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**Pushing the limits**

Field-effect transistors have been made with organic materials but need further optimization before they can be used in applications such as flexible displays. Torsi et al. (p. 1462) measured the field-effect mobility of electrons in α-sexithiophene from over a temperature range from 4 to 350 kelvin and obtained an excellent fit to their data with Holstein's model, which describes the transport as small polaron motion, or hopping transport, for the higher temperature conditions. These results indicate that materials with lower polaron binding energies should be sought.

**With the crust on**

Magas derived from the mantle may interact with the crust during their ascent. A key problem in tracing the origin of the magmas is resolving crustal contamination. Kersting et al. (p. 1464) examined a suite of volcanoes lying astride thin but chemically distinct continental fragments in Japan. The chemical variations among the volcanoes change across the crustal boundary, implying that even thin continental crust has modified the mantle magmas.

**Viral protein versus p53**

The transcriptional regulatory protein p53 controls the expression of proteins that regulate cell growth, and p53 mutations are frequently associated with human cancers. Dobner et al. (p. 1470) found that an adenovirus protein, E4orf6, can inhibit p53 transcriptional activation. E4orf6 binds to the carboxyl terminus of p53 and prevents the amino terminus of p53 from interacting with TAFII131, a TFIID component in the initiation complex.

**A mechanism for deep earthquakes**

The structural transformation of serpentine, an abundant mineral in subducting slabs under high pressures and temperatures, is considered to be a primary cause for the deepest earthquakes (450 to 650 kilometers) recorded along subduction zones. Irfune et al. (p. 1468) studied the structure of serpentine in a multianvil apparatus. At pressures from 14 to 27 gigapascals and relatively low temperatures (200 to 300 degrees Celsius), serpentine became amorphous and dehydrated and rapidly recrystallized at higher temperatures. Deep earthquakes, assumed to occur at higher temperatures, may result primarily from the dehydration of serpentine.

**Chromatin connection**

The packaging of DNA into chromatin helps regulate transcription. SPT6, an essential gene in the yeast Saccharomyces cerevisiae, has been implicated in the control of chromatin structure. Bortvin and Winston (p. 1473) found that Sp16 mutations cause alterations in chromatin structure in vivo. The Sp16p protein interacts directly with histones and can also mediate the assembly of nucleosomes in vitro in an adenosine triphosphate-independent manner.

**Controlling calcium**

Coordinated regulation of cellular functions requires interaction between signaling pathways. Jayaraman et al. (p. 1492) provide evidence for regulation of intracellular calcium concentrations by a tyrosine kinase of the Src family. Activation of the T cell receptor caused the tyrosine kinase Fyn to associate with the inositol 1,4,5-trisphosphate (IP3) receptor, a calcium channel that releases calcium from intracellular stores. Phosphorylation of the IP3 receptor increased the probability of opening of the calcium channel. The results reveal a mechanism by which activation of nonreceptor tyrosine kinases in response to stimulation of receptors on the cell surface can then cause an increase in intracellular concentrations of calcium.

**Environmental estrogens**

Chemicals in the environment that act like natural estrogens have been suspected to have the potential to disrupt normal reproductive function of exposed organisms. However, these compounds are much less potent than natural estrogens. Arnold et al. (p. 1489; see the Perspective by Simmons, p. 1451, and the news story by Kaiser, p. 1417) tested the effects of combinations of two environmental estrogens on binding and activation of the estrogen receptor. Combinations of the compounds were 10 to 1600 times more potent than the individual compounds in activating estrogen receptor-mediated transcription. The synergistic biological activity of the compounds reflects synergistic binding to the estrogen receptor.
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Immunological Tolerance

In the 22 March issue, three papers on immunological tolerance (Reports, J. P. Ridge et al., p. 1723; M. Sarzotti et al., p. 1726; T. Forsthuber et al., p. 1728) were featured, as well as a major comment on them in Research News (E. Pennisi, p. 1665). Because these papers purport to overthrow the major tenets of modern immunology, they have received even wider publicity over the news wires and in many daily newspapers.

While the research reported in these papers is competently done, and the results interesting, it is unclear how the inferences and conclusions drawn by the authors could have passed peer review. Nor is it clear why the authors' elaborations of these inferences should have been so uncritically reported in Research News.

It has been demonstrated for almost 30 years that there is nothing mystical about the fetal or neonatal period. The fetus of many species may express immunological competence to many different antigens at different stages of gestation and even beyond birth (1), and the mouse has long been known to slowly expand its immunological repertoire during the neonatal period (2).

