From Ability to Measure Cell Survival
Come New Radiotherapeutic Strategies

by Lester J. Peters, M.D.
Professor of Radiotherapy and Head, Division of Radiotherapy

(This article is a brief version of Dr. Peters’ chapter, “Basic Principles of Radiobiology in Head and Neck Oncology,” in Cancer in the Neck: Evaluation and Treatment, edited by David L. Larson, Alando J. Ballantyne, and Oscar M. Guillamondegui, and to be published this year by Macmillan.)

Cellular radiation biology was born when it became possible to measure the effect of radiation on the viability and reproductive capacity of single cells. Since a cell’s reproductive integrity determines its ability to form a clone, radiation biologists define cell death as loss of the cell’s clonogenic capacity.

Cell death is not always obvious immediately after radiation exposure. Studies have shown that most cells killed by radiation die while attempting mitosis, and this may occur after several apparently successful cell divisions. But because the essence of clonogenic survival is the ability to reproduce indefinitely, a cell is considered sterilized if none of its progeny retains the ability to reproduce. Generally, the higher the radiation dosage, the fewer divisions will the cell accomplish before it dies.

Interphase death, a less common type of cell death from radiation injury, occurs soon after radiation exposure and is believed to be caused by damage to the plasma membrane. In the head and neck region, the serous cells of the salivary glands, but not the mucous cells, undergo interphase death after even low radiation doses, which accounts for the acute changes in salivary flow and composition in patients undergoing radiotherapy.

Irradiation may also enhance apoptosis, a natural phenomenon in which defunct or injured cells collapse into electron-dense bodies and are ingested by adjacent parenchymal cells.

Loss of Tissue Function

Loss of an organ’s function after irradiation is the result of depletion of the total number of functional cells, not a decrement in function of individual cells. That is why, depending on their kinetic and organizational status, the functional response of tissues to radiation varies so widely. Tissues in which cells turn over rapidly—with fast cycles of stem-cell replication, maturation, and division—will show evidence of radiation injury soon after exposure, but the rate of onset will not be highly dose dependent. Most epithelia and the bone marrow are in this group. Depending on the extent of stem-cell depletion, these tissues may recover all their functions after radiation.

Late radiation injury occurs in tissues that have slow cell turnover—such as bone, neuroglial, and endocrine tissues—and in differentiated parenchymal cells that may recover reproductive function as a response to tissue loss. The extent of delayed injury depends on radiation dosage, and its severity tends to increase with time because of an avalanche phenomenon in which nondividing cells that harbor latent reproductive injury are drawn into the division cycle and undergo mitotic death.

Dose-Response Curves

Single doses. The deposition of radiant energy is random and discrete. Thus, cell killing by radiation approximates an exponential function, and radiation survival curves can be plotted on semilogarithmic coordinates, with the surviving fraction of clone-forming cells plotted on a logarithmic scale as a function of dose on a linear scale. On such a scale, exponential survival is represented by a straight line whose slope may be defined in terms of the mean lethal dose of radiation ($D_0$). This is the dose that would kill all cells in the population if the dose were targeted to the critical site of each cell. But because dose deposition is random, the mean lethal dose kills only an average of 63% of the cells in the population targeted.

For most mammalian cells exposed to X or gamma rays, the shape of the graph for the first few hundred rad is not exponential but curves downward on the semilogarithmic coordinates (Fig. 1). The curved portion of the survival curve, the “shoulder,” is the region of greatest interest to clinical radiobiologists because it marks the dose range of conventional dose fractionation.

Fractionated doses. In fractionated radiation, the shoulder on the survival curve reconstituted on page 2
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...tutes itself, provided that doses are separated in time by several hours. This means that after an adequate period of recovery, cells surviving the first dose of radiation respond to the next doses as if they had never been irradiated. This has important implications for hyperfractionation and accelerated fractionation, techniques that employ more than one radiotherapy treatment each day.

First described by Elkind and Sutton in 1959, the phenomenon of cell recovery from nonlethal radiation injury between doses is called “Elkind recovery.” A different type of intracellular repair mechanism, but probably involving the same enzymatic pathways, is called “potentially lethal damage repair.” This refers to the successful repair of DNA lesions by cells allowed to rest for several hours without a stimulus to proliferate before being assayed for survival.

