Editorial & Letters

EDITORIAL

Halting the March of the Immune Defenses

The cells of the immune system stand as sentries at our epithelial borders and are deployed in our peripheral lymphoid tissues to defend against the constant onslaught of microbial invaders. The components of the innate immune system use a limited repertoire of receptors to recognize molecular patterns common to pathogens and provide us with an early warning system to identify and ward off unfriendly challenges. But many pathogens have evolved tricks to sneak through and disarm these innate defensive barriers.

Thus, it is up to the adaptive immune system, consisting of T and B lymphocytes, to provide us with our ultimate defense against many pathogens and with a memory of these encounters when rechallenged by the same pathogen. The system is adaptive because it has a dynamic repertoire of antigen receptors. The repertoire changes with each encounter with a pathogen, with the goal being ever more efficient eradication. How mammals can develop and maintain such a lethal defense system without ultimately harming themselves is a question being actively pursued by many investigators. How does the system get stunted by developmental mutations? How are autoimmune attacks avoided? How is an immune response that has done its job removed from the front line? How are the inherent weaknesses of immune defenses exploited by pathogens? Some of the answers are revealed in three Articles presented in this issue of *Science*.

T and B lymphocytes develop, mature, and learn the difference between self and nonself in the thymus and bone marrow, respectively. Their antigen-specific receptors serve as highly specific sensors to detect pathogens. The receptor assembly process is rigorously tested at quality control checkpoints. Cells without receptors or with inappropriately autoreactive receptors are discarded. In the Article by Fischer and Malissen (p. 237), the critical importance of the events involved in the assembly of and signaling by antigen receptors at each of these developmental checkpoints is revealed by the human or murine immunodeficiencies that result from mutations in components of the assembly process, signaling apparatus, or response machinery. The lessons learned from studies of these human and murine immunodeficiencies are excellent examples of how study of clinical diseases and basic biology can synergize in the discovery process.

The immune system has powerful weapons to unleash against pathogens, consisting of antibodies, cytokines, and cytolytic activities. However, excessive or unrestricted use of this arsenal can result in injury to the host, as can occur in autoimmune diseases, or in the excessive response to some bacterial toxins, such as toxic shock syndrome and food poisoning. Thus, it is critical that an immune response be measured and self-limited. Insights into the regulatory constraints placed on B and T cell responses are summarized by Van Parijs and Abbas (p. 243). These regulatory mechanisms determine the basal state of the immune system and help to limit the magnitude and duration of the adaptive immune response. It is interesting, as the authors note, that these key regulatory mechanisms do not appear to be redundant. Without backups, the failure of these regulatory mechanisms results in an immunologic army that is out of control.

Unfortunately, every army has its weaknesses, and microorganisms have developed a variety of strategies to exploit those of the immune system. The current pandemic of the human immunodeficiency virus is a consequence of its direct attack on one of the critical components of the immunologic armamentarium, the $CD4^+$ T cell. Ploegh describes some of the other elegant strategies adopted by pathogens to evade the immune system (p. 248). Some organisms have targeted intracellular antigen processing and presentation. This compromises the ability of the host to display antigenic peptides by interrupting the peptide antigen presentation by class I or class II major histocompatibility complex molecules on the cell surface. Thus, the immunologic army that cannot see the enemy cannot fight the enemy. Other pathogens have acquired variant cytokines, receptors, regulators of transcriptional responses, or inhibitors of apoptosis to evade, confuse, or inhibit the immune defense system.

Continued study of how the immune system can be tripped up, either through mutation or by deliberate assault, can potentially provide therapies to ensure that our immune defenses cannot just match, but beat, the world's pathogens at their own game.

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LETTERS

Connections

Readers describe what can happen when scientists cross national borders for collaboration and education (right, Red Sea Program participants). Researchers discuss the microscopic anatomy of "regenerating axons." And could the Internet suffer a "tragedy of the commons"?

Mideast Peace and Scientific Collaboration

The News & Comment article "As Mideast peace process lags, science endures" by Jocelyn Kaiser (6 Mar., p. 1447) illustrates a human aspect of science often neglected in the media. I would like to offer an example of such collaborations with the potential to help heal enmities between two peoples.