We have known for almost 100 years that the mammal cannot distinguish between noxious and benign antigens; indeed, Paul Ehrlich's 1897 side-chain theory of antibody formation (a selectionist precursor of Burnet's Clonal Selection Theory) fell from favor precisely because of the demonstration that a host of nonpathogenic substances might induce an immune response. The concept of a "danger signal," with its implication of an evolutionary basis, is not viable.

We have known for well over 30 years that the balance between active immune response and tolerance induction (and maintenance) depends on a wide variety of factors, including the physical and chemical nature of the antigen, dose, timing, mode of access to the immune system, and so forth; we have long known also that the adult may be rendered tolerant under appropriate conditions (3).

The balance between tolerogenic and immunogenic dose, between B and T cell tolerance, between one and two signals, and the entire question of self-nonsel has been debated widely since Burnet's original formulation. Burnet's initial theory has been modified substantially by later data; to raise it now as a straw man to be demolished is not reasonable. These questions are scarcely new.

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References

Response: Neonatal tolerance has fascinated the immunologic community for 50 years, resulting in apparently conflicting publications that can be broadly divided into three groups which state that neonatal antigen exposure causes (i) clonal deletion, (ii) suppression, or (iii) an immune response (see Silverstein's letter). The prevalent view has been that the neonate is immune privileged.

The three reports in the 22 March issue may have resolved this controversy and demonstrate why neonatally induced immunity has been perceived either as clonal deletion or suppression. In our report (p. 1728), for...
example, we showed that memory cells lose lymph node homing receptors and lose their ability to migrate to lymph nodes (figure 1 in the report). Hence, when lymph node responses are studied, as has been the case in the past, the lack of antigen reactive cells seemed to suggest that these cells were clonally deleted, which substantiated the clonal deletion model for neonatal tolerance. But, as we have shown, the memory cells were simply redistributed in the organism (figure 1 in the report). Furthermore, we have shown that neonatally induced T_{H2} immunity results in apparent suppression when T_{H1} immunity is measured (table 1 in the report). The previous data, which seemed to conflict, reflect a single mechanism: induction of T_{H2} immunity.

Clearly, the currently favored clonal deletion model is insufficient to fully explain self-tolerance. Our reports have added two important aspects to this discussion. First is Matzinger’s danger model, on which she comments below. Second, our findings substantiated the active T cell tolerance idea, showing that what was thought to be “suppressor cell”-mediated self-tolerance actually translates into T_{H2} cell-mediated effects.

With regard to the “wide variety of factors” that can define outcome, there has not been a basic understanding of the rules that govern the outcome. This is where the impact of our studies lies. Matzinger and her colleagues showed that it is the type and activation state of the antigen-presenting cells that decide whether a response is engaged or tolerance results. Sarzotti and her co-workers determined how the dose of the virus affects response. Our own report showed that the adjuvants can reliably guide the response to the T_{H1} or T_{H2} directions.

I agree that “these questions are scarcely new,” but for the first time there may be a satisfactory answer concerning the mechanism that underlies neonatal tolerance.

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Response: Roughly two millennia before Copernicus, Aristarchus proposed a heliocentric model to explain the motion of the planets. Why was it ignored? Thomas Kuhn’s suggestion was that, at that time, there might have been no general dissatisfaction with the reigning paradigm (Earth at the center) and therefore no reason to abandon it (1). By the time Copernicus suggested his version, the motion of planets could no longer be easily explained by the view that the Earth was central, and the intellectual community was ready for a “new” idea. During that period of almost 20 centuries, there had been many findings that did not fit with the ruling paradigm, but most of them went unrecognized, examples of the “retrorerecognition” phenomenon (2), whereby clear anomalies in a paradigm are recognized only after a new conceptual framework has been set forth to replace the defective one.

Roughly 100 years ago, as Silverstein points out, Ehrlich thought that the immune system’s primary function was to detect and protect against noxious pathogens. It seems that this view was replaced by Burnet’s self-nonself model because the latter was better able to explain two new phenomena, the ability to raise immune responses to nonnoxious substances (3) and the discovery of neonatal tolerance (4). Over the ensuing years, both of these findings were extensively examined and, in both cases, some clear anomalies appeared, many of which were ignored. For example, a variety of nonpathogenic substances can indeed induce immune responses, but, as Charles Janeway has emphasized, they almost never do in the absence of immunological adjuvants, which contain bacterial products (5). Thus, the mere presence of “foreignness” is
not enough. Some essence of pathogenicity is also required.

