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The University of Texas MD Anderson Cancer Center

James M. Bowen
The University of Texas MD Anderson Cancer Center

A REPORT TO PHYSICIANS

OncoLog

THE UNIVERSITY OF TEXAS SYSTEM CANCER CENTER
M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE

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Newsletter Becomes OncoLog

by James M. Bowen, PhD, Vice President for Academic Affairs

This is the first issue of *OncoLog*, a report to all physicians regarding the status of cancer research and treatment at The University of Texas System Cancer Center M. D. Anderson Hospital and Tumor Institute. Formerly called the *Newsletter* and distributed bimonthly, *OncoLog* becomes, with this issue, a quarterly publication.

A REPORT TO THE PHYSICIANS OF TEXAS
newsletter

A REPORT TO PHYSICIANS
OncoLog

As a publication of the UT Cancer Center, *OncoLog* has been redesigned to meet the needs of our readers more effectively. The educational value of the contents will be emphasized to keep you informed of advances in diagnosis and treatment methods at UT MDAH. Its mission will be to present the most recent developments in patient care, significant diagnostic progress, and current clinical and basic science research activities. It will also serve to keep you informed about continuing cancer education conferences being held at UT MDAH that may be of interest and value to you.

The UT Cancer Center was originally established to serve as a major referral hospital as well as a clinical and basic science research facility, with the fourfold mission of patient care, education, research, and prevention. The Office of Academic Affairs is responsible for the dissemination of current and relevant information that will aid the physician in the early detection of cancer and the follow-up treatment of cancer patients. *OncoLog* will continually strive to serve as a significant resource for the physician in maintaining current oncologic knowledge in professional practice.

We encourage your active participation in *OncoLog* and invite you to suggest topics to be included in future issues. With your cooperation and assistance, *OncoLog* will achieve its goal of serving as an educational aid to you, the physician.

Prolactinoma, a Prevalent Gonadoinhibitory Tumor, Responds Well to Treatment

Prolactinoma, a benign, prolactin-producing pituitary tumor, is the most common tumor in the human body and occurs in 30% of the population. Since 1969, when human prolactin was first isolated, physicians at UT MDAH have successfully treated approximately 350 patients with prolactinoma, which can be a cause of sterility in both men and women.

Prolactinoma produces excess prolactin in the body and has both an indirect and direct effect on the gonads, according to Naguib A. Samaan, MD, PhD, chief of the Section of Endocrinology in the Department of Internal Medicine. The increased prolactin level indirectly affects the gonads by acting on the hypothalamus to prevent the pulsatile production of the luteinizing hormone releasing factor, while it directly inhibits formation of sperm and ova at the gonadal level and suppresses gonadal steroidogenesis.

In women, the combination of these effects may cause infertility, menstrual irregularity, galactorrhea, reduction of vaginal secretions, or painful intercourse. Men may suffer infertility, impotency, or, in rare instances, galactorrhea or gynecomastia. In children, prolactinoma may inhibit normal growth and sexual development. In addition, individuals with large, invasive prolactinomas, which destroy the pituitary tissue and bulge outside the pituitary fossa, may develop impaired lateral vision, brain compression, headaches, rupture in the sphenoid sinus causing rhinorrhea, or other endocrine-related disorders. If a patient exhibits any of these symptoms or has a family history of pituitary tumors, hypercalcemia, and pancreatic tumors, the attending physician should suspect the presence of prolactinoma and refer the patient to an appropriate treatment center for diagnostic testing, particularly since some cases of prolactinoma may be familial or may be a component of Type 1 multiple endocrine neoplasia, according to Dr Samaan.

A primary diagnostic tool to detect prolactinoma, used at UT MDAH and at other hospitals treating patients with the disease, is a radioimmunoassay that measures the level of serum prolactin, a test that Dr Samaan established soon after prolactin was isolated in humans. To obtain an accurate measurement of a patient's serum prolactin level, physicians at UT MDAH perform the test at least three times while the patient's serum prolactin is at basal level and then four additional times after injecting the patient with thyrotropic releasing hormone (TRH). Patients with

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Prolactinoma. . .