A number of Jewish scientists have participated in a collaboration between U.S. universities and Saudi Arabia. While on the faculty at Yale University School of Medicine, during discussions with Saudi and Yale collaborators, I wrote a computer application designed to help improve the care (and our understanding) of several severe pediatric illnesses in Saudi Arabia. I also spent some weeks as a guest of the sponsoring institution, King Faisal Specialist Hospital and Research Centre, living in downtown Riyadh and working with Saudi scientists and physicians. Others Jewish scientists at Yale and several other U.S. universities were similarly involved in clinical care and medical research collaborations. I enjoyed much hospitality and learned a lot from the intercultural discussions with my hosts.

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Southeast Asian Scientists and U.S. Graduate Programs

I enjoyed reading the article "Scientific growth faces fiscal crisis" by Jeffrey Mervis and Dennis Normile (Science in Southeast Asia, 6 Mar., p. 1466). One of the primary reasons that only sporadic attention is given by Americans to research efforts in Southeast

namics of congestion? Huberman and Lukose address this question of scale by formulating a prediction concerning the marginal distribution of delays for packets sent through the Internet. But because the packets in the sample they studied were generally sent with periods of less than 1 second between them, this approach assumes that social forces have effects visible on such small time scales. But we wonder whether other factors might instead dominate.

A crucial property of Internet traffic—the sole overt mechanism that maintains the network's stability and avoids "congestion collapse"—is that the rate at which the TCP transmits data "adapts" to network congestion (as evidenced by packet drops). In the presence of drops, a TCP sender is required to effectively halve its sending rate. This adaptation occurs on scales between those of round-trip times and those of "timeout" timers, often hundreds of milliseconds to seconds. Furthermore, a significant body of TCP research (2) has shown how this behavior can lead to cyclic oscillations in traffic loads. Thus, the network already has built into it a mechanism that will introduce delay variation on the time scales studied in the report, even in the absence of social forces coming into play.

Two other aspects of the study merit further measurement and analysis so that social forces and other mechanisms shaping congestion might be distinguished from each other. The first is that measuring congestion with the use of end-to-end round-trip times can be elusive because variations in delay at different points in the network, on both the forward and reverse path, become conflated together into a single aggregate increase in delay. Attributing the variations to a single "hot spot" becomes difficult. This question could be pursued by attempting to use the social forces model to predict what pattern of packet arrivals one would expect to observe at a fixed location in the network, and then comparing that prediction with results from "link-level" studies already available. [The "self-similarity" study (3) mentioned in the report is one of these; the autocorrelations analyzed in that study are different from those mentioned in the report.]

The second area that would benefit from a revisit concerns the end-to-end path studied. Huberman and Lukose selected a path including a particular trans-Atlantic link because it "is one of the most congested in the world," which historically is correct. However, they also report that "[o]f the 10,000 packets sent, 179 of them timed out and were removed," presumably because they were dropped by the network. This result reflects a packet loss rate of about 1.8%, which corresponds to only modest congestion. Traffic studies have found trans-Atlantic links to typically suffer from loss rates more than five times greater (4). Thus, if the loss rate was indeed 1.8%, then Huberman and Lukose should rethink the idea that the measurements reflect a heavily congested link for which the effects of social forces would naturally be most visible.

In summary, we find the empirical evidence offered to support the social forces explanation of congestion patterns—namely, the approximate fit of the delays to a log-normal distribution—not particularly compelling. The fit merely means that one cannot (yet) directly rule out the model. Such a fit is necessary evidence, but points such as those we raise above must be addressed if the evidence is to also prove sufficient.

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4. V. Paxson, *Proc. SIGCOMM '97, Cannes, France, Sep. 1997*, pp. 139–152.

Response: The main issue raised by Crowcroft *et al.* is that our "social forces" model is not exclusively proven by the latency measurements we made. Their central argument is that because the network already has built into it a TCP mechanism that drops packets, it will introduce delay variation. But when the TCP drops packets, it only means that they will have to be resent, which just adds an intermediate stage to the buildup of latency. Thus, while TCP is a "congestion control" algorithm from the point of view of routers, it does little to alleviate congestion from the point of view of users.

This and other considerations made us bring the user's utility maximizing behavior to the center of the analysis of congestion. Such a view allows one to ignore the details of the network's workings because it focuses on what users care the most about: latency.

Crowcroft *et al.* also point out that "a significant body of TCP research" has shown how this packet-dropping behavior "can lead to cyclic oscillations in traffic loads," and yet, we did not observe any signatures of periodic behavior in the power spectra of the data that we obtained. Rather, the observations were in agreement with the predictions of our social model. This point highlights the fact that research which does not take account of user behavior can produce results that are inconsistent with the empirical measurements we presented.

