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Stamina-Building Drug Linked to Athletes' Deaths

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Correction Appended

A genetically engineered drug that was created for people suffering from kidney failure has become the latest substance to be abused by athletes seeking enhanced stamina and performance. The consequences, in some cases, may be deadly.

The drug is recombinant erythropoietin, known as EPO, which was developed by the Amgen Corporation and approved by the Food and Drug Administration in 1989 for the treatment of chronic anemia in patients with kidney failure. It was later approved for treatment of AIDS-related anemia.

But some athletes and trainers have found that the drug can enhance athletic performance by increasing red blood cells, and thus the body's ability to carry oxygen. Doctors and blood specialists say the drug may be implicated in the deaths of as many as 18 European professional bicycle racers in the last four years. Drug Called a Factor

Only anecdotal evidence links EPO to these deaths. But the specialists say they believe the drug was a factor in at least some of the deaths.

"There is no absolute proof, but there's so much smoke that most of us are convinced," said Dr. Randy Eichner, chief of hematology at the University of Oklahoma. "You just don't get 18 deaths in 4 years, mysteriously, with 10 of them attributed to cardiac problems."

By increasing the red blood cells, the drug thickens the blood, and normal dehydration in a race concentrates the blood further.

"Pretty soon you have mud instead of blood; then you have trouble," Dr. Eichner said, adding that the thick, sticky blood can cause clotting, stroke or heart failure. Dark Side of Biotechnology

The problem with the drug demonstrates a dark side of biotechnology: the difficulties that drug makers face in assuring that their products are used for the intended purpose.

Recombinant EPO is a genetically engineered copy of a hormone normally produced in the kidney, and is considered safe and effective if used properly.

There is little question that EPO can enhance an athlete's performance. A study of 15 Swedish athletes by the Stockholm Institute of Gymnastics and Sports found an improvement of nearly 10 percent in aerobic performance after use of the drug.

Injecting the drug enhances athletes' performance in aerobic endurance events. In addition to bicycle racers, marathon runners and cross-country skiers are suspected of abusing the drug. But no deaths have been reported in sports other than bicycle racing. Drug Is Not Detectable

Because the drug is a model of a naturally occurring protein, it is not detectable by any existing test. This makes it even more attractive to athletes, who are routinely screened for use of drugs like anabolic steroids or amphetamines.

In the United States, Amgen limits distribution of the drug to kidney dialysis treatment centers. Sports physicians say the drug is not readily obtainable here but add that it not hard to get in Mexico or Europe.

Physicians say they believe athletes began using the drug almost with the beginning of clinical trials in 1986. Then the deaths began. In 1987 five Dutch racers died suddenly. In 1988 a Belgian and two more Dutch riders died. In 1989 five more Dutch riders died, and last year three Belgians and two Dutch riders died. Transfusions of Extra Blood

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One of them was Johannes Draaijer, a 27-year-old racer from the Netherlands who finished 20th in the 1989 Tour de France. In February 1990 he died in his sleep of a heart blockage a few days after completing a race in Italy. A doctor had pronounced him fit to ride in that race, and an autopsy did not specify the cause of death. But in a television interview afterward, his widow said she hoped the death would serve as a warning to other athletes who take the drug.

Because several companies were simultaneously pursuing approval of EPO in Europe, "the drug was available for clinical trials in large quantities," said Dr. John Adamson, president of the New York Blood Center who is leading the United States trial of Amgen's drug.

Dr. Adamson said the drug's potential for abuse was soon apparent because athletes were already known to be enhancing performance by having transfusions of extra blood, known as blood doping, or by training at high altitudes, which prompts the body to produce extra red blood cells.

EPO therapy for kidney-failure patients raises their red blood cell level to 33 percent of blood volume from 25 percent; athletes injecting the drug are increasing their normal level of about 45 percent to 55 to 65 percent.

With the dehydration that occurs in a long race, the blood concentrates further, to as much as 70 percent.

An article by Dr. Allan J. Erslev of the Jefferson Medical College in Philadelphia in the May 9 issue of The New England Journal of Medicine about the striking benefits of EPO therapy for anemia patients also concluded that its use by athletes, coupled with dehydration, could be "the cause of possible life-threatening thromboses."

While no deaths have been attributed to the drug in the United States, sports physicians and athletes say they have heard repeatedly about its use at cycling and long-distance running events.

"I began hearing about EPO two to three years ago through the grapevine in running circles," said John Treacy, a silver medalist in the 1984 Olympic marathon. "The story was there was this new drug that would take over from blood doping, and that it was much better."

Len Pettyjohn, coach of the Coors Light cycling team, which is competing in the 11-day Tour Du Pont in the Middle Atlantic States this week, said: "We've all heard about EPO. I could only speculate on its use now, but it wouldn't surprise me. I don't think any Americans are using it, but anybody doing something like that is certainly not going to talk about it."
Education Program Started

Jan Gisbers of the Netherlands, coach of the PDM team, which is also competing in the race, said he had not heard of anyone in cycling using the drug. Any rider on his team who used any medical substance without the approval of the team's doctors would be dropped from the team, he said.

To discourage abuse of the drug, Amgen has begun an educational program, including symposiums for athletes and sports physicians. Amgen, which has an exclusive license to sell the drug in the United States for kidney patients, had total sales of the drug of \$304.2 million in the fiscal year ended March 31.

Ortho Pharmaceuticals also sells the drug for other illnesses in the United States, and it is manufactured and sold by several companies abroad.

"We heard the stories early on," said Daniel Vapnek, Amgen's senior vice president for research. "We are very concerned about abuse."

Because EPO cannot be detected in any test, some sports physicians have suggested that Amgen add a biological or chemical "marker" to the drug that would show up in screening. But Mr. Vapnek said this was not feasible. Allergic Reaction Feared

"The erythropoietin we manufacture and use clinically is very close to the natural protein made by a person's kidney," Mr. Vapnek said. "If you try to modify the protein in any way you have a potential to make it immunogenic," in which case patients' bodies would have an allergic reaction.

EPO is the second genetically engineered drug known to be abused by athletes. The other is human growth hormone, which was developed by Genentech Inc. for the treatment of

dwarfism in children. Athletes began to use the hormone in the 1980's because they believed it promoted the growth of muscle tissue. No deaths have been attributed to growth hormone.

Genentech has tightly restricted the distribution of growth hormone, and says it believes that it can track more than 90 percent of the patients receiving its drug.

Lacking a test, or an ironclad restriction of supply, the only solution may be education. Some experts fear this may only increase abuse by making athletes more aware of the drug. Others say that once the truth about the risk of EPO abuse is better known, fewer athletes will be tempted to try it. A recent issue of the Anabolic Reference Update, a newsletter that generally promotes steroid use, concludes, "EPO's risks outweigh benefits."

Edmund R. Burke, manager of the 1984 United States Olympic cycling team, said: "You have to tell them, 'EPO can do wonders for your aerobic capacity. The problem is, it can also kill you.' "

Correction: *May 26, 1991, Sunday* A picture caption last Sunday with an article about a stamina-building drug linked to athletes' deaths misstated what is known about the death of the Dutch cyclist Johannes Draaijer. An autopsy did not specify the cause, and it is not known conclusively whether he had used the drug.

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