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prolactinoma have basal serum prolactin levels that are higher than normal and blunted serum prolactin responses after TRH stimulation. Because high prolactin levels may also be caused by oral contraceptives, analgesics, hypotensive agents, or hypothyroidism, standard procedure requires analysis of serum prolactin levels two months after patients cease taking drugs that may affect the level. Plasma estradiol in the women and testosterone in men are also measured, since they are usually suppressed in patients with prolactinoma. If the disease is suspected, sophisticated x-ray methods are used to confirm the diagnosis.

The two most common radiographic methods employed at UT MDAH to diagnose prolactinoma are computed axial tomography (CAT) and polytomography. These methods clearly delineate the pituitary gland and can reveal a tumor as well as suprasellar extension. The results of these procedures determine the appropriate treatment—either drug therapy or surgery—for each patient.

If the prolactinoma is not visible on the polytomogram or CAT scan but the patient exhibits many of the symptoms of the disease, he or she may have hyperplasia of the prolactin-producing cells or a prolactin-producing microadenoma, a small pituitary tumor 1 cm or less in diameter. Under these circumstances, the patient receives bromocriptine, a drug that inhibits prolactin secretion from the pituitary gland. Physicians at UT MDAH do not perform exploratory surgery to confirm the existence of a microadenoma; the risk of damaging the pituitary gland, though slight, is not worth the potential benefits, according to Dr Samaan.

Bromocriptine relieves the symptoms in 90% of the patients who receive it—those with hyperplasia or microadenomas not demonstrable by x-ray, those not wishing to undergo surgery, and those not responding to surgery. Menstruation begins or returns in women, and fertility is restored in both men and women. Evidence indicates that bromocriptine may even shrink a pituitary tumor, although it is not a cure for prolactinoma; if the patient stops taking the drug, the prolactin level rises again. Although the drug does not cause any severe reactions in patients or congenital defects in children of women who take the drug, it may cause nausea, vomiting, diarrhea, or syncope, especially when first taken. Therefore, bromocriptine is administered in small, gradually increasing doses so that the patient may build up a tolerance to it.

If the tumor is visible on the polytomogram or CAT scan and the patient is willing to undergo surgery, transphenoidal microdissection is performed, using the microscopic undervision dissection technique. This method enables the surgeon to reach the pituitary gland through an incision under the lip, into the gums, between the septum and the surrounding mucous membrane, through the sphenoid sinus, and into the floor of the pituitary fossa. Ordinarily, the tumor grows superficially from the anteroinferior aspect of the pituitary gland and when removed leaves the normal pituitary tissue intact.

After surgery, the patient usually recovers quickly and returns home on the fourth day. Four to 12 weeks later, most symptoms disappear and prolactin levels return to normal in 85% of the cases. Of the responding patients who desire to have children, 85% to 90% do so without complication. In adolescent female patients whose sexual development was inhibited, menarche begins soon after surgery, and in both male and female adolescents, secondary sexual characteristics appear. Those patients who do not respond to surgery, usually those with large invasive tumors, receive bromocriptine to inhibit high prolactin levels. Men and women beyond the reproductive age may receive adjuvant radiotherapy.

Although physicians have been very successful in treating patients with prolactinoma, its cause remains a mystery, according to Dr Samaan. Studies at UT MDAH have shown that symptoms often appear in women who have high estrogen levels, naturally occurring during pregnancy or produced exogenously by birth control pills. In addition, the incidence of the disease is four times greater in women than in men. Although Dr Samaan does not directly implicate excess estrogen as a cause of prolactinoma, animal experiments have shown that estrogen can produce hyperplasia or a microadenoma from prolactin-producing cells. In women, estrogen may unmask a preexisting asymptomatic prolactinoma or may stimulate development of potential tumor cells.

While studies at UT MDAH may eventually lead to an understanding of the cause and prevention of the disease, Dr Samaan now focuses on treating individuals with prolactinoma. Based on postmortem studies, 25% of the population suffers from prolactinoma without ever knowing they have the disease, he explained, adding that many of these individuals marry and needlessly remain childless.