The picture with neonatal tolerance has also been clouded considerably since the original pioneering experiments. As Silverstein mentions, there have been scattered examples in which neonatal immunity rather than tolerance was seen. We referred to some of these in our paper and have since been made aware of others (6). Altogether, these studies showed that neonates were able to make many different kinds of responses. They cleared viruses, generated graft-versus-host disease, and made T1,1 and T1,2 responses; and a few experts in the field began to understand that neonatal tolerance was more complicated than had first been envisioned. Yet many immunologists were unaware of the complications, and recent textbooks continue to describe neonatal tolerance in terms of the immaturity of the neonatal T cells (7).

Why have the anomalous findings had so little impact?

Perhaps this was another case of retro-recognition. The findings simply didn’t fit with a paradigm that had found its strongest early support in the original neonatal tolerance experiments, and there was no alternative model to fit them into. If youthful immune systems were able to respond to a variety of antigens, making a variety of responses, how could self be distinguished from nonself? Although some scientists attempted to deal with the problem by changing the temporal model to a spatial one (moving tolerance into the thymus, where the T cells, rather than the individual, are immature), these models could not easily account for tolerance to tissue-specific peripheral antigens, and no self-nonself model can account for new antigens that might appear throughout life.

Looking back, a historian of science might wonder what would have happened if Peter Medawar’s group had gotten a different result. Although Burnet’s Clonal Selection would certainly have prevailed as the modern operating model, what would have happened to self versus nonself? Perhaps Clonal Selection would have served as a mechanism to generate specific responses to dangerous pathogens and to allow for antigen-specific memory.

Our results, in combination with those of the other groups showing that neonatal mice can respond, open up the possibility of a new model based on clonal selection but not on self and nonself. Although the results, by themselves, do not disprove the self-nonself model (8), they do undermine one of its experimental underpinnings and are more easily placed in the context of the “danger” model (9), which suggests that the immune system is primarily concerned with detecting and protecting against “dangerous” pathogens and that tolerance is a continuous process regulated throughout life by each bodily tissue. We were pleased that Silverstein reminded us of Ehrlich’s early views. We could be in far worse company.

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Response: Our report demonstrated that the susceptibility of newborn mice to a virus was not the consequence of a "slowly expanding immunological repertoire" but an example of immune deviation (1) driven by the relatively high dose of virus encountered by the neonatal immune system. The development of type 1 or type 2 responses is determined by the dose of virus inoculated in newborn mice and influences the development of protective immunity. Our report and those of Ridge et al. and Forsthuber et al. used non-"mystical" concepts and approaches (dose of antigen, type of APCs, adjuvants) known to the immunological community for a long time. However, in combination these approaches offered a simple and comprehensive explanation of immunological nonresponsiveness in newborn mice.

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References

The three reports on immunological tolerance provide intellectual support for the clinical observation (1) of down-regulation of cellular immune responses in patients receiving allogeneic blood transfusions. This is particularly well documented in organ transplantation, surgery, and cancer. Recent evidence from both animal and human studies suggests that the high doses of alloantigen involved in clinical transfusions induce a Th2 immune response, and the expected down regulation of the Th1 response (2, 3). The trauma of surgery alone causes Th1 responses, compatible with Matzinger's "danger" theory. Allogeneic transfusions also have been successfully used to treat two disease processes that likely represent overactive Th1 immunity in adults—repetitive spontaneous abortion (4) and rheumatoid arthritis (5). These observations in humans support the point made by the authors that manipulation of immunity in adults may be more feasible than previously believed on theoretical grounds.

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Abelson on Nuclear Power

I was delighted to find the editorial "Nuclear power in East Asia" by Philip H. Abelson in the issue of 26 April (p. 465). During the last several years, I have opened each issue of Science to look first for an editorial by Abelson. Even with the many other assets of the magazine, Abelson's editorials stand out because of their singular societal value.

The members of AAAS and, for that matter, the people of the United States owe a debt of gratitude to Abelson, not only for his lifetime of public service through science, but also because of his insistence that we make sense when we think about major societal issues involving science and technology.

Abelson's moderate, rational voice, using relevant scientific data and speaking with the wisdom of a long life of public involvement, provides a model for us who would occasionally step outside the confines of our scientific disciplines and commit ourselves to serving the larger society and helping build a better world.

