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CANCER OF THE BREAST: THE SURGEON'S DILEMMA

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SUDDENLY, after 50 years of complacent acceptance of radical mastectomy, the surgical world is plunged in doubt. On the one hand, Urban and Baker[1] and Wangensteen[2] advocate extension of the radical operation to include resection of the internal mammary nodes; on the other, there is mounting evidence that simple mastectomy gives better results than the conventional radical operations.[3]

Since even in the most skillful hands the conventional radical mastectomy may cause disfigurement and dysfunction, it is important to determine whether it is really necessary to employ it routinely. To date there is no proof that the results of radical mastectomy are better than those of simple. Pathologists may theorize on the rationale of eradicating cancer by extended surgery,[4] but in the final analysis it is the survival of patients that counts. So little is known about the ways of cancers and the complex relationships of tumors to their hosts that theoretical considerations based on the traditional concept of the spread of cancers are of little value.

In the traditional concept of the spread of cancer, the tumor is at first localized, later spreads to the regional lymph nodes, and finally throughout the body. According to this concept the most extensive operation performed at the earliest possible moment should give the best chance of cure.

In opposition to this concept is the theory that Gatch[5] has long held and that MacDonald[6] has named *biologic predeterminism*. In this concept, the course of the disease is thought to depend chiefly upon the biologic properties of the tumor and the resistance of the host. In cancer of the breast, the principle of biologic predeterminism is sustained by the studies of Park and Lees[7] which indicate that it is impossible to prove that the course of cancer of the breast is influenced by any form of surgical treatment.

The present crisis in our thinking about cancer of the breast was precipitated by McWhirter[8] in Edinburgh, Scotland, who subjected a population group of more than a million people to a careful clinical experiment. All cases of cancer of the breast that occurred in this population group were included, regardless of how they were treated, or whether they received no treatment at all. Ackerman,[4] who reviewed McWhirter's material, did not agree with McWhirter's conclusions but had little criticism of the basis for the diagnosis or of the completeness of the follow-up.

In the United States the results of McWhirter's experiment have been widely misunderstood. Many surgeons believe that McWhirter showed that irradiation is as effective as radical mastectomy. Nothing could be farther from the truth. McWhirter's results indicate that although irradiation controlled local recurrences, it had little effect upon the survival of patients with cancer of the breast. The chief significance of the Edinburgh experiment is that it suggests that in some cases radical mastectomy may *shorten* the period of survival. In all operable stages of the disease, McWhirter found that the results of simple mastectomy were superior to those of radical mastectomy.

McWhirter's study is divided into three five-year periods. In the first period, the majority of the operable cancers were treated by *radical* mastectomy. In the second period, postoperative irradiation was added. In the third period, most of the operable cancers were treated by *simple* mastectomy and irradiation. In order to eliminate factors of selection, the results in each of these successive periods were listed under the type of treatment that predominated during that period, so that in the group considered to have been treated by simple mastectomy and irradiation there are some patients who had no treatment, some who had only irradiation, and some who had radical mastectomy, but most had simple mastectomy and irradiation.

McWhirter found that roentgen therapy given after radical mastectomy reduced the incidence of local recurrences but made no significant change in the survival rates. However, when the treatment was changed from radical mastectomy to simple mastectomy, irradiation being given in both instances, the survival rates at five and at ten years after operation were increased by more than 10 per cent. From this experiment McWhirter has drawn two conclusions: (1) that in many cases irradiation can control local recurrences, and (2) that by not dissecting the axilla, dissemination of disease is avoided and the survival rate is increased.

It is interesting that from an opposite approach, with emphasis on meticulous and extended operations, Haagensen and Stout[9] are working toward identical conclusions. They now emphasize the desirability of taking biopsies of mediastinal and supraclavicular lymph nodes before performing a radical mastectomy, and advise that if these nodes are involved, treatment should be solely by irradiation. Their results with this method of treatment are reported to be excellent, because they do not operate on the types of cancer that operations are apt to spread.

There is mounting evidence that the regional lymph nodes, even when

involved by cancer, may act more often as a barrier to further spread than as a source of dissemination. Williams, Murley, and Curwen[3] at St. Bartholomew's Hospital in London, England, analyzed the results of various types of operations that were performed 25 years ago during the height of the vogue for radical mastectomy. Fortunately there was one surgeon, Sir Geoffrey Keynes, who treated a large number of cancers by local excision, local implantation of radium needles or by simple mastectomy, but almost never by radical mastectomy. The survivals of his patients were longer than those of the surgeons who did radical mastectomies, and Williams, Murley, and Curwen concluded that with or without irradiation, simple mastectomy gave better results than radical mastectomy at St. Bartholomew's Hospital.

