Breast Cancer: Reports of New Therapy Are Greatly Exaggerated

As anyone who keeps up with the news knows, a major new treatment for breast cancer has been discovered in Italy. The good news was broadcast on radio and television and published on the front pages of newspapers across the land. *Time* (1 March) reported the story under a headline that announced "Spectacular Hope," and *Newsweek* ran the story with a picture captioned "Breakthrough." The salvation of women with breast cancer, we were told, lies in the use of three drugs administered for a year after the usual surgery. The effectiveness of these drugs is so "dramatic," reporters wrote, that all doctors should begin using them right away.

The authority behind all this good news is James F. Holland, a well-respected chemotherapist at the Mount Sinai School of Medicine in New York. In an editorial in the 19 February issue of the *New England Journal of Medicine*, Holland proclaimed that, as a result of an Italian study reported in the lead article in the same issue of the journal, it will now be possible to "admire more in Milan than La Scala." He called the study, by Gianni Bonadonna and his colleagues at the Istituto Nazionale Tumori in Milan, a work of "monumental importance" and said their work with combination drug therapy "has produced results nothing short of spectacular." Holland noted that "Much research remains to be done," but went on emphatically to declare that "this fact should not impede the adoption of the treatment by qualified physicians for patients who cannot participate in this research."

This is all very nice, but for one minor point. Breast cancer has not been cured in Italy or anywhere else. And while the Bonadonna study is an important one, its significance has been greatly exaggerated, because of Holland's enthusiasm for it. (Because of illness, Holland was not available to elaborate on his position.) In retrospect, Franz J. Ingelfinger, editor of the *New England Journal of Medicine*, concedes that the editorial might have been toned down. He does not like to "fiddle" with editorials written by persons who are recognized authorities in their fields, he says, but adds that in this case some changes might have been in order. "We certainly should not have called it a study of 'monumental importance,'" he acknowledges.

National Cancer Institute (NCI) officials agree. Vincent T. DeVita, Jr., head of the division of cancer treatment, says, "The Bonadonna study is good. We're very proud of it, but it is hardly monumental." NCI's deputy director Guy Newell says, "The study is exciting, there's no doubt about it. But you have to remember how early in the game it is. We may just be delaying recurrence of the disease. And these drugs are highly toxic. We don't know what their effect will be in the long run."

NCI Response Is Low-Key

When encouraged by Holland and others to call a press conference to coincide with the study's publication, NCI refused. Instead, they issued a decidedly unspectacular press release that blandly began, "The rate of breast cancer recurrence after initial surgery has been decreased with drug therapy in a study conducted by Dr. Gianni Bonadonna. . . ." To persons familiar with the field, it was news we'd heard before. Only the names were changed. About a year ago, a similar release told that a study in this country, headed by Bernard Fisher (University of Pittsburgh School of Medicine), indicated that drug therapy after surgery appeared to be a good thing.

The NCI release recounted the salient facts: in the Italian study, which was supported with about $300,000 of NCI money, women who received a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) after surgery fared better than those who received no postoperative therapy at all. Only 5.3 percent of the 207 women who received CMF have had a recurrence of cancer. In contrast, 24 percent of 179 women who got nothing did have recurrent cancer. The release also points out that the patients in the study have been followed for an average of only 14 months, although some have been observed for 27 months, since the study began.

No one denies that these data are important. The question is, just how important? NCI director Frank J. Rauscher's assessment was low-key. "The results from Milan are encouraging: they will provide the basis for a combined approach to treatment of breast cancer with involved lymph nodes," he said, and added that this study, viewed in conjunction with the Fisher study, "supports the rationale for applying drugs early in the treatment of cancer to destroy microscopic tumor cells that may have spread to distant parts of the body."

For years, investigators have been working on the theory that by the time a breast cancer patient gets to surgery, there are probably microfoci of tumor cells elsewhere in the body, especially if the cancer has already spread from the breast to nearby lymph nodes where tumor cells can get into the lymphatic system and travel freely to new sites. Chemotherapists reason that the way to deal with these microfoci, if indeed they are present (the Bonadonna study supports the belief that they are), is to go after them with drugs. Chemotherapy, which is still regarded skeptically in some circles, became recognized as a useful form of treatment during the 1960's, when investigators were successful in treating childhood leukemia, Wilm's tumor, and a handful of other rare forms of cancer. It was logical to extend the concept to the treatment of breast cancer, which is diagnosed in about 89,000 women a year. Early, small-scale studies were conducted and, although the results were not overwhelming, they were encouraging.