Radiation characteristics. The biologic effect of a given absorbed dose of radiation may vary markedly according to type of radiation. We know, for example, that kilovoltage X rays are 10% to 15% more effective rad for rad than 60Co gamma rays. Protons and high-energy electrons spread by a scanning electron pencil beam, but not by a scattering foil, are also biologically more effective by about the same factor.

All of these beams have low linear energy transfer (LET), which means that the density of ionization produced by them is sparse. Irradiation with other particles—for example, fast neutrons or heavy nuclei—produces tracks of dense ionization, so that these beams are said to have high LET. High-LET beams are much more damaging to biologic material than low-LET beams, because cells have little or no ability to repair intracellular damage between doses of high-LET radiation. Another difference is that cell killing by high-LET beams is less influenced by oxygen content and cell age distribution in the tissue.

Effect of oxygen. Hypoxic cells are more resistant to radiation injury than well-oxygenated cells. Oxygen seems to fixate labile radiation injury that would otherwise be repaired within milliseconds of irradiation. Thus, although the same number of lesions is produced by irradiation whether oxygen is present or not, many more lesions are repaired if oxygen is absent.
Dose Fractionation: The Four R’s

We have known for years that the results of radiotherapy are better when the total dosage is divided into many small increments instead of being delivered as a single dose or in a few large increments. The rationale for this is based on the four R’s of radiobiology.

Repair of radiation injury. When doses of low-LET radiation are fractionated, the shoulder on the survival curve reconstitutes itself between doses. This results in sparing from radiation injury as a function of the size and shape of the survival curve shoulder as illustrated in Fig. 2. Panel A shows a survival curve whose shoulder has a steep initial slope and little curvature, whereas the survival curve in panel B has a shallow initial slope and more curvature. With fractionated doses of radiation, there is much greater sparing of cells, characterized by the survival curve of panel B. Research has shown that cells of tumors and acutely reacting normal tissues tend to be type A and that cells of late-reacting normal issues tend to be type B. Thus, dose fractionation has a therapeutic advantage because most tumor cells are less spared by fractionation than are late-reacting, normal tissues.

Reoxygenation. Studies of hypoxic, radioresistant cells in solid tumors have shown that the oxygen status of such cells improves between dose fractions. Many reasons have been proposed for the reoxygenation phenomenon. Whatever the mechanism, its clinical significance is that the delivery of fractionated doses of radiation reduces the formerly hypoxic tumor cells’ chance of surviving closely timed and repeated irradiation.

Redistribution. When radiation is given in multiple fractions, the opportunities for irradiating a given cell during a sensitive phase of division are high, especially in the case of cells whose turnover rate is fast. This is true for both acutely reacting normal and tumor tissue, but not for late-reacting normal tissue that has a low turnover rate. The difference enhances the possibility of controlling the tumor and avoiding late injury to normal tissue.

Regeneration. During courses of radiotherapy, all tissues, normal and neoplastic, may respond to depopulation by increasing their cell production. As with redistribution, this mechanism is most dramatic in acutely reacting normal tissue and tumors, in contrast to late-reacting normal tissue and tumors whose slow turnover time is usually not affected by radiation injury and does not, therefore, trigger a regenerative response. The regeneration mechanism is a major determinant in deciding the best duration of radiotherapy in any given situation. Protraction of treatment spares acute reactions but allows regeneration. Split-course regimens do the same. In patients in whom the regenerative potential of the tumor is predicted to be high, accelerated fractionation is indicated.

Altered Fractionation Schedules

In the United States, the term “conventional fractionation” generally means incremental doses of 180 to 200 cGy delivered five days per week for six to eight weeks. Our recent attempts to improve the therapeutic ratio have led us to administer multiple fractions per day with two new schedules: accelerated fractionation, in which the overall treatment time is reduced and two daily close-to-conventional dose fractions are given, and hyperfractionation, in which the overall time is conventional or slightly longer and the total dosage is increased by giving two small dose fractions a day.

The basic principle of accelerated fractionation is to prevent treatment failure caused by tumor cell regeneration during treatment. Hyperfractionation, in contrast, is based on the fact that smaller fractions increase the tolerance of late-reacting normal tissue, thus allowing the total dosage to be higher while increasing injury to tumor but not normal cells (Fig. 2).

Tumor Regression and Regrowth

In general, tumors with the most rapid cellular turnover rate will respond most rapidly to radiotherapy. Those with a low cell turnover rate will respond more slowly and are sometimes mistakenly thought to be radioresistant.

