The Thomas E. Jones Memorial Lecture*

Changing attitudes toward the treatment of cancer

A personal reminiscence

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As a result of the devotion and generosity of the Jones family, a number of distinguished surgeons have been honored by being invited to give the Jones lecture. None has felt more honored than myself, because no other one had been introduced to surgery by the hands of the master himself. It was my privilege to learn both the technique and the philosophies of surgery from Dr. Tom Jones.

This year the Jones Lecture has a particular poignancy, for it is devoted not only to the memory of Dr. Tom Jones but also to that of Dr. John Jones, a surgeon who in his own field of cardiac and thoracic surgery was as superb as was his older brother in the field of surgical oncology. With the exception of Dr. Charles and Dr. Will Mayo, I know of no other brothers who have made such unique places for themselves in surgery. We who remain at the Cleveland Clinic are proud of these two men whose careers the Clinic played a part in shaping.

In 1934 and 1935, when I was a Resident in General Surgery at the Cleveland Clinic, under

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Dr. Thomas Jones, many surgeons were thinking in terms of ever-expanding operations for cancer. Pneumonectomy was in its infancy, as was resection of the esophagus for cancer. Some surgeons were performing total gastrectomies routinely for cancer of the stomach. The "Commando" operation was being developed for cancers of the mouth. Radical neck dissection was being advised by some in the treatment of thyroid cancer. Radical pancreaticoduodenectomy was about to be introduced by Dr. Whipple. Cystectomy with implantation of the ureters, radical prostatectomy, pelvic exenteration for cancers of the cervix, and many other radical and supraradical surgical innovations were taking place, even to the extent of hemicorpectomy—removal of the lower half of the body—for sarcomas involving the pelvis. This was the exciting era of exorcism in which I entered the practice of surgery. It was an era of excessive hope and of considerable irresponsibility.

I threw myself vigorously into the competition for fame and fortune. Having had my internship under Dr. Evarts Graham, I felt bold enough to perform the first total pneumonectomy to be done at the Cleveland Clinic. The patient died. I performed the first total gastrectomy at the Clinic in a patient with linitis plastica, and I was deeply hurt when 2 months later the patient died of abdominal carcinomatosis before my report of the successful operation could reach print. I performed four or five esophagectomies for cancer, one with the stomach transplanted into the chest and anastomosed to the cervical esophagus; but that was in the days before antibiotics and knowledge of thoracic surgery. Sooner or later all of my esophageal patients died of complications of the operations. I remember also resecting the mandible ("Commando" operation) for an extensive cancer of the mouth. This was a triumph until the patient went home and bled to death from a ruptured carotid artery. By this I do not mean to disparage the results of radical operations for squamous cell carcinoma of the head and neck. In this type of cancer there is little tendency to systemic metastasis, and radical operations, when skillfully performed, are effective means of cure.

Pancreatic cancer stands at the opposite end of the spectrum of metastasis. Nearly always by the time it is discovered it has already metastasized. In 1937 I performed the seventh reported Whipple operation. It was for an adenocarcinoma of the head of the pancreas in a 37-year-old man. Continuity of the bile duct was reestablished by anastomosis of gallbladder to stomach. In 1937 who knew that the stomach would digest the gallbladder wall, stenose the anastomosis, and result in jaundice? Who could predict that within a few months the absence of both bile and pancreatic juice would result in such a failure to absorb fat that the patient would have a complete deficiency of vitamin D, resulting in horny skin, night blindness, and death at reoperation? Ironically, at autopsy, there was no evidence of metastatic cancer—the only patient with adenocarcinoma of the pancreas ever operated on at the Cleveland Clinic who would have remained well for 5 years (if he had survived the complications of the operation).

Most of the other types of radical

operations I did not do because I considered them to be out of my field. But, young and reckless as I was, I balked at the radical neck dissection for cancer of the thyroid. Having seen much of my father's enormous thyroid practice and having grown up under the tutelage of the great thyroid pathologist, Allen Graham, I knew that undifferentiated cancers were by definition incurable and that the encapsulated angioinvasive follicular cancers did not metastasize to lymph nodes. At that time the medullary cancers were not recognized. Consequently, it was only the papillary carcinomas that could give any excuse for doing a radical neck dissection.

