pertensive effects of ACE inhibitors and angiotensin-receptor blockers may differ from the dose–response relation for the antiproteinuric effects. In addition, he cites studies suggesting that the antiproteinuric effect of ACE inhibitors and angiotensin-receptor blockers may be additive. Although this is an exciting area of current research, larger studies will be needed to determine the optimal level of urinary protein excretion and the optimal doses of ACE inhibitors, angiotensin-receptor blockers, and combinations of these two classes of agents to slow the progression of nondiabetic kidney disease.

Andrew S. Levey, M.D.

Tufts–New England Medical Center
Boston, MA 02111

Testing Medications in Children

TO THE EDITOR: The development of medications appropriately adapted for the health needs of children should not be focused exclusively on national regulatory structures. Steinbrook (Oct. 31 issue)[1] correctly points out the strong gains made in the United States during the past five years through the development of both requirements and incentives for research in pediatrics. At the same time, as he indicates, children involved in studies threaten to slip through the gaps when government programs are not properly complemented by robust ethical frameworks for clinical trials involving children.

The ethical and safety challenges faced by parents, pediatricians, and authorities when they are making decisions about pediatric trials are global issues. Focusing solely on national instruments will not provide sufficient protection for our children, at home or abroad. In part, this relates to the "crisis mode due to failed patient recruitment efforts" in the United States. At times, trials involving children are conducted abroad, where the necessary patients are more plentiful and there is a greater need for the research. As the inspector general of the Department of Health and Human Services has pointed out, there is little capacity in the United States for ethical oversight of these trials,[2] and internationally, protections for children in clinical trials are limited.[3]

Scientific expertise and ethical expertise, as well as experience in the application of medicines in pediatrics, are widespread. Plugging the gaps in medicines for children means working toward an international ethical framework supported by international sharing of data. Anything less is not acceptable for our children.

Francis P. Crawley, Ph.L.

European Forum for Good Clinical Practice
3010 Kessel-Lo, Belgium
fpc@efgcp.org

Ronald Kurz, M.D., Ph.D.

Confederation of European Specialists in Pediatrics
3010 Graz, Austria

Hidefumi Nakamura, M.D., Ph.D.

National Center of Child Health and Development
Tokyo 157-8535, Japan

1. Steinbrook R. Testing medications in children. N Engl J Med 2002;347:1462-70.
2. The globalization of clinical trials: a growing challenge in protecting human subjects. Washington, D.C.: Office of the Inspector General, Department of Health and Human Services, September 2001. (Accessed January 30, 2003, at http://oig.hhs.gov/oei/reports/oei-01-00-00190.pdf.)
3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guideline: clinical investigation of medicinal products in the pediatric population. July 20, 2002. (Accessed January 30, 2003, at http://www.ich.org/pdfICH/e11step4.pdf.)

TO THE EDITOR: There are many parallels between pediatric and geriatric practice with regard to the use of medications. In children and the elderly, practitioners often have nothing more on which to base prescribing decisions than "educated guesses about doses, safety, and effectiveness." The imperative for enhanced testing of medications in the elderly is at least equivalent to that for children.

Steinbrook reports that a combination of federal laws, regulations, and targeted funding for research has increased the number of medications studied in pediatric clinical trials. Despite many efforts to encourage the inclusion of more elderly persons in clinical trials of drug therapies, elderly subjects rarely account for more than a small fraction of participants.[1,2] Guidelines issued by the Food and Drug Administration (FDA) in 1989 to enhance the participation of elderly persons in clinical trials have been largely ineffective.[3] A "geriatric use rule," issued by the FDA in 1997, does require drug companies to include a separate geriatric-use section in the

labeling of their drugs, but it does not require companies to perform additional studies, as the pediatric rule does.[4]

In summarizing recent progress regarding the testing of medications in children, Steinbrook has provided a blueprint that should be given serious consideration as a means of addressing many similar issues with regard to the population of geriatric patients. According to Dr. Richard Gorman, chair of the Committee on Drugs of the American Academy of Pediatrics, "We are entering what could be the golden age for kids and pharmaceuticals." Regrettably, the same cannot yet be said for the elderly.

Jerry H. Gurwitz, M.D.

Meyers Primary Care Institute
Worcester, MA 01605
jgurwitz@meyersprimary.org

1. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061-7.
2. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA 2001;286:708-13.
3. Center for Drug Evaluation and Research. Guideline for the study of drugs likely to be used in the elderly. Rockville, Md.: Food and Drug Administration, 1989.
4. Center for Drug Evaluation and Research. Guidance for industry: content and format of geriatric labeling. Rockville, Md.: Food and Drug Administration, October 2001.

DR. STEINBROOK REPLIES: Since my health policy report was written, there have been developments with regard to the pediatric rule. The rule, an FDA requirement that manufacturers assess the safety and effectiveness of new drugs and biologic products in pediatric patients, had been challenged in federal court by the American Association of Physicians and Surgeons and other plaintiffs. On October 17, 2002, U.S. District Judge Henry H. Kennedy, Jr., ruled that the FDA had exceeded its authority when it established the rule and enjoined the federal government from enforcing it.[1] In December 2002, the Bush administration said that although it would not appeal the decision, it would back legislation that would write the pediatric rule into law.[2,3] If the new Congress enacts such legislation, the legal case will become moot.

Robert Steinbrook, M.D.

1. Kennedy HH Jr. Memorandum opinion. Association of American Physicians & Surgeons, Inc., Competitive Enterprise Institute, and Consumer Alert v. Food and Drug Administration and Department of Health and Human Services, civil action 00-02898. U.S. District Court for the District of Columbia, October 17, 2002.
2. Adams C. White House to back testing drugs on children. Wall Street Journal. December 17, 2002:D4.
3. Bush administration will seek new legislation for mandatory pediatric drug testing. Press release of the Department of Health and Human Services, Bethesda, Md., December 16, 2002.

A Case of Venlafaxine Abuse

TO THE EDITOR: Antidepressants are rarely abused except by persons who also abuse alcohol or other drugs.[1,2] We describe a case of venlafaxine abuse, which to our knowledge has not been previously reported.

A 38-year-old man presented to the emergency department with chest pain. Cardiac problems were ruled out after thorough evaluation, including electrocardiography and measurement of cardiac enzymes. The patient reported a history of major depression and of amphetamine dependence in remission. Every three months, he saw a psychiatrist, who prescribed extended-release venlafaxine at a dose of 225 mg per day.

Six months before presentation, the patient had become unemployed. He had considered using amphetamines, but decided against it. Awaiting an appointment with his psychiatrist, he increased his daily dose of venlafaxine to 337.5 mg by taking one and a half pills, an amount that produced a sudden, amphetamine-like "high." He then ingested two 225-mg pills. This higher dose did not produce a similar effect. Through experimentation, he discovered that crushing the venlafaxine pills produced quicker highs. He started ingesting crushed venlafaxine at doses of up to 3600 mg per day. When he ran out of the medication, he obtained early refills from the pharmacy and then contacted his primary care physician for another venlafaxine prescription. After consuming these pills he contacted the pharmacy for additional refills. When the pharmacist refused, the patient obtained another prescription from his primary care physician by claiming to have misplaced his pills and then purchased the drug at a different pharmacy. After he approached his physician for an additional supply of venlafaxine, the physician became suspicious and referred him to his psychiatrist. The patient instead acquired more venlafaxine illicitly. He continued to ingest increasing amounts of venlafaxine, until the ingestion of a 4050-mg dose produced chest pain, necessitating the visit to the emergency department.