

# This Week in the Journal

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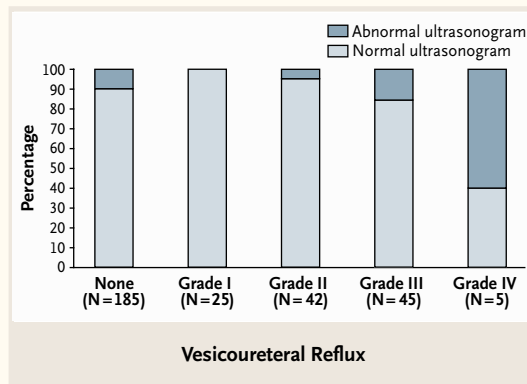
## ORIGINAL ARTICLES

### Imaging Studies after a First Urinary Tract Infection in Children

Renal imaging is recommended for children after a first documented urinary tract infection. In this prospective study, 309 children between the ages of one month and two years underwent renal imaging studies (technetium-99m–labeled dimercaptosuccinic acid scanning and renal ultrasonography) within 72 hours after the diagnosis of urinary tract infection, voiding cystourethrography one month later, and repeated scanning six months later. Management was not changed by the finding of ultrasonographic abnormalities (in 12 percent of the children). Monitoring with urinalysis and culture appears to be as effective as imaging studies.

**The routine performance of imaging studies in young children after a first urinary tract infection appears to be of little clinical value.**

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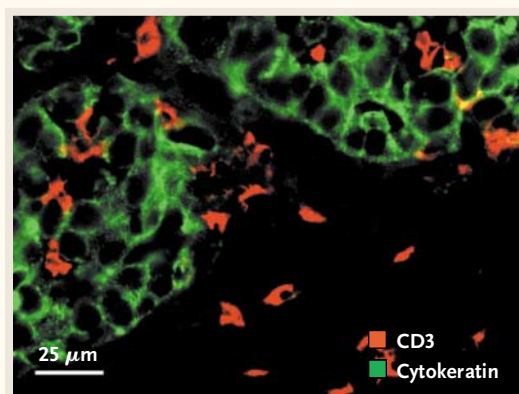


### Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

The outcome of treatment in advanced ovarian cancer can vary considerably among patients with similar clinical and pathological findings. In this immunohistochemical study of tumors from 186 patients, the presence of T cells within the tumor was strongly associated with a good outcome, whereas the absence of T cells correlated with a poor outcome.

**These results constitute strong, indirect evidence that an antitumor immune response has a potent influence on the outcome of advanced ovarian cancer. Similar results in studies of other neoplasms support the thesis that the immune system participates in the defense against cancer.**

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## THIS WEEK IN THE JOURNAL

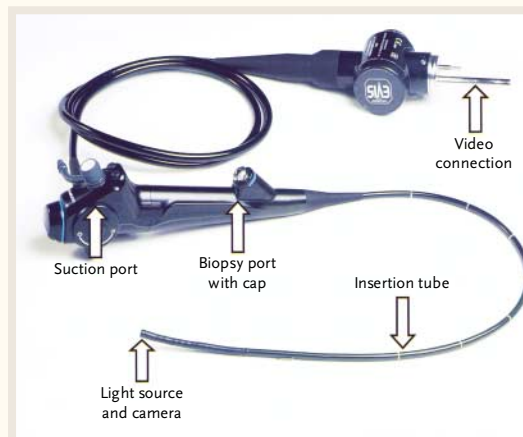
## ORIGINAL ARTICLE

**Outbreaks of *P. aeruginosa* Associated with Defective Bronchoscopes**

Two reports in this issue describe outbreaks of *Pseudomonas aeruginosa* infections in hospitals. In both cases an increase in the frequency of pseudomonas infections was associated with bronchoscopy. In one study, isolates from the patients were genetically related to isolates from bronchoscopes that had loose caps on their biopsy ports.

**Endoscopes are the devices most commonly associated with nosocomial outbreaks of infection. The outbreaks described in both studies involved bronchoscopes with defects that rendered disinfection procedures ineffective. This experience emphasizes the need for close surveillance for such infections and for better methods of recalling defective medical devices.**

SEE PAGES 214 AND 221; PERSPECTIVE, PAGE 191



## SPECIAL ARTICLE

**Retained Sponges and Instruments**

This study compared characteristics of patients with retained sponges or instruments after surgery, identified through a large malpractice insurer, and control patients who underwent the same types of surgery but did not have retained foreign objects. Independent predictors of the retention of a foreign body included emergency surgery, an unplanned change in procedure, and higher body-mass index. Counts of instruments and sponges were less likely to have been performed for patients with retained foreign bodies than for controls, although in the majority of cases, such counts were performed and were recorded as being correct.

