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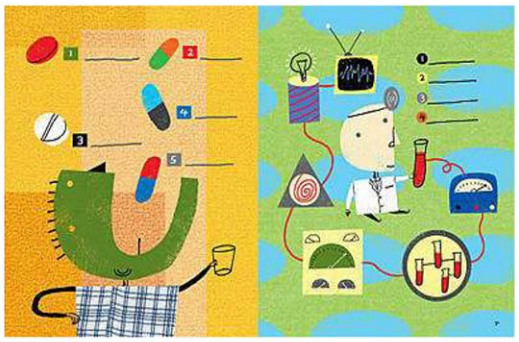

Drugs and the Definition of Disease

Jeremy A. Greene

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Preface

> The way to live the longest is to acquire a chronic disease and take good care of it. —SIR WILLIAM OSLER

This week, in clinics and hospitals across the country, thousands of perfectly healthy-feeling adults will receive a diagnosis for a disorder that they did not know they had. There are several such disorders: imperceptible to patients, they produce no fevers, no chills, no headaches, no stomachaches, no pains. Neither are they immediately perceptible to physicians or other health providers; there is no lesion to be seen with an ophthalmoscope or suspicious sound to be heard with a stethoscope, no tell-tale skin finding or sense to be made from piecing together disparate observations into a cohesive diagnosis. These are diseases that bear no immediate relation to symptoms but rather are connected to a statistical likelihood of developing symptoms in the future, pathologies—such as high blood pressure, mild diabetes, or elevated cholesterol—that are measurable only with the aid of an intervening diagnostic technology. Although patients who receive these diagnoses are typically encouraged to change their diets, get more exercise, and pursue other therapeutic lifestyle changes, for most people these diagnoses lead directly to the prescription of a drug they will take every day for an indefinite period, if not for the rest of their lives.

This book is concerned with the modern predicament of the subjectively healthy but highly medicated individual, a type that is becoming more and more common among the adult population of the United States. Americans on average filled ten prescriptions per person in 2003; those over age sixty-five filled an average of twenty-five prescriptions in that year. Dominant in this prescription practice are a set of drugs that modify conditions of risk and also happen to be the top-selling therapeutic agents in the pharmaceutical landscape. The widespread use of such agents supports an industry with worldwide sales rapidly approaching $500 billion and now represents the fastest-growing segment of health care expenditures. Because the preventive efficacy of these drugs has been determined only at the level of the population, individual patients who consume medications for asymptomatic conditions do so without knowing whether they will, in fact, ever receive any benefit from their pharmaceutical regimen. For the many thousands who experience side effects from these medications, the only certain result of their diagnostic and therapeutic experience is, ironically, a set of iatrogenic symptoms.

And yet the promotion of this pharmacopoeia of risk reduction is not merely a marketing ploy on the part of drug manufacturers or a bid by physicians for more office visits. Among those lobbying for the broader use of these drugs have been public health advocates, well-respected scientists, eminent clinicians, and many patient-activists and disease communities themselves. Although their actions have contributed to the endorsement of widespread use of prescription drugs, these actors have not all simply been "bought off" by the drug industry. An enormous wealth of data—hundreds of long-term, randomized, placebo-controlled clinical trials representing millions of patient-years—have indicated that for many populations of asymptomatic patients, steady consumption of risk-reducing drugs has generated visible benefits in the prevention of heart disease, stroke, blindness, and renal failure. In the past three decades, as broad guidelines have supported increasing use of such drugs on a preventive basis, the number of actual strokes and heart attacks in the United States has significantly declined.

The data behind the doctrine of pharmaceutical prevention are convincing, but the production and dissemination of that medical knowledge and its translation into medical practice is not insulated from the marketplace. In every step of the process we see an amalgamation of marketing and research: in the early stages of drug development, when a promising compound is conceived in terms of its potential market size; in the conduct of clinical trials, whose grow-

ing expense and largely private funding makes them increasingly accountable to shareholders as well as to scientists and regulators; and in the process of educating physicians and the public about the expanding use of these medications, which takes place largely through a promotional network of pharmaceutical representatives and direct-to-consumer advertising. In the course of several decades, disease has become simultaneously an epidemiological event and a marketing event.

