NEWS

Preventing Toxicity With a Gene Test

To test or not to test? That is the question clinicians are asking about screening for genes that affect how the body metabolizes drugs

For more than 30 years, doctors have been using a powerful cell-killing compound to cure leukemia in children. This wonder drug—6-mercaptopurine (6MP), synthesized by the late Gertrude Elion and George Hitchings—has saved thousands of lives. But it has a dark side. Researchers discovered more than 20 years ago that it is extremely toxic in patients with an inherited metabolic flaw. The drug can accumulate rapidly, wiping out essential bone marrow and leading to infections.

About 8 years ago, teams led by William Evans of St. Jude Children's Research Hospital in Memphis, Tennessee, and Richard Weinshilboum of the Mayo Clinic in Rochester, Minnesota, pinpointed flaws in an enzyme-producing gene called *TPMT* on chromosome 6. A DNA test became available in the 1990s. It tells patients whether they are in one of three risk categories: standard, with a copy of the normal *TPMT* gene from each parent; slightly elevated, with a deficient gene from one parent; or extremely high, with two deficient genes. People in the last category, roughly 1 in 300 Caucasians, should not receive standard 6MP therapy, physicians say. It could kill them.

Only one fatality has been reported in the medical literature: In 1993 a heart-transplant patient in Germany received a drug in the same class (a thiopurine) to suppress immunity and died of sepsis. Afterward, a blood test revealed a metabolic deficiency. But many young leukemia patients have suffered well-documented, life-threatening bouts of 6MP toxicity.

This makes a strong case for genetic testing before prescribing 6MP, argue cancer researchers such as Evans and Howard McLeod of Washington University in St. Louis, Missouri. The tests might be used not just for cancer therapy but also for the drug's unapproved or "off-label" treatment of inflammatory diseases. But the medical community remains skeptical. Like other promised benefits of genomic medicine, this one has run into complaints about its cost ($100 to $300 per test), technical issues about how to recalibrate drug doses, and doubts about physicians' ability to understand test results. Such real-world headaches seem to keep pushing the human genome sequence's payoff just beyond reach.

Pinpoint vulnerability. William Evans's group at St. Jude Children's Research Hospital patented a gene test that spots patients who are likely to overdose on 6-mercaptopurine (6MP).

Indeed, several influential physicians recently declared that testing for *TPMT* risks should not be mandated. Doing so, they say, could endanger patients by causing delays in therapy. Several pediatric cancer specialists have also said they don't want the government even encouraging prospective *TPMT* testing. Therapy should be guided by experience and well-established blood cell counts, they say, not a gene test. For now, the U.S. Food and Drug Administration (FDA) seems unlikely to recommend one.

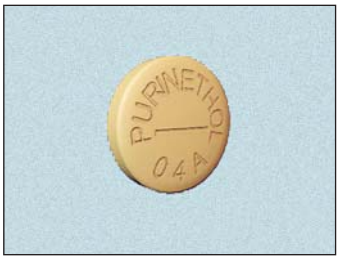
The resistance has surprised champions of genomic medicine. A leader in pharmacogenetic studies, Russ Altman of Stanford University, acknowledges that genotyping for drug risks has been a hard sell. In all, says FDA pharmacogenetic expert Larry Lesko, about 20 drug labels now mention reactions that may be influenced by genetic differences, but none recommends a gene test or related dose guidelines. Adds Altman: "Everyone thought *TPMT* would be the big one to do first. I must admit there is not a single case of a genetic variation where the standard of care is to test first. … We have not yet broken through."

Still, the *TPMT* case suggests that genomic medicine is gaining momentum, albeit slowly. Genotyping to prevent adverse drug reactions may indeed be one of the first applications to win broad acceptance, but the pace will depend a lot on how physicians respond. Patients who face risks of toxicity may be among the first to recognize the benefits, and they may bring along the doctors.

No advice, thanks

The question of whether to add an advisory on gene testing to the 6MP package label is now before FDA. The agency's new administrator, Mark McClellan, has said that one of his top five priorities is to raise the profile of genomics in FDA decisions. Partly because of McClellan's interest, says Lesko, the agency is taking a look at 6MP.

