sive primary care that is focused on patients with complex health care needs, with the aim of providing better care at a lower total cost through reductions in the use of hospitals and emergency departments.

Care management, with its cost-reducing potential, will not spread widely in the health care system without substantial changes in payment policy. If hospitals profit from unnecessary readmissions, they are unlikely to adopt effective hospital-to-home care-management programs. If primary care practices are not reimbursed for the work of a registered-nurse care manager, they will not hire one unless they share in the savings generated by reducing hospital admissions and emergency department visits. Other obstacles include nursing shortages and the paucity of training programs for nurses to become effective care managers.

The evidence is strong that well-designed care management can substantially reduce costs for patients with complex health care needs. Cost-control measures, particularly in Medicare, must be targeted to the group of patients who account for the great majority of health care expenditures. Investment in care management should become a focus of the cost-containment discussion that is now dominating the debate over health care reform.

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American Roulette — Contaminated Dietary Supplements

Pieter A. Cohen, M.D.

In one of the most dangerous cities in the United States, one portly police sergeant has more to worry about than crime. His doctor had been encouraging him for years to lose weight, and like millions of other Americans, he decided to try a weight-loss supplement to help him shed his extra pounds. But instead of losing weight, he lost his job. According to the label, his diet pills, which were imported from Brazil and sold in the United States, contained vitamin E, centella, senna, and cascara, among other "natural" ingredients. Not included on the label was the amphetamine detected in his urine drug screen. The now-unemployed sergeant is not alone. Such contaminated supplements represent an emerging risk to public health.

In August 2009, the U.S. Food and Drug Administration (FDA) discovered more products, most of them labeled as dietary supplements, that contain a wide variety of undeclared active pharmaceutical ingredients. Now, more than 140 contaminated products have been identified, but these represent only a fraction of the contaminated supplements on the market. Unfortunately, lenient regulatory oversight of dietary supplements, combined with the FDA's lack of resources, has created a marketplace in which manufacturers can introduce hazardous new products with virtual impunity. Although manufacturers have since 2007 been required to report serious supplement-related adverse events to the FDA, the great majority of the estimated 50,000 adverse events that occur annually remain unreported.

This trend is particularly alarming given that, according to a recent National Health Interview Survey, about 114 million people — more than half the adult population of the United States — consume dietary supplements. These supplements, which include botanical products, vitamins and minerals, amino acids, and tissue extracts, are regulated by the FDA under the 1994 Dietary Supplement Health and Education Act (DSHEA). Before 1994, herbal products were considered food additives, and their manufacturers were required to show

proof of safety before marketing them. Since the passage of the DSHEA, dietary supplements are presumed to be safe and can be marketed with very little oversight.

The regulatory environment for dietary supplements is poorly understood by both consumers and physicians. According to a 2002 Harris Poll, the majority of consumers believed that dietary supplements are approved by a government agency, and two thirds thought that the government requires that labels on supplements include warnings about their potential side effects and dangers. Physicians are also misinformed. A recent survey of more than 300 residents in internal medicine from 15 U.S. training programs showed that one third of the respondents believed that dietary supplements require FDA approval, and the majority did not know that adverse events suspected to have been caused by supplements should be reported to the FDA.[1]

The DSHEA presents serious obstacles to the FDA's ability to detect and eliminate contaminated supplements. A wide range of dietary supplements have been found to be contaminated with toxic plant material, heavy metals, or bacteria. Of particular concern are the dozens of dietary supplements that are contaminated with prescription medications, controlled substances, experimental compounds, or drugs rejected by the FDA because of safety concerns. These potentially hazardous ingredients have been detected in products marketed for patients with diabetes, high cholesterol, or insomnia but are most frequently found in products that promise sexual enhancement, optimal athletic performance, and weight loss.

Recent events involving dietary supplements marketed for weight loss, which have been consumed by an estimated 15% of U.S. adults, illustrate this growing problem. In July 2009, the FDA expanded its alert to include 75 tainted weight-loss products that contain undeclared medications. Analyses by the FDA have found the stimulant sibutramine in weight-loss supplements at levels amounting to three times the maximum recommended daily dose. Several of the unapproved anorectic ingredients detected in dietary supplements have been linked to serious adverse events: rimonabant to suicide and fenproporex to both addiction and suicide. The inclusion of furosemide and other diuretics in some of these supplements may result in dehydration and hypokalemia; other contaminants, such as benzodiazepines and antidepressants, mask the side effects of stimulants while conferring an increased risk of dependence. Some weight-loss pills, including many from Brazil, combine multiple medications in a single formulation.[2]

