It was demonstrated in the early 1940s that changing the hormonal milieu of certain cancers could result in their regression and that administration of a simple chemical compound could produce similar results. These observations have led to a continuing search for systemically administered agents that can produce profound and lasting effects on human cancer. The search has proceeded along two parallel tracks: empirical screening has produced useful drugs, most frequently natural products; mechanism-based syntheses have given us others. In addition, some drugs have come from serendipitous observation.

This is the 10th article of a series in this journal that has documented progress in systemic therapy over four decades.\textsuperscript{1-9} For most of this time, emphasis was placed on cytotoxic and hormonally active agents. More recently, the role for biologic agents has become apparent, and it is now clear that the explosion of knowledge in molecular biology has contributed to the development of additional types of therapeutic agents. It therefore seems appropriate to broaden our perspective to include a wide variety of systemic cancer treatments—this is reflected in the evolution of the title of this essay.

The development of combination chemotherapy was a major conceptual advance. By targeting multiple biochemical processes, it became possible to progress from achieving minor effects to complete, long-lasting remission. Cure of a dozen types of advanced cancer with chemotherapy is now well established. Adjuvant chemotherapy is now well established. Adjuvant chemotherapy is a major factor in the cure of others. These are, for the most part, tumors of nonepithelial origin, and they occur predominantly in young people. Progress in the most common tumor types has been less impressive. However, multidisciplinary planning and treatment and judicious integrated use of surgery, radiation therapy, and combination chemotherapy have produced complete remission and increased survival in a proportion of those refractory cancers. It is now clear that neoadjuvant or induction chemotherapy can increase survival in some cancers and has a major role in organ preservation in others.

Special techniques of drug administration (e.g., hepatic arterial infusion and chemoembolization) increase survival in some circumstances. It is recognized that dose attenuation may seriously limit the effectiveness of chemotherapeutic regimes, and it is important therefore to administer drugs in full dose. It is less certain, however, that very high-dose chemotherapy supported by bone marrow or peripheral stem cell transplantation confers a definite survival advantage. This major uncontrolled clinical experiment is continuing. Peripheral blood stem cell transplantation appears to be easier and cheaper than bone marrow transplantation and equally effective. It is replacing bone marrow transplantation in many centers.

The concept of chemoprevention is now firmly established. It is possible to cause regression of premalignant lesions, to block the development of second prima-
ry cancers and, in specific circumstances, to achieve regression of established cancers with “differentiating” agents.

Several additional drugs have become available. The microtubule-active agent paclitaxel has shown useful antitumor effects in several neoplasms. It is registered in the United States for the treatment of breast and ovarian cancer. The related drug docetaxel has also shown activity and is being studied. Gemcitabine, a new pyrimidine analogue, has antitumor activity in squamous cancer of the lung and head and neck and in other solid tumors. Two water-soluble derivatives of camptothecin, topotecan and irinotecan, are inhibitors of type 1 topoisomerase. They are at least as active as camptothecin without its limiting toxicities. Vinoerlbine is a semisynthetic vinca analogue that shows promising activity with at least quantitatively different toxicity from that shown by the parent drugs. The purine analogues fludarabine, 2-chlorodeoxyadenosine, and 2-deoxycoformycin have shown high levels of activity in low- and intermediate-grade lymphomas and hairy cell leukemia.

The development of blocking agents to the serotonin 5-HT3 receptor (ondansetron, granisetron, and others) as antiemetics is a major advance in potentiating the use of highly emetic chemotherapeutic agents.

Many cytokines have been cloned, purified, and studied. Each cytokine reacts with a specific cell-surface receptor. The term “interleukin” has been used to classify cytokines. The list now includes interleukin-1 through interleukin-12; interferon-α, interferon-β, and interferon-γ; tumor necrosis factor; and colony-stimulating factors. Of these, interleukin-2, the interferons, and the hematopoietic growth factors have reached wide clinical application.

The development of tumor-specific monoclonal antibodies led to efforts to use them clinically in cancer therapy. These have achieved little success. However, conjugation of monoclonal antibodies to drugs, plant or bacterial toxins, or radioisotopes has produced limited but encouraging success.

The demonstration that angiogenesis is necessary for tumor growth has led to the development of angiogenesis inhibitors that suppress tumor growth in vivo. The most promising of these are in clinical trials.

Although only a small number of biologic agents have reached regular clinical use, there is no longer any doubt that these substances represent a group of effective therapeutic tools. Their interactions are complex, and it is not yet possible to categorize their activities simply. Their continued development will cause them to emerge as another important class of systemic antitumor drugs.