(Physicians desiring additional information should write or call Naguib A. Samaan, MD, PhD, Department of Internal Medicine, MDAH Box 65, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030, (713) 792-2840.—ED)

A REPORT TO PHYSICIANS
OncoLog

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Laboratory Research Continues to Advance Methods of Cancer Diagnosis and Therapy

by James M. Bowen, PhD, Vice President for Academic Affairs

In a recent presentation, Dr Bowen responded to questions about the future of cancer research. His examination of recent technology developed through basic science and its successful application to cancer diagnosis and treatment confirmed his optimism about that future. Here he summarizes the presentation.

A friend who is a medical reporter recently asked me, "Don't you think it's true that cancer research has topped out? We've admittedly made a number of important accomplishments over the past 20 or 30 years, and now we're trying to apply those accomplishments as best we can, but we really don't have much to look forward to over the next 10 or 20 years."

My competitive spirit was aroused, and I made a fairly detailed analysis of new technologies based on basic cancer research. I hope to convince you that cancer research is in a time of explosive advancement, producing new understandings and new technologic capabilities that will change the field forever. I could use many examples for this, but the ones I have chosen represent: (1) major advances in our understanding of biologic systems, (2) major advances in our ability to exploit these understandings with new or recently evolving technology, and (3) particular applications of basic research and their rapid translation into the patient care area.

I want to begin with a brief description of the basis for a cancer cell's behavior. A fact that we take for granted, but which has particular significance in the context of understanding cancer, is that all the complex tissues and functioning systems that comprise the living body originate from a single cell. A sperm cell and an egg unite to produce an embryonic cell, and that original cell begins to divide, entering a period of tremendous proliferation. A series of highly ordered, highly regulated changes then begins to occur in subsets of the cell population so that highly differentiated tissues arise.

The important common denominator of differentiation is that all of the information needed to become any specialized cell in the body resides in every cell of the body. For that reason, an extremely complex and highly inclusive regulatory system must exist so that a kidney cell remains a kidney cell and so that if that kidney cell dies, it is replaced with a kidney cell and not a brain cell or a muscle cell. For every tissue there must be at least one gene for a substance that instructs those cells of that specific tissue to remain in place, to produce their products or carry out their specified function. When those cells divide to replace cells lost to aging or damage, the regulatory gene must control replacement with the appropriate kind of cell. An aberration in that regulatory activity can produce aberration in differentiation.

One of the characteristics of the evolving differentiation sequence is that cells become less and less prone to grow and proliferate, less and less competitive with other cells in their environment, and more and more focused on their functional activity. Kidney cells grow only to keep up with the body's growth or to replace lost kidney cells. Loss of either the functional aspect of the product of that regulatory gene or of the ability of that cell to respond to the signals from that regulatory gene tends to reverse the cell's progress on the path of differentiation, changing it to a more proliferative, more competitive, less functionally focused cell. When that functional backtracking reaches a certain level, the cell is no longer normal but rather possesses the behavioral characteristics we associate with disease, particularly with cancer.

Now let me briefly review the background of cancer therapy. The original modality of cancer therapy was surgery. When it was discovered that tissues were susceptible to destruction by x-rays, gamma rays, and other sources of radiation and that rapidly proliferating tissues were more sensitive to radiation than normal tissues, radiotherapy became an important second modality. It extended the ability to kill tumor cells, allowed therapeutic measures to be taken in areas inaccessible to the surgeon, and helped us to control distant spread and metastasis.

In the late 1940s and early 1950s, chemotherapy was added to the treatment choices. The basis for chemotherapy, like that of radiotherapy, is that the most rapidly proliferating cells are the most sensitive to cytotoxic substances, while normal, more differentiated, nonproliferative cells are more likely to survive. Also much like radiotherapy, chemotherapy extended the physician's ability to treat cancer that had spread or was too small or inaccessible for surgery. Many new drugs have proved effective, and many treatment advances have come from careful studies of the optimal combination of chemotherapy with surgery and radiotherapy.

Within the past 20 years, attention has also turned to manipulation of the body's immunologic defenses against tumor cells. These early studies have suggested a fourth therapeutic modality, immunotherapy, which encompasses our attempts to understand, exploit, and augment the body's own defenses. From there, we have enlarged our conceptual views to include a broad area that we term biologic response modification, defined as any therapeutic approach that augments any of the body's defenses against external encroachment or internal aberration.

