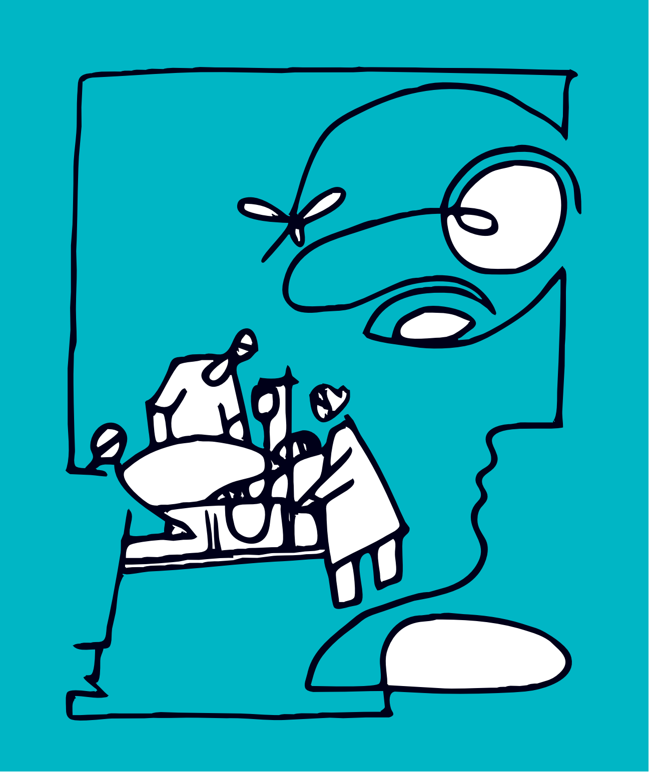

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GREATER THAN
THE SUM OF ITS PARTS

PATIENTS WITH THE SAME CONDITION MAY REQUIRE DIFFERENT TREATMENTS | BY KRISTIN OHLSON

Imagine that two people have survived a car crash and are rushed to the same emergency room. They present the same mix of physiological red flags: Both have suffered trauma to the body and blood loss. Both have similarly abnormal readings for blood pressure, respiration, heart rate, and other factors. The ER team rushes to set their bones, close their wounds, give them blood, and offer other standard treatments. Both patients seem to be stable after 24 hours. Yet days later, one dies in the ICU of multiple organ failure and the other survives.

When faced with trauma or severe infection, the body unleashes a fusillade of cellular and molecular events to reduce blood loss, fight pathogens, and eliminate damaged tissue. Sometimes, though, the response is so overwhelming that it destroys the body it is trying to protect. Why does one patient's inflammatory response save him, while that of another leads to systemic shock or multiorgan failure?

"The inflammatory response is like a game of chess," says Gilles Clermont, assistant professor of critical care medicine at the University of Pittsburgh and an attending physician at UPMC Presbyterian." We're very good at knowing exactly how the pawn moves and how the queen moves, but we are still not good at knowing how the whole game works." In other words, critical care specialists may know what a certain enzyme is doing but don't understand overall how individual patients will fare in this high-stakes game. "It all has to do with one genetic makeup compared to another," Clermont adds.

Before Clermont joined what's now Pitt's Department of Critical Care Medicine in 1994, he had done graduate work in physics and never lost his interest in that subject, especially in the study of complex systems. This field of study examines how dozens of processes create a global system that is dauntingly more complex and mysterious than the sum of its parts; in particular, researchers in this field look at the indirect effects resulting from the interdependence of many seemingly unrelated or distantly related processes. The study of complex systems has been applied to diverse areas---from environmental woes to economic cycles. Clermont's own graduate thesis discussed complex systems in language formation. At some point in the ICU, he looked at a patient in the throes of inflammation and realized that here, too, was a complex system. He began to imagine a diagnostic tool that could assess the integrated effect of all the inflammatory processes at work in an individual patient and offer custom therapies.

With the help of a National Institutes of Health grant, Clermont and Pitt specialists in mathematics, immunology, surgery, and statistics began developing software that uses mathematical modeling to simulate the interaction of more than 20 key processes involved in the inflammatory response. When this tool receives its final tweaks, emergency and ICU physicians will prepare data for it by taking blood samples from a patient at several timed intervals, even as they begin treatment, and measuring the patient's changing levels of immune cells and cytokines. As they feed this data into the computer model, it will gauge the action and energy of patients' inflammatory responses over time and reactions to treatments.

"The model 'learns' you as it gathers information," explains Clermont. "When we take your last blood sample, it will have zeroed in on who you are as an individual and what will drive your outcome many days down the road." He believes the model will not only be able to determine what kind of drug or combination of drugs a particular patient needs, but it also will be able to determine the best time to administer the dose.

Clermont and his team are still developing the model with animal and human data; a working clinical version probably won't be ready for another three years. However, a partnership between the Pitt team and LaunchCyte, a company that commercializes biotechnology breakthroughs, may deliver another promising application sooner. The partners have founded Immunetrics, a company that markets a version of the software designed to reduce the cost of drug development as well as speed the development of drugs for inflammation-related diseases like sepsis, a frequently fatal response to infection that afflicts 750,000 Americans every year. Using this tool, pharmaceutical and biotech companies could test the action of promising compounds before they ever reach the stage of costly animal trials. In addition, they may be able to run virtual clinical studies that account for the millions of combinations of criteria---the type of patient enrolled, the timing of the drug administration, the dose, etc.---to design more productive human trials.

"This method will replace a lot of trial and error," says Tom Petzinger Jr., CEO and chair of LaunchCyte. "And with the computer, you can do a lot of marginal experiments, too---the ones no one wants to try because they're such long shots." ■