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Volunteers at Risk

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Clinical research can be a risky endeavor. In this issue of the *Journal*, Suntharalingam et al.¹ describe the events that occurred when six healthy volunteers received a dose (0.1 mg per kilogram of body weight) of TGN1412 — a superagonistic humanized monoclonal antibody that stimulates and expands T-cell populations independently of the ligation of the T-cell receptor. In all six patients, the cytokine-release syndrome developed, including multiorgan failure. Two of the patients required mechanical ventilation, and all received renal-replacement therapy. All six had severe hypotension, and peripheral ischemia developed in one patient to the extent that surgical treatment was required.

Analysis of the infused TGN1412 has, to this point, indicated that it met the specifications of the manufacturer — that is, it was sterile and pyrogen-free and contained the expected amount of protein without contaminants. Thus, the response observed is likely to represent a clear example of an iatrogenic “cytokine storm” without the background of another illness. On the basis of the experimental data that had been gathered before the testing of this monoclonal antibody

in humans, the biologic and subsequent physiological changes were unexpected. Also in this issue of the *Journal*, Sharpe and Abbas speculate on the biologic events that occurred when the patients received this treatment.² Although the data clearly show the occurrence of a cytokine storm, research is ongoing to determine exactly what happened and why. We await those results.

All six volunteers, who subsequently became patients, survived in part because of the extraordinary intensive care delivered during the critical stages of their illness. The routine treatment of such severe illness reflects a remarkable development in critical care medicine, made possible in part by the countless patients who had previously put themselves at risk as each piece of the critical-illness puzzle was dissected.

While biologists are at work trying to understand the sequence of events that led to the clinical changes seen in these volunteers, regulators are at work trying to retool the system to minimize the possibility that such unexpected events will ever recur. It is certainly possible to change the way in which novel agents are tested to minimize the number of subjects who are put at risk.

As long as we continue to manipulate biology in new ways, we probably cannot prevent all such events from occurring. We must do what we can to minimize risk, but the future health of the world population demands that we not let adverse events put an end to medical progress. We must treat those at risk with respect and great care, but the work must go on. The troubling fact of the matter is that without people who are willing to place themselves at risk to advance our knowledge, we will be frozen in our current state

of understanding. And this state simply may not be good enough to enable us to meet the next unexpected challenge that comes our way.

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Editor's note: An interim report of the expert scientific group of the U.K. Secretary of State for Health on phase 1 clinical trials is available at www.dh.gov.uk/Consultations/LiveConsultations/LiveConsultationsArticle/fs/en?CONTENT_ID=4137501&chk=x%2BoJ/%2B. The group is seeking comment on the report from interested parties through September 14, 2006.