# Cancer Institute Unilaterally Issues New Restrictions on Mammography

In the continuing controversy over the routine use of mammography in screening for breast cancer, the case for x-raying the breast to look for tumors in women who have no symptoms seems to be getting weaker and weaker. Therefore, despite the fact that the American Cancer Society (ACS) continues to defend routine mammography, the National Cancer Institute (NCI) finally has decided that it will no longer endorse mammography for mass screening of women under 50 unless they have a personal or family history of breast cancer. Last week the NCI issued new, rigid guidelines that restrict the use of x-rays in the Breast Cancer Detection Demonstration Project (BCDDP) that it has cosponsored with the ACS since 1973.

At present, the guidelines bear only the imprimatur of the NCI, ostensibly because the ACS's own breast cancer task force cannot review them until it meets in June. Asked whether it is likely that the ACS will put its name on the guidelines after that meeting, one cancer society official said, "Sure. We have little choice but to go along if the NCI insists on this position. They're putting up most of the money. Considering that we're talking about a project with some 270,000 women, we can hardly do it without them."

From the project's beginnings about five years ago, there has been disagreement between the NCI and the ACS about how it should be organized. A number of NCI researchers wanted the project set up as a controlled clinical trial, with some women getting physical exams and others getting physical examination of the breast plus mammography. But cancer society officials, motivated by a desire to make the latest technology available to the largest number of women, argued for a so-called "demonstration" project instead, in which mammography would be offered to all women in the program in order to demonstrate that it is valuable in detecting breast tumors early—when they are small and, presumably, curable. It was 1972 when the project was being planned. The "war on cancer" had just begun. Politically the time for a mass attack on a lethal form of cancer was ripe. The ACS prevailed. Frank J. Rauscher, Jr., then director of the NCI, was persuaded that a demonstration project made sense and the National Cancer Advisory Board voted—without much enthusiasm—to approve it. At the time, questions about the risks versus benefits of x-ray exposure that now dominate the mammography debate were somewhat perfunctorily answered in mammography's favor. Today, Rauscher, who recently left NCI to become vice president for research at the ACS, is of mixed mind on the subject. While recognizing the validity of some of the criticisms of the project, Rauscher worries that the controversy is "giving mammography an undeserved bad name. The radiation dosage is decreasing all the time," he told *Science*. "Mammography is getting safer and maybe better but we're going to have a hard time a couple of years from now convincing women of that, even if we get absolutely firm data that it is."

But it is not Rauscher who is mammography's staunchest supporter within the ACS. Rather, it is Arthur I. Holleb, a breast cancer surgeon who is the society's senior vice president for medical affairs. Holleb, who has seen plenty of breast cancer first hand, speaks with the conviction of a physician who believes that the epidemiologists and others who talk about statistics and such simply do not understand how important it is to find breast tumors early or that mammography—particularly with newer techniques—is doing that job. "Will there never be an end to the 'biological determinists' and 'therapeutic nihilists' who minimize the importance of early diagnosis and prompt treatment, yet rush their wives to the physician's office at the first suspicion of possible cancer?" he asked in a letter written to NCI in 1973 in response to criticism of mammography screening. Probably not.

What had been underground attacks on the NCI-ACS mass screening program that were relatively well suppressed for years, came to light with great clarity more than a year ago when John C. Bailar III, editor of the *Journal of the National Cancer Instititue*, published his own arguments on mammography's risks. Then, open controversy about the value of mammography for screening erupted last summer, at a meeting at NCI, where those who oppose and those who favor mammography joined the issue (*Science*, 13 August 1976). In the ensuing months, the intensity of the debate has escalated as clinicians, whose views are epitomized by the position of the ACS, have tried to undo the damage they believe has been caused to women who were convinced by news stories that mammography is dangerous. In October, Benjamin F. Byrd, Jr., a surgeon who was 1976 president of the cancer society, and currently is head of its breast cancer task force, declared, "We know there are more than 245,000 American women with undiscovered breast cancer, and we will not abandon them."

