centres would allow more detailed surveillance and could inform prospective intervention studies on the prevention and treatment of bacteraemia.¹ Along with greater understanding of the evolutionary biology of these strains of bacteria,^{7,8} better management of community acquired MRSA, and more rational use of antibiotics (antibiotic stewardship), such surveillance could greatly improve the management of invasive staphylococcal infection and save lives.

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Further lessons from the TGN1412 tragedy

New guidelines call for a change in the culture of research

As eight young men assembled at a London hospital on 13 March this year, they had no idea that within an hour their lives would be changed irrevocably and they would have contributed to a fundamental rethinking of the development and testing of new drugs. The first trial of TeGenero's TGN1412 (a T cell agonist) in humans took place at Parexel's clinical pharmacology research unit at Northwick Park Hospital, London. The events that followed fuelled speculation not only into the conduct of the trial and the nature of the drug, but also into aspects of research as diverse as comparative molecular biology, bioethics, and health economics.¹

The Medicines and Healthcare Products Regulatory Agency initiated an investigation, but the *BMJ* and other journals called for a more far reaching inquiry independent of the regulatory agency that had approved the trial. On 5 April the agency released its interim report,² and the government announced that an independent Expert Scientific Group, chaired by Professor Gordon Duff, would be appointed "to learn from the Parexel clinical trials incident." On 25 July this group released their interim report and recommendations.³

Inevitably, the report has pleased some people and disappointed others.^{4,5} Although it shows common sense, thoughtful reflection, and even vision, it fails to answer all the questions asked by the *BMJ*. Part of the problem is that the expert group was given a narrow remit, which focused on the biology and mechanics of high risk "first in man trials." In contrast, the *BMJ* had asked that the events of 13 March be interpreted in the context of the broader social and economic forces that shape research, because things happen for reasons related to the systems that create these factors.⁶

Critics of the trial highlighted many factors that should have indicated the potential for disaster. However, people who are disappointed with the report must understand that the expert group wisely avoided the appearances of a "judicial style inquiry." The group

refrained from criticising the parties involved, but reading between the lines shows that many things could have been done better and that these factors were compounded. Another difficult task the group faced was creating a balance between improving safety without being accused of "stifling innovation." Many pieces of the puzzle are still missing (including the clinical data that were withheld from the report, pending publication), and in the end more questions are asked than answered.

The recommendations fall into several broad categories: preclinical development that is both directed and consultative; evidence based transition to testing in humans; more open regulatory and ethical review, including independent scientific expertise; and most importantly, the need for more transparency.^{7,8} Although the report is carefully couched in the language of the terms of reference, the reader will realise that the findings have profound implications for all aspects of human research and drug development. There is a Buddhist story about seeking truth, in which disciples enter a darkened temple and on emerging compare their experiences of encountering an elephant. Although each witness to the inquiry described a part of the elephant, it is not clear that the expert group actually realised that there was an elephant in the temple.⁹ Specifically, they did not engage the many voices that have pointed to a collapse of integrity in research and the crisis in evidence based medicine that has been built on a corrupt database.^{10,11}

It would be easy just to concentrate on the technicalities. For instance, one thing that is clear is "that the preclinical development studies ... did not predict a safe dose in humans." The group's recommendations on dosing are sensible and prudent—for instance, shifting the threshold from one at which adverse effects are observed to one at which biological effects are observed. The deeper issue is why are we asking these questions now? Should they not have been self evident? Another recurrent theme of the report is the

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need to retreat from a blind obsession with a regulatory “process” and “correct” procedures to the use of sound clinical judgment based on all relevant information and common sense, on a case by case basis. A good example is the regulatory clock, in which agencies guarantee to provide an approval within a timeframe embedded in regulations, and which has probably done more harm than good. The recommendation that “the clock should be stopped” is timely in an environment that pressurises regulators to bring drugs to market faster.

Among the more far reaching recommendations are those that place more responsibility on sponsors and investigators to prove that it is necessary to perform a clinical trial in humans. Even more wide sweeping is the emphasis on openness in development and regulatory and ethical review, and a burial of the sacred cow of proprietary information. Even so, the expert group was reluctant to grasp some of the more prickly nettles. These include advocating a single integrated and publicly accessible database in conjunction with the World Health Organization and resisting the claims that more emphasis on safety threatens the swift delivery of lifesaving drugs to the bedside and forces research overseas. A closer look at the contributions of pharmaceutical research to improving global health might draw a different conclusion. Although witnesses emphasised the word “unprecedented,” this does not mean that it won’t happen again.

The concerns and recommendations of the expert group about the rapidly changing environment of research are commendable. Concerns include the commercialisation of research and its loss from clinical and academic centres; the prevalence of inexperienced and small start-up biotechnology companies reliant on venture capital; lack of training and adequate facilities; and the failure to plan for and deal with adverse events. The new ethical guidelines from the royal colleges will lend a supporting voice to some of these aspects of the report.^{12 13}

Will the report of the expert group make a difference? That will depend on the quality of the

public debate and the responses to the consultation, the deadline for which is 14 September. It will also depend on the degree of resoluteness that the group displays in recommending the need for a more fundamental inquiry and action, the extent to which the affected parties embrace their vision, and the willingness of those parties and the Department of Health to implement them fully.

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What to tell patients about radioiodine therapy

Avoid close contact with other people, don't try to conceive, and take your radiation certificate when flying

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In this week's *BMJ* Gangopadhyay and colleagues report the case of an unfortunate patient who activated an airport radiation detector six weeks after receiving radioiodine ¹³¹I therapy and was consequently subjected to intense examination and interrogation (p 293).¹ No clinical practice guidelines cover this type of problem. So, on current evidence, how should doctors advise patients who are about to receive radioiodine therapy?

Each year radioiodine is administered to 10 000 people for hyperthyroidism in the UK.² After injection or ingestion, radioiodine initially concentrates in the thyroid gland and then circulates through the bloodstream, with 80% excreted renally. While the radioactive urine is stored in the bladder, until it is voided, the gonads are irradiated: after an adminis-

tered dose of 750 MBq of ¹³¹I the testes receive a radiation dose of 17-19 mGy and the ovaries 28-31 mGy.³

To reduce the risk of any radioactive germ cells causing irradiation of the fetus, the Department of Health Administrations of Radioactive Substances Advisory Committee (ARSAC) recommends that male and female patients should be advised to avoid conception for four months after treatment.⁴ The American Thyroid Association suggests a period of 6-12 months.⁵ Also, although currently no evidence shows that treatment is associated with an increased incidence of infertility in women,⁶ men should be warned that they may have a reduced sperm count and temporary infertility for up to two years after therapy.⁵ We can reassure patients about future conception, as there is no association between the calculated internal

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