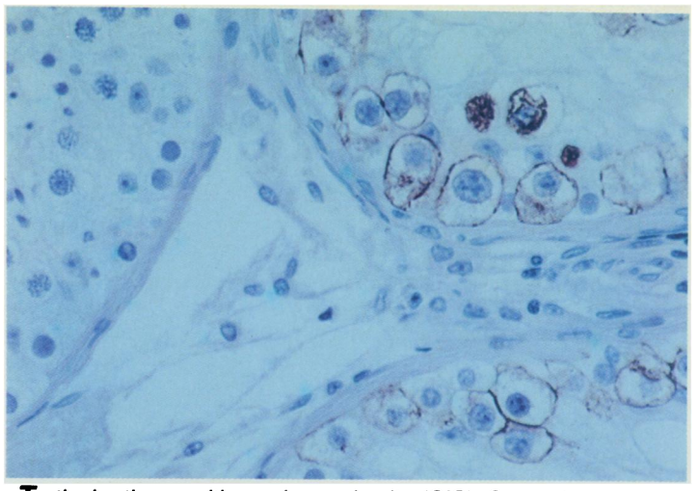
Manhood's Cancer

Increasingly, some young cancer patients are being asked to evaluate the price of fertility

By JANET RALOFF



Skakkebaek

Testicular tissue with carcinoma in situ (CIS). Seen at upper and lower right of photo, these harbingers of cancer appear as irregularly shaped, deeply stained rings with enlarged nuclei.

Testicular cancer tends to be a young man's disease. In 1993, U.S. physicians diagnosed some 6,600 cases, accounting for about 1 out of every 91 new malignancies in men. Though relatively rare, it nevertheless is the most common cancer in American males age 15 to 35.

Over the past several decades, the incidence of this disease has increased worldwide. Moreover, risk of the cancer varies dramatically between populations. For instance, at 7.8 new cases per 100,000 males in the population, the testicular cancer risk faced by Danish men is more than five times that faced by men in neighboring Finland. In the United States, where the incidence falls about midway between the rates of these two groups, there is a sharp polarity by race. Whites are about seven times as likely to develop the cancer as blacks.

While the overwhelming majority of people with testicular cancer survive — typically 90 percent or more — balancing a young man's desire to maintain his fertility against the risk of a cancer recurrence presents physicians and patients with a dilemma.

At issue is whether to actively look for signs of quiescent disease — by taking a biopsy of the second testicle — when the first testicle and its tumor are removed.

Most U.S. physicians recommend a wait-and-see approach. If a second cancer occurs, the remaining testicle is removed.

In several European countries, however, the trend is toward recommending immediate biopsy. A growing body of studies indicates that in most cases, the small percentage of men who will go on to develop a tumor in the second testicle (typically 2 to 5 percent) already possess characteristic cellular abnormalities — essentially, localized seeds of cancer — that can be identified in a sample of testicular tissue.

When physicians find signs of this precancerous condition, they offer to irradiate the second testicle. This kills the precancerous cells while sparing the organ, which produces the male sex hormone testosterone. However, radiation treatment also kills the testicle's sperm-producing cells, rendering the man infertile.

These two tacks toward cancer follow-up reflect differences in attitudes about risk management. They also could have legal repercussions. Doctors who do not offer to biopsy the second testicle may find themselves vulnerable to litigation if another cancer develops — especially if it's a lethal one.

Patients, too, face difficult tradeoffs. Those electing biopsy must balance the peace of mind that comes from knowing their cancer status against the risk of a positive finding — and a call for treatment that guarantees infertility. Patients who opt not to undergo biopsy may prolong fertility, but at the risk of later castration.

No one knows what causes testicular cancer. However, in 1972, Danish endocrinologist Niels E. Skakkebaek published a paper describing unusual cells in the testes of men who later developed the disease. Because he suspected the cancer evolved from these abnormal cells, Skakkebaek termed the apparent cancer precursors "carcinoma in situ" (CIS).