This book follows three overlapping narratives of drugs and diseases to explore the central confluence of marketing and epidemiology that underlies the contemporary doctrine of pharmaceutical prevention. Each two-chapter part of the text revolves around a single drug and a single disease during a time period pivotal in their mutual definition. The aim of this case-study method is to offer enough detail and context to trace how both drug and disease came to alter each other in their therapeutic embrace. The three stories overlap, share attributes and actors, and weave together to describe a consistent set of structural developments and sea changes in therapeutic knowledge and practice over the past half century.

Part 1 hinges on the relationship between Diuril (chlorothiazide) and hypertension. By the end of the twentieth century, hypertension (high blood pressure) had become the paradigmatic disease of risk, overwhelmingly diagnosed and pharmacologically treated on an asymptomatic, preventive basis. But in the mid-1950s, when Diuril was being developed as a therapeutic compound, high blood pressure was considered a treatable diagnosis only in patients with felt symptoms. Chapter 1 traces the interplay of marketing and research in the development and launch of Diuril within the newly formed Merck Sharp & Dohme, the hybrid combination of the scientifically acclaimed Merck Research Laboratories and the well-honed marketing and sales institution of the Sharp & Dohme Pharmaceutical Company. This chapter is largely based on a close reading of internal company documents found at the Merck Archives and traces in detail the practices by which drug promotion and disease promotion became intertwined in the pharmaceutical corporation. Chapter 2 follows Diuril after its launch and describes the varied roles the drug itself played in the production of a widespread consensus on the treatment of asymptomatic hypertension.

Part 2 maps the role of Orinase (tolbutamide) and other new oral antidiabetic drugs in the 1960s and 1970s as the diagnosis of adult-onset diabetes transformed from a frankly symptomatic process into a practice of preventive

screening. Chapter 3 examines the public documents of the Upjohn Company and the business and clinical literatures surrounding the launch of Orinase and its connection to expanding diagnosis of prediabetes and other asymptomatic forms of the disease. The community of American diabetologists, long divided over the proper relationship between the management of diabetes and the physiological control of blood sugar levels, viewed both the relative ease of an oral dosage and the asymptomatic category of prediabetes with ambivalence and some skepticism. A decade after the first oral antidiabetics were released, researchers conducting the University Group Diabetes Project (UGDP)—a large-scale, multi-arm clinical trial assessing the usefulness of oral antidiabetic agents—shocked the clinical world with a proclamation that treatment with Orinase did not decrease the risk of cardiovascular mortality in diabetic patients but instead dramatically increased that risk. As the Food and Drug Administration (FDA) attempted to alter Orinase's package labeling to limit the usage of oral drugs to overtly symptomatic patients, the subsequent publicity sparked a controversy over the role of clinical trials in the regulation of clinical practice that roiled for well over a decade. Chapter 4 looks at these disputes over Orinase's promotion, labeling, and cardiovascular effects in the aftermath of the UGDP study, with a focus on the role of the patient and the practicing physician caught between the arguments of Upjohn, the FDA, radical consumer groups, the American Medical Association, and other parties. Both private and public organizations, all claiming to represent the interests of the ultimate consumer, were now set against each other in the fray. As a commodity targeted toward a well-organized and well-identified patient population, Orinase highlights the contested role of the patient as consumer in the pharmaceutical negotiation of disease.