After a course of radiotherapy, the prognostic significance of residual tumor depends on tumor type. Most squamous cell carcinomas of the upper aerodigestive tract, for example, have a moderately rapid turnover rate, so that the presence of residual tumor at the end of radiotherapy may mean that the tumor has not been controlled. For this reason, such a patient will often undergo additional boosts of radiotherapy or limited

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surgical procedures to remove residual disease. Conversely, slowly proliferating tumors such as prostate cancers may show little response at the end of treatment and yet be cured.

Different rates of tumor regression after radiotherapy make it difficult to interpret the results of biopsies done during the postirradiation period. Because destruction by radiation is not usually expressed until cells attempt mitosis, histologic examinations cannot reveal whether intact tumor cells have retained their clonogenic ability. In the absence of clinical evidence of regrowth, biopsies of residual tumor should not, therefore, be done. Patients with residual disease should be closely monitored, but biopsy confirmation of recurrence should be sought only if tumor regrowth is clinically evident.

Combinations of Radiotherapy and Surgery

The essential rationale of combining radiation and surgery is that the two complement each other. Surgery is most effective in removing gross tumor masses that limit radiotherapy, whereas subclinical extensions of disease, the cause of surgical failure, are readily treated by irradiation. Integrated treatment in many cases offers a better prospect of cure than either modality alone. If postoperative irradiation is necessary because of the extent of primary disease in a patient who has no cancerous nodes in the neck, neck dissection is not needed because any subclinical disease will be sterilized by postoperative radiotherapy. Conversely, for a patient whose primary tumor will be treated by definitive radiotherapy, but in whom neck dissection is indicated because of nodal disease, beam energies and port arrangements should be selected with the goal of avoiding an increase in the risk of surgical complications.

Failure of Tumor Control

Reviewing the causes of radiation therapy failure helps us to identify the ones that can be avoided by the best possible application of current ideas and techniques, those not amenable to any modification of technique, and those that are potentially remediable by new treatment strategies. Cancers of the head and neck region lend themselves to evaluation of treatment failure because they are generally easier to stage and to monitor than tumors at other sites.

For the first half of the century, radiosensitivity was considered to be a simple function of histologic character, and histologically different tumor types were classified as being radiosensitive, moderately radiosensitive, or radioresistant. Furthermore, within the moderately radiosensitive group, differences in sensitivity were attributed to anatomic location. Squamous carcinoma of the mobile tongue, for example, was considered more sensitive than squamous carcinoma metastatic to the cervical lymph nodes. This conclusion can be traced to the fact that higher doses of radiation could be delivered to the tongue by interstitial techniques. Although it is undoubtedly true that tumors of certain histologic types are more radiocurable than others, this does not necessarily imply differences in inherent cellular radiosensitivity as opposed to epigenetic and environmental factors, such as the proportion of tumor stem cells, tumor cell kinetics, and oxygen status.

Recently, Deacon et al. (Radiother Oncol 2:317-323, 1984) collated the published data on the in vitro survival of human tumor cell lines of diverse histologic types. The authors found a broad correlation between surviving fraction at 200 cGy and category of tumor ranked at five levels of perceived clinical radiosensitivity (Fig. 3). It is clear, however, that the cellular radiation response within each tumor category varies markedly and that the ranges of sensitivity for the most sensitive and most resistant clinical categories overlap. These data also demonstrate the range of radiosensitivity of human tumor cell lines to small doses of radiation that would be greatly magnified in a fractionated course of treatment. Current research is aimed at establishing assays whereby the cellular radiosensitivity of individual patients' tumors can be measured before therapy is begun.

![Fig. 3. Initial slope of cell survival curve indicated by surviving fraction at 200 cGy, in relation to clinical response categories of A, neuroblastoma, lymphoma, myeloma; B, medulloblastoma, small cell lung carcinoma; C, breast, bladder, cervical carcinoma; D, pancreatic, colorectal, squamous lung carcinoma; E, melanoma, osteosarcoma, glioblastoma, renal carcinoma.](image)

Tumor volume is one of the fundamental determinants of radiocurability. This principle is illustrated in Table 1 with regard to control of cervical node metastases from squamous carcinoma of the laryngopharynx. These data show not only a decreasing probability of control with increasing size of lymph node within each dosage range, but also a dose dependence for control within each size range.