Although still in its infancy, gene therapy has become a reality. There is now convincing evidence that deletion or mutation of the p53 tumor suppressor gene is associated with tumor growth and progression and that transfection of cells with the normal gene, which can now be accomplished in vivo, results in tumor inhibition. Studies are being done in humans in which genes are being inserted into cells ex vivo and reimplanted into the human host. It is clear that gene expression can be altered and that this can result in therapeutic activity. Additionally, the protein products of tumor suppressor genes have been produced and shown to have tumor-inhibiting activity in vitro and in vivo. Studies are under way in humans to confer genetic resistance to anticancer drugs on normal hematopoietic cells to enhance the therapeutic index of those drugs.

Clinical studies of possible anticancer agents based on “antisense” strategies (specific binding to RNA to prevent expression of the encoded protein) have begun and represent a promising avenue to new and effective cancer therapies.

Immunotoxins are created by linking a cytotoxic molecule (e.g., plant tox-
### Table 1

**Influence of Chemotherapy on Advanced Cancer**

| Cure | Cure - Adjuvant Chemotherapy |
|------|-----------------------------|
| Gestational trophoblastic tumors | Wilms tumor |
| Acute lymphoblastic leukemia | Osteogenic sarcoma |
| Hodgkin’s disease | Rhabdomyosarcoma |
| Non-Hodgkin’s lymphoma (children) | |
| Diffuse large cell lymphoma | |
| Burkitt’s lymphoma | |
| Testicular tumors | |

| Complete Remission with Increased Survival | | Response with Some Prolongation of Survival |
|---------------------------------------------|---------------------------------------------|
| Breast cancer | Prostate cancer | Multiple myeloma | Neuroblastoma |
| Small cell carcinoma of the lung | Hairy cell leukemia | Ovarian cancer | Colorectal cancer |
| Acute myeloblastic leukemia | Chronic granulocytic leukemia | Endometrial cancer | Liver cancer |
| Non-Hodgkin’s lymphoma, indolent | | |

| Minor Response - No Demonstrable Prolongation of Survival | | Organ Preservation - Neoadjuvant Chemotherapy |
|----------------------------------------------------------|---------------------------------------------|
| Non-small cell lung cancer | Cervical cancer | Breast cancer | Soft tissue sarcomas |
| Head and neck cancer | Melanoma | Laryngeal cancer | Anus cancer |
| Stomach cancer | Cancer of the adrenal cortex | Bladder cancer | Esophageal cancer |
| Pancreatic cancer | Soft tissue sarcomas | Osteogenic sarcoma | |
Mechanism of action for chemotherapeutic and biologic agents.
### Polyfunctional Alkylating Agents

- Mechlorethamine
- Chlorambucil
- Melphalan
- Thiotapec
- Busulfan
- Cyclophosphamide
- Ifosfamide

**Major Toxicity**
- Therapeutic doses moderately depress peripheral blood cell count; excessive doses cause severe bone marrow depression with leukopenia, thrombocytopenia, and bleeding. Maximum toxicity may occur two or three weeks after last dose. Dosage, therefore, must be carefully controlled. Hemorrhagic cystitis occurs with cyclophosphamide and ifosfamide; can be prevented by mesna. Alopecia. Nausea and vomiting

### Antimetabolites

- Methotrexate
- 6-Mercaptopurine
- 6-Thioguanine
- 5-Fluorouracil
- 5-Fluorodeoxyuridine
- Cytarabine
- Fludarabine
- 2-Chlorodeoxyadenosine
- 2-Deoxycoformycin
- Gemcitabine

**Major Toxicity**
- Oral and digestive tract ulcerations. Bone marrow depression with leukopenia, thrombocytopenia, and bleeding. Toxicity enhanced by impaired kidney function. Alopecia

### Antibiotics

- Doxorubicin
- Bleomycin
- Dactinomycin
- Daunorubicin
- Plicamycin
- Mitomycin C
- Mitoxantrone

**Major Toxicity**
- Stomatitis. Gastrointestinal injury. Alopecia. Bone marrow depression. Cardiac toxicity at cumulative doses over 500 mg/m² (doxorubicin and daunorubicin) may be modified by continuous infusion. Pneumonitis and pulmonary fibrosis at cumulative doses over 400 u (bleomycin).
- Hypocalcemia. Hepatic toxicity (plicamycin). Nausea and vomiting