When papillary carcinomas were occult (not palpable in the thyroid) and occurred in young people and metastasized extensively to lymph nodes, we used to call them "lateral aberrant thyroids." To do a radical dissection for this supposedly benign disease would have been unthinkable. But as more and more children were subjected to radiation of the neck for benign disease or for no disease at all (as was the case when the thymus glands of infants were irradiated), the incidence of papillary carcinoma grew by leaps and bounds until soon it constituted 70% of all thyroid cancers instead of the 18% that it had been prior to 1937. By then we had found that almost always there was a primary cancer in the thyroid, that "lateral aberrant thyroids" were metastases from this primary, and that the unique fact about papillary cancer was that survival was not at all related to the extent of nodal involvement. A young person with a postradiation papillary cancer involving 40 nodes would be no more apt to die of the disease than one who had only one or two nodes involved even if treated by an operation far less extensive and less mutilating than the standard radical neck dissection. Moreover, following the analogy of thyroid cancer in rats controlled by thyroid hormone, I found that if suppressive doses of thyroid were given, the pulmonary metastases of the papillary cancers that occurred after radiation of young people's necks usually disappeared or failed to grow so long as the thyroid was taken. For these reasons, I did not often do radical neck dissections for papillary cancer, but removed the lobe on the affected side, the isthmus, and the major part of the contralateral lobe. Total thyroidectomy was performed only when nodes were involved on both sides or when both lobes of the thyroid were grossly involved. The affected group of nodes were removed in their fibrofatty envelopes without removing muscles or sacrificing nerves. The survival following these operations was as high as that reported by others following total thyroidectomy with radical neck dissection. Analysis of our figures by statisticians of the National Cancer Institute showed that patients younger than 45 years treated for papillary cancer of the thyroid had normal age-adjusted life expectancies. I began to view papillary carcinoma in young people not as a true cancer but as a sort of thyroidosis similar to endometriosis whose cells were capable of implantation or of metastasis, but whose growth could be controlled by eliminating the stimulating hormone. For whoever heard of any other cancer with 40 nodes involved in which the patient could be cured? My position in respect to

radical neck dissection has now been accepted, for in the past 2 years even the most firm advocates of routine radical neck dissection for papillary carcinoma have relented and now admit that lesser and more cosmetically acceptable operations give equivalent results.[1]

In the early 1920s, Dr. Thomas Jones, who later would become head of the Department of Surgery of the Cleveland Clinic, visited the famous Mr. Miles, in London, and learned there how to do the combined abdominoperineal resection of the rectum. He also spent some time at Memorial Hospital in New York observing the use of radium in the treatment of cancer.

Dr. Jones was as close to being a surgical oncologist as anyone was in those days. By 1935 most of his practice was in the field of cancer. Each afternoon in the Clinic he would treat a number of patients with cancers of the mouth or skin with radium plaques or radium seeds. (At that time the Clinic was the only institution in this part of the country that had a radium emanation plant.) He also treated cancers of the cervix and of the endometrium by radium and sometimes cancers of the rectum by radium seeds. Usually, for patients with rectal cancers, he did the radical abdominoperineal resection, even when the cancer was at or a little above the level of the reflection of the peritoneum. That was because in Dr. Jones's hands the mortality of patients who had undergone abdominoperineal resection and end colostomy was less than 2%, whereas in those preantibiotic days the risk of a low anastomosis was much higher.

Among the most extraordinary of Dr. Jones's achievements were his results in electrocoagulating low lying cancers of the rectum, with or without the addition of radon seeds. He treated nearly a hundred rectal cancers in this way with no immediate mortality and with a survival rate comparable to that of the abdominoperineal resection in patients with lesions of comparable size and location. The operation was reserved chiefly for physicians and friends and for the aged or the feeble. He never wrote of it or talked of it. The abdominoperineal resection was his favorite operation, and he did it with consummate skill, often completing the entire procedure in less than an hour. I do not think that even the excellent results of electrocoagulation could ever have lured him away from the procedure which he referred to as "my operation" and for which he was so justly famous. When Dr. Jones died suddenly of a ruptured aneurysm of the heart, it was while dressing to perform a combined abdominoperineal resection.