Subsequently, in an interview published in this March's issue of *Reader's Digest*, Byrd spelled out the society's position in full, making it very clear that the ACS has not been persuaded by those who fear mass screening with mammography can do more harm than good. Byrd's assertions include the following:

- . . . women without symptoms who are 35 and over should have at least one mammogram.
- Mammograms should be done at the physician's discretion in women with a higher than normal risk of breast cancer. In this group, I believe, are women with chronic cystic mastitis; lumps and thickenings in the breast; nipple discharge or other nipple abnormalities; a personal history of breast cancer; a family history of the disease; early onset of menstruation; no history of pregnancy; first full term pregnancy after age 30. In addition, mammography is a valuable adjunct to diagnosis in women who have unusually large breasts, which are difficult to examine. In the NCI-ACS experience, about 80 percent of women 35 to 50 meet one or another of these criteria.
- . . . the results of mammography in discovering early, curable breast tumors are indisputable. . . .
- And even if there is a slightly increased risk of her getting the disease in the distant future, there's also an excellent chance that by that time science will have learned how to control breast cancer.

In light of the ongoing debate about mammography, it is apparent that many scientists do not agree with Byrd's assertions. Indeed, definitive remarks such as his have done nothing to ease strained relations among various factions in this battle, particularly coming as they did just when the NCI was about to release the reports of three groups it had commissioned in 1975 to evaluate mammography's benefits and risks. Taken together, the final reports of the Ad Hoc Working Groups—on epidemiology, pathology, and radiation—deal mammography screening a stunning blow.

In considering the arguments for and against mammography, it is important to bear in mind that they are made strictly in the context of its use as a tool for *mass screening* of apparently healthy women. At issue is whether we know enough about the risks and benefits of mammography to offer it broadly as a public health measure, as though it were polio vaccine.

[For the present, at least, there is little controversy about its use diagnostically—for the woman with a lump in her breast, although even this has been called into question. In a recent paper in the *Journal of the American Medical Association* (7 March), investigators from Mount Sinai School of Medicine in New York report on cases in which mammography failed to confirm the presence of tumors that had been felt by doctors on clinical examination. As a result of the false-negative mammograms, they observe, surgery was delayed. They do not, however, argue against diagnostic mammography. Instead, they conclude that no one should ignore physical findings just because a lump doesn't show up on an x-ray.]

Radiobiologist Arthur C. Upton of the

# Battle to Legitimize Laetrile Continues Unabated

The intensely emotional controversy surrounding Laetrile, the illegal substance used to combat cancer, has erupted into the headlines again. On 30 April, Indiana became the third state to legalize Laetrile. And in early May the Food and Drug Administration conducted two days of court-ordered public hearings on the drug in Kansas City.

The hearings stem from an injunction issued in 1975 by Oklahoma district court judge Luther Bohanon which permitted a group of terminal cancer patients to bring supplies of Laetrile across the border from Mexico, where it is manufactured, for their own use. The FDA appealed the ruling. Last October the 10th Circuit Court of Appeals ruled that the FDA's record of support of its case was "grossly inadequate" and remanded the case to Bohanon with instructions for the FDA to hold hearings and compile a better record. Findings are due within a month.

Chances are practically nonexistent that the FDA will budge one iota on its position, which is that Laetrile, which is produced from apricot pits, is an "unlicensed new drug" of dubious safety and zero efficacy against cancer (*Science*, 10 September 1976).

That stance is backed by the National Cancer Institute, the American Cancer Society, the American Medical Association, and most physicians.

Yet try as they might, none of these groups has been able to put the lid on Laetrile. Supporters of the drug (which they claim is not a drug but a natural food substance), including such groups as the Committee for Freedom of Choice in Cancer Therapy, have become more numerous and better organized than ever.

In addition to winning several court injunctions allowing patients to obtain Laetrile without harassment, they have succeeded in getting pro-Laetrile bills through the legislatures of Alaska, Florida, and Indiana. The Indiana law, passed over the veto of physician-governor Otis R. Bowen, is the most far-reaching one. It not only permits physicians to administer Laetrile but permits sale and manufacture of the substance (federal law still prohibits interstate commerce in apricot pits for manufacture of Laetrile). Related measures have been passed by one house in each of five states, and are pending in 28.

Meanwhile, Laetrile proponents think they have found a champion in Congress in the person of Representative Steven D. Symms (R–Idaho) who has introduced a "Medical Freedom of Choice" bill. This measure, which has 97 cosponsors, would repeal the 1962 amendments to the Food, Drug, and Cosmetic Act that require a drug to be proved effective as well as safe before marketing. A Symms aide explains that the purpose of the bill is to facilitate the flow of new drugs onto the market and reduce testing costs, and that it is "*not* a Laetrile bill." The effect, however, would be to remove the major stumbling block—proof of efficacy—to its marketing.