I hope Abelson's editorials will continue to appear frequently and that we all will do our part to help our fellow citizens, especially law- and policy-makers and members of the media, understand.

In doing so, we will honor Abelson in a manner he richly deserves.

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Abelson provides interesting information regarding the growth of the nuclear industry in East Asia, along with comparisons to the "diminished" situation in the United States. The comparative data on reactor numbers, construction time, capacity, and design are enlightening. One issue not discussed by Abelson, however, is the disposal of nuclear waste from the many new reactors planned and recently built.

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Abelson remains crosswise with the majority view that disfavors nuclear power in the United States. Like his many negative editorials about the U.S. Environmental Protection Agency's human health protection policies and regulations, his opinions on nuclear energy in the United States have long belonged in the Round File.

We've outlived the Manhattan Project, and the sooner that those who continue to champion nuclear power from that perspective acknowledge it, the better.

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"Obscure" Journal?

It is with some astonishment that I read in the Research News article "Superconductivity turns 10" by Robert F. Service (29 Mar., p. 1804) that J. Georg Bednorz and K. Alexander Muller "published a cautiously worded paper on 'Possible High Tc Superconductivity' in an obscure German physics journal . . ." (italics mine.

Isn't it astonishing that Heisenberg and others published their seminal works on quantum mechanics in the same "obscure" journal, Zeitschrift für Physik, admittedly many years ago?

Even leading physicists with English as their mother tongue, like P. A. M. Dirac and J. Bell, did not publish regularly in journals like Physical Review, as a recent article in Physics World [9 (no. 4), 3 (April 1996)] has pointed out: "Bell's most famous paper appeared in a journal called Physics, which is now defunct." Thus, there is scientific life even outside the prestigious journals.

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Corrections and Clarifications

In the News & Comment article "Clotting controversy" by Jock Friedly (29 Mar., p. 1800), the affiliation of George Broze should have been given as Washington University in St. Louis, Missouri.

Letters to the Editor

Letters may be submitted by e-mail (at science_letters@aaas.org), fax (202-789-4669), or regular mail (Science, 1200 New York Avenue, NW, Washington, DC 20005, USA). Letters are not routinely acknowledged. Full addresses, signatures, and daytime phone numbers should be included. Letters should be brief (300 words or less) and may be edited for reasons of clarity or space. They may appear in print and/or on the World Wide Web. Letter writers are not consulted before publication.
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Science Slighted in UN Habitat II Agenda

Many of the world's academies of science are upset that a United Nations (UN) meeting on improving global living standards has given science and technology the brush-off. They expressed their concerns as government representatives gathered this week in Istanbul for the UN's Conference on Human Settlements, also known as Habitat II. According to U.S. National Academy of Sciences (NAS) leaders attending a meeting of 72 academies held in Istanbul in connection with the UN conference, the group drafting the Habitat II agenda included only one sentence of a paragraph on the importance of science and technology that the NAS and other academies had suggested 5 months ago. Chemist Sherwood Rowland, NAS foreign secretary, is concerned about the potential impact. "The framers of the 100-page agenda do not see that any major technological advances are needed for the amelioration of the problems of cities," Rowland says.

Last week, the academies signed a statement asking world leaders to give more attention to technical possibilities for improving the quality of life in urban areas—such as investing in better sanitation systems and using computers to track the course of infectious diseases. Rowland was to present the statement to a Habitat II committee this week. But even if wording is added to the document, he worries that the delegates' attitude could "undermine any effort to improve the quality of science and technology as applied to the problems of the cities."

Flouting Criticism, NBC Replays Origins Show

When a TV program called The Mysterious Origins of Man aired in February, scientists protested that it promoted pseudoscience and misled the public (Science, 8 March, p. 1357). The program, hosted by Charlton Heston, suggested among other things that evolution is a questionable theory, that human civilizations began more than 100 million years ago, and that scientists have conspired to suppress important archaeological evidence.

Now, it seems, the scientific outcry has backfired. The National Broadcasting Company (NBC) will air the show again on 8 June, and its press release uses the outrage of university professors as a selling point for this "program that dares to challenge accepted beliefs." The production company, B.C. Video Co., even has a World Wide Web site devoted to the controversy (and to selling videotapes) (http://rumba.ics.uci.edu:8080/ faqs/mom.html).

"It's a pathetic way to make a buck," says Jere Lipps, director of the Museum of Paleontology at the University of California, Berkeley. "The program's first showing made science teaching more difficult. ... Showing it again as science is irresponsible." David Schwimmer, a paleontologist at Columbus College in Georgia, says: "That anyone would nurture this level of ignorance is scary." Schwimmer has used the show as a teaching aid by analyzing the claims and evidence with students.