It's the second drug to undergo an explicit genetic risk review but only the first to be evaluated as possibly requiring a gene test before use. The other one was a new drug, atomoxetine, approved by FDA in January for treatment of attention deficit hyperactivity disorder. The manufacturer, Eli Lilly of Indianapolis, Indiana, agreed to include information in the package informing doctors that patients who have a toxic reaction or fail to benefit may



Expanding use. Despite known genetic risks, the cancer drug 6MP and a related compound are now widely prescribed for inflammatory diseases.

CREDIT: (TOP) ST. JUDE CHILDREN'S RESEARCH HOSPITAL

have a gene-driven metabolic irregularity. It also mentioned that a test is available to help analyze such irregularities—with no suggestion that the test be done in advance.

Because the toxic effects of 6MP are greater than those of atomoxetine, FDA asked an outside panel to consider whether the label for 6MP should go further and recommend gene testing in advance to prevent toxicity. At a critical review on 15 July, pediatricians on the FDA's Oncologic Drugs Advisory Committee (ODAC) were not enthusiastic. The panel agreed that the 6MP label should be modified to include more information about inherited *TPMT* deficiency—but no recommendation for gene testing.

The most disturbing potential risks discussed at the ODAC session concerned children with acute lymphocytic leukemia (ALL) who developed new cancers after being treated with 6MP and cranial irradiation. In a 1999 study, Mary Relling, a pharmacist-researcher at St. Jude, reported that half the children (three of six) who developed these fatal tumors over an 8-year period had at least one abnormal gene. To lower the risk of secondary tumors, cranial irradiation is not combined with 6MP therapy today. But Relling thinks that *TPMT* deficiencies may have contributed to earlier tragedies, and she's confident that testing would reduce the risk of toxicity in routine therapy.

Naomi Winick, an oncologist at the University of Texas Southwestern Medical Center in Dallas, representing the 238 institutions in the Children's Oncology Group (COG) that treat 80% of pediatric patients in North America, isn't persuaded. She says *TPMT* testing would not have prevented the tumors, and she doesn't think the cases are relevant to the debate. She told the FDA panel that the data are too sketchy to justify routine *TPMT* screening.

"I'm not against genetic testing," she explained in a telephone interview. "I just don't think it's necessary for this test to be mandated before giving [6MP]." She objects to the added cost and complexity. More than 2000 children are treated for ALL in North America each year, she points out; if one patient in 300 is at risk for a genetically determined 6MP overdose, "most hospitals would never see one." She fears that the tests would spread alarm and compromise therapy. "This drug has been used for 30 years," Winick notes; cancer therapists manage its toxicity every day by watching blood counts that enable them to cut the 6MP dose before the consequences are irreversible.

A greater risk, Winick told ODAC, is that doctors might become overly cautious, delaying 6MP therapy or reducing doses too much after discovering that a patient has a single *TPMT*-deficient gene. Although about 10% of Caucasians have at least one risky gene, no validated studies have been published indicating how much the 6MP dose should be reduced for them, she and others point out. "Leukemia is a fatal illness," Winick reminds: "I worry about [6MP] *under*dosing."

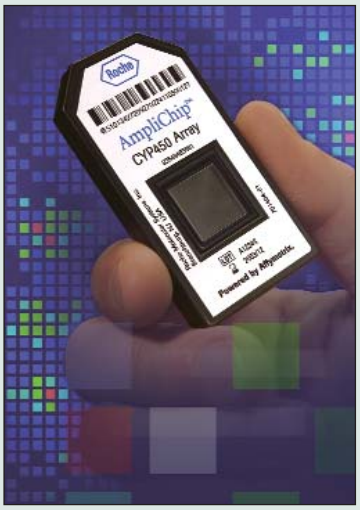
Pro-testers

Physicians care deeply about their patients and are "understandably conservative" about adopting new technologies, says Mayo's Weinshilboum, who also briefed the ODAC panel. And they're wary of gene testing. But he says: "I would prefer to see a recommendation for testing prior to drug therapy." Both the Mayo Clinic and St. Jude now routinely genotype ALL patients for *TPMT* genes before giving 6MP. But most do not. Even Evans of St. Jude says he understands that cost is a barrier, but he thinks that, "ideally, everyone

First Check My Genome, Doctor

The dangerous reactions some people have to the cancer drug 6MP may offer the most dramatic case for gene testing (see main text), but many other vulnerabilities may soon be checkable with a simple DNA test.