Let me emphasize that biologic response modification is complementary to surgery, radiotherapy, and chemotherapy. The initial tumor burden must be reduced by surgery, by radiotherapy, or by chemotherapy before biologic response modifiers can be used to control those last few tumor cells and to prevent recurrence of either that same tumor or another tumor.

Interferons are the most remarkable biologic response modifiers we have studied. They represent the cell's own system for defending itself against the encroachment of a virus or other substance or agent that mimics foreign genetic material. Interferon does not act on the cell in which it is made: Interferon is in fact a "messenger molecule" that leaves the cell in which it is induced and is taken up by a recipient cell. The recipient cell responds to

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Radiotherapy Plays Vital Role in Treatment

Adjunctive radiotherapy for patients with malignant epithelial tumors of the parotid gland greatly reduces the risk of tumor recurrence after surgery, according to a recent retrospective study conducted at UT MDAH. The study also verified that the facial nerve, when not grossly involved, can be safely preserved with irradiation, even when its proximity to such a tumor might indicate otherwise. The study was conducted by Oscar M. Guillamondegui, MD, Department of Head and Neck Surgery, and Gilbert H. Fletcher, MD, Mary Jane Oswald, BS, David McNaney, MD, and Marsha D. McNeese, MD, all of the Department of Radiotherapy.

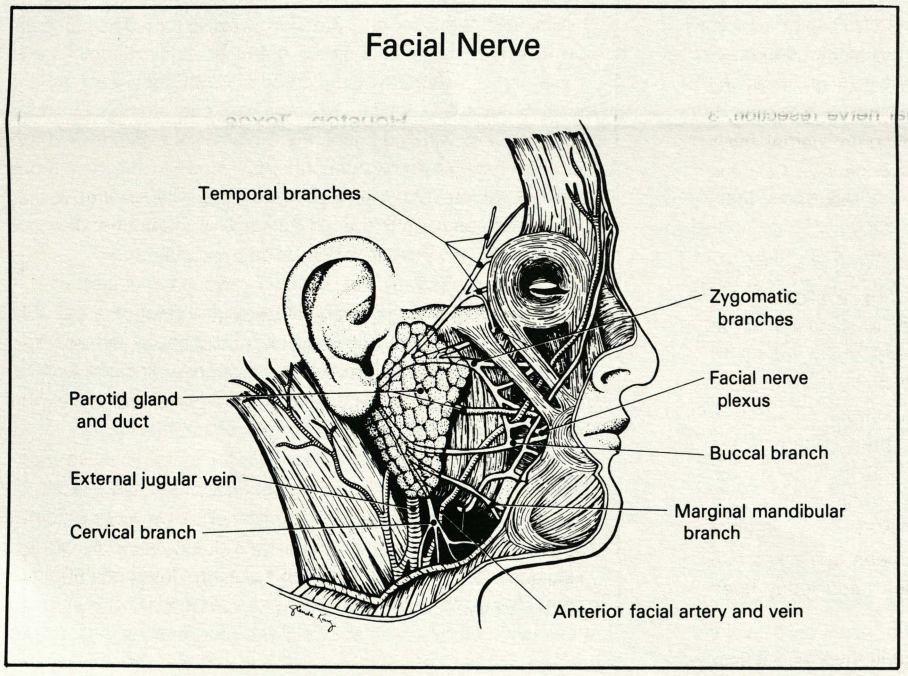
Adjunctive radiotherapy has been used systematically at UT MDAH since the middle 1960s for selected patients with malignant parotid tumors. Until recently, however, adequate evaluation of its controlling effect has been difficult, according to Dr Guillamondegui, because parotid tumors sometimes recur many years after initial treatment. Consequently, the precise role of irradiation for these patients has remained unclear, and no recommended treatment program has been widely accepted. Therefore, this study was undertaken to determine the overall benefit of adjunctive radiotherapy for patients with malignant epithelial tumors of the parotid gland and to clarify the clinical situations in which its use is effective.

