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65 Bleecker St., New York, NY 10012
Tel: (212) 477-9600 Fax: (212) 505-1364
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THE FIRST WORD

Solitaire

Don't expect any single therapeutic to completely control septic shock syndrome. As far as we understand it, toxic shock is an escalating positive feedback loop in the inflammatory system. But that system is not completely mapped and there are holes in our understanding of how the parts fit together. At this point, trying to stop the toxic-shock cascade system with a single drug is like trying to stop a runaway freight train by poking a stick in its wheels.

With a third company getting its comeuppance in phase III trials, investors are perhaps entitled to wonder, however briefly, whether the folks involved are grasping or just dim. We prefer (in keeping with our family motto, *semper pollyanna*) another possibility: Toxic shock is still keeping some secrets to itself. A year ago, Cynthia Schmeichel ended "Septic Shock—What Do Physicians Want?" (*BioTechnology* 10:264-267, March, 1992) this way:

It must be remembered that the septic cascade is complex. It involves multiple mediators and the activation of several interacting inflammatory systems. No single approach is likely to be as efficacious as the intelligent combination of a reliable diagnostic screen, aggressive assault on the infecting organism, and (if all else fails) pharmaceuticals that neutralize critical mediators and prevent cellular adhesion and activation. As one of the investigators developing immunotherapies observes, "Patients with sepsis will eventually be treated like cancer patients with a very expensive armamentarium of four to five different pharmaceuticals, rather than with competitive inhibitors of the cells and mediators involved in the development of toxic shock."

None of this is going to be welcome news—not to the companies hoping their single-molecule claims will turn into the Homestake Mine, and not to cost-cutters convinced that pharmaceutical and biopharmaceutical companies are out to bilk the little guy. But it shouldn't surprise anyone: We're not in Kansas anymore. We're dealing with a tremendously complex, incompletely understood system whose normal controls have completely broken down.

What, really, are the chances of a single compound bringing the whole to heel?

Klondike

This issue sees us waiting out the flu, playing idle games between bouts with the keyboard and waiting for the spots on the wall to stop moving around quite so much. So we've played too much Klondike, to keep some minimal load on an idling mind. Otherwise, one supposes, the engine will run out of control (excursion, the engineers call it) like an unloaded turbine or diesel. But even the devils of idleness have lessons to teach. Consider, a friend pointed out to us: Solitaire is a well-defined system with a very limited number of elements and a finite number of states. Yet it can be terribly deceptive.

Some games look as though they're won before they begin. The cards seem to line themselves up almost as soon as they are turned over. But then something happens. The system hits a snag, or a wall, and suddenly goes no further.

Other games look pretty black at the beginning. . . literally. But again something happens. At the last minute the key card appears and everything else falls into place.

If a system as simple as solitaire is that hard to predict, what in the world do we expect from a game as complex as clinical trials, played by companies holding only a single pharmaceutical hand?

—DOUGLAS K. MCCORMICK