As the movement grows, the conflict has become increasingly ugly. Mixed with the political conservatism of many of Laetrile's chief promoters is a more fundamental suspicion of constituted authority and the medical establishment in particular. At the FDA hearings, for example, Emil J. Freireich of the University of Texas Medical School at Houston and the M. D. Anderson Cancer Hospital said: "You surely cannot believe that a quarter of a million of American physicians are sitting on a cancer cure just so they can get rich?" He was answered with a chorus of yeses from the audience, many of whom had been borne to the hearings on chartered buses.

The Laetrile craze may be a fad, but it has already proved to be one with an unusually long life and one that is still growing. The adamant stance of the government seems only to add fuel to the fury. The FDA insists that allowing the stuff on the market would encourage its use as an anticancer drug despite any disclaimers on the label, but there are a good many people who sympathize with cancer sufferers who believe they should be allowed to use anything they think might help them. Indeed, the *New York Times* on 5 May came out with an editorial in the form of a dialog on Laetrile that concluded "After all, shouldn't people be allowed to choose their own placebo, for better or for worse?"

Another way to try to defuse the controversy would be to bypass animal studies (which have been negative or inconclusive) and go to a human trial of the drug. The Washington *Star* quotes Lewis Thomas, president of the Sloan-Kettering Institute for Cancer Research, as saying: "ordinarily no one would think of doing a clinical trial on a drug that has essentially been found ineffective in animal tests. However, this is a special case. With all the claims being made, I now think a clinical trial would be appropriate." Such a trial, however, would be extremely difficult to devise and would be unlikely to change anyone's mind.

The Laetrile issue is like a toadstool sprung up and nurtured in a murky environment of public distrust—in government, scientific research, and, in particular, physicians. "Practicing physicians," says John Jennings of the FDA's Bureau of Drugs, have "concentrated on diseases rather than patients. Laetrile practitioners are good at treating patients. . . . It's a message to all of us that we have to recapture the confidence of the population at large."

—C.H.

State University of New York at Stony Brook (and a candidate for the job of NCI director) headed the ad hoc working group that looked at the question of breast x-rays inducing unnecessary cancer, concluding that an exposure of 1 rad would increase an individual woman's risk of getting breast cancer by 1 percent of the normal risk of getting it no matter what. That means a 0.07 percent risk rises to a risk of 0.0707 percent. For the individual woman, Upton notes, that risk is very small indeed and, he says, "I'm not anxious to see mammography [for diagnosis] fall into disrepute. But when we go to mass screening we're in a different ball game. Even a small risk to the individual gains significance when applied to millions in the population." Thus, the Upton group estimates that exposing 1 million women to a 1-rad dose might induce 110 to 240 excess cases of breast cancer. If such examinations were to be repeated annually, the number of breast cancers that might be caused by mammography climbs to 3100 to 6700. "It would not be sound public health policy to advocate routine mass screening of large numbers of asymptomatic women unless the predicted benefits would clearly outweigh the presumptive risks, however small the latter might seem to the individual," the report states. Furthermore, the problem of determining risk is compounded by the real-life fact that most mammograms today deliver a radiation dose of more than 1 rad. Says Upton, "Things are improving in this regard but certainly not everyone is at 1 rad now, though I believe it is an achievable goal."

The salient points in the new NCI guidelines are these:

- Mammography will still be offered to women over the age of 50, in whom the incidence of breast cancer is highest. However, this policy will explicitly be reevaluated during coming months. Contrary to conventional thinking about the value of mammography screening in women over 50, the ad hoc groups question the assumption that benefits outweigh risks even in older women.
- Asymptomatic women under 50 will not be given a mammogram unless (i) the particular woman has previously had cancer in one breast, in which case one would want to watch carefully for signs of a lump in the remaining breast; or (ii) a woman's mother or sister has had breast cancer, inasmuch as there is good evidence of genetic susceptibility to the disease among immediate relatives. Here, the NCI has pared a long list of so-called "risk factors" down to the two it considers to be most certain.