Records of 77 patients (35 males and 42 females between 10 and 80 years of age) admitted to UT MDAH between 1954 and 1977 with malignant epithelial parotid tumors were reviewed. All patients had been treated with surgery and adjunctive irradiation at the site of the parotid gland (5000-6000 rad, usually using the electron beam in combination with ^{60}Co or 18-25 MeV photons). Fifty-six patients had received additional irradiation (5000-6000 rad) to the cervical lymph nodes. The total number of local and regional recurrences were calculated; tumor recurrences were then related to histologic type and grade of disease, extent of residual disease, and extent of facial nerve resection.

The results of the study indicated that adjunctive radiotherapy greatly reduces the recurrence rate of malignant parotid tumors: The overall control rate was 87%. Of the 77 patients, only six had recurrences in the primary site and four had recurrences in the cervical lymph nodes, yielding a local recurrence rate of 7.8% and a regional recurrence rate of 5.2%. (One patient had both local and regional recurrence and was included in both groups.) This local recurrence rate is at least four times less than local recurrence rates reported for patients treated with surgery alone.

No definite correlation between histologic type of tumor and tumor recurrence was found, although slightly more recurrences appeared in patients with adenocarcinomas. The different cell types and the number of local and regional recurrences of each were as follows: malignant mixed tumors, 1 local recurrence in 13 patients; adenocarcinomas, 3 local and 2 regional recurrences in 17 patients; low-grade mucoepidermoid carcinomas, 0 recurrences in 9 patients; high-grade mucoepidermoid carcinomas, 1 local and 2 regional recurrences in 15 patients; acinic cell carcinomas, 0 recurrences in 5 patients; adenocystic carcinomas, 1 local recurrence in 15 patients; unclassified tumors, 0 recurrences in 1 patient; and other types, 0 recurrences in 2 patients. These findings indicate that the various histologic types of malignant epithelial parotid tumors are radiosensitive.

A correlation between tumor radiosensitivity and histologic grade of tumor (high grade, low grade, or unknown) was determined based on the number of mitoses per high power field.



For many patients with malignant tumors of the parotid gland, radiotherapy as an adjunct to surgery both reduces the recurrence rate and obviates facial paralysis through the preservation of the facial nerve.

# of Patients with Malignant Parotid Tumors

Of the 77 patients included in the study, 63 had tumors of a histologically high grade, and all 10 local and regional recurrences developed in patients from this group. The low-grade mucoepidermoid and acinic cell carcinomas, which are noninvasive and slow-growing, did not recur.

Adjunctive radiotherapy was also found to be effective in controlling limited residual disease, often present in or near the surgical margin or in nerve sheaths after excision of the parotid tumor mass. As support for this finding, the study showed no correlation between extent of residual disease and tumor recurrence, as follows: gross residual disease, 1 local and 1 regional recurrence in 14 patients; microscopic residual disease, 2 local and 1 regional recurrence in 26 patients; no residual disease, 3 local and 2 regional recurrences in 33 patients; and unknown amount of residual disease, 0 recurrences in 4 patients.

A most important finding, which again illustrates irradiation's control of residual disease, should settle the controversy surrounding facial nerve preservation in these patients, a practice that often precludes total ablation of parotid tumor cells: Patients whose facial nerves had been preserved had no higher incidence of tumor recurrence. Thus, in most patients, possible or known residual disease on or near the nerve sheath had been controlled by irradiation.

Preservation of this vital nerve, which runs through the parotid gland, has been a primary concern of physicians who treat patients with malignant parotid tumors, according to Dr Guillamondegui. With complete resection of the facial nerve, which supplies motor fibers to all facial muscles, the patient suffers facial paralysis. Therefore, in many instances, the preferred treatment has been to preserve this nerve, if not grossly involved, and to control potential residual disease in the nerve area with irradiation.

Confirming the benefit of this approach, the study related the extent of facial nerve resection to the number of local and regional recurrences, as follows: total facial nerve resection, 3 local and 2 regional recurrences in 21 patients; partial facial nerve resection, 1 local and 1 regional recurrence in 21 patients; no facial nerve resection, 2 local and 1 regional recurrence in 35 patients.