**The implication of these findings is that specific characteristics of both patients and their surgical procedures are associated with an increased risk of retention of a sponge or instrument. This type of analytic approach may be useful in elucidating other medical errors and suggesting strategies for their prevention.**

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## CLINICAL PRACTICE

**Suspected Appendicitis**

An otherwise healthy 22-year-old woman comes to the emergency department with acute abdominal pain of 18 hours' duration in the right lower quadrant. On physical examination, she is afebrile, with tenderness on deep palpation in the right lower quadrant, and has no peritoneal signs. Pelvic examination reveals tenderness in the right adnexa without a mass. How should this patient be further evaluated?

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# Ensuring Safe and Effective Medical Devices

David W. Feigal, M.D., M.P.H., Susan N. Gardner, Ph.D., and Mark McClellan, M.D., Ph.D.

Over 8000 new medical devices are marketed in the United States each year. Before marketing, manufacturers of high-risk, or class III, devices provide the Food and Drug Administration (FDA) with scientific clinical evidence that the devices are “safe and effective”; 50 to 80 of these devices receive FDA approval annually. Some 3500 medium-risk (class II) products are approved for marketing by the FDA after the manufacturer has submitted a 510(k) notification. The device must be “substantially equivalent” to an existing marketed device, as demonstrated by product-specific performance requirements or “special controls.” Only 8 percent of 510(k) notifications have special controls that require clinical data. Over 4000 new, low-risk (class I) devices are marketed each year; they are exempt from the requirement for FDA approval. Systems that monitor manufacturing quality, including plans for corrective and preventive actions, are required for all products. All recalls and certain types of problems must be reported to the FDA.

Although drugs are molecules with short half-lives and long market lives, devices are often complex durable equipment with short market lives. Drug-related injuries are not commonly caused by manufacturing problems, but faulty design and manufacturing are frequently the cause of device-related injuries. Devices can malfunction, break, and cause injury because of errors in their use. New devices are also less likely than drugs to have their safety established clinically before they are marketed. Effective surveillance of marketed medical devices is an important aspect of consumer protection. In this issue of the *Journal*, Kirschke et al. (pages 214–220) and Srinivasan et al. (pages 221–227) report on bacterial infections associated with bronchoscopes.

What should we strive to accomplish by surveillance of medical devices on the market? We can im-

prove the safety and effectiveness of devices by identifying serious low-frequency events that were not reported before marketing, detecting unintended changes in risk due to design or manufacturing modifications, and assessing risks and benefits over longer follow-up periods or in high-risk populations. We can also identify “real-world” problems associated with the learning curve and other human factors in the use of new devices, as well as interference between new and existing devices.

Spontaneous reporting of adverse events (medical-device reporting) has been an important surveillance tool, particularly for the identification of unusual, unexpected, and severe events. Other surveillance methods include long-term follow-up of participants in clinical trials conducted before marketing, post-approval studies, and new trials to evaluate expanded indications or subsequent generations of the device. Manufacturers can identify problems by monitoring complaints, product failures, and corrective actions and can assess human factors as part of the training provided for the use of a new product. Problems are also identified through FDA field inspections and investigations.

The FDA requires that manufacturers and clinical facilities report certain types of injuries associated with medical devices, and voluntary reporting by health care providers and consumers is encouraged. Manufacturers must report device-related deaths, serious injuries, and certain malfunctions. The FDA received more than 120,000 reports in 2002. Clinical facilities are required to report device-related deaths to the FDA and manufacturers and are required to report serious injuries to manufacturers. In 2002, clinical facilities submitted over 2500 reports to the FDA, and health professionals and consumers submitted 3500 voluntary reports.

A product recall is one of the corrective actions

that may result from identification of a design flaw, manufacturing problem, or another problem with a medical device. The problem may have been identified on the basis of a report of a malfunction or an injury. Over 1000 devices are recalled each year. Almost all recalls are initiated by the manufacturer. About half the recalls involve problems classified by the FDA as posing a low clinical risk; most of the rest involve problems classified as posing an intermediate risk. About 10 to 20 recalls each year involve high-risk problems; the effectiveness of these recalls is monitored by the FDA, which has the authority to initiate such a recall.

