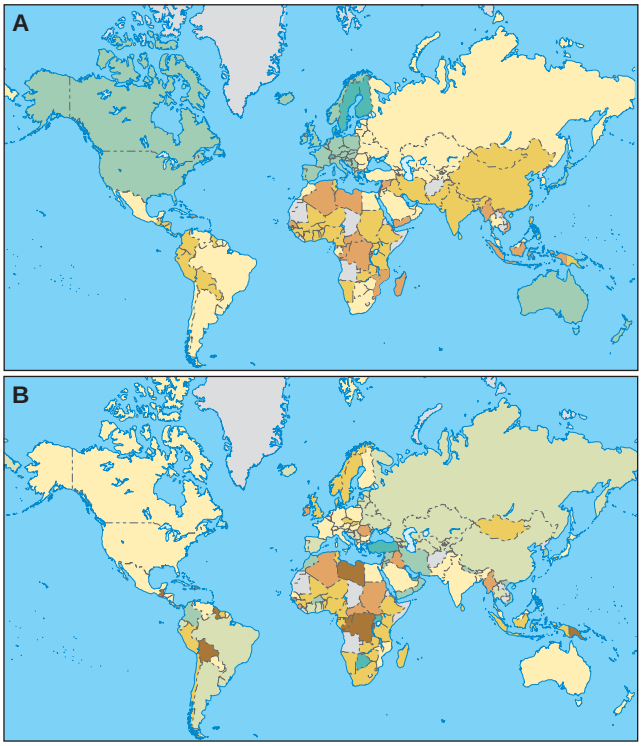
Worldwide Scientific Publishing Activity

IF WE VIEW SCIENTIFIC ACTIVITY AS AN indicator of wealth, and if we believe that publishing activity in peer-reviewed journals is correlated to scientific activity, then we can take the amount of papers published by individuals of a nation (divided by its total population) as an indicator of that nation's wealth. In the case of scientific activity, there is the expectation that it not only reflects today's wealth, but also promises future wealth through the practical application of the scientific knowledge generated.

We analyzed this indicator using the MEDLINE database of biomedical journal articles (*1*), which contains entries including the main address of the authors and the date of the publication. A first static analysis (measuring the papers published per inhabitant during 1996–2001) offered no surprises (see panel A of figure). The differences between First, Second, and Third Worlds are easily seen in a 10-fold difference in the amount of articles published per inhabitant.



We analyzed over 4.2 million entries from MEDLINE corresponding to articles published during 1989–2001. We identified the countries in the authors' affiliations for 4.0 million entries. Countries that became independent after the dissolution of former countries during the period analyzed were counted as one country (namely, the Union of Soviet Socialist Republics, and the former federal republics of Yugoslavia and Czechoslovakia). The population of each country as of May 2002 was taken from (*4*). (A) Approximate amount of publications for the years 1996–2001 per million inhabitants by country: dark green, 10,000; light green, 1000; yellow, 100; light brown, 10; dark brown, 1. (B) Ratio of the number of publications for 1996–2001 to the number of publications for 1989–95: green tones, positive trend; yellow, stable trend; brown tones, negative trend. Gray indicates that no publication corresponding to that country was found.

Being aware that developed countries dominate the process of publication and that this might bias the analysis (*2*), and in order to show the evolution of scientific activity in different areas of the world, we analyzed the relative evolution of publication activity in two periods, a parameter that should be independent of the dominance of developed countries in publishing. This comparison yields a disturbing result (see panel B of the figure): Most countries with low levels of publication (brown in panel A) also suffer from a negative publication trend (brown in panel B). This means that, unfortunately, the gap between scientifically active countries and the rest is apparently widening rather than closing.

Scientific funding agencies worldwide should take this into account. As claimed repeatedly (*3*), projects that train scientists from developing countries and help create research groups in those countries must be promoted, because we feel that scientific development will bring these countries socioeconomic development and because the global scientific community cannot afford to waste the intellectual capacity of developing countries.

CAROLINA PEREZ-IRATXETA[1,2] AND MIGUEL A. ANDRADE[1,2]

[1]European Molecular Biology Laboratory, Meyerhofstr. 1, 69117 Heidelberg, Germany. [2]Max-Delbrück-Centrum für Molekulare Medizin, Robert-Rössle-Str. 10, 13125 Berlin, Germany. E-mail: cperez@embl-heidelberg.de (C.P.-I.), andrade@embl-heidelberg.de (M.A.A.)

References
1. National Library of Medicine. See www.ncbi.nlm.nih.gov/PubMed/.
2. R. Barré, Indications of world science today, *UNESCO World Science Report 1998* (UNESCO, Paris, 1998), pp. 20–28.
3. R. Koenig, *Science* **284**, 1760 (1999).
4. The World Gazetteer. See www.world-gazetteer.com/.

