Diminished returns for cancer therapy

Therapeutic trials of juiced-up white blood cells and an immune system stimulator are yielding disappointing results in cancer patients, according to data presented by the method's developer, Steven A. Rosenberg of the National Cancer Institute. He is now working on revisions of the approach.

Last year, Rosenberg and his colleagues described preliminary results as promising, and the process was widely heralded as a novel approach to cancer treatment. But after the first flush of success, the numbers are beginning to pale. In the initial report, 11 of 25 cancer patients in whom no other treatment had worked had a 50 percent or more reduction in tumor size, including one in whom signs of cancer disappeared (SN: 12/7/85, p.359).

At a talk given at the National Institutes of Health last week, Rosenberg said that only seven of the 104 patients treated thus far have had a complete disappearance of their cancer. Another 25 have had a measurable reduction in tumor size, with 15 of them having at least a 50 percent reduction. One patient died three days after completion of the therapy, Rosenberg says.

"Most patients do not respond," says Rosenberg, who also characterizes the treatment as "very toxic." One problem not addressed by Rosenberg at the meeting is infection with hepatitis A. Several such cases have occurred in patients receiving the treatment at other institutions involved in the evaluation. According to a National Cancer Institute spokesperson, clinical trials at the outside institutions were halted the first week in September until the source, suspected to be in the medium used to grow the immune cells, is identified and eliminated.

In the therapy, white blood cells are removed from the patient, incubated in the immune system stimulator interleukin-2, and put back into the patient along with more interleukin-2.

While recognizing that the combination treatment has its problems, Rosenberg maintains faith in the general idea behind it. "I'm hoping that we've demonstrated that this kind of approach is at least capable of mediating tumor regression," he says.

He has already tried a further refinement, using white blood cells taken from the tumor itself. Following successful animal trials (SN: 10/4/86, p.222), a 36-year-old man with melanoma was treated in November.

Rosenberg is also trying straight interleukin-2, and he said at the meeting that so far two people have died as a result of leaky capillaries induced by the treatment. He and his colleagues report in the Dec. 12 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION on 10 patients treated with high doses of interleukin-2. Three patients had partial regressions, though one of them failed to respond to a second treatment and died of a secondary tumor several months later.

Cancer specialist Charles G. Moertel of the Mayo Clinic in Rochester, Minn., in an accompanying editorial, expresses pessimism about interleukin-2, which he notes has "unacceptably severe toxicity and astronomical costs . . . not balanced by any persuasive evidence of true net therapeutic gain." *—J. Silberner*

Gene therapy restores mouse fertility

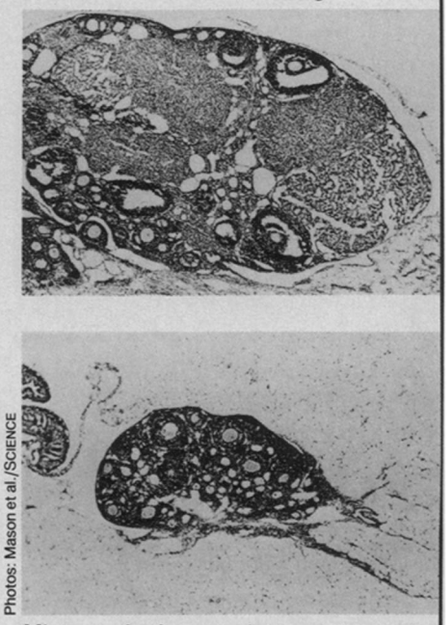
A gene deletion causing infertility in mice has been pinpointed and corrected in recent work, illustrating some curious facts about how genes can express themselves in specific tissues. Using a special breed of hypogonadal (*hpg*) mice, researchers have found that the hereditary form of infertility found in these mice is caused by a deletional mutation of about half of the gene coding for the precursor of gonadotropin-releasing hormone (GnRH) and GnRH-associated peptide (GAP). The peptide pair stimulates the release of key reproductive hormones.

Homozygous mice inherit the *hpg* gene from both parents and suffer from hypogonadism, characterized by immature sexual behavior, arrested gonadal development and infertility. But scientists at Genentech, Inc., in South San Francisco produced fertile *hpg* homozygotes by introducing DNA fragments containing the mouse GnRH gene into normal eggs later implanted into surrogate mothers. Subsequent mating of the progeny with *hpg* mice yielded fertile *hpg* homozygotes. Hormonal levels and tissue development in these mice were comparable to those in normal mice.

According to researcher Anthony J. Mason of Genentech, the most significant finding was not the successful gene therapy, but the first discovery of neural-specific expression of a gene. Mice that had received the GnRH gene through gene therapy showed a normal number of GnRH-containing neurons in the brain, whereas untreated *hpg* mice did not. These neurons are part of the hypothalamic-pituitary-gonadal axis essential in maintaining the delicate balance of GnRH release.

Although GnRH and GAP are absent in the brains of untreated *hpg* mice, an abnormal GnRH messenger RNA (mRNA) is present in the hypothalamic neurons, making the *hpg* GnRH gene one that is capable of producing specific mRNA but incapable of translating the mRNA information into a protein product.

Others have found similar tissue-specific expression elsewhere. For example, a group at the University of Warwick in Coventry, England, reports in the Nov. 21 CELL that muscle protein genes injected into fertilized eggs of the clawed toad *Xenopus borealis* are expressed almost wholly in muscles.



Photos: Mason et al./SCIENCE

Micrograph of ovary of a treated hpg *female (top) compared with that of an untreated* hpg *female.*

Results of the two-year *hpg* mouse study, which also included scientists from the National Institute of Mental Health in Bethesda, Md., and the University of California at San Francisco, are reported in the Dec. 12 SCIENCE. As Mason told SCIENCE NEWS, there still are unanswered questions. Why does a DNA segment restore functions lost through a deletion nearly three times its length? And why are there gene products found in the liver of the treated animals?

Earlier this year, the Genentech team reported the isolation of the gene for precursors of GnRH and prolactin-release-inhibiting factor in humans and rats. No mutation such as that described in the *hpg* mouse was found, although there are forms of hypogonadism found in humans. However, there is no direct clinical application of the newly described gene therapy to treating human infertility problems. The technique, called germline gene transplantation, is unacceptable in humans under current biotechnology guidelines (SN:10/18/86, p.252).

—D.D. Edwards