

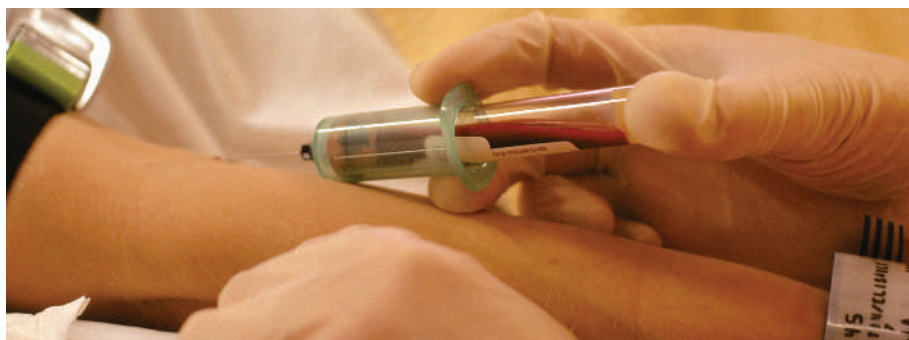
NEWS

London's disastrous drug trial has serious side effects for research

A drug trial that took a shocking turn in London last week may have far-reaching effects on policy. Its failure, experts say, could change restrictions on clinical research and increase scrutiny of the private companies that carry out the majority of clinical trials.

"There's going to be a lot of soul searching," says Thomas Murray, a bioethicist at the Hastings Center, a think tank in Garrison, New York.

As *Nature* went to press, two previously healthy young men were in critical condition and another four seriously ill at Northwick Park Hospital in London. On 13 March, they received intravenous injections of TGN1412, an antibody made by Boehringer Ingelheim for TeGenero, a small, privately owned biotechnology firm in Würzburg, Germany. The drug was being developed to fight autoimmune diseases and leukaemia. Parexel International, a contract research organization based in Waltham, Massachusetts, that operates in 39 countries, was running the trial for TeGenero.



IMAGESTAT/ALAMY

"Was informed consent adequate? Were the right subjects selected? Were the right doses given? This better have been done right, or some tough questions are going to come up for the private, commercialized research sector," says Arthur Caplan, a bioethicist at the University of Pennsylvania, Philadelphia.

Within one to two hours of being injected, the six volunteers suffered violent reactions that included headache, backache, nausea, a drop in

blood pressure and, ultimately, multiple organ failure. The trial was the first test of the drug in humans; it was immediately suspended by the UK Medicines and Healthcare Products Regulatory Agency, which is now investigating.

Thomas Hanke, chief scientific officer for TeGenero, says that the company had "no pre-clinical evidence whatsoever" that the drug might be unsafe, and that no adverse effects had been observed in rabbit and monkey studies.

THE DRUG TEST: WHAT WENT WRONG?

What is the drug?

TGN1412 is a monoclonal antibody being developed by the German company TeGenero. It is designed to direct the immune system to fight leukaemia, or relieve joints inflamed by rheumatoid arthritis.

How does it work?

The antibody stimulates a subset of immune cells called T cells by binding to a receptor molecule on their surface called CD28 — a pivotal molecule in the immune system. Normally, a T cell needs two incoming signals before it is activated: one from CD28 and a second from a separate T-cell receptor. TGN1412 is unusual because it overrides this basic control mechanism: when it binds to CD28, it activates the T cell without the need for a second signal.

What could explain the patients' reaction?

Doctors do not yet know, but multiple organ failure could be due to a contaminant in the medicine, the wrong dosage or the drug acting on the immune system in an unexpected way. Immunologists suspect that TGN1412 may have triggered T cells to release a toxic flood of molecules called cytokines. Or perhaps T cells attacked the body's own tissues, ignoring the safety mechanisms that normally keep them in check.

Are similar drugs already in use?

There is one, called anti-CTLA4 antibody, which binds to a different receptor on T cells and boosts the effects of the CD28 receptor, albeit to a lesser degree. Scientists working with this drug have seen side effects in human trials — including skin rashes

and gut reactions, some of which can be controlled with steroids. Anti-CTLA4 antibody is now in late-stage clinical trials to treat certain cancers.

Were there problems during animal tests with TGN1412?

TeGenero says that it saw no problematic side effects in tests on rabbits and monkeys. But researchers know that an antibody designed to bind to and rouse human CD28 may not work in the same way as the slightly different animal versions of the same molecule.

Will the drug be abandoned?

Immunologists are divided. Some warn that the approach is inherently dangerous. Others hope that TGN1412 or drugs like it might still find a use if researchers can learn to control its side effects or target specific tissues.

Helen Pearson

B. STANSALL/APP/GETTY IMAGES





SHIP ENDURES RECORD-BREAKING WAVES
Storm shows extreme seas may be more common than thought.
www.nature.com/news

But some observers say the company should have been more cautious, because the drug aimed to bypass the immune system's natural control mechanisms (see "The drug test: what went wrong?"). "You are going beyond the regulatory network, so all hell can break loose," says Angus Dalgleish, an immunologist at St George's Medical School in London.