When initially presented with this hypothesis, "most people didn't believe it," recalls pathologist Ivan Damjanov of Jefferson Medical College in Philadelphia. "But it's not controversial anymore," he says, adding that the potential of testicular CIS to transform into a cancer has been well accepted since about the mid-1980s. And because visual examination cannot distinguish which CIS cells may develop into an invasive tumor, he observes, "we therefore treat all of them as if they will."

Moreover, he notes, visual clues offer no indication of how quickly such a transformation might occur. "So we don't know whether we have to take it [the CIS] out tomorrow or can leave it for 2 weeks, even 2 years."

Like fetal germ cells, the noninvasive CIS cells lack the mature structure that characterizes the sperm-making or sperm-nurturing cells into which they were supposed to have evolved. CIS cells also produce several biochemical signatures of fetal cells — such as an enzyme present in embryonic cells migrating from the yolk sac to the genital regions.

But to the trained eye, Damjanov notes, CIS cells don't look like normal fetal cells: "They look like cancer." Moreover, Skakkebaek adds, they bear an abnormal genetic signature. With 60 to 70 chromosomes each, these cells possess a dozen or two too many.

Over the past 20 years, Skakkebaek, now chief of the Department of Growth and Reproduction at University Hospital (Rigshospitalet) in Copenhagen, has observed CIS cells in adults as well as young boys. Initially, he observed them in testicular biopsies from infertile men who went on to develop testicular cancer. Later, his group found CIS cells in a 10-year-old boy undergoing surgery to correct his cryptorchidism (undescended testes); within 10 years, the boy had developed testicular cancer.

More recently, Skakkebaek's team has biopsied young boys with other conditions that have been linked to testicular cancer — for example, hypospadia, a partially unfused penis, or intersex, a condition in which some of a boy's cells lack the male, or Y, chromosome. At least one Danish researcher has even observed CIS cells in a fetal testis.

The similarity of CIS cells to fetal cells and their appearance even in young children suggests that these testicular antecedents of cancer probably form during fetal life, then lie dormant for decades, Skakkebaek now believes.

"We think hormones that become active in puberty may play a role in the pro-

liferation of these cells," he says. "When a child is born, he may have just a few. With age, [the cells] may proliferate."

Physicians confirm a testicular tumor by examining a suspicious gonad after its removal, according to the National Cancer Institute. This is because biopsying a tumor-bearing testicle runs the risk of dislodging any cancer cells that may have turned metastatic — gained the ability to seed new cancers throughout the body. Because CIS cells are not invasive, biopsying them does not pose a similar risk.

If a pathologist observes invasive disease in the excised gland, doctors will conduct further tests to gauge whether and how much the malignancy has spread — thereby assessing the need for follow-up surgery and for postsurgical radiation therapy, chemotherapy, or both.

In the United States, most doctors then advise patients to perform monthly self-examinations (sound advice for all men) and to report suspicious signs — such as a hard lump, testicular enlargement, or buildup of fluid in the scrotal sac. If signs point to a second cancer, the remaining testicle is removed.

Losing one testicle should not prevent a man from fathering a child. Infertility and other problems typically arise when doctors must take the second gonad. Loss of both testes also leaves a man vulnerable to "a sort of male menopause," notes urologist Timothy B. Hargreave of Western General Hospital in Edinburgh.

Insufficient testosterone can lead to a softening of bones, hot flashes, lethargy, and a waning interest in sex. Though doctors can prescribe lifelong administration of testosterone to head off such symptoms, the hormone isn't well absorbed through the intestine. So the most effective treatments usually involve weekly injections or longer-duration implants of the hormone under the skin, Hargreave notes. Over a lifetime, this can prove "a bother for everybody concerned," he says, explaining why many European physicians seek to preserve the endogenous source of the hormone — the remaining testicle.

Moreover, Skakkebaek observes, men who lose both testicles often develop psychological problems that hormone-replacement therapy cannot address.

