

and where various polysaccharides are deposited, will likely be important in creating improved raw materials for biofuels.

The major conclusion reached by Burton *et al.* is that CslF proteins are involved in  $\beta$ -glucan biosynthesis. However, as is often the case, this important advance raises many additional questions. For example, the amounts of  $\beta$ -glucan were low in the transgenic plants and the polysaccharide could be detected only in selected cells, even though expression was driven by a strong constitutive genetic promoter. Burton *et al.* speculate that  $\beta$ -glucan

biosynthesis may also require “ancillary factors.” If so, we need to find out what these factors are and determine their biochemical functions. Do CslF proteins synthesize both sugar linkages of  $\beta$ -glucan? Or does CslF make one linkage while an “ancillary factor” makes the other? The work of Burton *et al.* opens up many opportunities for studying  $\beta$ -glucan biosynthesis and adds CslF to the list of Csl proteins with known functions. Still, the roles of the many other cellulose-like synthase gene products remain a mystery. Indeed, why are there so many? More food for thought.

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## GEOPHYSICS

# Dangerous Tectonics, Fragile Buildings, and Tough Decisions

Roger Bilham

When the going gets tough, it is merely a matter of time before rupture on a plate boundary gets going—again. Stresses from Indonesia’s December 2004 moment magnitude ( $M_w$ ) = 9.2 earthquake took 92 days to reach across the island of Simeulue before they propelled a second great earthquake, this time to the south. Deformation in this 28 March  $M_w$  = 8.7 Nias earthquake was captured in unprecedented detail, as reported on page 1897 of this issue by Briggs and his colleagues (1). At that time, the authors were documenting the effects of its December predecessor, which, at  $M_w$  = 9.2, was the largest earthquake in 40 years.

Had the March Nias quake with its rupture length of 400 km occurred simultaneously with that of the earlier 1600-km-long neighbor, the total energy release would have been equivalent to a  $M_w$  = 9.3 earthquake. But it didn’t, and the reasons for its hesitation now pose interesting questions, the answers to which have important consequences for nations in the path of plate collisions in Southeast Asia. Each end of this new 2000-km-long rip along the northeast edge of the Indo-Australian plate now points suggestively at adjoining segments of the plate boundary that are themselves considered overdue for rupture (2, 3). Why did the rupture stop where it did, and could the plate boundary conceivably rip further?

Simeulue, an island similar in size and shape to Long Island, New York, lies above a wrinkle in the plate boundary—ground zero to both the December and March earthquakes, and, apparently, a barrier tough enough to prevent through-

going slip. Such barriers pin the ends of earthquake ruptures, yet no one is certain how they do it (3–5). Slip often nucleates from them and/or to them, and occasionally straight through them, as was the case in contiguous great Japanese earthquakes that sometimes rupture individually and at other times simultaneously (6). Dual behavior is vexing because it implies that barriers cannot always be relied on to arrest rupture, adding a chaotic element to forecasting the locations of likely future events. Barriers prevent small earthquakes from becoming big earthquakes at all scales, and many problems in seismology would benefit from a better understanding of their physics (7). Serendipitously, the Simeulue barrier afforded a veiled view of some of its secrets during the flurry of postseismic deformation studies that followed December’s earthquake.

The time history of vertical deformation there is recorded in the growth and kill fields of a million tiny corals (8). In December the northern end of the island rose 1.4 m. Near-shore corals responded to the twisting and bending of their island, dying where exposed to the tropical sun, but establishing new thriving colonies safely below the lowest tides. On 28 March 1.6-m uplift of the southern end of the island again checked their growth, establishing yet lower, optimum growth levels from which Briggs and co-workers have pieced together an elegant four-dimensional time history of distortion of the island’s shorelines. The complex deformation of Simeulue and its neighboring islands was confirmed by data from Global Positioning System receivers placed throughout the islands (and mainland) monitoring the aftermath of the December event.

The measurements indicated clearly why the March earthquake, unlike the December catas-

The occurrence of four fatal earthquakes within and around the Indian plate in the last 5 years, including two great ones, highlights the need for earthquake-resistant construction and replacement throughout the region.

