has been awarded to MedImmune. Other approaches to vaccine development involve DNA, adenovirus vectors,[13] and cell-culture manufacturing techniques to increase the speed and capacity of vaccine production. These approaches are promising, particularly since reverse-genetics reassortant vaccine candidates can be generated within weeks.[14]

Thirty years ago, the United States attempted to respond to the threat of pandemic influenza with a vaccine approach. Now, armed with a greater understanding of the science, we have the capacity and the responsibility to embark on multiple, parallel avenues of vaccine development. In addition, we need efficient, rapid, high-yield, low-cost manufacturing innovations; the rapid generation of candidate vaccines for other, potentially pandemic influenza viruses (including emerging clade-2 influenza A [H5N1] viruses); and the rapid movement of those vaccines into clinical trials. In turn, this effort will require creativity along the entire pipeline: in the development and manufacture of candidate vaccines; the synchronization among countries of regulatory approaches; the resolution of issues concerning liability and intellectual property; ensuring the efficiency of clinical trials; and the use of methods to stockpile and rapidly deploy these vaccines. To do otherwise, with the pandemic clock ticking, could prove to be too little, too late.

Dr. Poland reports serving as the chair of a data monitoring and safety board for an investigational trial of an influenza peptide vaccine being conducted by Merck Research Laboratories. No other potential conflict of interest relevant to this article was reported.

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Serious Adverse Drug Effects — Seeing the Trees through the Forest

Jerry H. Gurwitz, M.D.

The medical community and the public have been buffeted by a steady stream of news linking the use of widely prescribed medications with serious health risks. The latest in this barrage of unsettling reports is an article by Park-Wyllie et al. that appears elsewhere in this issue of the *Journal*[1] regarding the association of the fluoroquinolone gatifloxacin with dysglycemia.

The authors describe the findings of two population-based, nested case–control studies involv-

ing outpatients 66 years of age or older who had received treatment with various broad-spectrum antibiotics. The first study demonstrated a substantial increase in the risk of emergency department treatment or hospitalization for hypoglycemia after outpatient therapy with gatifloxacin, as compared with the risk in a reference group comprising patients who received macrolide antibiotics. Analyses of the risk of hypoglycemia that is associated with other antibiotics suggested a small but statistically significant increase only with use of levofloxacin but no increase with moxifloxacin, ciprofloxacin, or second-generation cephalosporins. In the second study, patients receiving gatifloxacin had more than 16 times as high a risk of hyperglycemia as did patients receiving macrolide antibiotics. No increase in the risk of hyperglycemia was noted for any of the antibiotics studied other than gatifloxacin. Similar findings were observed in both studies, regardless of whether the study subjects were receiving treatment for diabetes mellitus.

Although safety concerns are of paramount importance with regard to the association of both hypoglycemia and hyperglycemia with gatifloxacin treatment, these findings are highly unusual and interesting from a pharmacologic perspective. As Park-Wyllie et al. emphasize, adverse effects of the same drug that are directly opposite are extremely rare. Although the biologic effects of gatifloxacin on glycemic control in humans have not been fully elucidated, the dysglycemic effects of gatifloxacin are plausible on the basis of studies in animals.

On February 16, 2006, the manufacturer of gatifloxacin announced that the drug's label would change. According to a Food and Drug Administration (FDA) press release, "Since the approval of gatifloxacin in 1999, there have been rare cases of life-threatening events reported globally in patients treated with the drug. Most of these events were reversible when properly managed, but a few had fatal outcomes."[2] A letter from the manufacturer to health care providers specifies the addition of diabetes mellitus as a contraindication to use of the drug and cautions that special care should be taken in the use of gatifloxacin among elderly patients, "who may have unrecognized diabetes, age-related decrease in renal function, underlying medical problems, and/or are taking concomitant glucose-altering medications" — circumstances that could place them at increased risk for serious dysglycemia.[3]

With the availability of this new information regarding gatifloxacin-associated dysglycemia, what measures can be taken to ensure that the drug is prescribed as safely as possible and to limit any risk of harm to patients? Changes in labeling, as described above, are the most common response to new safety information relevant to a drug during the post-marketing period. A black-box warning is the FDA's strongest labeling requirement for high-risk medicines.[4] As the name implies, such warnings are separated from the other text in the labeling by a prominent black border. However, the new warnings for gatifloxacin were not deemed to require a black box, a decision that probably warrants reconsideration in view of the findings reported by Park-Wyllie et al.