Failures of tumor control have been attributed to tumor cell hypoxia, to tumor cell regeneration and the failure of normal cells to redistribute, and to other causes. But the surest cause of radiotherapy failure is geographic miss or underdosing because of poor technique, and these must always be excluded first in any analysis of treatment failure.
Table 1. Control Rates* as a Function of Size of Node and Radiation Dose in Squamous Cell Carcinomas of the Laryngopharynx

<table>
<thead>
<tr>
<th>Size</th>
<th>&lt; 3 cm</th>
<th>3-5 cm</th>
<th>&gt; 5 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 65 Gy</td>
<td>15/26  (58%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 65 Gy</td>
<td>86/95 (91%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≤ 70 Gy</td>
<td>-</td>
<td>3/9    (33%)</td>
<td>1/9 (11%)</td>
</tr>
<tr>
<td>&gt; 70 Gy</td>
<td>-</td>
<td>11/13 (85%)</td>
<td>11/15 (73%)</td>
</tr>
</tbody>
</table>


*Determinate group.

The Therapeutic Ratio

The tolerance of normal tissues within a radiation treatment field determines the safe maximum dosage. Because the probability of normal tissue injury is dose related, tissue tolerance must be specified in terms of the probability of acceptable injury in a given clinical situation. Obviously, this will vary according to severity of complications and the gravity of the disease being treated.

For some normal tissues—the cervical spinal cord, for example—radiation injury is so devastating that it is totally unacceptable, and tolerance levels are set well below the dose that would produce this complication. This makes it impossible to use radiotherapy for most tumors close to the spinal cord, except for highly sophisticated particle beams that can be tightly and narrowly focused.

For less serious normal tissue injuries, tolerance will depend on the clinical circumstance and the philosophy of the radiation oncologist. Most physicians who treat patients for cancers of the head and neck regard a complication rate of about 5% to 10%, excluding complications involving the central nervous system, as acceptable when they determine total dosage limits.

Using radiation treatments that are too conservative will increase the number of patients in whom tumor control fails, whereas excessive dose escalation will raise the proportion of severe complications. The ultimate goal of all radiotherapeutic research is to increase the therapeutic ratio either by rendering tumors more susceptible to cure by ionizing radiation or by making normal tissues more resistant to injury.

Radiotherapy Tailored to Patient’s Disease

One of the most exciting new developments in radiotherapy is the prospect of being able to tailor treatment to the cellular radiosensitivity of a patient’s tumor. To illustrate this, Dr. Lester J. Peters displayed a tray of cultured tumor cells collected for a test developed in the Division of Radiotherapy.

A biopsy sample is taken from the patient’s tumor, he explained, and the tissue is broken up into single cells, which are then placed in each well of the specially coated culture dish. Rows of cells are irradiated with increasing doses from zero to 500 rad, and the numbers of cells that have survived and grown in each well after two weeks of incubation are then counted (see photo and graph).

Photo of cell tray (A) and graph (B) show tumor cell survival test that enables radiologists to design treatment for an individual patient’s tumor.

“With this system we can construct a survival curve that tells us what the effect of radiation is on that patient’s tumor—to see whether it is a sensitive or relatively insensitive one. We can test the cells with different types of radiation, with neutrons or X rays, and with a combination of drugs and radiation.

“So we’re getting to the point where we expect to be able to predict the outcome of standard treatment and make appropriate modifications if they appear necessary. One such modification might be the use of hyperfractionated treatment, that is, giving two small dose fractions each day instead of the standard daily treatment.”

Since Peters came to MDAH in 1981 to head the radiotherapy division, hyperfractionation protocols have been applied to squamous cell carcinoma of the head and neck, breast, and ovaries, and other such protocols are on the way.

Still, most patients come in expecting to be treated once a day, for six or seven weeks.

“...
Diagnosing the Rare Lesion: Ovarian and Omental Ependymomas

Immunocytochemical analysis was recently used by three pathologists at MDAH to diagnose lesions, typically intracranial, that appeared in the ovary and omentum of two patients. According to the pathologists, fewer than 50 ependymomas have been reported that appeared outside the central nervous system. The ependymomas in both MDAH patients were difficult to diagnose because of the rarity of such tumors in the abdominal cavity.