Collecting Biological Materials

I READ RICHARD STONE'S PROFILE OF biologist Gary Strobel ("Biologist gets under the skin of plants—and peers," News Focus, 31 May, p. 1597) with great interest. I would like to know if Strobel abides by local regulations about collection and exportation of biological materials in the many countries where he has worked. I deeply hope that Strobel does not see Third World countries merely as raw materials providers for technological developments, for which our people must later pay high royalties. The use of Third World (and all) natural resources should result in mutual and equitable benefits. And, as Strobel may understand, this is much more than simply returning a portion of the profits to the local communities. Third World countries are under tremendous pressure to comply with patents and royalties from developed countries (and many times these patents are derived from Third World resources); scientists all around the world should be encouraged to comply with each country's regulations about the collection and exportation of biological materials.

VIRGINIA ABDALA

Instituto de Herpetologia, Fundacion Miguel Lillo, Miguel Lillo 251, 4000 Tucuman, Argentina.

Response

I HAVE ALWAYS OBTAINED PERMISSION TO collect materials wherever I have gone. In addition, I acquire all necessary permits from the U.S. Department of Agriculture to bring disease-free samples into the United States. The arrangement generally is that if an organism proves valuable, then the supporting organization and I will discuss the disposition of financial benefits that the local community may derive. This plan is laid out at the outset. One of the main goals of the program is to help scientists in developing countries improve their scientific infrastructure. This is accomplished in a multitude of ways, including giving investigators opportunities to work in my lab for advanced training. In addition, local investigators are invited to become involved directly in the research. This has been true with scientists from Nepal, China, Morocco, Venezuela, Israel, Papua New Guinea, India, and Korea, to name a few countries with which I have been involved. Many people do not understand that to find a successful drug is difficult and expensive, and therefore a lot of time cannot be spent discussing matters of income where income may not ever exist. Discovery is the least expensive of all of the steps required in drug discovery. Ultimate drug development may cost up to $300 million. Compounds fail for many technical reasons, including toxicity, availability, side effects, and inability to reach the appropriate site. Nevertheless, it is absolutely critical to me that local people get energized about the novel and important biological prospects that exist in the forests around them and be encouraged to study them and learn about their promise and potential. It is also essential that more efforts be made to save these important biological resources before they disappear forever.

GARY STROBEL
Department of Plant Sciences, 206 Ag BioSciences Building, Montana State University, Bozeman, MT 59717, USA. E-mail: uplgs@montana.edu

C-Reactive Protein and Atherosclerosis

THERE IS A CREDIBLE ALTERNATIVE HYPOTHESIS that may explain the challenging observation that many states not heretofore regarded as inflammatory are associated with minimal C-reactive protein (CRP) elevation, discussed in Gary Taubes' article "Does inflammation cut to the heart of the matter?" (News Focus, 12 April, p. 242). Many other noninflammatory factors (demographic, genetic, life-style, and medical) can be added to those cited in the article, including depression, chronic fatigue, poor physical conditioning, high-protein diet, hypertension, insulin resistance, and albuminuria. Many of these conditions indicate suboptimal physical status and may reflect tissue injury. CRP has long been used clinically to evaluate the presence and degree of inflammation (*1*), classically defined as the response to tissue injury. I propose that tissue injury itself causes CRP elevation, even when no inflammatory response is apparent. Minor CRP elevation would thus identify individuals who bear an increased burden of tissue damage, resulting from a variety of causes (*2*). It is highly likely that among these is cumulative oxidative stress, which is strongly implicated in the pathogenesis of aging (*3*). Such biologically older individuals have a greater likelihood of manifesting diseases associated with aging or of dying (*4*).

Inappropriate use of screening tests can be harmful (*5*), and many have concluded that routine use of CRP testing is premature (*6*–*12*). CRP testing does not meet three major criteria for an effective screening test (*13*): (i) Accuracy is uncertain; we have no idea of how many individuals are incorrectly identified as high risk (*14*). (ii) Reliabili-

ty is weak; published estimates of within-subject variability (*15–17*) indicate that CRP measurement could differ by 71 to 84% from an earlier reading. (iii) The likelihood of beneficial intervention is unknown. We don't know how to intervene (we don't understand the mechanisms underlying the observed associations), and we don't know if intervention alters outcomes. Taken together, these considerations argue in favor of caution before plunging ahead.

IRVING KUSHNER

MetroHealth Campus, Case Western Reserve University, 2500 MetroHealth Drive, Cleveland, OH 44109, USA. E-mail: ikushner@metrohealth.org