Part 3 is concerned with the fall and rise of high blood cholesterol (hypercholesterolemia) as a treatable clinical category. It narrates the contingent development of Mevacor (lovastatin) and the therapeutic consensus around the treatment of high cholesterol between the late 1970s and the 1990s. Chapter 5 documents the failure of earlier cholesterol-lowering formulations and dietary regimens to gain currency in clinical practice and the resultant collapse of consensus on the advisability of treating high blood cholesterol at all. This destabilization of high cholesterol as a diagnosis reached its nadir in the late 1970s, amid conflicting accounts of the utility of drug, diet, and regimen. When Merck began to mobilize its efforts to bring Mevacor to market in 1987, its marketing staff approached the task of rebuilding a therapeutic consensus through far-

reaching public-private promotional campaigns in concert with the newly founded National Cholesterol Education Program of the National Institutes of Health, emphasizing the rational design of the drug and encouraging the general population to "know your number." The scope of this promotional campaign, and the subtlety of its integration with epidemiological and basic science research, represents a striking development in the style and content of pharmaceutical marketing in the years since the 1958 launch of Diuril. Chapter 6 follows the social lives of Mevacor and cholesterol in the decades since the launch of the statins, exploring the relationships between commercial clinical trials, expert guidelines, and promotional strategies in the expansion of the target populations for cholesterol-lowering therapy. As therapeutic reformers placed the randomized clinical trial at the center of public health strategies and clinical guidelines, the private funding of postmarketing trials became a vital link between economies of medical knowledge and economies of pharmaceutical development.

This complex nexus of drug and disease, risk and diagnosis, medicine and marketplace now lies at the foundation of mainstream American medical practice, but it is a structure that has only recently been set in place. Looking back a half century reveals an America with few pharmaceuticals of risk reduction, a nation that viewed chronic disease largely as a process of inevitable decay, and a pharmaceutical industry that concentrated much more on the development of new classes of drugs than on the expansion of its markets to encompass more and more subjectively healthy people. How did we arrive at a state where the line between the normal and the pathological became a numerical abstraction? How did these asymptomatic diseases come to be, and what new relationships between health and illness, doctor and patient, individual and population do they represent? What forces have allowed pharmaceuticals to become crucial to the definition of disease and the philosophy of health promotion? These historical questions are urgently relevant to our times.

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The Pharmacopoeia of Risk Reduction

> By means of his oracles, a Zande can discover the mystical forces which hang over a man and doom him in advance, and having discovered them he can counteract them or alter his plans to avoid the doom which awaits him in any particular venture. Hence a man's future health and happiness depend on future conditions that are already in existence and can be exposed by the oracles and altered.
>
> — E. E. EVANS-PRITCHARD, 1937

The audience assembled in the hotel ballroom October 29, 1957, came from surprisingly diverse backgrounds: some had started their careers as salesmen, others as financial analysts, basic research scientists, or practicing physicians. But the group gathered in the Boca Raton Club for the fifty-first annual meeting of the American Drug Manufacturer's Association was focused on a common set of interests: the financial and material future of the prescription drug industry. In the decade or so since the end of World War II, pharmaceutical manufacturers had seen the scope of their business expand dramatically, the structure of their firms grow outward, and the pace of their new-product development accelerate at an impressive rate. The industry was progressive and forward-leaning, and the audience assembled to hear the address given by Charles Mottley—Pfizer's chief of operations planning—was keen to hear what he had to say about the pharmaceutical future.

Mottley asked his audience to consider the paradoxical long-term influence that antibiotics—at that time the most lucrative sector within the pharmaceutical market—were beginning to exert upon broader health statistics. Antibiotics had effectively reduced the frequency and severity of infectious disease,

but they had also effectively reduced their own potential market. "There seems to be an important lesson here for the drug industry," he continued. "As the industry does a good job of producing efficacious drugs and helps to win a given campaign . . . the net result is to limit the potential market." If the industry was to have a viable future, it would be necessary to grasp the nature of this irony and work to invert it. Drugs needed to *grow* their markets, not shrink them. Mottley told his audience that the expanding prevalence of chronic disease already evident by the late 1950s offered the perfect opportunity to redesign the drug-disease relationship. "Trends are developing in the cause of death statistics," he concluded, "which indicate that 'tomorrow' greater proportions of people are likely to suffer fatal accidents or be afflicted with diseases, such as cancer and cardiovascular involvements, for which there are, as yet, no really effective drugs."[1] As chronic diseases gained in importance from the 1950s onward, Mottley suggested, and as a chronic pharmacopoeia developed alongside them, new concepts of disease and treatment could be explored to maximize the long-term growth potential of pharmaceuticals. Conditions that patients would necessarily have for the rest of their lives—coupled with treatments that could be taken every day for an indefinite period—had the makings of a market that could result in sustainable growth.