Full castration "is really a pity," he says. "And in our clinic, we consider it a failure when we have to remove the second testis."

A different risk-benefit calculation prevails west of the Atlantic, as John P. Donohue outlined 15 months ago during a workshop in Copenhagen. "My current practice has been to adopt a passive approach to the question [of biopsying the second testicle]," said Donohue of Indiana University Medical Center (IUMC) in Indianapolis. In general, he added, U.S. urologists "have had a similar philosophy."

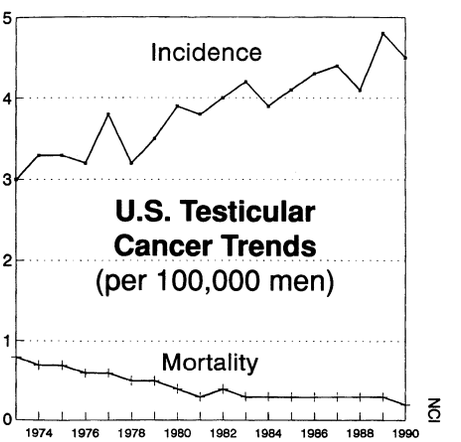
In the absence of tumors, CIS cells have not been associated with metastases. As a result, Donohue says, "we have not felt any great urgency to detect [their] presence." Moreover, he notes, because no more than 1 in 20 survivors of testicular cancer will ever develop a second malignancy, "we have not felt that this risk factor was sufficient to justify a biopsy in every case." Exceptions to this rule are patients believed to be at especially high risk, such as those born with one or more undescended testicles or those with a history of infertility.

Finally, he argues in the proceedings of the Copenhagen meeting, "medical practice in the United States is strongly influenced by a very aggressive legal system." Even minor postbiopsy complaints can result in litigation, he says.

Concern over possible side effects of major risk factor, undescended testes at birth.

Further evidence that the risk of this cancer may be subject to prenatal influences comes from a 1983 study comparing 108 young Los Angeles men with testicular cancer to a similar number of their cancer-free neighbors. Robert H. Depue of NCI and his coworkers found that men born to women administered estrogen or another female hormone during pregnancy were eight times as likely to develop testicular cancer as those whose mothers had not received such hormonal exposures.

This study has led some researchers to question whether a proliferation of estrogen-mimicking pollutants in the environment might help explain the rising rates of testicular cancer (SN: 1/22/94, p.56). — *J.A. Raloff*



Clues to the rise in testicular cancer

Though no one knows what factors predispose a man to develop testicular cancer, data from Denmark suggest that some share of cases might trace to environmental factors. In contrast to their Scandinavian neighbors, Danish men face an unusually high risk of this cancer. One might chalk this up to simple genetic differences were it not for Denmark's experience during World War II, argues Henrik Møller of the International Agency for Research on Cancer in Lyon, France.

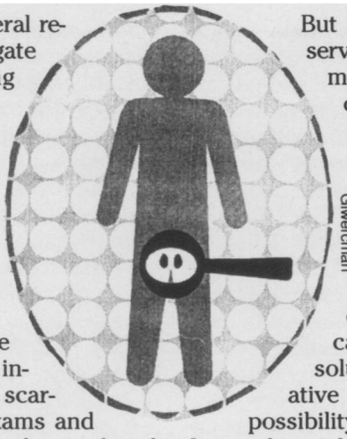
German occupation troops effectively isolated Denmark from commerce with the outside world. Something about this isolation appears to have altered risk, Møller maintains, because Danish men born during the war years have experienced far lower rates of testicular cancer than those born earlier or later. Moreover, he says, the timing of this dip in cancer incidence suggests that maternal changes — probably in diet — affected the rate of fetal CIS development in male offspring.

However, he adds, when or whether that CIS transforms into a true cancer may be affected by the man's subsequent lifestyle and exposures. For instance, one study linked the amount of exercise a young man engages in to his risk of testicular cancer. The more he exercises, the lower his risk.