The NCI's decision to take this tough, conservative stand on mammography—a stand many scientists believe is long overdue—is based on data from the three review studies and on information that the heads of many of the 27 NCI-ACS screening centers were not paying any attention to the vague "interim guidelines" that were issued jointly by NCI and ACS last August. Those guidelines, written with the ACS's pro-mammography stance very much in mind, said, in effect, that no woman under 50 should have a mammogram—unless she or her physician want her to. Given the fact that many of the BCDDP center directors stated quite clearly that they support mammography screening, it is no surprise that most of them chose to interpret the interim guidelines loosely. The new guidelines are not subject to such interpretation.

### Risk from Mammography Very Small

The likelihood that breast x-rays will cause cancer is small but real. The data indicating that mammography catches tumors early, thereby saving lives, are not very solid (preliminary data from the BCDDP on this point are being evaluated now). And the cost of mammography in dollars and time is very high. The committees decided the evidence does not stack up on mammography's side. The final reports of the ad hoc working groups are low-key but surprisingly straightforward. Cumulatively, they constitute an indictment of mammography for mass-market use. Instead of promoting it wholesale, the reports say in restrained but clear tones that the cancer institute should conduct controlled clinical trials to find out exactly how mammography should be used. (The NCI and ACS have resisted this notion ever since 1972, when the two organizations first planned the breast cancer screening program at the ACS's initiative.)

The decision to issue new, strict guidelines to the screening centers was not an easy one. Nonetheless, NCI acting director Guy Newell and Diane Fink, the head of NCI's division of cancer control, decided the time had come. On 22 April, Fink circulated the new guidelines at a meeting of the heads of the 27 centers who reluctantly agreed to accept them. An ACS representative was present, but the guidelines subsequently were not circulated among members of the society's breast cancer task force, a sore point with some of them. On 27 April, Newell and Fink discussed the situation with National Institutes of Health (NIH) director Donald S. Fredrickson, who had wanted clearer, stricter guidelines from the start. On 3 May, Fink presented them to the advisory committee for her division, again getting approval. And, so, the decision was made.

The ACS, with no official response to the guidelines, issued no formal comment on the NCI reports, which were available early in March. Even the NCI itself responded cautiously at first. It sent out an "it may not be as bad as it seems" statement which says that, maybe by June, when preliminary data from the current NCI-ACS program are evaluated, there will be evidence showing that, because of the program, lots of tumors are being detected earlier than ever before.

According to Fink, in the four and a half years that the NCI-ACS project has been running, about 14 percent of the small (1 centimeter or less) invasive tumors that have been found in women under 50 were detected by mammography alone. But just what this means remains to be determined. The NCI has commissioned yet another special advisory committee to try to find out. By conducting pathological analyses of each of the small invasive tumors and the in situ, noninvasive tumors that have been identified by mammography, on a case-by-case basis, the committee hopes to answer questions about whether mammography really is picking up early cancer or whether some of what is being called early cancer is simply benign cystic disease. It is expected to complete its review by the beginning of this summer.

One thing that has disturbed cancer society officials about the NCI's decision to issue new guidelines now is that the analyses of the data from the BCDDP projects are not yet in. The data that argue against mammography screening are inferred from the HIP (Health Insurance Plan) of Greater New York study that was begun in 1963 at a time when mammographic techniques were not nearly as sophisticated as they are today. Confident that the evidence from the NCI-ACS project will vindicate the use of mammography in finding cancer early, some ACS people are clearly unhappy that the NCI was unwilling to hold off on the new guidelines until fall.

Upton's report raises questions about the radiation risks of mammography. The report of the Pathology Working Group, headed by NCI pathologist Louis B. Thomas, raises questions about mammography's benefits. Of some 60,000 women enrolled in the HIP study since 1963, 582 have developed breast cancer. By contacting some 90 hospitals in the New York area, Thomas and his col-

leagues were able to collect tissue slides from more than 80 percent of those cases, which they proceeded to evaluate to see whether their opinions about the size and nature of the cancers matched those that were on the record. They paid particular attention to cancers reported to be found by mammography alone; that is, tumors not detected by manual examination (palpation) of the breasts.