The show's independent producer, Bill Cote, says he and NBC are "shocked that scientists are overreacting," adding that "NBC's extensive legal department put us through the wringer until we presented a balanced view."

Bill Blocks Computer Purchase

Supercomputers, by definition, are the fastest machines in the world. But buying one can be excruciatingly slow if you're a federally funded research lab—especially if you choose not to buy American. Last week the saga of the National Center for Atmospheric Research (NCAR) in Boulder, Colorado, which had raised lawmakers' ire by considering a Japanese machine (Science, 17 May, p. 941), took another turn when legislators added language to a spending bill that would stop NCAR's funding agency, the National Science Foundation (NSF), from signing off on the deal.

NCAR researchers want the best tool for global climate modeling, while legislators want to prevent foreign companies from "dumping" products at below-market prices. On 17 May, NCAR announced it had picked the NEC Corp. of Japan, rejecting offers from U.S.-based Cray Research Inc. and another Japanese company. NCAR planned to negotiate a contract worth up to $35 million. But 3 days later, the Department of Commerce wrote to NSF that it believed the machine's cost of production "is substantially greater" than NEC's bid and that such a purchase would harm U.S. supercomputer makers. And on 30 May, the House panel that sets NSF's budget declared no money in the bill could be used to pay anyone who "approves a contract for the purchase or lease of a supercomputer"—if Commerce officials conclude it is being sold below fair-market value.

NCAR, on orders from NSF, is reviewing NEC's winning bid to see if it reflects the company's true costs. The Commerce investigation is continuing, says a spokesperson, and a positive finding could lead to fines against NEC. Meanwhile, NSF officials are seeking a compromise that will satisfy Congress and give researchers what they want.

Ariane 5 Failure Throws Euro Space Science Off Course

As Science went to press, Europe's Ariane 5 rocket had just pirouetted out of control during its maiden flight, forcing engineers to destroy it. The 4 June disaster could deal a double blow to European space science, setting back solar studies and indirectly affecting the international crewed space program.

When it went down, Ariane 5 took with it four satellites it was carrying into orbit as part of an ambitious project to study Earth's magnetosphere—the region around our planet which deflects particles from the solar wind (Science, 24 May, p. 1095). That mission is lost. And unless the Ariane 5 program can quickly get back on course, the failure could cast a shadow on Europe's participation in the International Space Station as well. That's because the cash-strapped European Space Agency had negotiated a deal with its partners—the United States, Canada, Japan, and Russia—in which ESA would pay its share of station operation costs not with cash, but with flights of Ariane 5, ferrying supplies to and from the station.

European space officials are trying to put a bright face on things, saying they hope to solve Ariane 5's problems before its next flight in the fall. "This was an experimental flight," French space minister François Fillon told a press conference at Ariane 5's launch site in French Guiana after the failure. "We are going right ahead to prepare the second launch."
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Estrogen Receptor Binding to Estrogen Response Element

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PRODUCTS & MATERIALS

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Karyotyping Software
Oncor Karyotype is a software package for Macintosh or IBM-compatible computers to augment or replace manual karyotyping methods or to work in conjunction with fluorescence in situ hybridization analysis. It can also be configured as a complete system with a high-resolution digital camera or a less expensive video camera. Oncor. Circle 138.

Statistical Software
Unistat is statistical software for life sciences and biomedical research. Version 4.0 integrates seamlessly with the Microsoft Office suite of programs via OLE2 automa-

tion. A stand-alone statistical package, it also functions as a Microsoft Excel add-in. It is possible to start Excel with Unistat menus and toolbar, process data in Excel, and run Unistat just like an Excel Wizard. Unistat. Circle 139.

DNA Ligation and Screening Kit
The Ligator Rapid DNA Ligation and Screening Kit reduces the time needed to clone DNA fragments and identify recombinants. The ligation of inserts containing cohesive overhangs or blunt ends can be performed with high efficiency in just 5 min at room temperature. Ligation of polymerase chain reaction products with A-overhangs into T-vectors can be performed in 1 hour at 16°C. Following ligation and transformation, the Ligator in-well lysis screening technique allows screening of colonies for insert-containing plasmids in less than 1 day without having to isolate DNA and perform restriction digests. Epicentre Technologies. Circle 140.

Sequencing Primers
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