Prostate Cancer Consensus Hampered by Lack of Data

A consensus panel was unable to decide on clear-cut recommendations for treatment of early prostate cancer because the necessary data simply do not exist

ABOUT a year ago, the National Cancer Institute suggested a consensus conference on prostate cancer. But some scientists said it was a bad idea. So little is known about the diagnosis of this cancer, its course, and the best treatment that a consensus panel is going to have a very hard time reaching any sort of conclusion, they said. The data that are available are retrospective and it is difficult if not impossible to compare data between institutions.

But the NCI pressed ahead with the conference anyway, arguing, says John Antoine of the NCI, that the data were not going to get any better if they wait and that "it is time to find out exactly where we are." A conference was held on 15 to 17 June at the National Institutes of Health, and it turned out that the skeptics were right. The consensus panel was so hobbled by the lack of solid information that it ended up making only the blandest of statements, one that is unlikely to help either patients or their physicians deal with this disease.

Panel chairman Robert Livingston of the University of Washington in Seattle conceded as much at a press conference following the meeting. "We are not dealing with a situation comparable to node-positive breast cancer where there are a host of randomized studies," he said. "We are dealing with a situation where data have been accumulating but they are difficult to compare and we don't have randomized controlled trials to help us. We can only offer vague guidelines." For that reason, he said, the goal of the consensus statement was to "stimulate the government to support randomized controlled clinical trials and to stimulate responsible members of the medical community to support [such] trials and to enter patients."

The panel was asked to decide how patients should best be diagnosed, which patients should have surgery and which radiation, when patients should have adjuvant therapy in addition to radiation or surgery to destroy the primary tumor, and, as always, what directions future research should take. Only the question on what future research directions should be was definitively answered.

Moreover, many important questions about prostate cancer were completely left out. For example, the panel was not asked about the best treatment for men whose cancer is not entirely confined to the prostate. Only about 15% of all prostate cancer patients have small tumors confined to the prostate when they are initially diagnosed. The panel also did not address questions of early diagnosis. "I'm not trying to tell you that detection isn't important—it is," says Livingston. "We desperately need better ways to detect early. But management [of prostate cancer] was the charge of the panel."

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The lack of reliable data even for the early prostate cancer was striking because prostate cancer is hardly an obscure disease. Cancer of the prostate, the gland at the base of the penis that produces seminal fluid, is the second most common form of cancer in American men. About 100,000 new cases are diagnosed each year, primarily in older men. The average age at diagnosis is 70. And although the disease has a reputation for being relatively benign and slow to progress, a certain proportion of men with prostate cancer will die of the disease if they are untreated.

One problem, however, is that no one knows which men with early prostate cancer will have a very slow-growing cancer and which will have a tumor that is rapidly growing and invasive. "We know that there are some patients that have a disease that has a benign natural history," Livingston says. "We also know that there is a patient population that has a tumor of the same size and that looks the same under the microscope and their disease will progress and kill them. Our present dilemma is that we don't have a tool to tell us which is which."

American doctors, reluctant to take a chance, tend to treat essentially all patients with radiation or surgery. Doctors in other countries are not always of the same mind. In England, for example, most patients with small tumors have limited surgery to relieve the obstruction and then, says Livingston, "they are left alone."

Because American men are so likely to be treated, there is all the more urgency to the surgery versus radiation debate. The drawback to surgery is that it usually severs nerves to the penis and leaves men impotent or, less frequently, incontinent. The drawback to radiation is that it may not destroy all of the tumor. In addition, it may cause impotence. A small number of radiation patients report that they are impotent after treatment, presumably because radiation damages blood vessels that supply the penis. According to the consensus panel, there are no good data on how many men receive surgery and how many receive radiation in this country, but it is clear that both techniques are widely employed.

Given a choice between impotence or death from disseminated cancer, most people would choose impotence. And the panel stressed that point. "We want to warn physicians that a patient's risk of dying should come first before the risk of impotence," Livingston says. However, the choice between surgery and radiation is not simple. First, it is not clear that the surgery patients and the radiation patients are really comparable. When they operate, physicians can actually see the extent of disease. If the disease is limited to the prostate and the prostate is removed, patients have less than a 10% chance of local recurrence in the next 15 years.

The only way to estimate the extent of disease in radiation patients is to ask the patient about his symptoms and to feel the prostate with a rectal exam. So it is never completely certain that the radiation patients whose disease, the physicians suspect, is limited to the prostate, actually have such

a small tumor. For this reason, says Livingston, it is not clear how to assess the finding that radiation patients have a "somewhat higher" rate of local recurrence of their cancer.

Another factor is that surgery seems to be improving. With new techniques, most younger patients may come through the operation with their potency intact. Patrick Walsh of Johns Hopkins University School of Medicine reported at the consensus conference on a surgical technique that involves a small incision made between the scrotum and the rectum that does not cut the tiny, weblike nerves that control potency. Of 340 men operated on by Walsh and his colleagues, 74% who were potent before the operation were also potent afterwards.

Walsh warns, however, that "age is a very important factor." Of the men who were in their 30's, all were potent after the operation. But only 14% of those aged 70 to 79 were potent afterwards and, says Walsh, "after age 70, it is highly unlikely that a man will be potent after a radical prostatectomy."

