The Continuing Breast Cancer Controversy

Over Ethics

There was a time, not really very long ago, when it was generally accepted that medical experimentation was ethical as long as the point of the experiment was important and the patients involved would not be unduly harmed. However, there is now growing concern about the ethics of human experimentation in general and, in particular, about the patient's rights and informed consent. As a result of these concerns, feelings about human experimentation have been changing. The attitudes both scientists and laymen have taken toward the National Surgical Adjuvant Breast Project are a case in point.

The study, which began in 1971, was designed to resolve the long-standing medical controversy over whether women with breast cancer that has not spread should have a radical mastectomy or a total, sometimes called simple, mastectomy, the former being more mutilating than the latter. It was decided that the only way to answer the question was to have a controlled clinical trial in which women who fit a certain protocol as far as the stage of their disease was concerned would have one or the other of the operations according to the dictates of a computer. Scientifically it makes sense, and there was no question about the importance of getting the answer the study was meant to provide.

But ethical questions came up anyway. At a meeting of the National Cancer Advisory Board in October 1972, the subject of breast cancer was on the agenda and, at that meeting, some of the members heard about—or at any rate became fully aware of—the surgical study for the first time (*Science*, 3 November 1972). At that meeting, board members also heard a great deal about combination chemotherapy, which has been successful in treating certain cancers such as leukemia. As a result some investigators would like to try chemotherapy on patients with breast cancer. There was much optimistic emphasis on the idea that early drug therapy, perhaps beginning right after surgery, would enhance a breast cancer victim's chances of long-term recovery.

The chemotherapy discussions prompted questions about the surgical breast project, questions asked both publicly during the meeting and privately later. Would any of the women in the study receive experimental chemotherapy? No, they would not. There was a question about whether women in the study were, therefore, receiving the best available therapy. Said one board member with a note of incredulity in his voice, "Are we supposed to endorse this [study]?"

But that issue, too, is complex. While there are some doctors who want to try chemotherapy right away, others argue that, because the drugs themselves cause serious side effects, including cancer, it may be unethical to give them to women with no evidence of cancer spread.

Questions were raised about informed consent, about just what the women asked to participate in the study were being told and whether the consent forms they signed told them clearly what was going on.

National Cancer Institute officials promptly promised the agitated members of the board a full report on the breast project.

In March 1973, Nathaniel Berlin, clinical director of the cancer institute, reported back to the board. In great detail he explained the various types of surgical procedures that were used, highlighted those that were most common, stressed the necessity of knowing whether the radical operation was really better, as many people think it is. And, he told the board that the study had not been undertaken lightly, that in fact several committees of the institute and of outside investigators had reviewed and approved the project on several occasions.

The board members appeared to be satisfied, and no further probing questions were raised about not giving drugs to women in the study. No one said a word about informed consent. Most members appeared to be satisfied that everything was in order.

Though the issue thus died as far as the cancer board was concerned, it did not go away. Lawyers for Washington's Center for Law and Social Policy, a public interest group, have charged that most of the women in the study were not fully informed of the facts, especially the one about letting a computer choose their operation.

The question here of informed consent is almost as controversial as the question of whether radical surgery is better than simple. Bernard Fisher of the University of Pittsburgh, who is head of the study, clearly feels that women have been fully informed and has emphasized the point that what they are told in person is more important that what they are told on a consent form.

Nevertheless, the consent forms have been revised "in accordance," Fisher says, "with the new HEW [Health, Education, and Welfare] guidelines for human experimentation." In the revised form, there is a sentence that reads, "The decision as to which form of treatment I receive will be made on the basis of randomization." Whether this revision is sufficient to allay criticism is doubtful.—B.J.C.

Over Surgery

The preliminary results* of a study on the surgical treatment of breast cancer indicate that radical mastectomy is no more effective in preventing cancer recurrence than total or simple mastectomy, according to Bernard Fisher of the University of Pittsburgh School of Medicine and chairman of the National Surgical Adjuvant Breast Project (NSABP). The study, conducted under the aegis of the NSABP, included almost 1700 women who were operated on for breast cancer between September 1971 and August 1974. It involved the cooperation of 35 medical institutions in the United States.

Women who participated in the study and whose cancer had not yet spread to the lymph nodes under the arm (as determined by a clinical examination) received either a radical mastectomy, a total mastectomy, or a total mastectomy plus radiation therapy. A radical mastectomy entails removal of the breast, the underlying chest muscles, and the lymph nodes. In the total mastectomy, the entire breast—but only the breast—is removed. In all cases, the type of operation the women underwent was determined by computer. Fisher reported that no significant differences in the efficacies of the three

* Presented at a conference sponsored by the Breast Cancer Task Force of the National Cancer Institute at the National Institutes of Health on 30 September 1974.

treatments under study have been observed at this time.

