Prediabetes can be understood as a mobile and efficient means of translating diabetes into an infinitely expandable market, a vision that coincided exactly with a public health goal of broader and earlier preventive measures to combat an ancient scourge. By equating the linear gradient of physiological parameters with the temporal progression of disease, the concept of prediabetes invested borderline test results with a sense of pathophysiological urgency.

Conclusion

Mild, hidden, chemical, early, or latent, the expansive taxonomy of adult-onset diabetes had by the end of the 1960s provided for an ample population of newly diagnosed diabetics, and by 1968 the National Health Survey revealed that over three-quarters of all known diabetics were being treated with oral hypoglycemics.[115] In that year alone, more than 3 million new prescriptions were written for oral antidiabetics—more than ten new oral agent prescriptions for every one new insulin prescription—and Orinase grossed over $40 million in sales.[116] In 1968 the average person living with diabetes had been diagnosed on the basis of blood sugar readings, offered a choice of oral antidiabetic agents, and told that in exchange for taking a pill a day for the rest of her life, she could reasonably hope to reduce her chances of diabetic complications, heart disease, and stroke. For the populations of asymptomatic diabetics detected and dosed, Orinase was intended to be a lifetime partner. As one Orinase salesman noted in a letter sent back to his supervisors with a copy of a prescription written for six hundred Orinase tablets, "the M.D. told the patient that he was going to be on Orinase for life and he might as well buy in quantity (. . . love that doctor)."[117]

This transformation in diabetes practice might superficially resemble the transformation in hypertension practice after Diuril, but there are significant differences. First, the therapeutic innovation represented by Orinase was not initially connected to claims of improved safety or efficacy, but instead emphasized palatability and ease of administration. This marketing of convenience encountered resistance and soon took on additional dimensions of enhanced safety (in terms of decreased hypoglycemic episodes) and increased efficacy (through better therapeutic compliance). Orinase's larger impact, however, came from its role in making possible the logic of diabetes screening and mobilizing the various categories of prediabetes that would come to be folded into the general category of diagnosable and treatable diabetes. Meta-

phorically, the shift from the needle to the pill encapsulated a general transformation of the therapeutic landscape of the 1950s and 1960s, as the injectable "miracle drugs" of the 1930s and 1940s like insulin and penicillin gave way to the tablets and capsules that were the wonder drugs of the post–World War II era. The daily integration of oral medications into outpatient life was essential to building a feasible pharmacopoeia of risk reduction.

Moreover, there was simply no analogue to prediabetes in the mild-to-moderate hypertension debates of the 1950s and 1960s.[118] What was in hypertension a single threshold separating the hypertensive from the normotensive became in the case of diabetes a territory all its own: a mobile buffer state that interposed itself between the normal and the pathological and in so doing actively stabilized both categories. Though never explicitly a disease, prediabetes allowed an articulation of an activist and expansionist mode of disease prevention and broader treatment. As a buffer, its two interfaces were both active: the interface between normal and prediabetes offered a demarcation of risk, while the interface between prediabetes and diabetes constituted a boundary of experimental therapeutics versus proven therapeutic indications. Prediabetes thus provided an epistemological two-step crucial to the mechanics of market and disease expansion.

This prediabetic state did not evaporate after serving its mediating purpose in the 1960s. Rather, definitions of prediabetic populations have continued to expand. The most recent instantiation of the prediabetic state is the contemporary category of "insulin resistance," sometimes explicitly referred to as a form of prediabetes.[119] As with previous categories of prediabetes, contemporary descriptions of insulin resistance denote a prepathological state that is defined in practice by borderline test results, a population whose blood glucose levels—whether fasting or following a glucose tolerance test—lie in the region just below the numerical thresholds for frank diabetes. Recently, a large multisite clinical trial, the Diabetes Prevention Program (DPP), has demonstrated that populations diagnosed with insulin resistance and placed on a regular regimen of Bristol-Myers Squibb's newer oral antidiabetic Glucophage (metformin) demonstrated a 31 percent reduction in three-year incidence of development of diabetes relative to placebo.[120] These results have been ratified with subsequent studies, and the pharmacological treatment of insulin resistance is steadily gaining favor in clinical practice.[121]

It is possible that within a few years, insulin resistance as a category will cease to exist and will instead be known as another variant of mild diabetes. If the

results of the DPP are upheld, the screening, detection, and treatment of insulin-resistant populations will offer a further step toward Elliot Joslin's 1931 call for large-scale measures for the prevention of diabetes, but they will also result in another vast increase in antidiabetic prescriptions, currently judged at about $750 per person per year.[122] They also suggest a further question: if the difference between insulin resistance and diabetes is now strictly a quantitative difference in test results, how long will it be before another study demonstrates the benefit of treating the next population with borderline laboratory values below the current threshold for insulin resistance? What logic can oppose the progress of this expansive pharmacotherapy of prevention?