What the Thomas group discovered was that a fair number of tumors 2 cm or larger in size were missed the first time around by both mammography and physical examination. For example, 41 percent of women with tumors 2 cm or larger had negative mammograms. Furthermore, there were 19 tumors listed in HIP data as being found by "mammography alone" that turned out to be relatively large—3 cm or more. Inasmuch as every woman who had mammography also had palpation, Thomas concludes that "It is difficult to understand how or why these could have been missed on clinical examination." Thus, the Thomas group decided that those 19 cases said more about the skills of the examining physician than they did about the virtues of mammography and deleted them from the "mammography alone" category. Taking all things into account, the group concluded that the original inferences about the benefits of mammography drawn from the HIP were overblown. However, Thomas emphasizes the fact that the HIP study never was designed to separate the value of mammography from clinical examination and says that, were new data to show that mammography really can pick up very early infiltrating cancer, he would be ready to change his mind about its value in screening.

The arguments against mammography screening appear to be based on cool scientific logic. Those for it often seem to be intuitive and come from physicians and surgeons whose daily business is the treatment of breast cancer. They maintain, though they do not have the hard data to prove it, that they are finding cancer earlier than ever before, that they, therefore, can offer women less mutilating surgery than is necessary for advanced cancer; and that—in the end—they are prolonging lives.

The fact of the matter in this terribly difficult case is that there is no objective way to say who is right. Radiobiologist Upton calls this a "paradigm of the kinds of problems we're facing on the uses of technology versus social costs." Neither the HIP study nor the NCI-ACS screening project were designed to answer important questions about the benefits of mammography, or how often it should be used, or on what group of women. NCI is under considerable pressure now to initiate such a study—or possibly studies—to find out Acting Director Newell supports that idea, saying "We really have to get some clean data on this, which probably means we'll have to start some completely new controlled clinical trials."

Brian E. Henderson, an epidemiologist at the University of Southern California at Los Angeles, who was a member of the NCI's epidemiology-biostatistics working group, strongly endorses Newell's view. "I think we should use mammography as little as possible until we learn how to use it," Henderson says, adding that for screening purposes he thinks it should be used "only in controlled clinical trials—even for women over 50."

The justificiation given for screening women over 50 is that they are more likely to get breast cancer than younger women, and that, because of changes that occur in breast tissue after menopause, it is easier to get a good picture of their breasts than it is in younger women with denser, more hormonally active breast tissue. In addition, Upton reports that there are some data suggesting that a woman's risk from radiation exposure decreases with age. If that is so, women over 50 are less likely to get breast cancer from the x-rays of mammography. On the other hand, Henderson points out that there are data that indicate a synergistic effect between radiation and hormones. Inasmuch as many women over 50 take estrogens, thereby approximating in some ways the hormonal status of a younger woman, there may be an argument against mammography in at least that group of older women.

The upshot is that the situation is extraordinarily confusing. It seems that there is no evidence that is clear-cut, and the answer to the "should she or shouldn't she" have a mammogram question is that nobody knows for sure. Given the present state of affairs, the NCI's position seems eminently sensible.

The resolution of the controversy is not in sight. But the next chapter will be written in September when Donald S. Fredrickson hosts what is euphemistically being called a "consensus" meeting on mammography. Among other things to be decided then is the question of whether the NCI, with or without the ACS, should embark on controlled trials, the results of which would be a decade in coming.—BARBARA J. CULLITON

# Smithsonian: "The Nation's Attic" Undergoing New Federal Scrutiny

These are trying times for the Smithsonian Institution. It is being pecked at by the Washington *Post*, poked into by the General Accounting Office (GAO), grilled in Congress and—the latest insult—has received Senator Proxmire's Golden Fleece Award of the month for allegedly worthless government projects (in this case, a Tzotzil dictionary).

Criticism has been directed both at the allegedly cavalier modus operandi of the secretary of the Smithsonian, patrician ornithologist S. Dillon Ripley, and at the way the institution handles its funds, 87 percent of which are supplied by the federal government.

There have been no formal accusations of illegality or impropriety in the Smithsonian's operations. Yet the cloud of question marks has prompted the institution's own Board of Regents to propose contracting for an independent study in order to clear the air. The GAO study continues.

As a semipublic, semiprivate organization, the Smithsonian has an unusual relationship to the federal government. It has always enjoyed considerably more flexibility in the use of its money than have federal agencies. In the past year or so concerns have been raised in Congress about the commingling of public and private funds; about whether the Smithsonian is relying too much on its own discretion in acquisition and disposition of properties that receive federal money; and about the nature of two private corporations administered by the Smithsonian.