The biggest player in this DNA diagnostics market is Roche Molecular Diagnostics in Pleasanton, California. It is seeking U.S. and European regulatory clearance for a battery of gene tests to be included on a single device, the "AmpliChip CYP450," a microarray developed with the genomics company Affymetrix of Santa Clara, California. The chip will test for variations in two genes: *CYP2D6* and *CYP2C19*. They affect how people process about 25% of drugs on the market, says Walter H. Koch, the company's senior director of pharmacogenomics. Initially, Roche plans to market it primarily for patients using antipsychotic and antidepressant drugs, the efficacy of which varies greatly depending on *CYP2D6* genes. Some people with *CYP2D6* variations also get no pain relief from codeine or related drugs. The company will translate the results for physicians into metabolic function categories, from poor to ultrarapid.



Gene screen. Roche and Affymetrix are seeking approval for a new pharmacogenomics device.

In January 2003, Seryx of New York City launched a genotyping service called Signature Genetics that also zeroes in on similar "cytochrome p450" enzyme genes as well as *NAT2*, a gene that affects the efficacy of anti-HIV medications. The service is marketed to physicians, who receive a 50-page footnoted analysis with the results to share with the patient. CEO Fred Mannausau says the company charges about $2000 for the initial test and a subscription of $350 a year for scientific updates. Mannausau said that "fewer than 1000" clients have signed up so far.

A handful of other companies are promising that they will soon have validated genotype assays ready to offer the medical community. Genaissance Pharmaceuticals of New Haven, Connecticut, for example, is planning a test for risky genes that can lead to the heart arrhythmia known as "long QT syndrome." But the number of commercial companies has declined sharply since the 1990s, from over a dozen to just a handful, says Michael Murphy, CEO of Gentris Inc., a North Carolina pharmacogenomics firm that processes genotypes for clinical trials. Koch confirms that "you don't see much pharmacogenetic testing going on in the clinic right now."

One of the main brakes on progress, says Christopher Austin, a former Merck executive now at the National Human Genome Research Institute in Bethesda, Maryland, is that "physicians are not generally familiar with the idea" that common gene variations can have a dramatic impact on how well drugs work. Says Richard Weinshilboum of the Mayo Clinic in Rochester, Minnesota: "We need to educate physicians broadly about the vocabulary and concepts that underlie genomic medicine."

There may be no cultural revolution in the next few years, Weinshilboum acknowledges. But students now in medical school are getting the message. He predicts that when they begin to practice, they will be ready for the new genomic technology—and it will be ready for them. **–E.M.**

CREDIT: ROCHE DIAGNOSTICS

would be tested before these drugs are prescribed." Some champions of testing—like Evans—acknowledge that they have a financial stake in it, which also raises questions about their objectivity. St. Jude and Mayo, for example, have an interest in key *TPMT* gene patents and have earned income from them.

But money isn't the issue, argues Nancy Keene, a patient advocate, member of the pediatric subcommittee of ODAC, and mother of a survivor of childhood ALL. Given the huge medical bills a cancer patient incurs, Keene says, $100 to $300 for one lifetime *TPMT* test doesn't seem extravagant: "I'm mystified by the resistance to a simple blood test that might save children's lives."

Early warning. Richard Weinshilboum of the Mayo Clinic demonstrated 23 years ago that 0.3% of patients have an inherited, life-endangering reaction to the drug 6MP.

Evans, likewise, fails to understand why tests are seen as perilous. Just the opposite, he says. Most cancer patients take several toxic drugs at once; a common response to seeing a patient's blood count drop with toxicity is to cut back slightly on all chemotherapy, he says. Doing so with homozygous *TPMT*-deficient patients, however, would mean skimping on the drugs they can tolerate while overloading them with the one (6MP) they cannot. Evans says the 6MP dose needs to be cut 90%—not given a typical "tweak" of 25%—while other doses can remain high. The gene test "allows you to zero in on the drug that's causing the problem."

Other testing advocates such as McLeod and Relling concede that research is needed on the 10% of patients who have a single deficient *TPMT* gene, but they still think the argument for testing is strong. These patients are most likely to cause confusion and receive unnecessarily low 6MP doses, Winick fears. Not enough is known about how they metabolize 6MP to make firm dose recommendations. But Relling points out that they tolerate far larger doses than homozygotes do and therefore can be managed as normal patients are—by monitoring blood cell counts.