Also of concern was whether the complications of adjunctive radiotherapy were too severe to warrant its application. Of the total patient population, only five, all of whom received adjunctive radiotherapy for extensive disease, suffered some long-term complications: osteonecrosis (two patients), soft-tissue necrosis (one patient), necrosis of the brain and temporomandibular joint (one patient), and myelitis (one patient). Three patients have been successfully treated for these complications; the patient with necrosis of the brain and the temporomandibular joint continues to suffer severe side effects; myelitis in another caused his death. These complications might have been minimized had the more advanced radiotherapy techniques used today been available.

The study has confirmed that adjunctive radiotherapy is a vital part of the treatment plan for selected patients with malignant parotid tumors: those with histologically high-grade tumors, locally invasive or metastatic disease, or gross or microscopic residual disease. The study has also established that, in selected patients, adjunctive radiotherapy allows the surgeon to preserve the facial nerve without increasing the risk of recurrence.

(Physicians desiring additional information should write or call Oscar M. Guillamondegui, MD, Department of Head and Neck Surgery, MDAH Box 69, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030, (713) 792-6920.—ED)

The University of Texas
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DEPARTMENT OF PEDIATRICS

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Life, Faith, Hope, and Magic

The Chaplaincy in a Children's Cancer Center

April 21-22, 1983
Shamrock Hilton Hotel
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Cochairpersons: Jan van Eys, MD, PhD, Department of Pediatrics, and Edward J. Mahnke, DD, Department of Chaplaincy and Pastoral Education

Interviews with parents and children during and after the experience with cancer indicate that religion is a primary source of support. Therefore, this conference will focus on the role of clergy members as an integral part of the health care team.

For registration information, write or call the 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.

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Research. . .

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the message by synthesizing a secondary protein that confers resistance.

We have identified two key areas of antiviral interferon activity. The so-called antiviral proteins, or inhibitory proteins, are produced against early stages of virus replication. These stages are so early that they are common to most viruses, which allows for a broad spectrum of interferon-induced resistance. For example, if interferon production is induced in the cell by influenza virus, that cell is not only resistant to influenza virus but to virtually every other virus.

Perhaps more important from the standpoint of cancer therapy is the fact that interferons not only recognize foreign genes and induce resistance in recipient cells, they also recognize aberrant genetic behavior patterns in uninfected cells. Thus, they act against the proliferative uncontrolled growth phases in cells such as some cancer cells.

Interferons inhibit the growth of cells in tissue culture. They inhibit the same tumor cells in a susceptible animal that they inhibit in culture. They may also inhibit normal cells that are in highly proliferative states, such as cells of the blood-forming tissues, cells of the gastric and colonic mucosa, hair-producing cells, and so on. But interferons are more effective inhibitors of tumor cells than of normal cells because the proliferation rates of tumor cells are often much higher than those of even the most rapidly proliferating normal cells in the body.

Interferons are also immunomodulators. They inhibit both the proliferation and function of some kinds of immune cells and enhance the proliferation and function of others. (Figure 1 summarizes these activities of interferon.) The immunomodulatory property is a two-edged sword, however, since large quantities of interferons may produce immune compromise. Nevertheless, the interferons are extremely important biologic response modifiers, which have already shown therapeutic benefits for breast cancer, melanoma, multiple myeloma, and a variety of other tumors.

Figure 1

BIOLOGIC ACTIONS OF INTERFERON

ANTIVIRAL
- Trinucleotide synthetase
- Protein kinases

ANTIPROLIFERATIVE
- In vitro—inhibits cells in monolayer suspension
- In vivo—inhibits tumor cells and normal cells

IMMUNOMODULATION
- Inhibition

(primary and secondary antibody responses)
(lymphocyte blastogenesis)
- Enhancement

(macrophage function)
(sensitized cyotoxic lymphocytes)
(natural killer cells)

One problem exists with interferon, however—it is species specific. In the early 1960s, drug companies committed millions of dollars to the production of kilogram quantities of chick interferon. It turned out, however, that a kilogram of chick interferon is a useful therapeutic agent only if you happen to be treating a sick chicken.

If we are to treat human disease with interferon we must have human interferon. The first clinical trial of interferon exemplifies this problem's significance: In Scandinavia about 16 years ago, 18 young patients with osteosarcoma were treated with interferon. To treat those 18 patients, all the interferon made from every blood donation in the entire country of Finland for one full year was needed.