In another field, the breast, there also was competition between radical and simpler treatments. My father, who was a little younger than Dr. Halsted, always held the master in profound disrespect. Dr. Crile ridiculed Dr. Halsted's time-taking, meticulous black-silk technique, and he thought Halsted's radical mastectomy was absurd. "If the muscles are so extensively invaded that you have to take all of them to remove the cancer, the disease has metastasized distantly and is incurable," Dr. Crile always said. He performed a neat, 30-minute modified radical mastectomy, using a transverse incision and thick skin flaps, just as we do today.

Dr. Jones always removed the muscles. Since he cut the skin flaps thick

and rarely used skin grafts, there was little difference in the postoperative course of his patients and my father's, although my father's looked better and had better motion of the arm. Nevertheless, I opted to pattern myself after my hero, Tom Jones. Was there ever a son in his 20s who thought his father did anything right?

Until 1955 I continued to perform the Jones-type radical mastectomy and often, in internal quadrant cancers, to divide the intercostal muscles and remove nodes of the internal mammary chain. By that time evidence had begun to accumulate suggesting that increasing the scope of operations did not necessarily increase the proportion of patients cured. Edwin Fisher, who was then working in Pathology at the Clinic, and Rupert Turnbull, in the Department of Colon and Rectal Surgery, were collaborating to show, for the first time, that most operable cancers were discharging viable cancer cells into the venous blood.[2] In Canada, McKinnon[3] was talking about the mortality of breast cancer and pointing out that treatment had little if any demonstrable effect on survival. Williams et al[4] were writing that Sir Geoffrey Keynes, who did few if any radical mastectomies and treated breast cancer by combinations of lesser operations and radiation (mainly from radium), obtained results as good as or better than those of other surgeons using radical mastectomy in the same hospital at the same time.

I knew Reggie Murley, one of the authors of the classic paper on Keynes' results, and it was he who persuaded me to put more credence in McWhirter's[5] reports of excellent survival following simple mastectomy and radiation. Impressed by the mounting evidence in favor of simplified treatment, I resolved to abandon radical mastectomy and to use modified radical mastectomy when I thought nodes were involved, and simple when I thought they were not. If, later on, nodes were to become palpably involved they would be removed by a conservative axillary dissection. Occasionally, when the tumor was small, peripheral, and apparently localized, it would be treated by partial mastectomy (11% of the operable cases).

In 1955 I was doing about half the breast surgery at the Clinic and my colleagues the other half. For 2 years they continued to do the radical operation, but as they saw my patients in follow-up and read the papers that were beginning to come out on simplified treatment, they too began to substitute the modified radical for the radical and to use simple operations in some of the more favorable cases. Since 1956 less than 0.5% of the operations for breast cancer at the Cleveland Clinic have been radical, and since 1971 more than 20% of the operations have been partial mastectomies with reconstruction of the breast. Despite this simplification of treatment, the proportion of patients surviving 5 and 10 years has increased steadily and the incidence of local recurrence is only 6%. The most likely explanation for the much higher incidence of local recurrence that is reported after the conventional radical mastectomy is best explained by laboratory studies showing that the growth of cancer is greatly stimulated by injuring tissue or interfering with its blood supply. For this reason, the thin-cut skin

flaps of the radical mastectomy trap cancer cells in the deep lymphatics of the skin and by devascularizing the skin they stimulate the growth of the cancer cells.

Encouraged by the success of more conservative treatment of breast cancer, I went back over our experience with electrocoagulation of rectal cancers, and found that the survival rate of Turnbull's patients (and a few of mine) after electrocoagulation of relatively small, low-lying, posterior or lateral cancers was better than that of similarly staged tumors treated by abdominoperineal resection. This was because the operation itself constituted a considerable risk; 10% was the average reported mortality, and in our hands there had been a 3% immediate mortality and 1% delayed, whereas there was no mortality after electrocoagulation.