Roupen H. Dekmezian, M.D., Nour Sneige, M.D., and Nelson G. Ordonez, M.D., Department of Pathology, demonstrated glial fibrillary acidic protein (GFAP) with immunohistochemical procedures, confirming the diagnosis of ependymoma in the two patients referred to this hospital. Ependymomas usually show a focal and distinct staining pattern for GFAP (Fig. 1).

Histologically benign and slow growing, ependymomas are neoplasms made up of differentiated ependymal cells, which are usually found in the lining of brain ventricles and the spinal cord’s central canal. Although ependymomas have been reported to occur in the sacral subcutaneous tissues, presacral peritoneum, ovaries, mesovarium, and broad ligament, the pathologists believe no report of an ependymoma in the omental peritoneum exists in the literature.

The two women in whom the ependymomas were found are both multiparous women who were in their late thirties when they first presented with pelvic masses. Both women are alive, one with stable disease and the other with no evidence of disease.

In the patient in whom the omental lesion was found, two tumor masses involving the omentum had been resected 13 years earlier. The two tumors, one 25 cm and the other 10 cm in greatest dimension, were removed. Her ovaries and fallopian tubes were normal, but the physician discovered an anterior vaginal septum, two cervices, and a uterus didelphys. A diagnosis of malignant mesothelioma was made, and the patient underwent a year of chemotherapy. When another pelvic mass was discovered, she was referred to MDAH because of the clinical impression of recurrent mesothelioma, and here the pathological material of the previously resected tumor was continued on page 7

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that a course of radiotherapy is a once-only treatment for any one part of the body, and that the temporary inconvenience is well worthwhile if it means an increased chance of cure," Peters said.

His department has emphasized hyperfractionated treatment of cancers involving the larynx and hypopharynx. "For patients who have advanced disease in these areas," he said, "the only surgical option is total laryngectomy, and that has many disadvantages beyond the patient’s loss of voice and having only a hole to breathe through. Besides the obvious psychological and communication problems, there are problems with showering, swimming, lifting heavy weights, and constipation.

"We hope to reduce the need for laryngectomies, and our data from the first 54 patients treated with hyperfractionated radiotherapy look very good," Peters said.

The fresh printout on his desk showed that, so far, 42 of 54 patients treated since 1983 were completely free of disease at the time of last follow-up. The status of two patients is unknown. Of the 10 patients known to have relapsed, only four have experienced recurrences at the treated site, the others having developed metastases or other new cancers.

Peters stressed that this analysis is premature, “but the results encourage us to continue this research initiative.”

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reviewed and diagnosed as an omental neuroectodermal tumor with ependymal differentiation. At laparotomy multiple tumor nodules measuring up to 10 cm in diameter were removed from the mesentery of the small bowel and from the pelvic peritoneum, ovaries, uterus, and liver. Surgeons performed a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and resection of multiple peritoneal tumor nodules. Cytologic and histologic studies confirmed the diagnosis, and chemotherapy followed.

The second woman, who had had a right ovarian dermoid cyst resected eight years earlier, was referred to MDAH after laparotomy revealed and surgeons removed a large, smooth-surfaced cystic ovarian tumor with multiple tumor nodules on the serosal surface of the uterus and in the omentum. The patient underwent a total abdominal hysterectomy, left salpingo-oophorectomy, and resection of multiple tumor implants. After a review of the pathologic material here, the lesion was diagnosed as ependymoma of the ovary. In a second-look laparotomy a year later following chemotherapy, microscopic foci of residual ependymoma were found in peritoneal washings and tissue biopsy specimens.

Sneige said the cytologic findings characteristic of ependymoma in the peritoneal washings included numerous isolated spindle and stellate cells having fibrillary cytoplasm and long, tapering cytoplasmic processes, and groups of the same type of cells forming true rosettes (Fig. 2).

Although the characteristic appearance of the individual tumor cells and the positive staining for GFAP in isolated cells and cell groups made the diagnosis possible, Sneige said there were some differences in the cytologic appearance of the two patients' tissues.

"Cell grouping varied considerably between the two cases," Sneige said, "though the cytomorphologic appearance of the single cells was identical. In the patient with the ovarian ependymoma, there were papillae, tubules, and cell clusters, which were indistinguishable from those seen in patients with low-grade serous or endometrioid carcinoma, in addition to the true rosette formation.

