-human monoclonal antibodies [2].

TUMOR METASTASIS

Exciting new information is emerging about the complex process of tumor metastasis. It has been noted that not all tumor cells are capable of metastasis and that

metastatic potential varies among particular cells of a tumor. Thus, although cancer cells must be tumorigenic to grow as a metastatic colony, metastatic propensity is distinctly separate from tumorigenicity [4,5].

Considerable progress has been made in recent years toward defining the biochemical mechanisms of tumor invasion and metastasis. An underlying principle is that cancer invasion and metastasis represent a complex, multistep process. Liotta [6,7] has proposed a three-step hypothesis that describes the sequence of biochemical events during tumor cell invasion of the extracellular matrix. The first step is tumor cell attachment via cell-surface receptors that specifically bind to components of the matrix, such as laminin (for the basement membrane) and fibronectin (for the stroma). In the second step, hydrolytic enzymes locally degrade the matrix, including the attachment components. This degradation may variably be achieved by the anchored tumor cell's secretion of hydrolytic enzymes, by induction of host cells to secrete enzymes, or by the activation of proenzyme already present in the matrix. The third step is tumor cell locomotion into the region of the matrix modified by proteolysis. The cyclic repetition of these three steps is probably required during continued invasion through the matrix and during the rest of the metastatic process.

A gene that in some way inhibits the formation of metastasis may be defined as a metastasis suppressor gene. Since tumorigenicity and metastatic propensity are independent processes, it follows that metastasis suppressor genes are distinct from tumor suppressor genes [4,8]. A metastasis suppressor gene may function by increasing the immunogenicity of the tumor cell in the host. It is now generally accepted that there are loci in normal cells that can suppress the tumorigenic phenotype and that can be inactivated by mutation. Cancer cells must be tumorigenic to grow as a metastatic colony; however, all tumorigenic cells are not necessarily invasive and metastatic. The metastatic phenotype is independent from the tumorigenic phenotype. It is proposed that multiple gene products are necessary for the expression of the metastatic phenotype. Genetic control of metastasis may be exerted by the increased expression of specific genes involved in the metastatic cascade.

CHEMOTHERAPY

Great strides have been made in cancer chemotherapy during the past 40 years. In a classic article, Bonadonna [9] described the effectiveness of chemotherapy in cancer treatment. Categories of cancer in which combination chemotherapy alone can cure a percentage of patients with clinically widespread disease include acute lymphoblastic leukemia, Hodgkin's disease, choriocarcinoma, testicular tumors, Wilms' tumor, small-cell lung cancer, and embryonal rhabdomyosarcoma. The incidence of complete remission is higher than the actual cure rate, indicating that relapse is due to the large fraction of drug-resistant cells existing in clinically disseminated cancer. Cure is achieved through a variety of intensive-dose regimens whose duration has been considerably shortened in recent years without compromising the end results. In some neoplasms such as acute lymphoblastic leukemia, Hodgkin's disease, high grade lymphomas, choriocarcinoma, and probably also in small-cell lung cancer, treatment outcome has been improved by the use of non-cross-resistant combinations. Neoplasms in which the combined modality approach with chemotherapy has improved relapse-free and total survival rates include the following: Wilms' tumor, breast cancer, anal cancer, Hodgkins' disease, and testicular tumors. Furthermore, there are some neoplasms such as soft tissue sarcoma, anal carcinoma, and osteogenic sarcoma in which less extensive surgery is needed when chemotherapy and radiation are used [10–12].

FLOW CYTOMETRY

The flow cytometric analysis of DNA content has been used to establish objective prognostic variables in a wide variety of neoplasms [13,14]. For certain hematologic malignancies and solid tumors, DNA ploidy has been shown to have an important prognostic value. For example, breast cancers showing aneuploidy and high S-phase fraction are more aggressive and have a worse prognosis than diploid tumors with low S-phase fraction [15]. However, a direct correlation between DNA ploidy and clinical outcome has not been consistently found in all tumor types. For example, in non-small-cell lung cancer, studies of DNA ploidy have yielded disparate results.

BREAST CANCER

Great strides have been made in the early diagnosis and treatment of breast cancer, primarily because of screening mammography, which can reduce breast cancer mortality by 20% to 30% in women over 50 years of age [16]. The two classic mammographic indications for breast biopsy are clustered microcalcifications and stellate masses. Less definite indications are asymptomatic density and architectural distortion. Biopsy for these indications will reveal cancer in 15% to 30% of cases. Despite the value of mammography in decreasing breast cancer mortality in women over 50 years of age, controversy remains as to whether such screening is cost-effective and how frequently mammography should be done, even in the over-50 age group. Several studies have tried to settle these questions, but no concrete answers are available [17,18]. It is hoped that detection and treatment of early breast cancers will not only be cost-effective but will also help patients avoid the problems of advanced disease.

Fisher *et al* [19] and Veronesi *et al* [20], in separate trials, have shown the effectiveness of breast-preserving treatment for patients with early-stage breast carcinoma, which combines resection of the primary tumor with a surrounding margin of grossly normal breast tissue (lumpectomy, partial mastectomy, segmental mastectomy, or quadrantectomy), with or without surgical staging of the axilla and radiotherapy for the eradication of residual subclinical disease. The goal of such treatment is to provide highly satisfactory cosmetic results without compromise of local tumor control or survival. Randomized clini-

cal trials have now shown that conservative surgery and radiotherapy are equal to mastectomy in achieving this latter goal.