It would be wrong to take away the impression that the expansive trajectory of treatable diabetes traces an unbroken line from the launch of Orinase to the successes of Glucophage. Lingering disputes over the value of glycemic control in asymptomatic individuals plagued the community of diabetologists in the 1960s much as lingering concerns over the value of normalizing blood pressure in moderate hypertensives had plagued the community of cardiologists. As practitioners grew somewhat more comfortable writing prescriptions on a preventive basis, leaders in both fields looked to federally funded long-term, multisite, randomized placebo-controlled clinical trials to settle their respective clinical merits. However, whereas the VA study of asymptomatic hypertension became a model for generating clinical consensus and translating therapeutic experience into a broad-based public health program, its diabetic analogue—the NIH-funded University Group Diabetes Project Study—tore open the fabric of therapeutic consensus. It is to that act of disruption that we will next turn.

CHAPTER FOUR

Risk and the Symptom

The Trials of Orinase

> Everyone here is claiming to be in the public interest, and when everybody is riding the horse of the public interest in a different direction, there is great controversy.
>
> —ROBERT F. BRADLEY,
> Committee on the Care of the Diabetic, 1975

Early in the afternoon of May 20, 1970, a report was leaked over the Dow Jones newswires that Orinase (tolbutamide), "a drug used to lower blood sugar in diabetic patients," might be harmful.[1] Orinase had been Upjohn's showcase success and sales leader for nearly a decade, and news of its possible toxicity spelled disastrous things for the company and its investors. Before the New York Stock Exchange closed that afternoon, Upjohn's stock had fallen in heavy trading. The next morning, the *Washington Post* reported the preliminary findings from the federally funded University Group Diabetes Program (UGDP)—the largest, longest, and most definitive study of diabetes therapy yet performed—with the implication that at least eight thousand patients a year may have already died as a result of Orinase consumption. As the story was picked up by the Associated Press, the Food and Drug Administration (FDA) hastily issued a press release that provided only the briefest abstract of the study and pronounced that the agency intended to revise the labeling of tolbutamide and other oral hypoglycemic drugs.[2] In the meantime, all hell broke loose.

At that time, hundreds of thousands of Americans were taking Orinase every day for mild (asymptomatic) diabetes, largely on the premise that the pill

reduced their long-term risk for diabetic complications and heart disease. Over the next few days, FDA commissioner Charles Edwards received hundreds of phone calls and letters from patients concerned to find that the drugs they were taking to reduce their health risks might actually be increasing them. "C.P.," a Virginia man, wrote: "I have a mild diabetes—the kind that shows up in blood tests only it does not show in normal urine tests. For the past two years have been taking 2 Pills daily Upjohn *Orinase* and using saccharin . . . Last week both were pointed out as dangerous to use as reported in the Wash Post. My Doctor thinks he should have more authoritative information before advising discontinuing or curtailment of these items. Could your office please advise on continued use of these items in view of frightening reports of Wash Post newspaper. I am 65 years old."[3] C.P. and the rest of the *Washington Post*'s readership were among the many Americans who learned of Orinase's putative toxicity before their physicians did.[4] This "premature announcement" of Orinase's toxicity, before the FDA had issued any warning to physicians and before the UGDP study was published in the clinical literature, unleashed a public debate over risk and asymptomatic disease that lasted more than a decade; created rancorous divides between advocates, researchers, and regulatory agencies; and left hundreds of thousands of diabetics, their families, and their physicians in a muddle of uncertain practice, contested information, and strained trust.[5]

If patients like C.P. were disturbed by the news of Orinase's toxicity, the news hit their physicians twice as hard. Those who learned of the controversy through the newspaper were relatively lucky compared to the thousands of physicians who first learned of the debacle from their agitated patients. Commissioner Edwards subsequently received the following letter from a "Poor Practitioner," who complained hotly of the difficulty he was thrown into due to the study's untimely publicity and the regulatory and epistemological uncertainty that followed:

> Dear Dr. Edwards:
>
> Now that my nurse, receptionist, and bookkeeper are no longer tying up the three telephone lines to discuss with patients who are extremely worried and apprehensive about the Orinase situation, I am able to obtain a free line to dictate this letter to your attention.
>
> I sincerely believe that the "public leak" by the F.D.A. to the newspapers, and Walter Cronkite in particular, is not only a very stupid and indiscreet action on the part of your agency, but I firmly also believe this transgresses any and all med-

ical ethic. This is a scare tactic to the general public who are using an ethical and adequate drug program and in so doing this, you are disrupting control balance of relationship of physician to patient and all other such relationships. You are further dictating by fiat medical practice and to make matters worse, you are using an unpublished study which has no logic, inadequate statistics and improper evaluation.