A recall is intended to halt the use of the product, either permanently or until the problem is corrected, and to alert clinicians to potential problems for patients already using or exposed to the device. Heart valves, knee and hip prostheses, endosseous implants, intraocular lenses, implantable cardioverter-defibrillators, respirators, infusion pumps, hemodialysis equipment, in vitro diagnostics, electrosurgical cutting and coagulation equipment, and endoscopes have been recalled.

Early identification of problems by health professionals can help prevent device-associated injuries. The Medical Device Surveillance Network is a new FDA program designed to promote early reporting and improve patient safety. The program will involve 250 acute care and extended care facilities. Data collection from the first 25 facilities began in 2002. The network currently includes 80 facilities. The first 224 reports included reports of 2 deaths and 17 serious injuries; 205 of the reports were voluntary.

This new approach may also help health care facilities minimize the risk of device-related injuries locally. Just as hospitals developed programs to prevent nosocomial infection, programs to prevent injuries from medical devices may be more effective when hospitals join in the efforts of manufacturers and the FDA. Ensuring that medical devices are safe and effective is everyone's business.

From the Center for Devices and Radiological Health (D.W.F., S.N.D.), and the Office of the Commissioner (M.M.), Food and Drug Administration, Rockville, Md.

# Risks and Benefits of Gene Therapy

Philip Noguchi, M.D.

Although most of today's gene-therapy trials are targeted to cancer, there is renewed interest in pursuing the goal for which gene therapy was invented: the cure of genetic disease. Recent studies from France, the United Kingdom, and Italy have provided encouraging results in the treatment of several forms of a rare, devastating disease of infancy, collectively called severe combined immunodeficiency. Each form of this disease is caused by a mutation in a single gene. In these studies, a modified retrovirus was used to insert, *in vitro*, a "corrective" gene into the host genome. "Corrected" cells were then returned to the patients, in whom an immune response subsequently developed (see Panel A of Figure). In a letter in this issue of the *Journal* (pages 255–256), however, Hacein-Bey and colleagues describe a serious adverse event—a leukemia-like disorder—in a young child, 30 months after a single gene-therapy treatment.

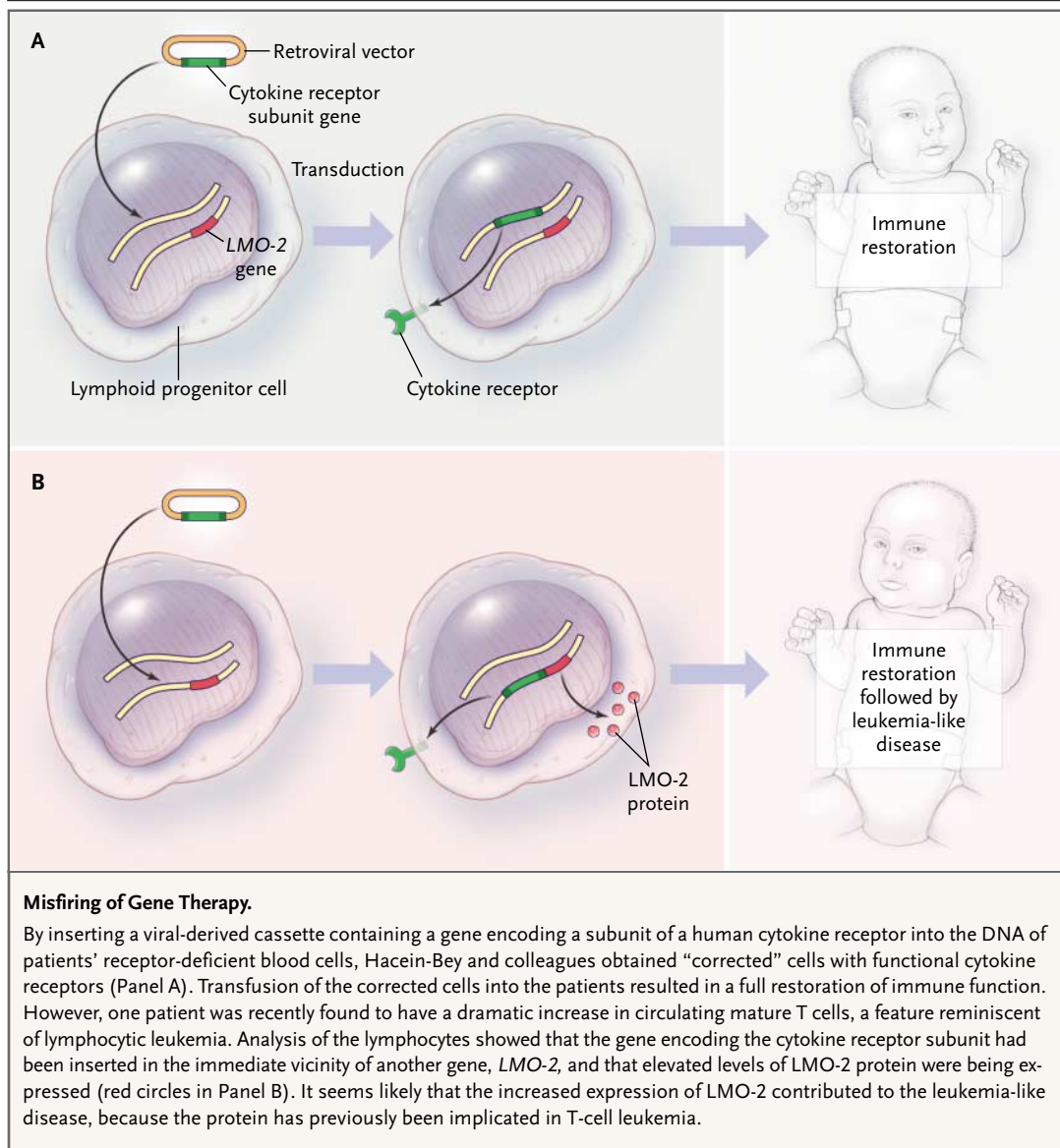
When Hacein-Bey and colleagues first suspected a problem during the trial in early September, they immediately informed the families of the patients. They also shared data with other investigators of similar gene-therapy trials, members of the broader gene-therapy community, and regulatory agencies. As a precaution, the Food and Drug Administration (FDA) put three similar gene-therapy trials on hold, and its Biological Response Modifiers Advisory Committee met in mid-October to discuss the future of gene-therapy trials for severe combined immunodeficiency in the United States.

