75% of new patients have been entered in the system. Other NCCN institutes are at various stages of implementing the guidelines. An implementation committee will meet in June and may establish a timetable, Winn said.

Three NCCN members have conducted pilot “compliance audits” to learn how well the guidelines reflect actual practice. All turned up some cases of non-compliance, often in the areas of diagnostic testing, where the guidelines call only for tests deemed to have an impact on treatment decisions. Stephen B. Edge, M.D., who conducted one of the audits at Roswell Park Cancer Institute’s breast cancer clinic in Buffalo, N.Y., said that the audit validated the NCCN methodology. It demonstrated that the guidelines did work as a benchmark for assessing quality of care, he said.

Edge’s clinic does not have the benefit of a full management information system but has developed a database to track patient care. Edge said that a full-time data manager spends about a fourth of her time maintaining the database in the clinic, which sees about 160 to 170 breast cancer patients a year.

Despite the resources required, Edge is a firm proponent of collecting and using data on patient management. “I think it’s useful and I think it will get to the point where third-party payers are going to demand it of us,” he said.

George D. Demetri, M.D., of Boston’s Dana-Farber Cancer Institute and a member of NCCN’s board of directors, agreed. “Much of the variation in practice is due to a lack of data,” he said. “Once you have a system, you wonder how you did without it.”

— Caroline McNeil

NCCN: Who Is a Member?

The National Comprehensive Cancer Network began with 13 members and now has 15, most in the East and on the West Coast. Other centers may join, said William McGivney, Ph.D., NCCN’s chief executive officer, noting that “there are gaps in the map.” Members are:

Arthur G. James Cancer Hospital and Research Institute
at Ohio State University, Columbus
City of Hope National Medical Center, Duarte, Calif.
Dana-Farber Cancer Institute, Boston
Fox Chase Cancer Center, Philadelphia
Fred Hutchinson Cancer Research Center, Seattle
Johns Hopkins Oncology Center, Baltimore, Md.
University of Texas M. D. Anderson Cancer Center, Houston
Memorial Sloan-Kettering Cancer Center, N.Y., New York, N.Y.
Northwestern University/Lurie Cancer Center, Chicago
Roswell Park Cancer Institute, Buffalo, N.Y.
St. Jude Children’s Research Hospital, Memphis, Tenn.
Stanford University Medical Center, Stanford, Calif.
University of Alabama at Birmingham Comprehensive Cancer Center
University of Michigan Comprehensive Cancer Center, Ann Arbor
University of Nebraska Medical Center, Omaha

Alfred Knudson: Two Hits Times 25 Years

Just over 25 years have passed since Alfred Knudson, M.D., Ph.D., then a scientist at the University of Texas M. D. Anderson Cancer Center in Houston, proposed his famous “two-hit” hypothesis of tumor suppression.

Although groups in the 1960s had theorized that genes must exist that suppress tumor development, Knudson was among the first scientists to propose a stepwise hypothesis of how these tumor-suppressing genes might be selectively turned off in certain familial cancer syndromes.

Knudson formed his famous hypothesis by comparing numerous case studies of inherited and noninherited forms of the rare eye tumor, retinoblastoma. Knudson proposed that children who inherit RB must be born with one hit, or mutation, already in the germline and later acquire a second, tumor-activating hit.

For children with noninherited forms of RB, Knudson speculated that the first hit comes not in the germline, but in an already differentiated retinal cell. He then proposed that this once-hit cell accumulates a second hit later in childhood that triggers the tumor, explaining why noninherited cases of RB tend to arise later than inherited forms of the cancer.

Later, Knudson focused his hypothesis on the RB gene itself. He theorized that each hit must arise in one of the two copies of RB, suggesting that both copies of the gene must be inactivated for a tumor to form in the retina.

In the gain-of-function 1970s, however, Knudson’s loss-of-function hy-
thesis fell mostly on deaf ears. But Knudson’s theory was eventually rescued from obscurity, championed, and proven to be largely correct by molecular biologists studying a number of familial cancer syndromes.

Today, Knudson is hailed as a pioneer of cancer genetics. Most experts point to his theory as laying the intellectual foundation that has allowed a generation of scientists to transform tumor suppressor research into one of the most productive areas in molecular biology.

Now in his 70s, Knudson is still going strong. He divides his time between Fox Chase Cancer Center in Philadelphia, where he has been since 1976, and the National Cancer Institute, where he serves as a special advisor and acting director of the Human Genetics Program.

During a break in his hectic schedule, Knudson recently met with the News and shared some of his thoughts on cancer genetics and where the field might be headed.

**News:** Do you think that we’ll one day understand how tumor suppressor genes and their proteins work?

**Knudson:** Well, I like to think so. Usually, when scientists make a discovery, there seems to be a simple explanation for it. Then, that leads to experiments, and you learn a lot of new things and it’s a mess. Eventually, the things you discover begin to converge and it starts to get simple again. I hope that we’re in the phase of going from the terribly complex down to the simpler.

**News:** Some scientists say that cancer research is in a golden age right now. Would you agree?

**Knudson:** Yes. I’m so old that my first year of medical school was the year that Avery’s paper [on bacterial transformation of cells in 1944] appeared. So, from my first year of medical school, I’ve gone from knowing that genetic material is DNA to having cancer genes in test tubes. It’s amazing. In fact, I sometimes think how can we get people to see that the last 50 years intellectually has been as great as the Golden Age of Ancient Athens or the Renaissance in Florence.