A similar report in this country by Meyer and Smith[10] shows that the results of simple mastectomy done on unselected cases in a community hospital were slightly better than those of the conventional radical operation (the five-year survival rate was 8 per cent higher). Small and Dutton[11] at the University of Rochester came to similar conclusions. Byrd and Conerly[12] at Vanderbilt University analyzed the survival rates of women who were aged, debilitated, or had advanced cancer, and who had undergone simple mastectomy, and compared these survival rates with those of women who had undergone radical mastectomy. They found that in the clinical stage I cases with no palpable involvement of the axillary nodes, the survival rates were slightly better after the simple than after the radical operation. Despite the more advanced stage of the disease in the clinical stage II cases treated by simple mastectomy the survival rates after simple mastectomy were remarkably similar to those after the radical procedure done in a more favorable group of cases. Finally, Deaton[13] in a survey of the world literature, reported that the survival rate following simple mastectomy was 5 per cent higher than that following radical mastectomy.

These observations are disturbing to our conventional thinking about cancer, and cannot be explained without drawing an analogy between the role of the lymph node in infection and in cancer. In an infection of the hand we view the axillary nodes as a barrier to systemic spread. We treat the local lesion and count on the natural resistance of the body to overcome the bacteremia and the lymph-node involvement. Surgeons have learned from bitter experience that they spread the disease if they excise lymph nodes that are involved by virulent infections. Yet in grade IV cancers, when blood vessels and lymphatics are filled with tumor cells, many surgeons do not hesitate to excise the lymphatic barrier.

The dissemination of cancer cells into the blood stream is much more common than we have realized. In 59 per cent of a series of 107 cases of operable cancers of the breast, lung, stomach, and colon, Engel[14] of Stockholm, Sweden, found cancer cells free in the blood of the veins that drained the cancers. Thirty-five per cent of grade II cancers had cells in the blood, 78 per cent of grade III, and 100 per cent of grade IV.

The two properties of cancer cells that enable them to enter the blood stream are their lack of attachment to surrounding cells and their ability to migrate by ameboid movement. These properties account for the exfoliation of living cells

that makes possible the Papanicolaou smear test for cancer of the cervix. The same properties cause internal migration and exfoliation of cells into the streams of body fluids. As Denoix[15] of Paris, France, has said, there probably is a time in the evolution of all cancers when they are systemically disseminated. The spread of the cancer therefore depends much more upon the resistance of the host and the ability of the circulating cells to implant and to grow than upon the type of surgical treatment.

Although we can avoid unnecessary manipulation of a cancer and although in some situation we can ligate the veins that drain a cancer before we disturb it, there is little else that we can do to prevent dissemination of cancer through the blood stream. But perhaps we can avoid its widespread dissemination through the lymphatics. The experiments of Zeidman and Buss[16] who injected cells of a transplantable cancer into the popliteal lymphatics of chickens, indicate that lymph nodes are effective barriers to the spread of cancer and localize the disease for long periods of time. This evidence should encourage us to study further the possible advantages of performing the initial operation for cancer of the breast within the lymph-node barrier.

The principle of local excision or destruction of a cancer within the lymph-node barrier has been employed for many years in the treatment of cancers of the lip, skin, and mouth, where treatment of clinically uninvolved lymph nodes often is deferred until the course of the disease can be evaluated. The advantage of simultaneous or prophylactic resections of lymph nodes in these cases never has been established. Indeed, in the treatment of some tumors such as melanoma, the opposite may be true. The survival rate following simultaneous dissection of the primary melanoma and palpable lymph-node metastases is almost nil, yet nearly half of the patients have been reported to survive more than five years when the primary is first removed and involved nodes are resected at a later operation.[17] In patients with lymph-node involvement from highly malignant tumors, it may be that the lymphatics are filled with cancer cells on their way to the lymph nodes. If so, wide resection of the nodes, before the primary tumor has been removed and before the cells in the lymphatics have been fixed or destroyed by the forces of body resistance, may disseminate the tumor more widely. In such cases, the challenge to the surgeon is much the same as it is in the treatment of infection. It is not so much to operate as early and as widely as possible as it is to determine as early as possible which lesions are adapted to surgical treatment.