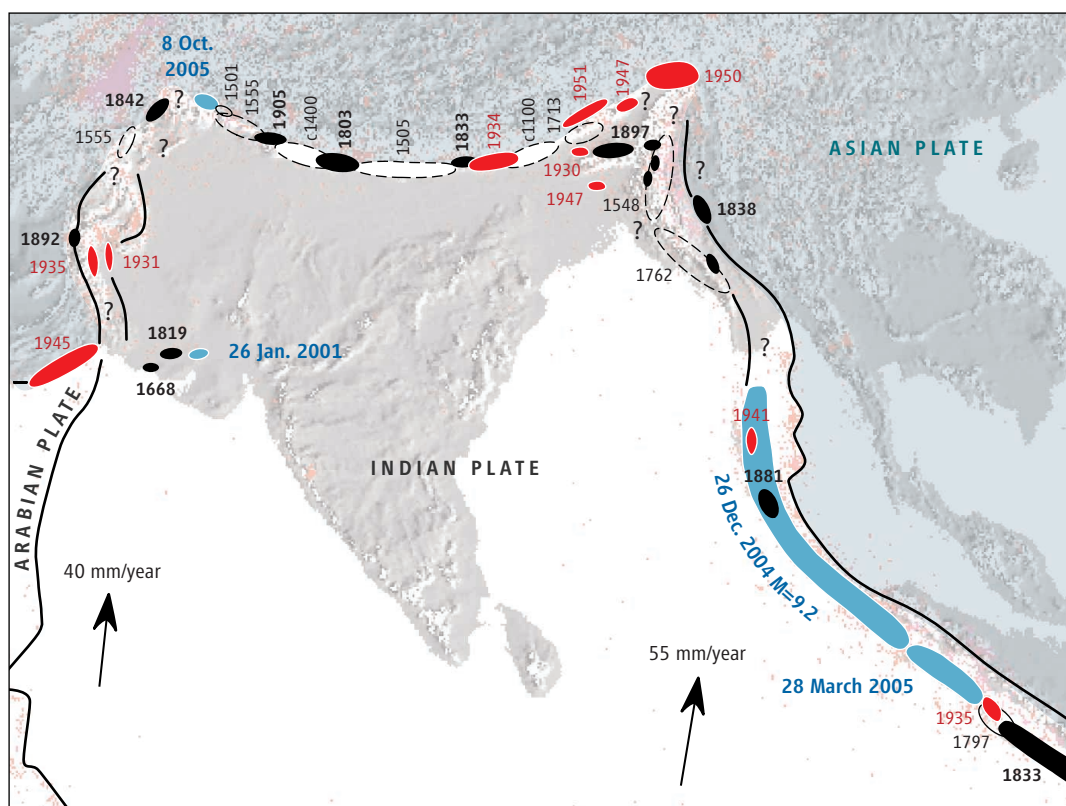
trophe, produced no substantial tsunami—energy release was one-fifth, rupture length one-quarter, and maximum uplift one-half that of the December earthquake, and most of the uplift occurred on land rather than beneath the sea.

But the measurements also captured Simeulue in the act of impeding, or seeding, rupture. The corals tell of a 20-cm uplift of the foundations to their watery homes in 2003 during a  $M_w$  = 7.3 earthquake. This modest ancestor to the two great earthquakes separated their slip areas but failed to trigger either event. Briggs and co-authors speculate that most probably the barrier corresponds to a scissors-like tear in the descending plate. Certainly, elucidation of its structure and rheological properties are now of great importance to understanding how it permitted earthquakes to nucleate to north and south, and may provide important clues applicable to earthquakes elsewhere.

These clues are more than of esoteric interest because numerous segments of Southeast Asia’s plate boundaries are today sufficiently mature to slip in massive earthquakes. They include not only segments of the Sunda arc east of the March earthquake that are clearly ripe for failure (2, 3), but also the region of the Indo-Burman ranges north of the December rupture, which has no recent history of significant slip, and where such slip must now be considered quite possible. They also include parts of the Himalaya and India’s western plate boundary.

The Indian plate has been cornered by four killer quakes in the past 5 years: the  $M_w$  = 7.6 Bhuj ( $\approx$ 18,500 dead), the  $M_w$  = 9.2 Sumatra-Andaman rupture ( $\approx$ 300,000 dead), the 28 March earthquake ( $>$ 700 dead) and most recently the  $M_w$  = 7.6 Kashmir earthquake (73,338 dead as of January 2006). This fatal

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**Disaster zone.** Earthquakes surround the northern edge of the Indian plate in response to its northward motion toward Asia. The most recent destructive ( $M > 7.5$ ) earthquakes are shown in black (1800 to 1905), red (1930 to 1951), or blue (since 2001). Historical earthquakes where known are shown in white (evidence from trenching or historical accounts), in dashed lines (incomplete data), or with a question mark (no data). In the millennium before 2000, the cumulative death toll in Indian plate boundary earthquakes amounted to fewer than 80,000 of which 50,000 occurred between 1930 and 1950. Earthquakes in the first 5 years of the new millennium have already claimed more than 380,000 lives.

sequence has no precise historical precedent in the Indo-Asian collision zone, and therefore, no easy answer can be offered to the most obvious of questions—is this the end, or are more catastrophic earthquakes poised to occur?