I deplore such action. I trust that it will not occur in the future over this or any drug. In the past, your direction has been to have the drug company release a news letter to physicians regarding dangerous or untoward side effects of drugs when they have been proven. In this case, you have done neither. I would hope very much that the F.D.A. would retract publicly its stand and correct this situation and future ones as they may occur.

Sincerely yours,
David L. Roberts, M.D.
Poor Practitioner[6]

The poor doctor Roberts and the hapless patient C.P. are but two of the thousands of minor actors in the public drama that became popularly known as the tolbutamide controversy. As it unfolded over the full course of the 1970s, this fight about Orinase and the UGDP trial proved to be one of the ugliest conflicts in the history of therapeutic investigation and came to involve a set of congressional hearings, an FBI investigation, and a court ruling challenged all the way up to the U.S. Supreme Court.[7] Eminent clinicians, typically reserved in public comments, took to calling each other "snake-oil salesmen," "unbridled sensationalists," and "drug-house whores."[8] Although the court proceedings had ended by 1984 and the dispute gradually disappeared from the pages of medical journals and popular newspapers, the debate never did reach a point of resolution.

I do not attempt in these pages to resolve the long-unsettled issue of whether Orinase reduced or increased the cardiovascular mortality of its consumers: now that Orinase has been replaced by newer generations of oral antidiabetic agents, the question has become largely irrelevant. Instead, I explore materials documenting the experience of how "street-level" actors like Dr. Roberts and C.P. came to terms with the diagnosis and treatment of asymptomatic diabetes at a time when its entire therapeutic rationale was under public scrutiny. The thousands of letters stored in the FDA dockets and administrative files during the tolbutamide controversy form a semi-ethnographic set of resources, docu-

menting the voice of the patient as consumer and coming to terms with the pragmatic and moral issues that connect pharmaceuticals, risk, and asymptomatic disease. The letters preserve expressions of a changing ethos of patienthood and provide a perspective on the relationship of pharmaceuticals and disease in practice that is not widely available.[9] Historians, sociologists, policy analysts, journalists, and others have examined the tolbutamide controversy as a case study in clinical trial methodology, an exercise in failed public relations and communication breakdown, and a demonstration of the incommensurability of clinical and biostatistical logics.[10] These analyses, however, fail to convey the extent to which this controversy blew up around a disease in the process of shedding its symptoms and a drug that was instrumental in that transformation.

The displacement and attempted restoration of the symptom in the diagnosis of diabetes are central to this story. As illustrated in chapter 3, Orinase helped catalyze the transformation of diabetes from a symptom-bound disease into a numerical diagnosis treated on a preventive basis. One of the original goals of the UGDP study—proposed just one year after the 1957 launch of Orinase—was to interrogate whether the treatment of diabetes in terms of number rather than symptom provided any measurable benefit for these newly diagnosed "mild diabetics," "chemical diabetics," "latent diabetics," and others with laboratory-detected abnormalities of carbohydrate metabolism. Consequently, when the preliminary UGDP results suggested that tolbutamide *harmed* its consumers, the FDA's initial actions focused attention on the symptom as a vital site of regulation. As tolbutamide's identity shifted from risk-reducing agent to risk-augmenting agent, reexamination of the drug's efficacy crept backward from therapeutic agent to disease entity, casting the validity of asymptomatic diabetes itself into question.

The attempt to "roll back" diabetes from an asymptomatic condition to an exclusively symptomatic disease, however, did not go unchecked. Once the curtain of diagnosis had shifted outward to include the asymptomatic, after hundreds of thousands of symptomless patients had come to think of themselves as diabetics, there was no simple path back. The ensuing controversy offers a unique opportunity to understand how the regulation of pharmaceutical products—and the corresponding definition of patients as consumers—became entwined in a crisis over medical authority in late-twentieth-century America.