It is thus very clear that if interferon is ever to be fully exploited as a chemotherapeutic agent and for its other potentials, we must have a larger source. How are we going to get human interferon if we don't have human cells? Basic science has placed the answer to that question in our hands through recombinant DNA technology. This technology is a beautiful example of the impact of basic research on therapy for cancer and other diseases because it was first developed as a solution to simple academic laboratory problems with no visible relevance to the treatment of cancer or any other disease.

In the course of their research, two scientists at Stanford University discovered that restriction endonucleases were able to break DNA molecules from any organism at specific points. These pieces could then be recombined with DNA pieces from any other organism, in any order. Since that discovery in 1973, many more restriction endonucleases have been discovered, each cutting DNA molecules at specific sites. Those pieces, too, could be recombined in any order from any organism. By inserting the resulting manufactured genes into an appropriate organism, the products of any added foreign genes can be expressed. (Figure 2 summarizes some of the biologic products available through recombinant DNA technology.)

Escherichia coli is the organism most often used as the recipient of foreign genes. It is a simple microorganism that is easy and inexpensive to culture, and it has genes that are always read in the same sequence—these genes are expressed absolutely predictably. When they mutate, the genes can be identified. More important, the microorganism will express any gene, no matter what its source, if it is inserted into its genome.

Thus, once the first human interferon gene was identified, it became a simple matter to apply recombinant DNA technology to splice that human gene onto the end of the bacterial chromosome. That bacterium then synthesized large quantities of human interferon. The first clinical trial of human interferon produced by recombinant DNA technology is under way right now. In most respects this interferon appears to be as good as human interferon produced by human cells.

Another area that has revolutionized an entire field of endeavor is hybridoma technology. A quick tour of immunology will make its significance clear: Although there are many different functional

Figure 2

RECOMBINANT DNA TECHNOLOGY IN CANCER RESEARCH

SYNTHESIS OF BIOLOGICALLY ACTIVE AGENTS
- Interferons
- Hormones
- "Tailored" antibiotics and other drugs

SYNTHESIS AND STUDY OF GENE PRODUCTS ASSOCIATED WITH THE MALIGNANT PROCESS
- Differentiation factors
- Phosphokinases
- Tumor cell growth factors

populations of immune cells in our bodies and in the bodies of all complex living things, they fall into two basic populations—those that produce antibodies (B cells) and those that directly interact with the target substance or target cell (T cells).

B cells have a remarkable set of properties. They contain within their own genetic makeup a programmability that puts to shame the finest computer ever devised by man. They are able to recognize an antigen, and realizing their own interactive capability, they produce antibodies absolutely specific for the antigen. The B cell is thus programmed, as are all generations of its daughter cells, to produce that antibody and that antibody only. A subpopulation of those programmed cells does stop making the antibody, but it retains the ability to produce that antibody whenever the body is exposed to the same antigen again.

These B cells, which reside in the spleen of highly evolved organisms, die very rapidly, usually within a few hours, if they are removed from the spleen. Thus, they have extremely limited growth potential. Like other cells of the body, B cells can undergo malignant change. The most important B cell cancer is multiple myeloma, which is sometimes known as cancer of the bone marrow because the malignant change occurs when the B cells are undergoing initial development in the bone marrow.

Myeloma cells have an interesting set of properties that contrast with those of their normal counterparts. If myeloma cells are removed from the body, and if they are given the appropriate nutrients, they can grow indefinitely, having lost the senescence mechanism of the normal B cell. In addition, their growth is unrestrained. They produce antibody protein, but in an unprogrammed form, and they produce it in quantities a hundred times greater than does the normal spleen cell. They are also able to grow in an appropriate animal. For example, mouse myeloma cells can be transplanted to a mouse of the same genetic configuration, and a new myeloma tumor will form and will keep on growing, ultimately killing the mouse. In addition, the cells lose the programmability of the normal cell, one of the characteristics of cancer cells in general. While the normally differentiated cell is focused on function, not growth, the cancer cell is focused on unrestrained growth.

