

## Death halts trial of kidney cancer drug

Last week, a biotechnology company halted a clinical trial designed to test the effectiveness of an immune system molecule known as interleukin-12 (IL-12) against advanced kidney cancer. The suspension came after 12 out of 17 enrolled patients were hospitalized and one of the 12 died.

The company, Genetics Institute, in Cambridge, Mass., has declined to describe the symptoms that the patients suffered because "it is too soon to determine what happened," says company spokesman Dennis Harp.

Initial information, Harp notes, indicates that the hospitalized participants appear to suffer from more severe versions of side effects observed in four preliminary clinical trials. The company has yet to make those side effects public.

Preliminary, or phase I, clinical trials are meant to establish safe dosages of an

experimental drug. The phase II trials that follow address the drug's activity against a disease or condition. The phase II IL-12 trial, which began in late May, employed a slightly different formulation of the drug that gave it a longer shelf life. This trial also used a slightly different dosing schedule, although dosages found safe in the company's phase I trials actually exceeded dosages given in the phase II trial.

Harp says the company has informed the Food and Drug Administration of the suspension and will thoroughly investigate the illnesses and death.

The incident could prove a significant setback for a molecule that holds promise as a treatment for conditions as varied as parasitic infections, AIDS, and cancer (SN: 8/20/94, p.120).

IL-12 is one of a class of immune molecules known as cytokines. Cytokines

serve as messengers, telling different parts of the immune system when to become active. IL-12 specifically activates white blood cells known as T1 helper cells. These cells call up a portion of the immune system that identifies and destroys cells infected with bacteria, viruses, and parasites.

IL-12's ability to rev up this so-called cell-mediated immunity results in resistance to a variety of infectious diseases. Mary Stevenson of Montreal General Hospital Research Institute has shown that IL-12 protects mice from malaria. And Christine A. Biron of Brown University in Providence, R.I., found that administering the molecule to mice controls infection with cytomegalovirus and lymphocytic choriomeningitis virus.

However, it is the molecule's promise as an agent against AIDS and cancer that has sparked the interest of the biotechnology industry. AIDS patients produce less IL-12 as their disease progresses, and a number of studies conducted in animals show that administering IL-12 eradicates tumors and confers immunity to the disease.

"From the perspective of an experimentalist, IL-12 is phenomenal in terms of what it does for resistance to infection," says Alan Sher of the National Institute of Allergy and Infectious Diseases in Bethesda, Md.

But like other cytokines, IL-12 has a dark side. Sher points out that some researchers link IL-12 to autoimmune diseases such as chronic inflammatory bowel disease. Both Stevenson and Biron found that mice already mounting an immune response to an infection began to suffer from toxic shock syndrome when given IL-12 at more than a critical dosage. At lower dosages, the mice made remarkable recoveries.

Biron speculates that animals already in the process of responding to an infection may have a more complicated reaction to the addition of IL-12.

Despite known side effects in animals, neither Sher, Biron, nor Stevenson can speculate what happened to the kidney cancer patients in the Genetics Institute's phase II trial. But they all fear that the incident could stop research on what Stevenson calls "a tremendously promising therapeutic."

David R. Parkinson of the National Cancer Institute in Bethesda, Md., says he doesn't "believe that at all." The phase I trials, he points out, show that IL-12 can safely be given to patients. Those trials, he says, produced side effects similar to those found for another cytokine, known as IL-2. With high doses of IL-2, patients suffer lower blood pressure, leakage of blood from capillaries, and other symptoms similar to shock.

Harp says that Genetics Institute plans to sort out the problems with the trial and return to phase I trials to put IL-12 back on track.

— L. Seachrist

## Progestin fails to cut breast cancer risk

Taking estrogen for 5 or more years may raise postmenopausal women's risk of developing breast cancer and of dying from the disease, a controversial new study shows. What's more, taking progestin does not reduce those odds, the researchers report.

Earlier studies produced conflicting results on whether estrogen, a hormone that helps lower postmenopausal women's likelihood of getting heart disease and other disorders, raises their chance of developing breast cancer (SN: 2/4/95, p.74). Taking progestin counteracts estrogen's effect of increasing women's susceptibility to uterine cancer, but few studies examined whether progestin also protects against breast cancer.

In the new study, women who had taken hormones for 5 or more years and who were still taking them showed a 30 to 40 percent higher incidence of breast cancer than nonusers, report Graham A. Colditz of Harvard Medical School in Boston and his colleagues in the June 15 *NEW ENGLAND JOURNAL OF MEDICINE*.

A woman who continually takes hormones from age 55 onward would have approximately 3 chances in 100 of developing breast cancer between age 60 and 65, Colditz explains. Without the treatments, she would have less than 2 chances in 100.

However, stopping hormone treatment for 2 or more years brings a woman's likelihood of developing breast cancer down to that of nonusers, they report.

The study had several confusing findings, notably that risk drops quickly

once women stop taking hormones, says William C. Andrews of Eastern Virginia Medical School in Norfolk. However, the large size of the study demands that researchers take its findings—which differ from many other investigators' results—seriously, he says.

To do the nationwide study, Colditz and his colleagues sent questionnaires to nurses age 30 to 55 asking about their health and health practices, including use of hormones. In 1976, when the study began, almost 24,000 of the nurses had entered menopause. By 1992, that number had increased to almost 70,000, and 1,935 of the women had developed breast cancer. Over one-third of the participants took hormones; about one-third of that group also used progestin.

The researchers failed to take into account certain behaviors that may increase a woman's chance of getting breast cancer, including drinking alcohol, argues R. Don Gambrell Jr. of the Medical College of Georgia in Augusta. Also, using a questionnaire prevented the researchers from finding out important details, such as what sort of treatments breast cancer patients received, notes Paul G. Stumpf of the Robert Wood Johnson Medical School in New Brunswick, N.J.

Indeed, the benefits of hormone therapy for postmenopausal women outweigh the risks, some researchers assert. Colditz, however, recommends that each woman weigh carefully the pros and cons of hormone therapy and consider whether heart disease or breast cancer poses a greater risk to her.

— T. Adler