Even more important than technical considerations of the lymph-node barrier are the biologic considerations of the cancer's growth. If we had some way to recognize, before operation, the pattern of the tumor's growth and spread we could avoid many of the dangerous operations that disseminate disease. At present there are only two ways of estimating preoperatively the biologic potential of a cancer. One is by observing its response to radiation therapy, the other is by observing its clinical course.

The response to irradiation is used by MacDonald[18] as an index of the operability of breast cancers. In clinical stage II cancers, in which axillary nodes

are palpable, he gives 1800 r over a period of two weeks, and if the nodes decrease in size by one third or more he considers the cancer to be biologically better adapted to irradiation than to surgery and relies solely on irradiation in the treatment of the metastases. If, on the other hand, there is little or no response, he performs a conventional radical mastectomy. Similar principles are being tested by the Grahams[19] in their use of the factor of radiation sensitivity in selecting cancers of the cervix for treatment by irradiation or by surgery.

An alternative biologic approach is to use the factor of time as an index of the tumor's biologic behavior. In this system the initial treatment of a clinical stage I cancer of the breast with no palpable nodes would be simple mastectomy or, occasionally, in carefully selected small peripheral lesions, wide local excision. The axilla is then periodically examined. If in a few months diffuse involvement of axillary nodes becomes apparent, intensive cobalt teletherapy is given. If systemic metastasis is apparent, endocrine therapy is tried. If, on the other hand, two or three years elapse before one or two movable nodes become palpable it is assumed that the resistance of the body to the tumor is high and that the tumor is better adapted to control by radical axillary dissection than by irradiation.

In clinical stage II cancers with palpable axillary nodes, if the history is short, the treatment is simple mastectomy and irradiation by the McWhirter technic. But if the patient states that the primary tumor has been present a year or more, if it is located in the upper outer quadrant, and if the palpable nodes are few and movable, radical mastectomy is performed.

Since there is evidence that irradiation may do harm as well as good, I believe that irradiation should not be applied prophylactically as a routine measure. The balance between the growth of the tumor and the resistance of the host is a delicate one that can be tipped easily in either direction. In experimental animals, Kaplan and Murphy[20] have shown that irradiation of radiation-resistant tumors is apt to hasten their metastasis, and Krebs[21] has found that irradiated cancers invade more extensively than do nonirradiated controls. Clinically too, a tumor sometimes seems to grow and spread more rapidly after irradiation, as for example in one of my patients in whom a local recurrence of a breast cancer treated by irradiation grew through the chest wall and pericardium and into the myocardium.

Even endocrine therapy is not without danger. Adrenalectomy, as Moore[22] has shown, may stimulate the growth of a cancer of the breast. Administration of androgens also may accelerate its growth.[23] Even oophorectomy is not free of this danger and should not be applied indiscriminately. In young women there are breast cancers that are in no way dependent on estrogens, but rather are dependent on the growth or on the mammotropic hormones of the pituitary, which may be cross-stimulated by oophorectomy. I have seen such a cancer in a menstruating woman, 42 years old, whose cancer grew more rapidly after roentgen sterilization of the ovary and then went into a striking remission when she was given desiccated thyroid, cortisone, and 20 mg. of stilbestrol daily to suppress the activity of the pituitary.

Apparently, with the possible exception of removal of the pituitary, there are no operations, no technics of irradiation, and no treatments with sex hor-

mones that are free of the risk of accelerating the growth of cancer of the breast. For the present, therefore, and until we develop a better understanding of the factors that control the spread of cancer, it may be best to avoid therapeutic generalizations and to base treatment on the biologic behavior and response to treatment of the individual cancer.

Summary

1. Since we know little of the factors that influence the spread of cancer, no valid generalizations can be made about the treatment of cancer of the breast.

2. At present there is no basis for advocating any single type of operation for operable cancers of the breast and there is no basis for employing a general policy, pro or con, regarding irradiation, removal of endocrine glands, or endocrine therapy.

3. Each patient with a cancer of the breast should be considered as an individual problem and treated according to the biologic behavior of the tumor and the resistance of the host.

4. Since there is doubt whether any of our treatments will often prevent the distant spread of cancer, a heavy burden of responsibility rests on the surgeon. The day is past when he can accept the credit for prolonged survival and consider himself free of responsibility if after the treatment the cancer spreads.

5. Surgery, irradiation, and endocrine therapy are double-edged swords that may harm as well as help.

6. The challenge to the surgeon is to control the cancer as well as possible and to do so with the least possible harm.

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