Reaction to the trial's outcome has been swift, and mixed. In an unexpected turn of events, Britain has seen more people enquiring into early trials, in which healthy volunteers take experimental drugs to determine their safety and dose range. "Paradoxically, there's been an upsurge in interest in these healthy volunteer studies," says Max Parmar, who heads cancer studies at the Clinical Trials Unit of the UK Medical Research Council. The men who were struck ill in the TeGenero trial had been paid £2,000 (US\$3,500) each to do the test.

In Germany, reaction has been rather different. The local public prosecutor in Würzburg is investigating whether any criminal wrongdoing was involved. And this week, the Paul Ehrlich Institute, which authorizes human trials of biological drugs, announced it will tighten regulation of the first tests of such drugs in people. "The central question is: why do you treat six people at the same time? Why don't you start with one?" says Johannes Löwer, president of the Langen-based institute.

Löwer says that his institute will start requiring sequential rather than simultaneous administration of 'high risk' monoclonal antibodies — those that, like TGN1412, activate central pathways of the immune system. He says that one-at-a-time administration — with days between injections — will also be required for experimental biologics if institute scientists are not convinced by animal-model studies, or no appropriate animal model exists.

Ethicists in the United States, meanwhile, have called for careful scrutiny of a newly loosened set of rules for the making and testing of drugs in early human trials (see page 406). And the \$10-billion business of contract research organizations, or CROs, has come under the microscope.

Caplan worries that such organizations are tacitly encouraged not to focus on protection for human subjects. "The CROs are often told: 'Just get us the data on the deadline.' They don't get asked questions about how that's being done." The Association of Clinical Research Organizations boasts that CROs conduct clinical trials 30% more quickly than the pharmaceutical companies that hire them.

A spokesman for Parexel says: "We believe that best practices were followed and the appropriate policies and procedures were adhered to."

Meredith Wadman

GRAPHIC DETAIL

GAS CENTRIFUGE

Magnetic Suspension Bearing
Top Scoop
Molecular Pump
Outer Casing
Rotor
Bottom Scoop
Stator
Bottom Bearing
Inverter

Indian Rare Earths Ltd.
408, Marathi Commercial Centre,
P/18-A, D. Anil Desai Road, West, Mumbai-400 028, INDIA.
Fax: 91-22-2496 0506 Phone: (022) 5890 4792-5
TENDER Advertisement No. IREADV196
Indian Rare Earths Ltd., Mumbai, India

Aluminium tubing has many uses, but these dimensions suggest that it could be for the outer casing of a centrifuge.

TP-719 Rs. 400/- 28.2.2006
Seamless Aluminium extruded tubes of 195 mm O.D. and 25 mm wall thickness as per specification

TP-719 Rs. 500/- 17.12.2003
Precision machining of special steel Thin Rod-R(L) with spherical tip.

TP-672/TPT Rs. 2000/- 25.1.2006 1030 hrs. 1130 hrs.
Manufacture and supply of Ø 150 mm x 1225 mm long Thin Wall Flow Formed Interstage Annealed Ultra Precision Tubes made out of MDN 350 grade free issue extruded preforms as per specification.

This advert may be for a supercritical centrifuge rotor assembly — one of the parts that is most difficult to build. An outside agent posing as a bidder might have been able to obtain far more detailed specifications from Indian Rare Earth.

Are adverts revealing nuclear secrets?

WASHINGTON DC

When US President George W. Bush was asked recently whether he thought India — with whom he had just announced a deal to export nuclear technology — was a responsible nuclear nation, he responded simply: "I do." But critics say a scan through the local papers is all it takes to show that New Delhi is blatantly circumventing US and European export controls, and publicizing nuclear secrets.

In a report released on 10 March, David Albright and Susan Basu of the Institute for Science and International Security in Washington DC reveal that a Mumbai-based company has frequently placed advertisements in Indian newspapers; the ads are for corporations to supply items that seem to be components of a uranium gas centrifuge.

They analysed almost 200 public advertisements placed since 1984 in *The Times of India* by Indian Rare Earths, a mineral-extraction company that they suspect is helping to further the government's uranium-enrichment programme.

Gas centrifuges are spinning canisters that can be used to produce uranium that is enriched in the fissile isotope uranium-238, for use in reactors or weapons. The technology is currently being pursued by nations such as Iran (see *Nature* 432, 432-437; 2004).

Not everyone is in agreement over how to respond to the ads. Arjun Makhijani, president of the non-profit Institute for Energy and Environmental Research based in Takoma Park, Maryland, points out that India never signed the treaty on the non-proliferation of nuclear weapons. So it is technically allowed to further its enrichment programme. "India is not breaking any rules," he says.

But Albright says the technically detailed descriptions being published in newspapers show India's lax control over its nuclear technology. "It's gotten ridiculous," he says. "India just can't turn its back on this, and neither can the United States."

Geoff Brumfiel