Women whose cancer had spread to the lymph nodes received either a radical mastectomy or a total mastectomy plus radiation to kill cancer cells in the lymph nodes. Again, no differences were observed in the cancer recurral rates in patients receiving the two treatments.

If the results of the study hold up, the next step may be a determination of the effectiveness of the segmental mastectomy or lumpectomy. In this procedure, the tumor plus the surrounding tissue is removed but the bulk of the breast is left intact. This operation is even more controversial—and raises even more ethical questions—than the total mastectomy, but Fisher believes that it is imperative to test its effectiveness because some surgeons are already doing it.

The results described by Fisher indicate that the more disfiguring radical operation, which is by far the most commonly used, may not be necessary for most women. Whether they will be accepted and applied by the medical profession remains uncertain in view of the controversy that has raged for years about breast cancer surgery. Although the physicians treating Mrs. Betty Ford, for example, were aware of the results of the NSABP study, they still elected to perform a radical mastectomy on the President's wife.

The inability to detect all positive nodes by clinical examination—almost 40 percent may be missed—is one reason some surgeons prefer the radical operation. Fisher said, however, that it is possible to remove nodes for pathological examination without doing a radical.

Adequate detection of positive nodes is important because the presence or absence of cancer in the lymph nodes is the most accurate indicator of a patient's prognosis. When the nodes are negative, 80 percent of the patients survive at least 5 years. The survival rate drops to less than 40 percent for those with nodal involvement, but another NSABP study described by Fisher showed that chemotherapy with L-phenylalanine mustard (L-PAM) may prolong the survival of such patients.

Administration of the drug is begun right after surgery when the patient is clinically free of disease. Until recently chemotherapy was not attempted until cancer recurred and was in the advanced stages. The increased survival was particularly striking for premenopausal patients but less significant for patients above the age of 49. Fisher said that he now routinely prescribes L-PAM for all younger patients with nodal involvement.

Additional chemotherapeutic trials with drug combinations are now planned. Paul Carbone of the National Cancer Institute said that clinical studies have indicated that combinations of extremely potent chemotherapeutic agents increase the remission rate or prolong the survival of patients with advanced breast cancer. Such studies will now be extended to postoperative patients who appear disease-free but are in the high risk group. Patients who do not have nodal involvement will not receive chemotherapy because their prognosis, which is already good, does not warrant exposing them to the hazardous side effects—including carcinogenicity—of the drugs.—J.L.M.

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RESEARCH NEWS

Diagnostic Medicine: The Coming Ultrasonic Boom

Current predictions are that the medical applications of ultrasound will equal or even surpass those of x-rays within 10 years. In fact, if these predictions are borne out, a veritable revolution in diagnostic medicine is in the making, for there appear to be few—if any—medical specialties in which ultrasound cannot play a role. At present, its clinical applications are most advanced in obstetrics, cardiology, neurology, and ophthalmology, but research is moving forward on a broad front and numerous additional applications are foreseen if not yet available.

Many investigators think that ultrasound may be the ideal diagnostic tool. It is externally applied and noninvasive; unlike x-rays it can distinguish between different soft tissues; and there is no evidence that ultrasound as it is used in diagnostic procedures damages biological tissues. The investigators stress, however, that additional research on the biological effects of ultrasound is required to definitively establish its safety.

Ultrasound examinations are limited mainly by the fact that both bone and gases strongly reflect high-frequency sound waves and thus interfere with their transmission through certain areas of the body including the skull, lungs, and gastrointestinal track.

The ultrasound procedures now used for medical diagnoses are essentially clinical forms of radar and can be called pulse-echo sonography. Ultrasound is generated by a transducer, made of piezoelectric material, that is incorporated into a probe. Piezoelectric materials vibrate at high frequencies when a pulse of electricity is applied to them. Ultrasound is defined as sound with frequencies greater than 20,000 hertz, but the frequencies of diagnostic ultrasound are usually above 1 million hertz. For most diagnostic procedures the transducer transmits sound waves for about 1 millionth of a second.

As the ultrasound travels through the body, it is reflected by interfaces between tissues with different acoustic properties. Reflected sound returns to the transducer, which serves as the detector during the time it is not transmitting, where the vibrations are reconverted to electrical signals that are recorded on an oscilloscope. The time required for the reflected sound wave to return to the transducer depends on the distance between interface and transducer and the properties of the structures through which it passes. Since ultrasound does not travel well in air, the transducer must be coupled to the body by a liquid.

Ultrasound has been extensively applied in the practice of obstetrics and gynecology (Fig. 1). There are two major reasons for this. The pregnant uterus is filled with fluid that is an excellent transmitter of ultrasound. And diagnostic ultrasound, which is not associated with known hazards to the developing fetus, is the preferred diagnostic alternative to x-rays, which are associated with known fetal hazards.

Ultrasound scanning of the uterus