Relling missed the ODAC meeting but was so disappointed with it that she wrote a sharp letter to FDA on 7 August. "The alternative" to testing *TPMT* genes, she wrote, "is to continue to use our arbitrary and unscientific approaches to dosage adjustments." She suggested simple answers to the fears expressed by the oncologists. The hypothetical concern that some doctors "might make a mistake" in interpreting data, she concluded, "is not an adequate justification for withholding information from all clinicians."

Concerns about 6MP have prompted Winick to ask COG to rewrite the protocols for treatment of ALL. Winick says the new guidelines will include detailed information on genetic risks, gene testing, and dosing of *TPMT*-deficient patients. No deadline has been set for finalizing them. Having observed COG's methods, however, patient advocate Keene thinks it may take years.

Off label

FDA's review focused exclusively on cancer, ignoring the biggest arena of thiopurine use: for inflammatory diseases. FDA did so because cancer therapy is the sole officially approved use of thiopurines. In reality, physicians prescribe 6MP and its cousin azathioprine, which is converted to 6MP in the body, far more widely to treat "off-label" conditions. FDA is unlikely to address this issue, says one biotech executive, unless someone files an application for a drug covering these uses. And that won't happen, he adds, because the drug is now generic and cannot earn the big profits required to support a new FDA filing.

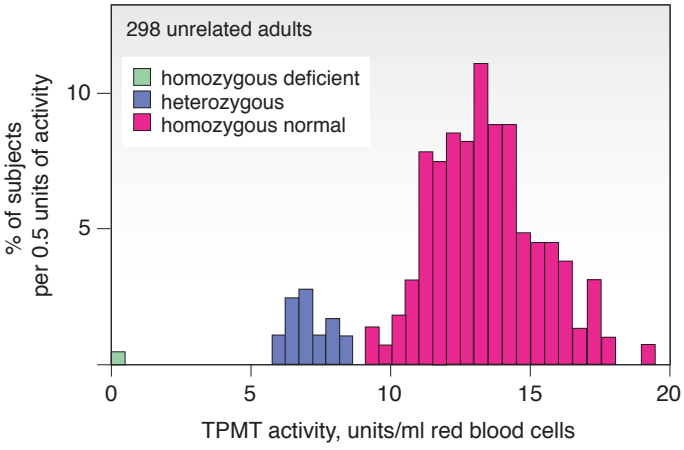
According to Prometheus Laboratories of San Diego, California, maker of a generic azathioprine called Imuran, most of its product goes to patients with ulcerative colitis, Crohn's disease, rheumatoid arthritis, and related diseases. Company spokesperson Beth Kriegel reports that data from IMS Health, a market research firm in Fairfield, Connecticut, indicate that as of June, 10 times more 6MP has been used by gastroenterology patients than cancer patients. Prometheus recently acquired an exclusive license to market the *TPMT* test, and gastroenterologists are its major clients. Still, it's not standard procedure to test before prescribing.

Some clinicians say that 6MP and related compounds may not be as dangerous in these applications as in cancer therapy because dose levels are set lower, at least at the start. But Winick suggests that there is a stronger argument for testing these patients: Unlike children with leukemia who get very frequent tests that could spot a declining blood cell count, indicating toxicity, she says, "I'm not sure that [off-label users] have a blood count done every week."

Although the prescribed drug doses are likely to be lower, the period of use can be long. One prominent gastroenterologist, Stephen Hanauer of the University of Chicago, says blood tests are done frequently enough to avoid serious toxicity. Hanauer last month won a grant from the National Institute of Diabetes and Digestive and Kidney Diseases to run a 15-center, 2-year trial of azathioprine to treat inflammatory diseases. "We rely on functional assays" that measure blood cell counts, he says, and they work just fine. If the count drops, the patient is taken off thiopurines. Nevertheless, many other physicians are looking at genotypes. Kriegel says the volume of tests performed by Prometheus, which sells the drug and the test, is rising; roughly 20,000 have been done to date.

Although drug regulators and oncologists remain wary of screening for *TPMT* genes, there clearly are patients out there who are ready to embrace the technology. If Kriegel is right, their numbers are growing.

—ELIOT MARSHALL



Alone and at risk. Weinshilboum's research revealed that patients cluster in three groups of TPMT enzyme activity; the one at the far left was TPMT-enzyme deficient and could not metabolize 6MP.

