

In a spin: the 1998 Tour de France was reduced to chaos (left) after drugs were found in the possession of Willy Voet, a Festina team employee.

bankrupt, partly as a result of court costs incurred after the middle-distance runner Diane Modahl challenged its decision to ban her following a positive test for testosterone. Modahl convinced the court that bacterial growth caused by a failure to refrigerate her urine sample properly could have led to a false positive result.

Hormone hunting

Given this, the IOC's decision to adopt the two EPO tests for the Sydney games is a genuine milestone in antidoping science. Recombinant EPO, a peptide of 165 amino acids produced by genetic engineering, is among the world's top selling pharmaceuticals. It is used to treat anaemias associated with disorders such as kidney failure. By boosting the production of red blood cells, it increases the flow of oxygen to the muscles. Some competitors in endurance sports such as cycling and distance running probably started using EPO as soon as it became available in 1987. Until now, there has been no way to detect this abuse.

In approving one of the EPO tests, the IOC is for the first time requiring athletes to give blood samples for doping control. Developed by Michael Ashenden and his colleagues at the Australian Institute of Sport near Canberra, the test measures the EPO concentration in blood as well as four other factors affected by raised EPO levels¹. Precursors of red blood cells, known as macrocytes and reticulocytes, are overproduced in bone marrow when EPO levels are raised, and they leak out into the circulation. So Ashenden's test measures the levels of red blood cells and these two precursors. It also measures the serum concentration of a protein called soluble transferrin receptor, which is involved in iron metabolism — and as such influences the production of the oxygen-carrying haemoglobin complexes found in red blood cells.

The other test, described earlier this year in *Nature*² by Françoise Lasne and Jacques de Ceaurriz of the French National Anti-Doping Laboratory in Châtenay-Malabry, near Paris, detects directly the presence of recombinant EPO in urine. The test is based on a subtle difference between human EPO and that produced *in vitro* for pharmaceuticals. The recombinant EPO has the same amino-acid sequence as the natural hormone but, because it is produced from non-human cells, it has a different number of sugar residues attached to it. As a result, the electrical charges on the two forms of EPO are different and they can be separated using an electrophoretic technique called isoelectric focusing.

To avoid the possibility of false positive

The lot of the dope police

Unlike the lives of the athletes they police, the work of the antidoping scientists is far from glamorous. Thousands of samples, each held in tamper-proof bottles, must be subjected to a set of standardized analyses. It is easy to get bored with the routine, says Wilhelm Schänzer, who heads the International Olympic Committee (IOC)-accredited doping control lab in Cologne. Last year, the 35 scientists in his lab tested 10,800 samples, 159 of which proved positive. Two-thirds of the positives were for anabolic steroids, most of the rest for stimulants such as ephedrine.

Each sample is divided into two, so that a retest can be done in the event of a positive result. For the retest, the athlete involved, or witnesses representing them, can attend. This is always "uncomfortable" for the scientists, says Jordi Segura, head of the IOC-accredited lab in Barcelona.

Doping control labs are also always on the alert for biochemical clues that athletes may have started to abuse a new compound for which no test is available, or which may not yet have been put on the banned list. Suspicions are usually aroused by the presence of unknown nitrogen-containing molecules in an athlete's urine. In some cases, it is possible to predict which drugs they are likely to experiment with. "We do try to anticipate the abuse potential of new drugs which come onto the market," says Schänzer.

results in Sydney, sanctions will only be taken against athletes who fail both tests. The blood changes tested for by Ashenden's method linger for two to three weeks after an athlete stops taking EPO, but the recombinant EPO itself is flushed out of the body within a few days. De Ceaurriz suspects that the performance-enhancing effects of EPO start to diminish three days after its last administration. Even so, he believes athletes can gain an advantage if they use EPO up to a few days before their competitions, and yet still test negative for the urine test. He says the tests will be most valuable in out-of-competition monitoring, where samples can be demanded at any time.

After watching the performance of the EPO tests in Sydney, IOC-accredited labs will decide whether to include them in their battery of standard tests. At the moment, these cost around 150 euros (US\$131) for competition samples and 100 euros for out-of-competition testing. The two EPO tests could add considerably to the costs. Wilhelm Schänzer, director of the IOC-accredited doping control laboratory in Cologne, calculates that Ashenden's blood test alone would add around 25 euros, not including the costs involved in blood collection.

The intensity of the war on doping will always depend on money, both for carrying



Testing times: Schänzer says that doping control can be a frustrating task.

What the antidoping scientists find most frustrating is the validity of their work being challenged by athletes' lawyers. "A new approach or methodology may take scientists years to develop, yet as soon as there is a positive test all the science is thrown into question," says Francesco Botrè, head of the IOC-accredited doping control laboratory in Rome. And if a disputed positive test ends up before an international arbitration panel, or even in court, it can be a harrowing experience for the scientists on both sides. "It is not that easy being beaten for hours by a barrister in a court-like setting," says John Honour, an endocrinologist at University College London who on several occasions has acted as an expert witness for accused athletes.

out the tests and for developing new ones. In 1998, the IOC decided to fast-track the development of the EPO tests by investing US\$1 million. This figure was matched by the Australian government.

A growing problem

But the IOC's antidoping research budget is so limited that this decision meant it had to abandon promising research into tests for hGH. Used to treat dwarfism, recombinant hGH first made its appearance in the mid-1980s. As usual, athletes recognized its fat-burning and anabolic effects long before the scientists. Even before the recombinant hormone became available, a publication called *The Underground Steroid Handbook* noted that hGH was already established in power-lifting and "within a few years will be a commonly used drug in all strength athletics". This prediction seems to have come true. The drug is often stolen from manufacturers and hospital pharmacies, and athletes have been caught carrying supplies. In February this year, 1,575 vials of hGH were stolen from a pharmaceutical importer in Sydney.

In the mid-1990s, the IOC and the European Commission co-funded a three-year international project called GH2000 to develop tests to detect this substance. The