### Steroid and Hormonally Active Compounds

- Androgen
  - Fluoxymesterone
  - Antiandrogen
  - Flutamide
- Estrogen
  - Ethinyl estradiol
  - Diethylstilbestrol
- Antiestrogen
  - Tamoxifen
- Progestin
  - Megestrol acetate

**Major Toxicity**
- Fluid retention.
- Masculinization/femininization.
- Hot flushes (sex hormones).
- Hypertension. Diabetes. Adrenal insufficiency

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**Table 2**

| Specific Agents Used in Cancer Therapy* |
|----------------------------------------|
| **Polyfunctional Alkylating Agents**   |
| Mechlorethamine                        |
| Chlorambucil                           |
| Melphalan                              |
| Thiotapec                              |
| Busulfan                               |
| Cyclophosphamide                       |
| Ifosfamide                              |
| **Major Toxicity**                     |
| Therapeutic doses moderately depress peripheral blood cell count; excessive doses cause severe bone marrow depression with leukopenia, thrombocytopenia, and bleeding. Maximum toxicity may occur two or three weeks after last dose. Dosage, therefore, must be carefully controlled. Hemorrhagic cystitis occurs with cyclophosphamide and ifosfamide; can be prevented by mesna. Alopecia. Nausea and vomiting |

| **Antimetabolites**                    |
| Methotrexate                           |
| 6-Mercaptopurine                       |
| 6-Thioguanine                          |
| 5-Fluorouracil                         |
| 5-Fluorodeoxyuridine                   |
| Cytarabine                             |
| Fludarabine                            |
| 2-Chlorodeoxyadenosine                 |
| 2-Deoxycoformycin                      |
| Gemcitabine                            |
| **Major Toxicity**                     |
| Oral and digestive tract ulcerations. Bone marrow depression with leukopenia, thrombocytopenia, and bleeding. Toxicity enhanced by impaired kidney function. Alopecia |

| **Antibiotics**                        |
| Doxorubicin                            |
| Bleomycin                              |
| Dactinomycin                           |
| Daunorubicin                           |
| Plicamycin                             |
| Mitomycin C                            |
| Mitoxantrone                           |
| **Major Toxicity**                     |
| Stomatitis. Gastrointestinal injury. Alopecia. Bone marrow depression. Cardiac toxicity at cumulative doses over 500 mg/m² (doxorubicin and daunorubicin) may be modified by continuous infusion. Pneumonitis and pulmonary fibrosis at cumulative doses over 400 u (bleomycin). Hypocalcemia. Hepatic toxicity (plicamycin). Nausea and vomiting |

| **Steroid and Hormonally Active Compounds** |
| Androgen                                  |
| Fluoxymesterone                          |
| Antiandrogen                              |
| Flutamide                                 |
| Estrogen                                  |
| Ethinyl estradiol                         |
| Diethylstilbestrol                        |
| Antiestrogen                              |
| Tamoxifen                                 |
| Progestin                                 |
| Megestrol acetate                         |
| **Major Toxicity**                       |
| Fluid retention.                          |
| Masculinization/femininization.           |
| Hot flushes (sex hormones).               |
| Hypertension. Diabetes. Adrenal insufficiency |
### Steroid and Hormonally Active Compounds

- Luteinizing hormone-releasing hormone agonist
  - Leuprolide
- Aromatase inhibitor
  - Aminoglutethimide
- Adrenal cortical compound
  - Dexamethasone

### Miscellaneous Drugs

| Drug          | Major Toxicity                                                                 |
|---------------|-------------------------------------------------------------------------------|
| Asparaginase  | Anorexia, weight loss, somnolence, lethargy, confusion. Hypoproteinemina (including albumin and fibrinogen). Hyperlipidemia, abnormal liver function tests, fatty metamorphosis of the liver. Pancreatitis (rare). Azotemia. Granulocytopenia, lymphopenia, and thrombocytopenia (usually mild and transient) |
| Altretamine   | Bone marrow depression. Peripheral neuropathy                                   |
| AMSA          | Bone marrow depression. Stomatitis. Hepatic dysfunction. Nausea and vomiting    |
| Carmustine    | Bone marrow depression, thrombocytopenia. Nausea and vomiting                   |
| Lomustine     | Bone marrow depression, thrombocytopenia. Nausea and vomiting                   |
| Steptozotocin | Hypoglycemia. Nausea and vomiting                                              |
| Mitotane      | Skin eruptions. Diarrhea. Mental depression. Muscle tremors. Adrenal insufficiency. Nausea and vomiting |
| Dacarbazine   | Bone marrow depression. Nausea and vomiting                                    |
| Hydroxyurea   | Bone marrow depression. Nausea and vomiting                                    |
| Etoposide     | Alopecia. Nausea and vomiting                                                  |
| Cisplatin     | Bone marrow depression. Renal tubular damage. Deafness. Nausea and vomiting    |
| Carboplatin   | Bone marrow depression. Nausea and vomiting                                    |
| Procarbazine  | Bone marrow depression with leukopenia and thrombocytopenia. Mental depression. Nausea and vomiting |
| Vinblastine   | Alopecia. Areflexia. Bone marrow depression                                    |
| Vincristine   | Areflexia. Muscular weakness. Peripheral neuritis. Paralytic ileus. Mild bone marrow depression |
| Levamisole    | None                                                                           |
| Cis-retinoic acid | Cheilitis. Stomatitis. Conjunctivitis.                                       |
| Paclitaxel    | Leukopenia. Peripheral neuropathy                                              |
| Docetaxel     | Leukopenia. Peripheral neuropathy                                              |