References

1. C. Gabay, I. Kushner, *N. Engl. J. Med.* **340**, 448 (1999).
2. I. Kushner, *Cleveland Clinic J. Med.* **68**, 535 (2001).
3. F. B. Johnson, D. A. Sinclair, L. Guarente, *Cell* **96**, 291 (1999).
4. T. B. Harris *et al.*, *Am. J. Med.* **106**, 506 (1999).
5. D. A. Grimes, K. F. Schulz, *Lancet* **359**, 881 (2002).
6. W. Koenig, *Clin. Chem.* **47**, 9 (2001).
7. F. Van Lente, *Clin. Chim. Acta* **293**, 31 (2000).
8. R. Munford, *N. Engl. J. Med.* **344**, 1959 (2001).
9. K. J. Krause, *J. Insur. Med.* **33**, 4 (2001).
10. S. S. Levinson, R. J. Elin, *Arch. Intern. Med.* **162**, 389 (2002).
11. B. Campbell, T. Badrick, R. Flatman, D. Kanowski, *Ann. Clin. Biochem.* **39**, 85 (2002).
12. I. Kushner, A. R. Sehgal, *Arch. Intern. Med.* **162**, 867 (2002).
13. U.S. Preventive Services Task Force, *Guide to Clinical Preventive Services* (U.S. Department of Health and Human Services, Washington, DC, ed. 2, 1996) (see www.odphp.osophs.dhhs.gov/pubs/guidecps/).
14. G. L. Horowitz, B. A. Beckwith, *N. Engl. J. Med.* **343**, 512 (2000).
15. E. M. Macy, T. E. Hayes, R. P. Tracy, *Clin. Chem.* **43**, 52 (1997).
16. P. A. Sakkinen *et al.*, *Am. J. Epidemiol.* **149**, 261 (1999).
17. C. Kluft, D E. De Maat, *Ital. Heart J.* **2**, 172 (2001).

Atherosclerosis and Inflammation

IS ATHEROSCLEROSIS AN INFLAMMATORY disease that can occur even in the presence of "low" or "healthy" plasma concentrations of cholesterol, as Gary Taubes' article "Does inflammation cut to the heart of the matter?" (News Focus, 12 April, p. 242) implies? The answer lies in what those terms actually mean. We have argued that labeling a pathophysiologic process "inflammatory" can be misleading, because inflammation always has an underlying cause (*1*). For example, even though the lung is full of inflammatory cells in Pneumococcal pneumonia, the disease is considered infectious—the root cause—but with an important, secondary inflammatory reaction. Regarding atherosclerosis, a large body of experimental evidence supports the "response to retention" hypothesis of early atherogenesis: Retained or trapped low-density lipoprotein (LDL) particles within the vessel wall become enzymatically and oxidatively modified, thereby provoking, among

other things, an influx of inflammatory cells that accelerate LDL retention, early lesion development, and ultimately the progression to life-threatening plaques [reviewed in (*2*–*6*)]. In an important, recent validation of this hypothesis, LDL that was genetically engineered to be poorly retained was found to be nearly incapable of producing early atherosclerotic lesions in vivo (*7*).

This brings us to the question of what is a "low" or "healthy" plasma cholesterol level. Human atherosclerosis is vanishingly rare when LDL concentrations are below 80 mg/dl, regardless of other risk factors (*2*), and no widely accepted animal models of atherosclerosis exist that arise from either genetic derangements of immunity or distal sites of chronic inflammation in the absence of plasma lipoprotein abnormalities. Although the cholesterol levels referred to in Taubes' article may seem low or healthy compared with the very high average values in Westerners, they are still above 80 and therefore merit serious concern.

Therapies directed at both lipoprotein retention and the responses—including inflammation—to retained material will have the greatest chance for continued successes against atherosclerosis. We must not neglect either the primary or secondary processes in this deadly disease.

KEVIN JON WILLIAMS[1] AND IRA TABAS[2]

[1]Division of Endocrinology, Diabetes and Metabolic Diseases, Thomas Jefferson University, 1020 Locust Street, Philadelphia, PA 19107, USA. E-mail: K_Williams@Lac.jci.tju.edu. [2]Division of Molecular Medicine, Columbia University, 630 West 168th Street, New York, NY 10032, USA. E-mail: IAT1@columbia.edu

References

1. K. J. Williams, I. Tabas, *N. Engl. J. Med.* **340**, 1928 (1999).
2. ———, *Arterioscler. Thromb. Vasc. Biol.* **15**, 551 (1995).
3. E. Hurt-Camejo, U. Olsson, O. Wiklund, G. Bondjers, G. Camejo, *Arterioscler. Thromb. Vasc. Biol.* **17**, 1011 (1997).
4. K. J. Williams, I. Tabas, *Curr. Opin. Lipidol.* **9**, 471 (1998).
5. A. Chait, T. N. Wight, *Curr. Opin. Lipidol.* **11**, 457 (2000).
6. K. J. Williams, *Curr. Opin. Lipidol.* **12**, 477 (2001).
7. K. Skålén *et al.*, *Nature* **417**, 750 (2002).

CORRECTIONS AND CLARIFICATIONS

PERSPECTIVES: "Flood basalts—bigger and badder," by P. R. Renne (7 Jun., p. 1812). In describing the flood volcanism occurring during the last several hundred million years, the wrong units were used to describe the implied magma production rate. It should have read "on the order of 1 km^3/year."

NEWS FOCUS: "How devastating would a smallpox attack really be?" (31 May, p. 1592). A sidebar to the story about smallpox models incorrectly stated that about 1250 in every million people vaccinated against smallpox in the past suffered from serious side effects. That number, taken from a 2001 report by the Advisory Committee on Immunization Practices (ACIP), also included mild side effects and adverse reactions. For adverse reactions the ACIP classified as "moderate to severe," the number is only 293.9 per million persons vaccinated. These include generalized vaccine (241.5 per million), eczema vaccinatum (38.5), progressive vaccinia (1.5), and postvaccinial encephalitis (12.3).

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.