Changes in drug labeling are often direct-mailed or faxed to doctors or other health care providers.[5] Unfortunately, several studies have suggested that such mailings do not result in changes in prescribing practice.[6] Furthermore, a recent study found that physicians and other health care providers frequently prescribed drugs in violation of warnings of important risks, including those contained in black boxes.[7] Although technologic innovations, such as electronic-health-record–based alerts, hold promise for reducing the risk of unsafe prescribing (especially related to drug–drug, drug–laboratory, and drug–disease interactions), such systems are not yet widely available, particularly in the outpatient setting.

If practitioners do not have access to sophisticated, computerized support systems, the safety of patients often hinges on the ability of the physician to recall a particular warning concerning an adverse drug effect and to make a mental connection with the clinical characteristics of the patient. Under such circumstances, prescribing errors are common. Pharmacy-based systems may increase the opportunity to intercept unsafe prescriptions, but such systems rarely link the pharmacist with clinical information regarding specific patients. In addition, drug information provided to patients (e.g., in pharmacy leaflets) is generally of limited quality, especially information relevant to contraindications, precautions, and how to avoid harm.[8]

Some observers have lamented the excessive delays from the time a drug is marketed to the

appearance of persuasive data regarding important safety issues.[9] Gatifloxacin was first marketed in 1999. Reports of dysglycemic effects appeared soon after the drug's approval, and Health Canada (the Canadian FDA) published a report about the drug in 2003. Is six years too long to wait for a high-quality, controlled epidemiologic study quantifying such important drug-related risks? The experience with gatifloxacin underscores the need for a comprehensive plan to respond appropriately and expeditiously to signals indicating potential drug-safety problems in order to reduce unnecessary complications and deaths.[10]

Gatifloxacin now takes its place among an ever-growing list of medications that have been associated with very serious adverse effects. The most immediate question is what should be done with gatifloxacin. It seems clear that the drug's place among broad-spectrum antibiotics available for outpatient use is tenuous at best. For every approved indication for gatifloxacin, there are safer, equally effective, and less costly alternatives. In comparison with other recent experiences regarding adverse drug effects, this choice should not be a difficult one for physicians, patients, regulators, and manufacturers.

No potential conflict of interest relevant to this article was reported.

This article was published at www.nejm.org on March 1, 2006.

From the Meyers Primary Care Institute, a joint endeavor of the University of Massachusetts Medical School, the Fallon Clinic Foundation, and the Fallon Community Health Plan — all in Worcester, Mass.

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Better Behavioral Health Care Coverage for Everyone

Sherry Glied, Ph.D., and Alison Cuellar, Ph.D.

People with private health insurance who seek care for mental health conditions generally face higher coinsurance and more limits to coverage — including limits on the numbers of outpatient visits and inpatient days — than do those who require care for other health conditions. These restrictions reduce the use of mental health services and force persons who have severe mental health problems to bear crushing financial costs for necessary treatment.[1]

Existing insurance limitations reflect previous experience. Efforts to extend parity coverage — equality of benefits — to federal employees in the 1960s failed as the use of services soared and persons with chronic mental health needs were much more likely than the average person to select plans with more generous coverage.[2] The RAND Health Insurance Experiment, conducted in the late 1970s, corroborated this pattern, documenting the fact that responsiveness to reductions in copayments for mental health was double that for general health services.[3]

The article by Goldman et al. in this issue of the *Journal*[4] provides the first controlled study of parity in insurance for mental health in two decades. The compelling evidence presented suggests that in today's environment, parity in health insurance coverage is both economically feasible and socially desirable.

The rise of managed behavioral health care organizations, which control costs through nonfinancial mechanisms, had led policymakers and advocates to revisit the question of parity. A series of case studies of experiments involving par-