"Though we could find no report in the literature linking ovarian ependymomas with psammoma bodies, a recent pathology report of ependymomas in the broad ligament noted psammoma bodies. When we found psammoma bodies in the tissue sections and peritoneal washings from the patient with ovarian ependymomas, we concluded that their presence in a papillary ovarian tumor is not pathognomonic of a Mullerian type of tumor. We knew the true nature of the tumor from the immunoperoxidase analysis," Sneige said.

![Fig. 2. In this peritoneal washing specimen, tumor cells are seen in clusters forming true rosettes.](image)

In explaining the histogenesis of ependymomas outside the central nervous system, some scientists have advanced the theory that the ependymomas originated in heterotopic ependymal rests or in the coccygeal medullary vestige of the embryonic neural tube. This theory is plausible in explaining ependymomas that arise in the sacrococcygeal area, because subcutaneous islands of ependymoma separated from the spinal cord have been found in the posteroctic region of many infants. The theory does not go very far, however, in explaining the origin of ependymomas in other locations. Islands of ependymoma are not known to exist in the female genital tract or the omentum. According to some scientists, the neural tissue of a teratoma after involution of other germ-layer components or a "unidirectional" teratoma composed only of neural tissue may be the origin of ependymomas in these locations.

Incomplete closure of the neural arch might enhance the possibility of ependymal heterotopia, and extraspinal ependymomas have been described in several patients with spina bifida occulta and cystica. But whether the uterine didelphys, duplication of the cervix, and partial anterior vaginal septum in one of these patients are associated with the ependymoma is uncertain.

Sneige said that these two unusual cases remind cytopathologists that rare ependymal tumors may occur in unusual sites and that immunocytochemical techniques are available to confirm the diagnosis.

(Physicians who desire additional information may write Nour Sneige, M.D., Department of Pathology, Box 85, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030.)
Large Bowel Cancer: Two New Books

Anthony J. Mastromarino, Ph.D., assistant vice president for research, is an editor of two new books on cancer of the large bowel.

Carcinoma of the Large Bowel and Its Precursors is volume 186 of Progress in Clinical and Biological Research (Alan R. Liss, New York, 1985, $48) and the proceedings of a 1984 conference held in Detroit. Coeditor is John R. F. Ingall, M.D., of the Department of Surgery, Wayne State University.

The conference was organized with the specific goal of gathering "the most useful information, of practical worth, in the current and future attack on colorectal cancer," the editors write in their foreword. Earlier detection and identification of premalignant lesions are the volume's particular emphasis.

"A singular feature . . . is the interrelationship of the authors to one another which conveys a sense of action in concert and an anticipation of better care to come," the editors write. "The sensitive issues of pathologically dictated radical surgery are examined and, without question, there is anticipation that the need for the latter . . . may diminish; perhaps the colostomy will become obsolete."

Among contributors are Gerald D. Dodd, M.D., professor and head of the UT MDAH Division of Diagnostic Imaging, who wrote "The Air Contrast Barium Enema—Indications and Validity," a richly illustrated chapter in which he analyzes techniques of single-contrast and double-contrast enema examinations, stressing the greater usefulness of the latter and explaining that colonoscopy and the double-contrast barium enema are complementary, not competitive, diagnostic procedures.

The book covers a wide spectrum of clinical diagnostic techniques and includes cautious interpretations of the applicability of animal research to clinical practice.

The other book, Large Bowel Cancer: Clinical and Basic Science Research, volume 3 of Cancer Research Monographs (Praeger, 1985, $37.95), was coedited by Michael G. Brattain, Ph.D., of Baylor College of Medicine.

In contrast to the clinical emphasis of the first book, this one summarizes the status of research of large bowel disease, stretching from the past decade's advances in fundamental genetic and biologic knowledge to improvements in the management of colorectal cancer. The book is drawn from a 1982 workshop sponsored by the National Large Bowel Cancer Project, whose headquarters were at UT MDAH, and it is dedicated to Murray M. Copeland, M.D., the project's first director and a former vice president of this institute's University Cancer Foundation.

MDAH staff members who contributed to the book include Birger Jansson, Ph.D., and Richard G. Martin, M.D. In addition to coediting the volume, Mastromarino is coauthor with Sandra Wolman, New York University Medical Center, of the chapter on markers of colonic cell differentiation.

Anthony J. Mastromarino