Another point raised is that "variations in delay at different points in the network, on both the forward and reverse path, become conflated together into a single aggregate increase in delay." Once again, our model was intended to describe the statistics of the congestion that a user is likely to see. Thus, this kind of aggregation is desirable for our purpose. Although the link level studies of the type proposed by Crowcroft *et al.* may be appropriate for the purpose of locating "hot spots" or bad routers, they would not account for overall latencies experienced by the users.

Finally, Crowcroft *et al.* state that, in our

Asia is the utilitarian and mercantilist nature of a good portion of U.S. science. This motive would seem to account for the preponderance of elite students from China, Korea, India, and—on the rare occasion—Indonesia or Thailand in science and engineering graduate programs in the United States. There seems to be little interest on the part of U.S. government agencies (not to mention academic mentors) in supporting non–upwardly mobile students from Southeast Asia (particularly from Malaysia, Indonesia, and Myanmar/Burma). U.S. science policy is predicated on fast results, and the criteria used to assess foreign student performance do not lend themselves well toward "Peace Corps–type" science. Thus, the majority of nonaffluent students in Southeast Asia will continue to be ignored equally by local government institutions and by self-serving U.S. science policies.

U.S international science policy should assist poorer nations in Southeast Asia in developing proactive education and science programs in order to raise the overall standards locally; we should not be in the business of mining elite talent in Asia to augment putative efforts toward U.S. scientific supremacy. Graduate science programs in the United States should return to their original purpose of educating all students, and end their present role of serving as would-be surrogates for the U.S. Immigration and Naturalization Service.

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Anatomy of "Regenerating Axons"

In their Report "Repair of adult rat corticospinal tract by transplants of olifactory ensheathing cells" (26 Sept., p. 2000), Ying Li *et al.* describe destroying unilaterally the upper cervical corticospinal tract (CST) of adult rats by focal electrolytic lesions and then transplanting homologous olfactory ensheathing cells (OECs) onto the injury site. They found that the transected CST axons grew through the transplant and elongated into the denervated caudal host tract, forming a continuous bridge across the lesion. These results are relevant because of the possibility of future applications in patients with spinal cord injuries. The anatomical findings shown in the report, however, call for some comment.

An example of the regenerated CST axons at 4 weeks after transplantation (figure 2 in the report) shows a fascicle of parallel, unbranched axons with occasional varicosities and no terminal clubs traveling in the transplanted area. These axons, however, do not exhibit the typical features of the regenerating CST axons (*1*–*3*). The morphology of the regenerating CST fibers is peculiar and makes them distinguishable from unlesioned CST fibers (*3*). One possible explanation for the results (figure 2 in the report) may be that the transplanted OECs modified the growing environment, affecting the regenerative pattern of the CST fibers. Alternatively, the axons depicted might not represent transected CST fibers that regenerated across the injured area, but CST axons that survived the lesioning procedure. The electrolytic method that was used in this study is likely to produce partial lesions of the CST, as demonstrated by the control group, where only 7 out of 21 rats (33%) showed a complete CST transection. In the transplanted group, the actual extent of the CST lesion was not determined. It would be interesting to know whether Li *et al.* observed Dextran-labeled terminal plexuses in the anterior horns of segments innervating the forepaw.

Another point concerns the demonstration with electron microscopy (EM) of Schwann-like OECs that formed peripheral-type myelin around regenerated CST axons. The EM technique per se cannot show conclusively that the myelinated axons (figure 3, B and C, of the report) represent CST fibers. These axons may derive from sources different from the pyramidal neurons. Li *et al.* identified the cells in figure 3B as Schwann-like OECs, but this determination is not justified because they did not label the OECs that were transplanted. It is known that the Schwann cells can migrate into injured SC areas and myelinate the regenerated axons that arise from dorsal root ganglion cells, as well as from intraspinal neurons (*2*, *4*, *5*). We cannot exclude the possibility that the axons seen with EM may represent CST fibers that were first demyelinated, but not transected, by the electolytic lesion, and then remyelinated with peripheral myelin formed by the Schwann cells. It is important to distinguish between the regeneration of transected CST axons, which may be potentially aided by the transplanted OECs, and the myelination of the regenerated axons, possibly by Schwann cells that have migrated into the lesion.

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