CREDITS: (TOP TO BOTTOM) MAYO CLINIC; SOURCE: R. WEINSHILBOUM/MAYO CLINIC

LETTERS

Crisis for Biodiversity Collections

ALTHOUGH WE AGREE WITH DONALD Kennedy about the importance of seed and other germplasm collections ("Agriculture and the developing world," Editorial, 17 Oct., p. 357), and we support the efforts of the Global Conservation Trust and the Consultative Group on International Agricultural Research to preserve these collections, many other critical biodiversity collections are facing challenges as well (*1*, *2*). The biological collections in natural history museums and herbaria also serve vital roles in protecting sustainable agriculture, including the identification and mitigation of invasive alien species, and enabling biological control. When the cassava mealybug threatened collapse of the staple diet of millions of Africans (*3*), successful biological control was achieved only after in-depth research on classification (systematics) with museum collections. These collections also allow identification of disease vectors and pollinators, document ethnobotanical practices, and support a vast array of other uses (*4*). Museum collections have a set of globally agreed-upon plans of action, including the Global Taxonomy Initiative and Global Strategy for Plant Conservation of the Convention on Biological Diversity, and the Global Biodiversity Information Facility (*5*),

> **"It is ironic that, just as the U.S. National Science Foundation increases funding for biodiversity research, many states are threatening to discontinue support for their [biodiversity] collections."**
>
> –MILLER ET AL.

but international investment has been insufficient. It is ironic that, just as the U.S. National Science Foundation increases funding for biodiversity research, many states are threatening to discontinue support for their collections (*6*).

SCOTT E. MILLER,* W. JOHN KRESS, CRISTIÁN SAMPER K.

National Museum of Natural History, Smithsonian Institution, Post Office Box 37012, Washington, DC 20013–7012, USA.

*To whom correspondence should be addressed. E-mail: miller.scott@nmnh.si.edu

References

1. S. E. Miller, L. M. Rogo, *Cimbebasia* **17**, 197 (2002).
2. Organisation for Economic Cooperation and Development (OECD), *Biological Resource Centres: Underpinning the Future of Life Sciences and Biotechnology* (OECD, Paris, 2001).
3. J. Zeddies, R. P. Schaab, P. Neuenschwander, H. R. Herren, *Agric. Econ.* **24**, 209 (2001).
4. House of Lords, *What on Earth? The Threat to the Science Underpinning Conservation*, HL Papers 118(i) and 118(ii) (Stationary Office, London, 2002).
5. S. Blackmore, *Science* **298**, 365 (2002).
6. R. E. Gropp, *BioScience* **53**, 550 (2003).

Synchrotron-Čerenkov Radiation

IN HIS NEWS FOCUS ARTICLE "MONEY SPINNER or loopy idea?" (12 Sept., p. 1463), Edwin Cartlidge reports on a conjecture that energy radiated by a charge in uniform, superluminal, circular motion would vary as $1/r$, rather than $1/r^2$, in the far zone. Such radiation combines features of synchrotron radiation (due to a charge in uniform circular motion) and Čerenkov radiation (due to a charge with superluminal velocity). This topic has been analyzed theoretically by Erber, Schwinger, and others (*1*–*9*), where it is predicted that the far-zone radiation pattern falls off as $1/r^2$, as must be the case for any energy-conserving radiation pattern emitted by a real, and hence spatially bounded, source. Observation of an interference effect between the synchrotron and Čerenkov components of such radiation has been reported by Bonin *et al.* (*10*).

An infinite line source could, mathematically speaking, emit cylindrical waves whose energy varies as $1/r$, as measured from the axis. But any real source with cylindrical symmetry must have a finite extent along its axis, and for distances that are large compared with the size of the source, the radiated energy falls off as $1/r^2$, as required by consistency with the laws of diffraction and conservation of energy.

Superluminal motion leading to radiation can be achieved by a single charge moving with velocity $v < c$, where c is the speed of light, in a medium of index of refraction n such that $v > c/n$ (Čerenkov radiation). Effective superluminal motion can also be achieved when an extended beam of charged particles, each moving with velocity $v < c$, intercepts a surface such that the point of contact moves with velocity $u > c$. An example of the latter is the electron beam in a Tektronix 7104 oscilloscope, whose "writing speed" can exceed c. In this case, the transition radiation that is emitted as the beam enters the surface of the oscilloscope faceplate takes on the character of Čerenkov radiation (*11*). If the oscilloscope were rotated about an axis perpendicular to that of the electron beam, the configuration would be that discussed in the article and so would produce synchrotron-Čerenkov transition radiation—with a $1/r^2$ falloff of the radiated energy.