The committee concluded that the molecular event that provided clinical benefit in the gene therapy tested by Hacein-Bey and colleagues was also the probable cause of the leukemia-like adverse event (see Panel B of Figure) and made some recommendations. It recommended that retroviral gene-transfer trials for severe combined immunodeficiency in the United States be allowed to proceed, but with careful attention to inclusion and

exclusion criteria, so as to provide the best ratio of benefit to risk, relative to other therapies. Related to this is the revision of consent documents. Children with severe combined immunodeficiency who have an HLA-identical donor should be excluded from gene-therapy trials because of the high success rate of bone marrow transplantation from a fully matched donor (greater than 90 percent success). But the trials should be available to children with severe combined immunodeficiency in whom transplantation from an HLA-identical donor fails and to those who do not have an HLA-identical donor (about 80 percent of the cases).

This relatively permissive response is based on the advantage of a successful treatment for severe combined immunodeficiency—reported clinical benefits that seem to be more robust than those associated with HLA-identical marrow transplantation—balanced against an as yet unquantifiable risk of the development of leukemia from insertional mutagenesis. The parents of children with severe combined immunodeficiency felt strongly about this point and argued that it is better that parents or guardians have the option to make an informed choice than to have no choice at all.

Because retroviral vectors are thought to insert themselves at random positions in the host genome, insertional mutagenesis as a potential risk of retroviral gene therapy has been debated for some years. That an instance of insertional mutagenesis first happened in humans during a clinical trial surprised some, but not those of us who regulate biologic products such as gene therapy. We take to heart the words of Robert Ingersoll: "In nature there are no rewards or punishments; there are consequences." Gene therapies are constructs derived from nature; they are not of nature. The manipulations needed to create genetic therapy add enormous complexity to considerations of safety and preclinical toxicity testing, and for every intended



consequence of a complex biologic product, there are unintended consequences. Biologic products, like all products, carry risks along with benefits.

Tractable diseases have been taken care of; those that have resisted more conventional approaches, such as severe combined immunodeficiency, are now being tackled. Each therapeutic effort that shows potential benefit needs to be scrutinized closely, with the knowledge that most clinical trials

fail to show benefit. We must remember that the evolution of medical practice is dynamic. As each new, unexpected adverse event arises, evaluation is carried out again and again, and in the process, new scientific ideas unfold that ultimately yield medically useful products.

From the Food and Drug Administration, Rockville, Md.