The conservative answer to this question is that we are witnessing a coincidence, a random fluctuation in the timing of earthquakes that occur at intervals of hundreds of years. History reveals numerous of these coincidences, however, which suggests that these clusters may be more common than can be explained by chance: in Mongolia (9), in the northern United States (10), and in the Pacific (11). Even in India a cluster of seven fatal earthquakes bracketed World War II, leaving 50,000 dead in their wake (see the figure). The comparative lull following this sequence has led to complacency in the rigorous application of earthquake-resistant building codes in India, despite the definition of a code in 1931 following the  $M_w = 7.3$  Mach earthquake near the start of this sequence.

The nonconservative answer is that several mature seismic gaps are known (12), and that the past 5 years have nudged these and neighboring regions toward failure (see the figure). The 1819 Allah Bund and 2001 Bhuj earthquakes have stressed regions within striking distance of

populations exceeding 20 million (Karachi and Ahmedabad). The 8 October Kashmir earthquake has stressed adjoining Himalayan regions, where no great earthquake has occurred since the 16th century (13). A 600-km-long region of the central Himalaya has apparently not slipped since 1505 (14). The more ancient the predecessor, the larger will be the future earthquake, and the recurrence of these Himalayan  $M > 8$  earthquakes would now threaten a dozen megacities in Pakistan and India. No  $M > 8$  earthquakes are known on the Chaman fault system that separates the western edge of the Indian plate from the Asian plate, and although it is possible that earthquakes here cannot exceed  $M_w = 7.7$ , similar to that suffered by Quetta in 1935, this earthquake is infamous for holding the previous record number of fatalities (35,000) for an Indian subcontinent earthquake before last October's Kashmir earthquake.

The question of why these recent earthquakes stopped where they did, and whether the increased stresses that now lay siege to their rupture termination points will succumb to failure sooner rather than later, is one that regrettably cannot be answered. Why do contiguous ruptures tarry? Coulomb failure models can tell us clearly where to expect failure (3, 15), but we remain clueless about the settings on the

delayed-action fuses that have now been lit.

Tough decisions now face the politicians and urban planners of Sumatra, India, Pakistan, Nepal, and Bangladesh. The simple solution, to toss money at seismic-monitoring technologies, is laudable but may be less effective in saving lives than community education. The proposed Indian Ocean tsunami warning system will cost far more than telling schoolchildren and their parents about the causes and effects of tsunamis. The half-million dwellings and 7600 schools that collapsed in Kashmir last October were almost entirely constructed in the past 20 years. They collapsed more from poor assembly than from severity in shaking. Correctly assembled buildings survived intact as beacons to education. The 26 January Bhuj 2001 earthquake occurred in a region long designated at high risk from future shocks, yet the earthquake-resistant code here was so unevenly applied that the same percentage of the population was killed by building collapse as occurred in 1819 when earthquake-resistant construction was unknown (16).

Most troubling is that although these three recent Indian plate earthquakes have raised public awareness of the precarious state of dwellings in their region, these earthquakes could have occurred in any of a dozen other locations surrounding the Indian plate with similar or worse effects. None of the recent earthquakes were direct hits on any of the numerous megacities that populate the plate. A death toll of more than 30% is typical of a direct hit from a quite modest earthquake beneath a city like Tangshan, Muzaffarabad, or Balakot. Such an event beneath Karachi, Lahore, Lucknow, Benares, Dacca, or Bombay would result in a disaster of unprecedented magnitude were it to occur, and it seems only a matter of time before it does (17). The well-intentioned frenzy of earthquake-resistant reconstruction that is now essential in the epicentral regions in response to the past 5 years of earthquake-induced collapse has not been attended by any similar frenzy of attention to reconstruction and retrofitting of the next dozen potential earthquake targets. That is not to say that urban planners are being complacent. New Delhi and other cities have started a retrofit campaign (18), but the costs are daunting and almost unimaginably expensive.

The diversion of funds to a project as simple and fundamental as safe dwellings for citizens of the Indian plate surely poses tough decisions for leaders of nations in the collision zone. It's tough luck for citizens of these nations if their leaders decide, through indifference, to ignore this early-millennium quadruple wake-up call. Unwavering common sense, rather than a knee-jerk reaction designed to score political points, appears to be the only solution to the world's earthquake-vulnerable populations. It is essential that the replacement of the ancient building stock of cities, be it a 20-year or 50-year turnover, be undertaken with mandatory earthquake-resistant code. This won't stop the

carnage immediately, but it will substantially reduce it, and it will make politicians and urban planners look less culpable than they do now.