In 1972, NCI launched a large-scale, controlled trial of the use of chemotherapy as an adjuvant to surgery in women whose cancer had already spread to the lymph nodes—the National Surgical Adjuvant Breast Project (NSABP), headed by Fisher.* Half of the women received L-PAM (L-phenylalanine mustard) after radical surgery; half received a placebo. It was apparent that women receiving the drug were doing better, particularly premenopausal women. In the 16 January 1975 issue of the *New England Journal of Medicine*, Fisher reported early data: "Treatment failures [recurrence of disease] occurred in 22 percent of 108 patients receiving placebo and in 9.3 percent of 103 women given L-PAM."

In spite of the fact that the data were preliminary, NSABP doctors and NCI officials felt the results so clearly justified the use of L-PAM following surgery that they changed the design of the study, eliminating the placebo group. "We felt we could not ethically withhold drug therapy from one group of women," says NCI director Rauscher, "once we had statistically sound data that it helps." Now, women in the "control" group of the study receive L-

*The first National Surgical Adjuvant Breast Project was begun under Fisher's leadership in 1957 to evaluate the worth of a drug called thiotepa after radical mastectomy. Surgeons had learned that in the course of the operation, some cancer cells spilled into blood and lymph and thiotepa was administered on the day of surgery and for 2 days after to eliminate those circulating cells. At the end of 5 years, there was no difference in recurrence rates between treated and control patients.

Plutonium Experiment Recalled

A generation-old experiment involving the injection of plutonium, an extremely potent carcinogen, into human subjects has finally gotten a public airing after years of obscurity. The project, initiated in the waning days of the Manhattan Project, seems appalling in light of the ethics of the 1970's, particularly since informed consent apparently was not obtained from the subjects. Yet, according to a scientist who tracked down 17 of the 18 subjects, the one-of-a-kind experiment proved to be of "inestimable use" in setting standards for plutonium workers. There is no evidence that any of the people suffered ill effects—in fact, although all were supposed to be terminally ill, three of them are still alive.

The experiment was conducted between 1945 and 1947, shortly after the construction of the first plutonium bomb, by investigators for the Manhattan Engineering District (MED). According to Patricia W. Durbin of Lawrence Berkeley Laboratory, there was an urgent need for data on the rate at which the human body excretes plutonium so that safe exposure levels could be set for bomb workers. Because ingested plutonium emits very weak radiation, the only way to measure its retention is through measurement of alpha particles in the urine. Experiments had been conducted in which plutonium was injected into rats and dogs but, says Durbin, because the two species excrete it at different rates, they offered no guidelines for humans.

So 18 patients, all of whom were thought to have fewer than 10 years to live, were selected at four hospitals—those at the universities of California, Chicago, and Rochester, and the MED hospital in Oak Ridge, Tennessee. They ranged in age from 4 to 69 and were afflicted with many things including cancer, heart disease, Cushing's syndrome, Addison's disease, and cirrhosis. Each was given a single intravenous plutonium injection that amounted, in most cases, to about 5½ times what was considered an acceptable amount to be ingested by a plutonium worker over a 50-year span. Informed consent is known to have been obtained in only one case, from a man who was injected in 1947, after the Atomic Energy Commission (AEC) had taken over from the MED.

Durbin and her colleague, R. E. Rowland of Argonne National Laboratory, have located information on all but 1 of the 18 subjects. Eight of them survived at least 8 years following the injections, and at least 3 of the 18 were autopsied. None of the available evidence shows that the plutonium injections influenced the course of the patients' diseases. As of 1974, four of the subjects were still alive. One was still ill and has since died, one had ulcers misdiagnosed as stomach cancer, another was freed of cancer after his leg was amputated, and the disease of the fourth was not revealed by Durbin. That year the AEC contacted the doctors of the four and asked them to tell them about the injections; this was done except in the case of the woman who was ill.