The standard radiation treatment, which is to irradiate the prostate 5 days a week for 7 to 8 weeks, can cost $7000 to $8000. Costs vary throughout the country, but surgery typically costs twice as much as radiation. So if the two methods are indeed comparable, it would certainly be more cost-effective to treat with radiation. A good clinical trial comparing surgery and radiation is on the panel's list for future research.

Other of the panel's suggestions for future research address the profound lack of good data available. For example, the panel wants clinical researchers to "accept a uniform method for data reporting and statistical analyses that will allow meaningful comparisons of treatment results reported by various disciplines," and to "agree upon a uniform clinical and pathological definition of stage A1 [the earliest stage] prostate cancer."

The panel says in its statement that patients should have available information on "the probability of cure, mortality, complications, and other side effects of radical prostatectomy and radiation therapy, the risk of impotence and incontinence for either treatment, psychosocial consequences of either choice, the extent and risk of pretreatment staging assessment tests, and the economic consequences of each form of treatment." But considering the dearth of information at the consensus conference, patients may have to await another consensus conference several years from now before they can have the more definitive information this panel deems essential. ■ GINA KOLATA

Cytokines Alter AIDS Virus Production

A central question in AIDS research is why an infected but otherwise healthy person suddenly develops signs of disease. The answer depends, at least in part, on understanding why cells that are silently infected with the AIDS virus suddenly begin to produce virus. Anthony Fauci and Thomas Folks of the National Institute of Allergy and Infectious Diseases (NIAID) find that cytokines, substances normally produced by activated lymphocytes and cells of the macrophage line, can stimulate a latently infected cell that carries the silent form of the AIDS virus in its genome to produce mature virus particles.

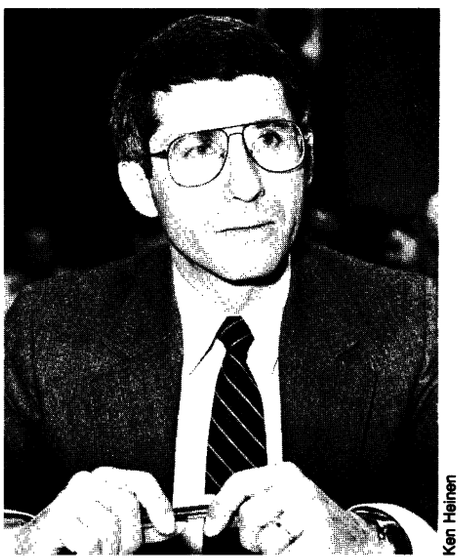
"Any of a number of things—mitogens, antigens, other viral infections, and normal physiological stimuli like cytokines—can convert a latent infection to a productive one," said Fauci in an interview at the recent AIDS meeting.* "So we are now at the molecular level and can give some scientific basis for conversion of latency to productivity."

In order to demonstrate the cytokine effect, the NIAID group first developed a line of cells that could carry the latent form of the AIDS virus (human immunodeficiency virus or HIV) in its genome and would suddenly produce virus with the appropriate stimulus. Their new U1 cell line fit the bill. Derived from a line of monocyte precursor cells that is chronically infected with HIV, the U1 clone also carries a latent virus infection.

The next step was to identify what factors trigger virus production from the chronically infected U1 cells. After finding that tissue culture fluid containing a mixture of cytokines stimulates HIV production, Fauci and Folks then identified which specific cytokine was active. "We tested recombinant lymphokines—interleukin-1, interleukin-2, gamma-interferon, tumor necrosis factor, and granulocyte/macrophage colony-stimulating factor (GM-CSF)," says Folks. "And only GM-CSF stimulates HIV production from infected U1 cells." In vivo, activated T lymphocytes produce GM-CSF, and in the U1 in vitro system the factor stimulates HIV production three- to fourfold. Folks also reports that gamma-interferon has the opposite effect because it strongly inhibits virus expression from the latently infected promonocyte cells.

A similar approach toward understanding interactions among cytokines and HIV infection led the NIAID researchers to a second conclusion: not only do cytokines appear to regulate the production of the AIDS virus from infected cells, but the reverse is also true. Latent infection of the U1 cells with HIV leads to increased cytokine production.

"The infection of U1 cells with the AIDS virus is associated with the regulation of gene expression for interleukin-1β (IL-1β), a cytokine normally made by activated monocytes," says Fauci. "So you have both sides of the coin. Some cytokines increase the expression of the AIDS virus, and the virus increases the expression of certain cytokines."



Ken Heinen

Anthony Fauci *reports that certain cytokines stimulate or inhibit AIDS virus production from infected cells in vitro.*

This increased production of IL-1β is at least somewhat specific to HIV infection because a more general stimulus—again, tissue culture medium containing a mixture of cytokines—does not have the same effect. What does mimic the effect of virus infection, however, is stimulation with phorbol myristate acetate (PMA), a drug that is known to activate the intracellular enzyme, protein kinase C. PMA also has an additional action; namely, it induces virus production from HIV-infected cells.

The new information means that normal physiological stimuli, in this case, cytokine synthesis and function, help to regulate the active production of the AIDS virus from latently infected cells. The new results also show that viral infection can trigger cytokine production. How the two phenomena are coordinated in vivo, specifically in an AIDS patient, is still unclear. ■

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*The III International Conference on AIDS was held 1 to 5 June in Washington, D.C.