The advantage of the radical operation was that it removed the nodes. But removal of the nodes does not improve survival as much as one might expect. Suppose we have 100 patients with small, low-lying rectal cancers. Seventy of them will have no nodes involved so that removal of the nodes would do no good. Eighty percent of the 30 who had involved nodes will die of cancer, leaving only 6 of the 100 who would be cured by removing the nodes. Since 4 of the 100 patients would have died as a result of the operation as compared to none after electrocoagulation, only 2 of the 100 would have been saved by it. This sounds as if there might be an advantage to the resection, but there are two other considerations. First, with resection there is a colostomy. Second, when one dies as a result of operation, one dies right then, whereas if one dies as a result of cancer being left in nodes, the majority of patients live between 5 and 10 years. Thus, if the patient were 65 at the time of operation and had a life expectancy of 10 years, he would lose 10 years of life if he died of the operation. If he died of cancer in nodes after coagulation, however, he would live for 5 years and lose only 5 years of life. A little calculation shows that in terms of months of life expectancy the lesser operation is better than the radical one. Another interesting observation was that failure to control the local cancer by electrocoagulation did not in any way jeopardize the chances of curing the patient by combined abdominoperineal resection. It was rare that this was necessary, but reassuring to know that it could be used.

In 1936 when I first started resecting cancers of the pancreas, I was highly enthusiastic about the procedure. By 1970, however, I had become disillusioned. No patient operated on at the Cleveland Clinic for adenocarcinoma of the pancreas had survived 5 years. The mortality rate had been acceptable as compared with that reported by others, but what was the use of resecting when most of the patients in the same stage of the disease would live longer after bypass and would not be subjected to the high risk of immediate postoperative death that was associated with pancreaticoduodenectomy?

My "moment of truth" arrived when I operated on a 47-year-old man with a small apparently localized cancer of the head of the pancreas. I resected it along with all of the pancreas, not even doing a biopsy for fear of disseminating the disease. Two months later he returned with abdominal pain and distension. Ex-

ploration showed carcinomatosis. That was the last Whipple operation that I did. Reviewing my results I am sure that when the postoperative mortality is included, patients with adenocarcinoma of the head of the pancreas live longer when the tumors are bypassed than when they are resected.

A study of the record suggests that expanding the scope of operations for cancer has increased morbidity and mortality, but that in most types of cancer has not improved survival. Neither has the addition of irradiation improved the results. This is because in most cancers the disease has metastasized systemically before it can be recognized and treated. Fortunately, new hope is arising as a result of treatment with modern, multiple-drug chemotherapy.

Chemotherapy, with a few exceptions, did not cure and did little to prolong life when used in the treatment of systemic metastases that could be recognized by symptoms or signs, or could be seen on roentgenograms or scans. But in Hodgkin's disease, lymphomas, Wilms' tumors, neuroblastomas and, most strikingly of all, in osteogenic sarcomas, there is increasing evidence that microscopic, unrecognizable deposits of cancer can be eradicated, or at least their clinical appearance can be greatly delayed when they are treated by intensive chemotherapy before they can be recognized. Now the same principles are being applied to cancer of the breast with promising early results. Already, however, as the studies enter their third year, the advantage to the treated patients seems to be diminishing. Whether the effect of chemotherapy with multiple agents is mainly due to the antiestrogen activity of the chemotherapy (the favorable results occur only in premenopausal women) or whether the delay of reappearance of cancer is in part, at least, a direct effect on the tumor and might be permanent are questions that cannot yet be answered.

In conclusion, it seems that the hope of the last generation of surgeons, that more radical surgery would effect more cures, has not been realized. Also the hope of radiotherapists, that the addition of modern radiation would increase the rate of cure, has not been fulfilled. Routine postoperative irradiation has reduced the incidence of local recurrence, as in cancer of the breast, but if no radiation is given and recurrences are irradiated as soon as they are discovered, the incidence of troublesome, uncontrollable, local recurrences is the same as in patients who received irradiation prophylactically. The moral of all these stories seems to be that surgeons and radiotherapists have been obsessed with the notion that maximum therapy should be given at the earliest possible moment. Step-by-step treatment has been held in disfavor. Surgeons have had little regard for the morbidity or mortality inflicted by treatment. The potentially involved lymph node has not been viewed either as an index of whether or not there is apt to be systemic metastasis or as a possible factor in maintaining immunity, but it has been thought of as a dangerous source of systemic spread that must be destroyed even at the expense of high morbidity and mortality. Now the question arises as to whether we are about to go through the same experience with chemotherapy. Will the next generation of patients be subjected to all the toxic side effects

induced by universal treatment with multiple, potent chemotherapeutic agents? Finally in terms of survival will this be any more worthwhile than were our radicalizations of surgery and extensions of the use of irradiation?

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