Durbin says the absence of contemporary written records indicates that everything was very secret and most communications were probably oral. She says that if there was any follow-up on the patients it did not last long—both the new AEC and the investigators involved felt embarrassed and ashamed about the study and wanted to put it behind them as quickly as possible.

Another reason for the lack of follow-up is that the sole purpose of the study was to find out how fast the body gets rid of plutonium. It was discovered that human kidneys are at least 50 times less efficient than animal kidneys at removing plutonium. "If animal data had been used," says Durbin, "permissible levels would have been set much higher."

Mention has been made of the experiment in various scientific journals throughout the years and in 1972 Durbin wrote it up for a book called *Radiobiology of Plutonium* (J. W. Press, University of Washington, 1972). The newsletter *Science Trends* gave the first news account of it after Durbin and Rowland presented a paper last October at a workshop on plutonium and radium. They concluded from their investigation of the study that "bone-tumor risk from plutonium is no greater than that from radium, and might be less." As for cancer of the liver, the other most likely site, the authors say the doses weren't high enough to make its occurrence likely. The experimental group was too small and the survival times too short, given the long latency period for cancer, for the project to have yielded any more definite information.—C.H.

PAM and women randomly assigned to the "experimental" group receive L-PAM plus 5-fluorouracil (5-Fu).

Before long, according to Fisher, patients receiving L-PAM plus 5-Fu will become the control group while women in the experimental group will be given one of three combinations of three drugs.† New protocols are before NCI now and will be reviewed within a week or so. "We are going about this in a very orderly manner," says Fisher. "First, we tested a drug versus nothing, then one drug versus two. Now, we'll look at other combinations. The point is to find the minimal treatment that will do the job with minimal toxicity. We're putting everything we know on the line in breast chemotherapy now. The next 10 years will be the ones that count in telling us whether we're succeeding."

While the NSABP study was going on, NCI investigators were experimenting with the three-drug CMF therapy, which they developed, and the Institute was anxious to initiate a controlled clinical trial using it. Fisher's group, which includes collaborators all over the country, was already tied up in the L-PAM study. NCI looked around the country for a large institution that would be willing to conduct the CMF study but found none. Surgeons at one leading institution, for example, refused to cooperate because they still do not believe there is a role for drugs in breast cancer therapy. So, the NCI turned to Bonadonna and his group in Milan. There is a lot of breast cancer in Italy and the Milan cancer institute sees a large number of patients, which is important if one wants to get useful data in a reasonable amount of time. And the group there was enthusiastic about doing the study. It was begun late in 1973 and has, by now, included 386 women, each of whom had radical surgery for breast cancer with lymph node involvement.

Bonadonna and his colleagues declare in their article that "These results should be considered with caution, since, at present, the effect of this therapy on survival and possible long-term side effects remain unknown." They call their results "promising" but say, "This optimism should be tempered by a few important considerations." It is too early to tell whether CMF therapy is merely delaying recurrence or actually lengthening survival. There is evidence, the Italian team notes, that breast cancer behaves as a "chronic disease" and may reappear as many as 20 years after initial surgery. Furthermore, it is not yet possible to tell whether the CMF

†The three-drug combinations are L-PAM + 5-Fu + Methotrexate, L-PAM + 5-Fu + C-parvum, an agent that stimulates the immune system, and L-PAM + 5-Fu + Tamoxifen, an anti-estrogenic compound.

combination, which is more toxic than single-drug therapy, is actually any better. Side effects include nausea and vomiting, temporary (maybe permanent) sterility, and, most serious, bone marrow suppression and a decrease in the number of white blood cells in circulation.

With Bonadonna's preliminary results in, the question of where one goes from here becomes difficult to answer. Is it ethical to withhold all postsurgical treatment from one group of women? Could such a study be conducted in this country where the present climate is one in which the ethics of human experimentation are foremost in everyone's mind? DeVita answers that he is not sure, saying that a case could be made on both sides. He, himself, would argue against "doing nothing" for women with positive nodes. However, because of the risks inherent in the drugs themselves, he would not recommend adjuvant therapy for women with no nodal involvement because 75 percent of them survive for 5 years or more with surgery alone. Newell says it is ethical to do nothing postsurgically for a control group as long as you do not know whether the drug therapy is any good and cites the decision on L-PAM in the NSABP study. Whether the protocol in the Italian study will be modified remains to be decided.