The same year that Mottley addressed the crowd at Boca Raton, medical journals carried the early results of the Framingham Study, the first major effort of the recently established National Heart Institute and the American Heart Association in their joint endeavor to better understand the "modern epidemic" of coronary heart disease.[2] In the wake of receding morbidity and mortality of infectious diseases, heart disease had emerged as the foremost killer of modern times, and the search for a cure, or at least a cause, of this epidemic had gained widespread popular attention.[3] As the Framingham investigators followed the cardiovascular history of some six thousand residents of this small Massachusetts city, they began to single out the predictive "prepathological" categories that would eventually become known as coronary risk factors. Some of the categories were apparently immutable demographic characteristics of an individual: age, sex, and family history. Others, such as cigarette smoking, were potentially modifiable behaviors. The central risk factors, however, were physiological variants believed to be mechanistically connected to heart disease: hypertension (high blood pressure), hypercholesterolemia (high blood cholesterol), and, later, diabetes (uncontrolled elevation of blood sugar).[4] Implicit in the initial Framingham publications, then, was a tantalizing new

possibility: control these deviations, and you can control chronic disease. As Jeremiah Stamler, a principal Framingham investigator, noted auspiciously in 1958: "It is highly feasible to assess risk of coronary heart disease in healthy persons—and to identify susceptibles . . . Elevated blood pressure and hypercholesterolemia can be lowered to or toward normal in many. Diabetes can be well controlled . . . Moreover, it is quite clear that the measures available for correcting abnormalities are simple, practicable, reasonable, and devoid of danger. It therefore seems entirely in order to propose that the medical profession apply the knowledge from recent studies to identify those susceptible to coronary heart disease and attempt to help them prophylactically."[5]

Mottley and the Framingham investigators were setting forth essentially the same program for the future of health care priorities. In the ensuing half century, their respective visions have become reality in the expanding diagnosis and pharmaceutical treatment of chronic diseases and their precursor states. Prescriptions for chronic disease categories now dominate the American pharmaceutical industry's domestic income, and the Framingham risk factors—particularly the three physiologically modifiable conditions of hypertension, diabetes, and hypercholesterolemia—have become common figures in contemporary clinical practice. Safe, effective, and specific therapeutic agents for each condition, unavailable in 1957, have since seen their markets multiply to represent three of the ten highest-grossing therapeutic categories in the world, collectively accounting for nearly $40 billion in sales in the year 2000 alone.[6] The midcentury proclamations of the marketer and the epidemiologist are fused together in the contemporary doctrine of pharmaceutical prevention.

The Therapeutic Transition

This book addresses the riddle that lies at the confluence of these two viewpoints. How is it that the priorities of public health—a field traditionally associated with the welfare state and private charity—have become so closely aligned with the marketing practices of the single most profitable industry in the American economy? What mechanisms have come to link pharmaceutical agents with the widespread detection and promotion of conditions of risk?