*Generic names are used throughout. Because doses may vary widely, depending on schedule, dose intensity, and combinations, original sources should be consulted. Where there may be multiple preparations with similar mechanisms of action, representative ones are shown.
ins, such as ricin; bacterial toxins; or radioisotopes) with a molecule that preferentially binds to a cancer cell receptor. Such immunotoxins have been shown to be cytotoxic to malignant cells and are being investigated in clinical trials.

Earlier reviews in this series noted that most anticancer agents interfere in a specific way with basic cellular mechanisms of DNA synthesis and replication, transcription to RNA, and protein synthesis (Figure). Our understanding of molecular biology has provided additional tools to perturb this axis. We can now block receptors or use them to attach and internalize toxins. We can block DNA synthesis, signal transduction, gene transcription, and protein synthesis.

The cytotoxic and biologic agents that we have are important clinical tools. Others will continue to be developed. As molecular tools are developed, they will be added to our armamentarium.

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**Table 3**

| Agent                         | Abbreviation | Target                                      |
|-------------------------------|--------------|---------------------------------------------|
| Interferon-α                  | IFN-α        | Antiproliferative, antiviral; augments natural killer cell activity |
| Interferon-β                  | IFN-β        |                                             |
| Interferon-γ                  | IFN-γ        | Antiviral; augments natural killer cell activity |
| Tumor necrosis factor         | TNF          | Stimulates T-cells; augments natural killer cell activity |
| Erythropoietin                | Epo          | Stimulates erythrocyte precursors           |
| Granulocyte colony-stimulating factor | G-CSF       | Stimulates granulocytes                     |
| Granulocyte macrophage colony-stimulating factor | GM-CSF       | Stimulates granulocytes, monocytes, erythrocytes |
| Macrophage colony-stimulating factor | M-CSF       | Stimulates monocytes                        |
| Interleukin-1                 | IL-1         | Stimulates T-cells                          |
| Interleukin-2                 | IL-2         | Stimulates T-cells                          |

*These agents produce a common pattern of toxicity characterized by fever, severe fatigue, and moderate leukopenia. The colony-stimulating factors often cause bone pain.
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Additional Reading
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American Cancer Society
National Conference on Cancer Nursing Research

The American Cancer Society, in cooperation with the Association of Pediatric Oncology Nurses and the Oncology Nursing Society, announces the Fourth National Conference on Cancer Nursing Research to be held January 23-25, 1997, at the Marriott Baypoint Resort in Florida. The conference brings together researchers, educators, and clinicians for an opportunity of scholarly exchange to bridge the gap between nursing research and practice.

The conference objectives are (1) to discuss state-of-the-art research in selected areas of practice, (2) to examine and discuss research outcomes in selected areas of cancer nursing, (3) to evaluate the application of research findings to cancer nursing practice, education, and future cancer nursing research, (4) to describe the empirical database for selected aspects of cancer prevention, detection, treatment, and rehabilitation, (5) to discuss application of state-of-the-art research methodologies to the study of selected aspects of cancer, and (6) to examine the implications of research findings to nursing practice, education, administration, and research.

Researchers are invited to submit abstracts for presentation or for poster sessions. Deadline for abstract submission is July 1, 1996. For more information, contact Terri Ades, RN, MS, OCN, Director, Detection and Treatment/Nursing, American Cancer Society, 1599 Clifton Road, NE, Atlanta, GA 30329-4251, telephone 404-329-7616.