The role of pathologic margins in treatment selection remains controversial. Recht and Harris [*21*] believe that margins have clinical meaning only when interpreted in relation to the histology of the primary tumor and that "negative" margins are not always needed to achieve a high rate of local tumor control.

Despite the significant progress that has been made in the diagnosis and treatment of breast cancer, some troubling issues remain. For example, adjuvant chemotherapy for node-negative patients is controversial. The single most important predictor of relapse after primary therapy for patients with breast cancer is the status of the axillary lymph nodes. Those patients with negative axillary lymph nodes have a better prognosis than those whose nodes are involved with metastatic cancer. Approximately 70% to 80% of all node-negative patients are free of disease at 5 years. However, some patients will experience a relapse and die of metastatic disease.

Results from recent clinical trials in which patients with node-negative breast cancer were randomly assigned to receive either adjuvant tamoxifen citrate (in estrogen-receptor–positive patients) or combination chemotherapy produced significantly superior disease-free survival rates when compared with no treatment [*22,23*]. However, none of the trials demonstrated a superior overall survival for patients receiving treatment. Although these results were encouraging, many onoclogists believe that adjuvant systemic therapy for node-negative patients remains investigational and should not be administered routinely.

Tandon *et al* [*24*] investigated the possibility that cathepsin D, an estrogen-induced lysosomal protease, might have value as a prognostic factor in breast cancer by studying frozen-tissue specimens from 397 patients. Among 199 patients with node-negative disease, but not among 198 with node-positive disease, high levels of cathepsin D proved to be a significant predictor of reduced disease-free and overall survival (median follow-up: 64 months). When the level of cathepsin D was related to other prognostic factors in the patients with node-negative disease, they found an association with aneuploidy but none with estrogen or progesterone receptors, tumor size, or the age of the patient. In multivariate analyses, a high level of cathepsin D was the most important independent factor in predicting shorter disease-free and overall survival in patients with node-negative disease. They concluded that cathepsin D may be an independent predictor of early recurrence and death in patients with node-negative breast cancer.

COLORECTAL CANCER

The role of adjuvant radiotherapy in rectal cancer, especially for Astler-Coller B2, C1, and C2 lesions, is becoming more widely accepted as standard therapy. Pahlman and Glimelius [*25*] described 471 patients with resectable rectal carcinoma seen between 1980 and 1985 who entered a randomized multicenter trial for comparison of pre- and postoperative radiation. Two hundred thirty-six patients were allocated to receive high-dose fractionated preoperative irradiation (total dosage: 25.5 Gy in 5 to 7 days) and 235 patients were to receive postoperative irradiation to a very high dosage level with conventional fractionation (60 Gy in a total of 8 weeks). The postoperative treatment was delivered only to a high-risk group of patients (Astler-Coller stages B2, C1, and C2). The postoperative treatment was not as well tolerated as the preoperative one. The local recurrence rate was statistically significantly lower after preoperative than after postoperative radiotherapy (12% versus 21%). In both groups, more patients developed a local recurrence if the bowel was perforated at surgery or if the resection line was microscopically close to the tumor. With a minimum follow-up of 3 years and a mean follow-up of 6 years, there was no difference in survival rates between the two groups.

Little success has been achieved in finding adjuvant therapy for patients with colon cancer. Recently, however, Moertel *et al* [*26*] described 1,296 patients with resected colon cancer that was either locally invasive (Stage B) or had regional nodal involvement (Stage C). They randomly assigned patients either to observation only or to treatment for 1 year with levamisole hydrochloride combined with fluorouracil. Patients with Stage C disease could also be randomly assigned to treatment with levamisole alone. The median follow-up time was 3 years (range: 2 to 5½ years). Among the patients with Stage C disease, therapy with levamisole plus fluorouracil reduced the risk of cancer recurrence by 41% ($p < 0.0001$). The overall death rate was reduced by 33%. Treatment with levamisole alone had no detectable effect. The results in the patients with Stage B2 disease were equivocal and too preliminary to allow firm conclusions. Moertel and associates concluded that adjuvant therapy with levamisole and fluorouracil should be standard treatment for Stage C colon carcinoma.

COST-BENEFIT ANALYSIS

In today's climate of escalating health care costs, much is written about cost-effectiveness and cost-benefit ratios. Millions of dollars are spent on treating patients with advanced cancer who never return to productive lives. However, there is another view that should be emphasized. Shibley *et al* [*27*] reported a cost-benefit analysis of the impact of cisplatin-based combination chemotherapy for treatment of disseminated testicular cancer. The annual estimated economic value of this treatment innovation in the United States is approximately $150 million. The estimate was based on the human capital approach, which conservatively values a human life in terms of economic productivity. Because testicular cancer predominantly strikes young adult males, the savings reported were due to the future earning potential of the survivors. A comparison of relevant National Cancer Institute costs for drug development and clinical trials versus annual savings realized indicated that the total costs over a 17-year period are recovered in less than 1 year.

This report is an example of health care cost-savings resulting from biomedical research findings. To present a balanced view, the authors emphasize that not all cancer treatment research yields a comparable economic return to society. However, they state that a net social economic return should not be the exclusive criterion determining whether research should be considered a success or failure.

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