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## IMMUNOLOGY

# An Antibody Paradox, Resolved

Martin Prlic and Michael J. Bevan

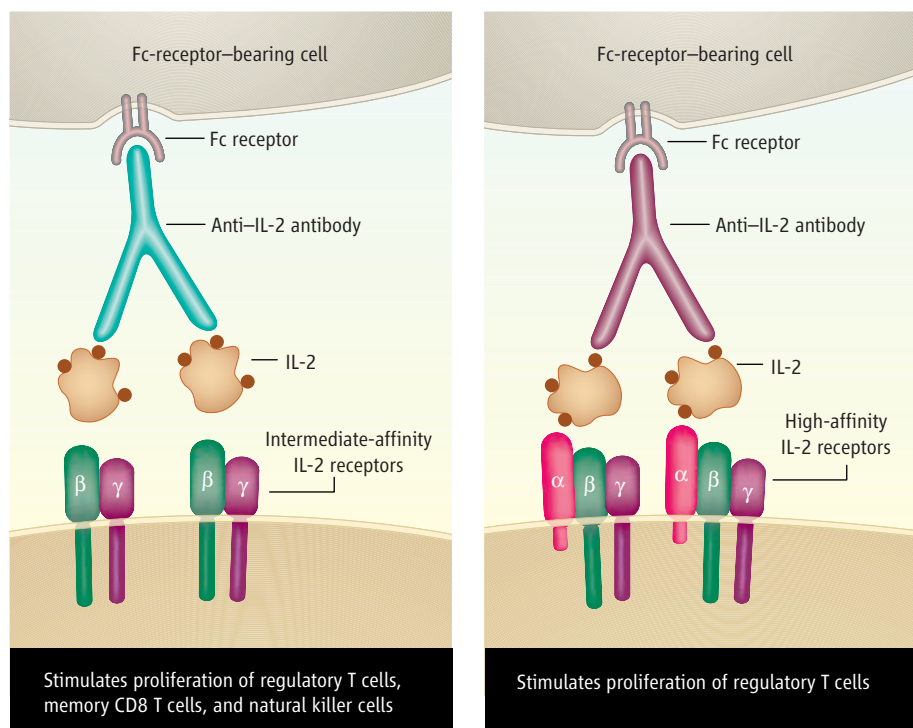
Lymphocytes are the epitome of migrant cells in the body, coursing through blood and lymphatic vessels, trafficking through lymphoid organs such as spleen and lymph nodes, and entering any tissue upon activation. Yet the numbers of these highly mobile populations of immune cells—B and T lymphocytes and natural killer cells—must be balanced and maintained to sustain lymphoid homeostasis. In the absence of such balance, autoimmunity or the failure to respond to an infection may result. Cytokines, soluble factors produced by lymphoid and nonlymphoid cells, provide signals for the survival, proliferation, and turnover of many subpopulations of lymphocytes. A report by Boyman *et al.* (1) on page 1924 of this issue shows that the balance of lymphocyte subpopulations can be dramatically skewed by the injection of monoclonal antibodies previously designated as cytokine-neutralizing antibodies. As it turns out, these antibodies paradoxically enhance the potency of the cytokine in vivo and disrupt lymphoid homeostasis.

Many of the cytokines involved in lymphoid homeostasis are members of the “common gamma chain” family of cytokines, so called because they all activate lymphocyte receptors that include a subunit called the  $\gamma$  chain. Interleukin-2 (IL-2) is the founder member of this family of cytokines, and is historically thought of as an acute cytokine—that is, one that is made and secreted in large quantities only by T cells (CD4 T cell subtype) that have been recently activated by antigen. Acute cytokines are also consumed by activated CD8 T cells.

The high-affinity receptor for IL-2 is a trimeric structure composed of an  $\alpha$  chain (CD25), whose expression increases in T cells shortly after antigen exposure, plus a  $\beta$  chain (CD122), and  $\gamma$  chain. In this way, activated T cells expressing the high-affinity receptor can respond to secreted IL-2 as a growth and differentiation signal. Nonactivated, “resting” T cells that do not express CD25 may express the two-chain

The immune effect of a cytokine bound to an antibody is paradoxically much stronger than that of the cytokine alone, suggesting a way to lower therapeutic doses and thereby reduce side effects.

intermediate-affinity receptor for IL-2 composed of CD122 plus  $\gamma$ . In addition to its acute role in the immune response to antigen, IL-2 is also a maintenance cytokine for regulatory T cells, another T cell subset (2). Regulatory T cells constitutively express the high-affinity, trimeric IL-2 receptor. To complicate things further, the cytokine interleukin-15 (IL-15) is necessary for the maintenance of memory CD8 T cells and



**Antibodies determine which lymphocytes get stimulated.** Monoclonal antibodies that bind to different sites on IL-2 can enhance, rather than neutralize, the potency of the cytokine in vivo and stimulate the proliferation of different subpopulations of lymphocytes. Possibly, polymerization of the IL-2 on the surface of cells bearing Fc receptors enhances the potency of IL-2 and causes these cells to proliferate.

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