KIRK T. MCDONALD

Department of Physics, Princeton University, Princeton, NJ 08544, USA.

E-mail: kirkmcd@princeton.edu

References

1. T. Erber, *Am. Math. Soc. Not.* **22**, A422 (1975).
2. T. Erber, D. White, H. G. Latal, *Acta Phys. Austriaca* **45**, 29 (1976).
3. J. Schwinger, W.-Y. Tsai, T. Erber, *Ann. Phys.* **96**, 303 (1976).
4. T. Erber, D. White, W.-Y. Tsai, H.G. Latal, *Ann. Phys.* **102**, 405 (1976).
5. T. M. Rynne, G. B. Baumgartner, T. Erber, *J. Appl. Phys.* **49**, 2233 (1978).
6. T. M. Rynne, *J. Appl. Phys.* **50**, 5572 (1979).
7. T. M. Rynne, T. Erber, *Appl. Phys. Lett.* **35**, 752 (1979).
8. T. M. Rynne, dissertation, Illinois Institute of Technology, Chicago, IL (1979).
9. T. M. Rynne, *J. Appl. Phys.* **52**, 6471 (1981).
10. K. D. Bonin, K. T. McDonald, D. P. Russell, J. B. Flanz, *Phys. Rev. Lett.* **57**, 2264 (1986).
11. K. T. McDonald, *Am. J. Phys.* **65**, 1076 (1997).

Response

THE ELECTROMAGNETIC FIELD ASSOCIATED with the vacuum version of synchrotron-Čerenkov radiation, i.e., the field generated by a superluminally rotating point source, has an infinitely large amplitude on the envelope of the emitted wave fronts, which is a surface extending from the source to the far zone (*1*). McDonald's contention that the intensity of this radiation is everywhere finite and decays like the inverse square of the distance from its source stems from a misinterpretation of the published analyses that he refers to, none of which are performed in the time domain. For the same reason that the singularity of a Dirac delta function cannot be directly inferred from an individual Fourier component of this function (which equals 1), the divergence that arises in the vacuum version of synchrotron-Čerenkov radiation is concealed by any analysis that is solely performed in the frequency domain (*2*, *3*).

Sources that move with a speed faster than that of light in vacuo cannot, of course, be pointlike (*4*). However, when the contributions arising from the constituent (point-

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted by e-mail (science_letters@aaas.org), the Web (www.letter2science.org), or regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

like) volume elements of an extended source are superposed, the divergence in question endows the resulting radiation field of a volume source with a (singularity-free) intensity that decays like $1/r$, instead of $1/r^2$, with the distance r from the source (*1*, *3*). This result, which is a mathematically rigorous consequence of the retarded solution of Maxwell's equations, does not disagree with those referred to by McDonald. The individual Fourier components of the field that is generated by an individual volume element of any of our extended sources agree with those that are derived in the context of synchrotron-Čerenkov radiation, and each exhibit the Airy-function oscillations (characteristic of the intensity fluctuations near caustics) that are observed by Bonin *et al.* (*5*). [There is, however, a fundamental difference between the radiation processes involving caustics in vacuum and in a medium: For high enough frequencies, the phase velocity of light in a medium will approach the velocity of light in vacuo and so will smooth out any sharp gradients in the field, but in the case of sources that move superluminally in vacuum, there is no agent to eliminate the singularities that appear in the field of a point source (i.e., in the Green's function for the radiation process).]

Nor is there a discrepancy between our results and the requirements of the conservation of energy. The focused wave packets that embody the nonspherically decaying pulses are constantly dispersed and reconstructed out of other waves, so that the constructive interference of their constituent waves takes place within different solid angles on spheres of different radii r [appendix D of (*1*)]. The integral of the flux of energy across a large sphere centered on the source is the same as the integral of the flux of energy across any other sphere that encloses the source. The strong fields that occur in focal regions are compensated by weaker fields elsewhere, so that the distribution of the flux of energy across such spheres is highly nonuniform and r dependent.

Finally, the superluminal source that is produced by the impact of an electron beam on the face plate of an oscilloscope does not correspond to the configuration discussed by Cartlidge in his article. The superluminal effects described in the report only arise from a volume-distributed source, from one in which there is an extended dense set of source points that approach the observer with the speed of light and zero acceleration at the retarded time (*1*–*3*).