Dr Cesar Milstein, a scientist in Great Britain, asked himself a very academic question: "What would happen if I fused a normal spleen cell with a multiple myeloma cell?" What happened when he did turned the field of immunology upside down. From his fusing of a normal antibody-producing spleen cell and a multiple myeloma cell, a hybridoma resulted (Figure 3). From the myeloma cell, the hybridoma obtained an indefinite life span, the ability to grow unrestrained both in tissue culture and in a suitable animal, and continuous immunoglobulin production capability. From the normal spleen cell, it obtained specific programmability. What resulted was a cellular factory that could forever produce a specific antibody in large quantities. If a clone is produced from a single hybrid cell, the programmability of a single B cell is available in large quantities. The resulting monoclonal antibody has absolute specificity.

All of the uses of this hybridoma technology for cancer therapy depend on one of the manifestations of the difference between cancer cells and normal cells—the expression of new chemical signals on the surface, recognizable by the immune system. It is possible to make monoclonal antibodies against a variety of these signal substances—say, a marker specific for ovarian cancer. The monoclonal antibody will not react with anything in the body except an ovarian cancer cell. It becomes an absolutely specific reagent for the diagnosis of ovarian cancer cells.

Monoclonal antibodies complexed to plastic spheres can be used to select a specific antigen from a mixture of a thousand different antigens. We can complex antibodies to a variety of substances, dyes, radioactive atoms, and even large complex substances such as drugs, and they do not lose their specificity. For example, suppose a patient has an ovarian tumor. If a drug that is potent against ovarian cancer is complexed to a monoclonal antibody specific for ovarian cancer, the drug can be delivered through the blood stream to the ovarian tumor and

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Figure 3

HYBRIDOMA CHARACTERISTICS

MYELOMA CELLS	NORMAL SPLEEN CELLS
• Indefinite life span	• Short extracorporeal life span
• Unrestrained growth	• Limited growth
• Continuous immunoglobulin production	• Programmable for monospecific antibody
• Growth in vitro and in vivo	• Specificity retention for life
• "Unprogrammed" immunoglobulin	

FUSION

CLONAL SELECTION

HYBRIDOMA
- Indefinite life span
- Growth in vitro and in vivo
- Continuous immunoglobulin production
- Specific, monoclonal antibody

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Research. . .

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nowhere else. Suppose the tumor has already metastasized to the liver, but the few hundred cells are undetectable. The monoclonal antibody doesn't care. It will deliver the cytotoxic drug to those few hundred cells hidden in the liver.

Another use for monoclonal antibodies is in the programming of killer T cells. Although there are a variety of ways these lymphocytes are directed, the most significant is by adsorption to antibodies produced against a given substance; the unprogrammed killer cells then become specific killer cells for whatever cell is carrying the specific antigen. If a few hundred molecules of a specific antiovarian tumor antibody produced by monoclonal techniques are attached to a patient's lymphocytes and those lymphocytes are returned to the patient, the killer T cells are no longer unprogrammed. They are T cells programmed to attack and destroy the ovarian tumor.

In certain kinds of systemic cancers, particularly those of the blood system, fairly large amounts of monoclonal antibody alone may destroy the tumor. Dr Evan Hersh and his colleagues in our Department of Clinical Immunology have just completed a small, limited protocol using monoclonal antibodies produced against a marker specific for a particular kind of human leukemia. In some patients, the skin reactivity of this leukemia completely disappeared after two or three courses of therapy.

I will now bring this discussion full circle and ask you the question that I was asked. With these advances in mind, has cancer research really topped out? Is there nothing to look forward to in cancer research over the next few years? The news of cancer research's death is greatly exaggerated, seriously mistaken, and shortsighted. Not only does it live, but new technology to exploit new knowledge has never been as promising. I believe new technologies will continue to change our entire view of the management of cancer and diseases like cancer within this century. The three kinds of cancer that produce 50% of all cancer deaths have been most resistant to all therapies that are now available—cancers of the lung, breast, and colon. However, new technologies are now being applied to these areas, particularly colon and lung cancers. We will begin to see our first truly successful inroads into the management of even these most refractory cancers in the next five to ten years.

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