Recently, unscrupulous manufacturers have made it more difficult for the FDA to detect undeclared ingredients by incorporating pharmaceutical analogues into their products. Analogues are created by modifying the original chemical structure of a compound — for example, by adding a hydroxyl group. It is suspected that these analogues are developed to evade detection by the FDA, making the products more difficult to regulate, and to reduce the risk of patent-infringement lawsuits. A recent analysis showed that more than half of 26 supplements marketed for the enhancement of sexual function contained analogues of phosphodiesterase type 5 inhibitors.[3] Because these analogues have never been studied in humans, their risks are unknown, but unexpected adverse reactions to analogues have already been documented. Reports from Britain, China, and Japan, for instance, link an analogue of fenfluramine to liver damage, including fulminant hepatic failure necessitating transplantation.[4,5]

Many contaminated dietary supplements are sold over the Internet, but they have also been found in mainstream retail stores in the United States. Many of the tainted products are manufactured in China, but they have also been produced closer to home. In July 2009, federal agents executed search warrants to investigate allegations that a California-based company, American Cellular Labs, was manufacturing supplements contaminated with anabolic steroids.

Given the potential for dietary supplements to result in side effects and adverse interactions with drugs, physicians should explicitly ask all patients about the use of such supplements. Contaminated supplements expose consumers to additional health risks: common side effects may be misdiagnosed, and drug–drug interactions overlooked. Of even greater concern, it may be impossible to prove that the culpable contaminants are responsible for life-threatening sequelae, leaving future consumers at risk.

Physicians should maintain a high index of suspicion for supplement-induced adverse effects — even when the components on the label are not known to cause the observed effects. When appropriate, physicians should have supplements tested in clinical laboratories to detect unreported substances, and they should always report to the FDA both suspected adverse effects

(through MedWatch, www.fda.gov/medwatch/report/hcp.htm) and suspected unlawful Internet sales of medical products (www.fda.gov/oc/buyonline/buyonlineform.htm).

The DSHEA has not ensured that hazardous dietary supplements will be identified or removed from the market in a timely fashion. I believe that Congress should give the FDA the requisite authority and resources to regulate dietary supplements so that the public can make well-informed decisions regarding the potential risks and benefits of consuming such supplements. Until that happens, millions of Americans will continue to be exposed to unacceptable risks in exchange for purported but unproven health benefits.

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Drug Shortages and Public Health

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Because the public discussion of drugs is dominated by considerations of their safety, effectiveness, and cost, it is easy to forget that medications have to be manufactured from raw materials before they can be prescribed. The continuing shortages of two medications for enzyme-deficiency disorders and of technetium-99m, the radioactive isotope most commonly used in cardiac studies, bone scans, and other diagnostic procedures in nuclear medicine, provide a salient reminder that adequate drug supplies cannot be taken for granted.

The viral contamination of a Genzyme manufacturing plant in Massachusetts, detected in June 2009, caused an unexpected shortage of imiglucerase (Cerezyme), for Gaucher's disease, and agalsidase beta (Fabrazyme), for Fabry's disease. The virus, vesivirus 2117, interfered with the growth of Chinese-hamster-ovary cells, which are used to produce biologic drugs. This problem led to a decline in productivity this year and to two similar instances in 2008, one at the Massachusetts plant and the other at a Genzyme facility in Belgium. The virus has not been shown to cause infection in humans.

Genzyme has managed the shortage of these very expensive drugs by using existing inventories and developing dose-conservation measures. The availability of imiglucerase has had to be limited to children and the most severely affected adults; the company is reviewing other requests through an emergency-access program. For patients with Gaucher's disease, the Food and Drug Administration (FDA) has also expanded access under "treatment protocols" to investigational medications from other manufacturers — velaglucerase alfa, from Shire Human Genetic Therapies, and prGCD, a plant-cell–expressed recombinant glucocerebrosidase enzyme, from Protalix Biotherapeutics. After the Massachusetts plant was decontaminated and additional viral monitoring procedures were implemented, manufacturing of imiglucerase and agalsidase resumed; Genzyme expects to ship drugs from the new production runs in November and December, and the shortages should be resolved thereafter.

Unlike the Genzyme situation, the global shortage of technetium-99m was predictable and will be prolonged. Technetium-99m is generated from molybdenum-99 (see diagram). Almost all molybdenum-99 is produced from highly enriched uranium (concentrations of 20% or more of uranium-235 by weight), and its production depends on nuclear reactors that are old and of doubtful reliability. In recent years, various reactors have been shut down unexpectedly for extended periods. The United States is the primary supplier of highly enriched uranium to these reactors and consumes the majority of the world's supply of molybdenum-99; however, none of the isotope is produced in this country for medical use.[1]

The irradiation of uranium-235 with neutrons produces fission fragments containing molybdenum-99 and other medical isotopes, such as iodine-131 and xenon-133. After the molybdenum is separated from the isotope mix-