ARZHANG ARDAVAN,[1] HOUSHANG ARDAVAN,[2] JOHN SINGLETON[3]*

[1]Clarendon Laboratory, Department of Physics, University of Oxford, Parks Road, Oxford OX1 3PU, UK. [2]Institute of Astronomy, University of Cambridge, Madingly Road, Cambridge CB3 0HA, UK. [3]National High Magnetic Field Laboratory, Los Alamos Laboratory, TA-35, MS-E536, Los Alamos, NM 87545, USA.

*To whom correspondence should be addressed. E-mail: jsingle@lanl.gov

References

1. H. Ardavan, *Phys. Rev. E* **58**, 6659 (1998).
2. H. Ardavan, A. Ardavan, J. Singleton, *J. Opt. Soc. Am. A* **20**, 2137 (2003).
3. H. Ardavan, A. Ardavan, J. Singleton, preprint available at http://xxx.lanl.gov/abs/physics/0301083.
4. B. M. Bolotovskii, V. L. Ginzburg, *Sov. Phys. Usp.* **15**, 184 (1972).
5. K. D. Bonin, K. T. McDonald, D. P. Russell, J. B. Flanz, *Phys. Rev. Lett.* **57**, 2264 (1986).

Open Access to Science and Culture

IN OCTOBER, THE MAJOR GERMAN RESEARCH organizations, together with a dozen other national and international research centers, signed the Berlin Declaration on Open Access to Knowledge in the Sciences and

Humanities (*1*). In accordance with the spirit of the Bethesda Declaration and the Budapest Initiative, the Berlin Declaration endorses fundamental changes in scientific publishing.

The declaration encourages researchers to publish their work according to the principles of the open access paradigm—to provide free access for all to scientific publications. These principles advocate the consistent use of the Internet for scientific communication and publishing. According to the declaration, means and ways should be developed to evaluate open access contributions and online journals to maintain the standards of quality assurance and good scientific practices. Furthermore, it advocates that open access publication be recognized in promotion and tenure evaluation and supports further development of existing legal and financial frameworks to facilitate optimal use of and access to scientific publications.

In one crucial point, the declaration extends the previous Open Access initiatives: The holders of cultural heritage are also encouraged to support open access by providing their resources on the Internet. This point stems from the European Cultural Heritage Online (ECHO) project, which develops solutions to make this heritage accessible via the Internet.

Publication is crucial for science. Free and unhindered access to humanity's knowledge sources increases the benefits that scientists and researchers bring to society and also strengthens the positions of individual scientists and researchers in competition with others. Just as scientists enjoy the right to use knowledge, scientists and researchers who come up with findings are obliged to make their work accessible to other scientists.

There is no doubt that the old system of print-based distribution is much slower and more restricted than the Internet. But for all its efficiency and effectiveness, the new electronic system of knowledge dissemination has to adhere to quality assurance standards and follow principles of good scientific practice, just as with print media. The new paradigm also has to be financially feasible. Funding agencies and research organizations must decide whether they see dissemination costs as part of research costs. The road is long, and as yet, it is uncertain whether the plan of fully exploiting the Internet to build a pool of knowledge will come to pass.

But is it really necessary to answer every question before supporting the right idea? Like the Web, science cannot be steered by central organizations. Good science finds its way forward, which means that good science finds efficient and effective instruments to be successful. However, science alone might not be strong enough to break existing legal and financial barriers, which is why research organizations like the Max Planck Society feel obliged to give the vision of open access a chance.

The Max Planck Society appeals to research and grant organizations to join its efforts, face the challenges, and embrace the unique opportunity offered to build a global open access platform for scientific and cultural knowledge. We are proud that now the major German research organizations have reached a consensus, too. However, there is still a lot of work ahead of us.

PETER GRUSS*

Max Planck Society, Hofgartenstrasse 8, D-80539 Munich, Germany.

*President of the Max Planck Society

Reference

1. The Berlin Declaration, with the list of the signatories, is available at www.zim.mpg.de/openaccess-berlin/berlindeclaration.html.

CORRECTIONS AND CLARIFICATIONS

News of the Week: "Preventing toxicity with a gene test" by E. Marshall (24 Oct., p. 588). The drug Imuran was incorrectly described as a generic drug. Imuran is a brand-name product of Prometheus Laboratories in San Diego, CA.