The issue of the risk imposed by toxic chemotherapeutic drugs is one not likely to be resolved for some time. Holland, in his editorial, has this to say. "The risks of carcinogenesis, fatal drug intoxication, and other morbidity are certainly much less hazard than the certain death that inexorably follows clinically evident metastatic cancer."

The other side of the issue was well expressed recently, also in the *New England Journal of Medicine*. Writing in response to publication of preliminary data from the Fisher-NSABP study, which received wide public attention because it came out about the time Mrs. Gerald Ford was having breast surgery, Mary E. Costanza of the Tufts–New England Medical Center Hospitals in Boston argued for caution. "All in all," she said in the 20 November 1975 issue, "there is reason to be skeptical as well as optimistic about the effects of long-term chemoprophylaxis against breast cancer. Unfortunately, no one can rationally weigh the benefits against the disadvantages, since final results are simply not yet available. . . . It is much too soon to regard chemoprophylaxis in breast cancer as a proved method of treatment." For now, she believes, it should not be undertaken by nonresearch physicians, "however well intentioned," but should be regarded as the experimental procedure it still is.

—BARBARA J. CULLITON

Science Indicators: New Report Finds U.S. Performance Weakening

American leadership in science and technology appears to be diminishing by most available indicators, according to data in a cautiously worded report just issued by the National Science Board, the policy-making body of the National Science Foundation.

The report, entitled "Science Indicators—1974," was transmitted to Congress by President Ford on 23 February.* It is the board's seventh annual report and the second to present measurements of the strengths and weaknesses of science and technology in the United States. The indicators reflect a varied mass of data, ranging from employment statistics to patent awards to literature citations and trade balances. By some measures, the United States has improved its performance in absolute terms in recent years, but other countries have improved even more, thus reducing the American lead. In other cases, the American performance has deteriorated in absolute terms.

The report resolutely refuses to reach any overall conclusion as to whether American science is healthy or weak and whether one should be content or alarmed about the trends that it documents. Staffers who had prepared the predecessor report, "Science Indicators—1972," had attempted to include a series of conclusions and recommendations in that report. But the material was excised because of opposition from the National Science Board and the Office of Management and Budget, which felt that the indicators were not adequate to measure the entire scientific enterprise and that even the limited indicators available were often difficult to interpret. So this time there was not even a serious attempt to tease a general conclusion from the data presented.

Nevertheless, for what it's worth, the bulk of the indicators that are used to compare the United States with other countries appear to be headed downward. This is true both of the indicators that measure the resources being put into research and development—such as money and manpower—and the indicators that measure the results coming out of a nation's research establishment, such as publications, Nobel prizes, patents, innovations, and productivity. Only two major output indicators—international exchange of technical "know-how" and balance of trade in research-intensive products—show improvement in the U.S. position.

The indicators provide new insight on the importance of basic research to technological innovation, and on the relation between the size of an industrial firm and its ability to innovate. They also reveal that the American public, far from being disenchanted with science and technology, has actually grown more supportive in recent years (see box, p. 1032).

Where possible, the performance of the indicators is traced over a decade and a half, from 1960 through 1974. Like its predecessor report, the new report deals primarily with the resources put into R & D, since these are relatively easy to measure. But it also sets forth new measures of research "outcomes," some of which were developed especially for this analysis, and it extends the coverage of some indicators that were used in the previous report.

Virtually every section of the report is hedged with caveats warning about weaknesses in the data or difficulties in its interpretation. But the general message of the figures seems to be that, while the United States is still ahead by many measures, its lead is being eroded.

The downtrend shows up dramatically, for example, in a study of technological innovation that was conducted specifically for this report by an outside contractor, Gellman Research Associates, Inc. The study investigated some 500 major new products or processes brought into commercial use over the past two decades. The list included such innovations as nuclear reactors, oral contraceptives, integrated

*The report is available from the U.S. Government Printing Office, Washington, D.C. 20402; stock No. 038-000-00253-8, $4.60. It was prepared with the assistance of the National Science Foundation's Science Indicators Unit, headed by Robert W. Brainard and Robert R. Wright.