Testicular cancer's rising incidence also argues for some environmental influence. "In Denmark, today's rate of getting a testicular cancer is three times higher than it was 50 years ago," says Niels E. Skakkebaek of Rigshospitalet in Copenhagen. The United States is also experiencing an "epidemic" in these cancers, according to the National Cancer Institute (NCI) in Bethesda, Md. Even where this cancer remains very rare — as it does in Finland — the incidence of it has been climbing, report Aleksander Giwercman of Rigshospitalet and his colleagues in a July 1993 supplement to Environmental Health Perspectives.

"The dramatic increases in testicular cancer incidence for young men over time suggest that an environmental factor that has also increased over time might be responsible," write Eric J. Feuer and his NCI coworkers in the agency's *Cancer Statistics Review 1973-1990.* However, they add, "given the magnitude of this increase, it is puzzling that the factor remains elusive." Indeed, they note, the "most consistent occupational association has been with employment in professional or white-collar occupations" and the

biopsy has prompted several research centers to investigate alternative CIS-screening techniques. Biopsies require cutting a slit in the scrotum and the membranous cover enveloping a testicle, squeezing out and excising a little tissue, then sewing the slits closed. Though perhaps only 3 to 5 percent of such procedures cause any bruises, swelling, or infection, all produce some scarring. And in follow-up exams and tests, that scar tissue can be confused with a developing tumor, Hargreave says — another reason "why there has been an ambivalence to widely using [biopsy]."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Hargreave's group has been studying fine-needle aspiration — the removal of a few cells through a needle — as a less-scarring option. How does its reliability compare to biopsy for finding CIS?

"The truthful answer is that we don't yet know," Hargreave told SCIENCE NEWS. However, he adds, work by Skakkebaek's team suggests that when CIS develops in adults, it's often widespread in the testis. Then, "if fine-needle aspiration is as good at sampling [as biopsy] — and in the hands of a competent cytologist it may well be — it would be far less invasive," he says.

But even if CIS is found, observes William R. Fair of Memorial Sloan Kettering Cancer Center in New York City, there remains the question of what to advise the patient. Because perhaps no more than 50 percent of men with observed CIS in a second testis go on to develop cancer, and because "there is no absolute assurance that a negative biopsy excludes the possibility of future contralateral [second-testicle] tumor development," he maintains that in the United States "we could be sued for treating CIS or for *not* treating CIS."

As a result, Fair argued at the Copenhagen meeting, "Perhaps it is better not to know whether or not CIS is present."

In Denmark, virtually all testicular cancer patients choose a biopsy, Skakkebaek notes. Biopsies are also offered and frequently performed in Germany. And for the past 4 years, the United Kingdom's Medical Research Council has been conducting a large study to quantify the value of biopsy.

The major reason patients choose not to undergo a biopsy is the dread of having to decide whether to irradiate the second testis if a precancerous condition is found. Though some men have fathered children between the time cancer was detected in their first and second testicles, many don't. In fact, Hargreave says, "by the time he's got precancerous changes, a man almost always has a very low sperm count."

If he has, Skakkebaek notes, a man can bank sperm for use in artificial insemination later. Or he can put off irradiation for a year or so while trying to have children.

Fair and Donohue both routinely offer testicular cancer patients the option of biopsying the second testis for CIS. "But to be very honest," says Donohue's IUMC colleague, urologist Richard S. Foster, "because the chance of having a contralateral testis cancer is very low, and because the outcome of those patients [who develop a second cancer] is very good, most patients in the United States opt not to have a contralateral biopsy."

Indeed, Donohue adds, U.S. patients have not appeared very anxious to learn whether they have CIS in the second testis. However, he conceded at the Copenhagen meeting, what a patient decides can be strongly influenced by his physician — "and urologists in the United States have had a passive approach to this question. If we gave a better explanation of the risk-benefit, there may be greater interest in having a biopsy." □