**News:** All of this progress must be incredibly rewarding to you.

**Knudson:** Well, I just feel lucky that I’ve lived through this time. You look back at the end of each decade and there’s a staggering list of things that have happened.

**News:** When cancer occurs, is it the number of mutations, or “hits,” that drive tumor development? Or is it the order in which the mutations arise that matters most?

**Knudson:** I tend to develop hypotheses. I don’t know whether they’re right or not, but they help me keep track of information. They tend to ask you to look for certain things that are coming down the path. And so, I must warn you, these hypotheses may be wrong.

Just to simplify things, I consider that there are three categories of tumors. One is the embryonal tumor. It arises in tissues where the stem cells are multiplying. So, there are many rounds of cell division before differentiation occurs. I made calculations on whether people who inherit one mutation in the germline could develop a second mutation, or hit, based on the usual rate of somatic mutations. I found that they could, that the ordinary mutation rates suffice for a second hit to occur. But I also calculated that people who do not inherit a germline mutation can develop a clone of cells that have one somatic mutation. Rarely, one of these cells may develop a second mutation and become a tumor. In fact, I have estimated that almost 30% of us have clones of once-hit cells in our retina, but differentiation occurred before a second hit could occur. I estimated that the second, cancer-causing hit happens to only 1 in 30,000 people.

**News:** So if you have this clone of cells with one “hit” or event, something else is going to go awry during cell division?

**Knudson:** Yes. The critical thing about the embryonal tissues is that a stem cell that is dividing and not differ-
entitatively is a very dangerous cell. It is the one type of cell that could accumulate several mutations. A second mutation may interfere with cell differentiation and cause a stem cell to lose control of its cycle. This apparently happens with non-hereditary retinoblastoma. So, you can’t just talk about mutation. You also have to talk about the development of the tissue.

**News: What is the second type of cancer?**

**Knudson:** They arise in tissues that bear a resemblance to the embryonal tissues. We see many of them in the Li-Fraumeni syndrome — rhabdomyosarcoma, osteosarcoma, breast cancer. Like embryonal tissues, the target tissues for these tumors have a growth spurt during adolescence rather than near birth.

Girls, for example, have muscle and bone growth, then the breast develops. This separates the breast from all other epithelial tissues that are targets for carcinoma. If a girl accumulates a mutation at puberty when the breast is growing, a clone will develop, as happens in embryonal tissues. In other words, puberty makes the tissue begin to look like an embryonal tissue, ... [but] it’s not as extreme. You’re not going to have as many cell divisions. But it is a dangerous time.

**News: What is the third type of cancer?**

**Knudson:** The third tissue is the common renewal tissue, such as epithelial tissue. You don’t have a physiological process that’s causing stem cell proliferation. In the gastrointestinal and genitourinary tract, and probably the tracheo-bronchial tree and skin, it seems to be necessary to mutate a gene that normally inhibits such proliferation. Now there is a great deal of interest in understanding the function of such genes, such the polyposis coli gene.

**News: And when we find out how one of these genes works, what might it tell us?**

**Knudson:** Well, these genes clearly are able to control a switch that might say, “I need to repair a tissue; therefore, I need stem cell growth. I want the stem cell to grow symmetrically. But once the tissue starts getting filled in, I want to go to A to A plus B, where A is a differentiating cell. It may go through 10 cycles of cell division, then there’s a stop that says, “Okay, enough now, complete differentiation.” So, there must be genes that control the switch from symmetric cell division to asymmetric cell division—and back again—in renewal tissues. Understanding such genes may provide clues on how to reverse the abnormalities produced by mutations in them.

**News: Each inherited cancer syndrome predisposes people to a specific spectrum of tumors. And for each syndrome, this spectrum is different. How can we begin to understand this in the future?**

**Knudson:** Well, you might expect that mutated genes such as RB or p53 in the germline would predispose to a lot of tumors because they seem to be central regulators of cell division. The reason that you don’t see some of the somatic tumors with mutated RB or p53 is there are too many steps. If you inherit a p53 mutation in the germline, and you still need several other steps, the impact of this inherited one is diluted. The tumors that will show up are the ones that require the fewest events. I think that’s why osteosarcoma and breast cancer are observed. Breast cancer in

---

**ORI Finds No Misconduct in Fisher Case**

The Office of Research Integrity of the U.S. Department of Health and Human Services found no evidence of scientific misconduct by Bernard Fisher, M.D., in its final report issued Feb. 28.

The ORI had investigated whether Fisher, in his capacity as the principal investigator and chair of the National Surgical Adjuvant Breast and Bowel Project (NSABP) at the University of Pittsburgh, had committed scientific misconduct by publishing NSABP research papers that may have contained falsified and fabricated research data submitted by St. Luc Hospital in Montreal, an institution participating in the NSABP.

ORI found in February 1993 that the principal investigator for the NSABP project at St. Luc hospital committed 115 instances of data fabrication and falsification in 99 patient records by systematically altering data to make it appear that his patients were eligible to participate in NSABP clinical trials.

The ORI determined that the papers published by NSABP after February 1993 (that contained St. Luc data) did not include falsified or fabricated data.