By most accounts, the emergence of a highly profitable set of therapeutics for previously untreated, asymptomatic, and flexibly defined disease entities occurred only as a result of the scientific achievements of clinical epidemiology. In this commonly received narrative, the epidemiological study of risk re-

duction preceded the development of risk-reducing therapeutics: disease entities were recognized first, and then drugs were developed to treat them. Medical historians have thus situated the Framingham Study as a pivotal moment in the articulation of risk in health and medicine, a moment when the laboratory and the clinic began to share their primacy in medical epistemology with biostatistics and the long-term epidemiological study.[7] The role played by pharmaceuticals in the renegotiation of disease has typically been left to speculation or discounted as an afterthought, the inevitable consequence of a natural "epidemiologic transition" from acute to chronic disease in economically developed nations.[8]

In the following chapters, I argue that that there was nothing inevitable about the development of a specific therapeutics of risk reduction and that the widespread adoption of these pharmaceutical agents speaks to a social history far more complex than a mere shift in the demography or in the epidemiological study of chronic disease. Rather, pharmaceuticals played a central and active role in the definition of these categories of illness. The adoption of mild hypertension as a disease was not automatic or self-evident: it hinged upon a set of promotional practices—somewhere between education and salesmanship—to give it credence in the eyes of medical practitioners and consumers alike. For diabetes and high cholesterol, asthma and dyspepsia, the same is true: our contemporary understanding of chronic disease is the product of epidemiological practices and marketing practices that have come to configure their common subject in increasingly similar terms.

Over the second half of the twentieth century, in concert with the emergence of specific, efficacious, and palatable oral medications, the domain of chronic diseases expanded from a core nucleus of long-suffering symptomatic patients to encompass broader and broader populations who bore no immediate symptoms. This book presents selected episodes in the emergence of the three principal treatable cardiovascular risk factors of our time—hypertension, diabetes, and elevated blood cholesterol—and the careers of three pharmaceutical products whose fates have become inseparable from the conditions they treated. All three conditions were ultimately transmuted by pharmaceutical agents: attenuated, expanded, and displaced from the realm of symptom, history, and treatment to one of screening, measurement, and prophylaxis.

Diuril, Orinase, and Mevacor are not historical actors in the traditional sense, but they were nonetheless crucial agents in the transformation of disease in the twentieth century. Each of these mass-produced tablets represents the

intersection of several interested parties who have competing stakes and claims; it is a site where the divergent trajectories of researchers, clinicians, patients, regulatory bodies, manufacturers, and insurers necessarily connect. In the postwar, ostensibly postinfectious era, the historical punctuation formerly provided by epidemics was replaced by a new sort of historical punctuation provided by pharmaceutical launches and marketing developments. Pharmaceuticals can also serve as portals into a distinctly social history; they form collective "sampling devices" through which we can observe the social tectonics underlying contemporary politics of health and normality. The stories of these three agents, linking discrete clinical categories and successive historical moments, work together to offer a central insight into the expansion and contestation of chronic disease categories in the late twentieth century.[9]

The program of pharmaceutical prevention cannot be reduced simply to a clever marketing effort or a centrally planned medicalization that generated artificial disease categories in order to transform every healthy American into a multiple-drug consumer. That argument overestimates the power of the research-based pharmaceutical industry and minimizes its substantial investment in scientific inquiry; it also echoes the 1970s use of the term *medicalization* as a paranoid polemic describing an omnipotent medical profession constantly seeking to expand its province over the healthy.[10] Although it is apparent that the autonomous stature of the medical profession has declined over the past fifty years while the resources of the pharmaceutical industry have grown substantially, the current politics of health cannot be described as a simple transfer in power from physicians to PhRMA (the industry lobby, abbreviated from Pharmaceutical Research and Manufacturers of America). The expansion of hypertension, diabetes, and high cholesterol to include previously healthy populations was indeed a process of medicalization, but it was not a concerted or monolithic strategy emanating from the board room of a pharmaceutical company or the American Medical Association. It was instead part of an overdetermined process that illustrates the porous relationship between the science and the business of health care and the centrality of disease categories in contemporary conceptions of health.

Since the 1950s, a set of related changes occurred—in demography and epidemiology; in policy structures surrounding biomedical research, pharmaceutical regulation, and clinical practice; in the R&D and marketing practices of the pharmaceutical industry; and in disease-centered activism—and each change played a substantial role in generating support for the pharmaceutical