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The Past 200 Years in Diabetes

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Diabetes was first recognized around 1500 B.C.E. by the ancient Egyptians, who considered it a rare condition in which a person urinated excessively and lost weight. The term diabetes mellitus, reflecting the fact that the urine of those affected had a sweet taste, was first used by the Greek physician Aretaeus, who lived from about 80 to 138 C.E. It was not until 1776, however, that Matthew Dobson actually measured the concentration of glucose in the urine of such patients and found it to be increased.[1]

Diabetes was a recognized clinical entity when the *New England Journal of Medicine and Surgery* was founded in 1812. Its prevalence at the time was not documented, and essentially nothing was known about the mechanisms responsible for the disease. No effective treatment was available, and diabetes was uniformly fatal within weeks to months after its diagnosis owing to insulin deficiency. In the intervening 200 years, major fundamental advances have been made in our understanding of the underlying causes of diabetes and the approach to its prevention and treatment (see timeline, available with the full text of this article at NEJM.org). Although diabetes is still associated with a reduced life expectancy, the outlook for patients with this disease has improved dramatically, and patients usually lead active and productive lives for many decades after the diagnosis has been made. Many effective therapies are available for treating hyperglycemia and its complications. The study of diabetes and related aspects of glucose metabolism has been such fertile ground for scientific inquiry that 10 scientists have received the Nobel Prize for diabetes-related investigations since 1923 (Table 1). Thus, as a result of the efforts of the past 200 years, there is much good news to report regarding diabetes.

Ironically, although scientific advances have led to effective strategies for preventing diabetes, the pathway to cure has remained elusive. In fact, if one views diabetes from a public health and overall societal standpoint, little progress has been made toward conquering the disease during the past 200 years, and we are arguably worse off now than we were in 1812. Two centuries ago, severe insulin deficiency dominated the clinical presentation of diabetes. Although it is possible that some people had milder forms of hyperglycemia at that time, they largely escaped clinical detection. In 2012, the commonly encountered spectrum of diabetes is quite different. Although severe insulin deficiency still occurs, it now accounts for only about 10% of cases overall and can be readily treated with insulin. The vast majority of patients with diabetes are overweight and have a combination of insulin resistance and impaired insulin secretion. The prevalence of this form of diabetes has been increasing dramatically, particularly in the past three to four decades, resulting in a worldwide epidemic that has made diabetes one of the most common and most serious medical conditions humankind has had to face.

Table 1. Nobel Prizes for Diabetes-Related Research.

Year	Category	Recipient	Contribution
1923	Medicine	F.G. Banting and J.J.R. Macleod	Discovery of insulin
1947	Medicine	C.F. Cori and G.T. Cori	Discovery of the course of the catalytic conversion of glycogen
1947	Medicine	B.A. Houssay	Discovery of the role of hormones released by the anterior pituitary lobe in the metabolism of sugar
1958	Chemistry	F. Sanger	Work on the structure of proteins, especially insulin
1971	Medicine	E.W. Sutherland	Discoveries concerning the mechanisms of action of hormones
1977	Medicine	R. Yalow	Development of radioimmunoassays for peptide hormones
1992	Medicine	E.H. Fischer and E.G. Krebs	Discoveries concerning reversible protein phosphorylation as a biologic regulatory mechanism

THE SCIENTIFIC BASIS OF CURRENT TREATMENT APPROACHES

STUDIES OF GLUCOSE METABOLISM

In the past 200 years, we have made dramatic advances in our understanding of the regulation of normal glucose metabolism. Beginning in the mid-19th century, Claude Bernard showed that blood glucose levels are regulated not just by the absorption of dietary carbohydrate but also by the liver, which plays a central role in producing glucose from nonglucose precursors.[2] Other investigators built on this discovery to identify the enzymes responsible for the synthesis and breakdown of glycogen,[3] the role of anterior pituitary hormones in glucose metabolism and the onset of diabetes,[4] the role of reversible protein phosphorylation by a protein kinase,[5] and the discovery of cyclic AMP and its role in hormonal action, particularly that of epinephrine and glucagon, both of which elevate the blood glucose concentration and contribute to diabetic hyperglycemia.[6]

THE ROLE OF THE PANCREAS AND THE DISCOVERY OF INSULIN

In 1889, Joseph von Mering and Oskar Minkowski found that removing the pancreas from dogs resulted in fatal diabetes, providing the first clue that the pancreas plays a key role in regulating glucose concentrations.[7,8] In 1910, Edward Albert Sharpey-Schafer hypothesized that diabetes was due to the deficiency of a single chemical produced by the pancreas; he called this chemical insulin, from the Latin word *insula*, meaning island and referring to the pancreatic islet cells of Langerhans. In 1921, Frederick Banting and Charles Best actually discovered insulin when they reversed diabetes that had been induced in dogs with an extract from the pancreatic islet cells of healthy dogs.[9,10] Together with James Collip and John Macleod, they purified the hormone insulin from bovine pancreases and were the first to use it to treat a patient with diabetes. The production of insulin and its therapeutic use quickly spread around the world. This series of events may be the most dramatic example of the rapid translation of a discovery in basic science into a benefit for patients. Once insulin injections became available, young people with insulin deficiency who had previously faced almost certain, painful death within weeks to months were able to survive for prolonged periods of time. Figure 1 shows a patient before and after she was treated successfully with insulin in 1922.[11]

INSULIN CHEMISTRY, BIOLOGY, AND PHYSIOLOGY

The dramatic discovery of insulin and the rapid demonstration that it is essential for human health stimulated intense interest in its chemistry and biology. A number of landmark discoveries resulted, some of which reached beyond diabetes research. For example, Frederick Sanger was awarded the Nobel Prize in Chemistry for developing methods to sequence the amino acids of proteins, and he used insulin as an example of his approaches.[12] Insulin was the first hormone for which the three-dimensional crystal structure was determined (by Dorothy Hodgkin, who had previously received the Nobel Prize in Chemistry for determining the structure of vitamin B_{12}). Donald Steiner's demonstration in 1967 that the two-polypeptide insulin molecule is derived from a

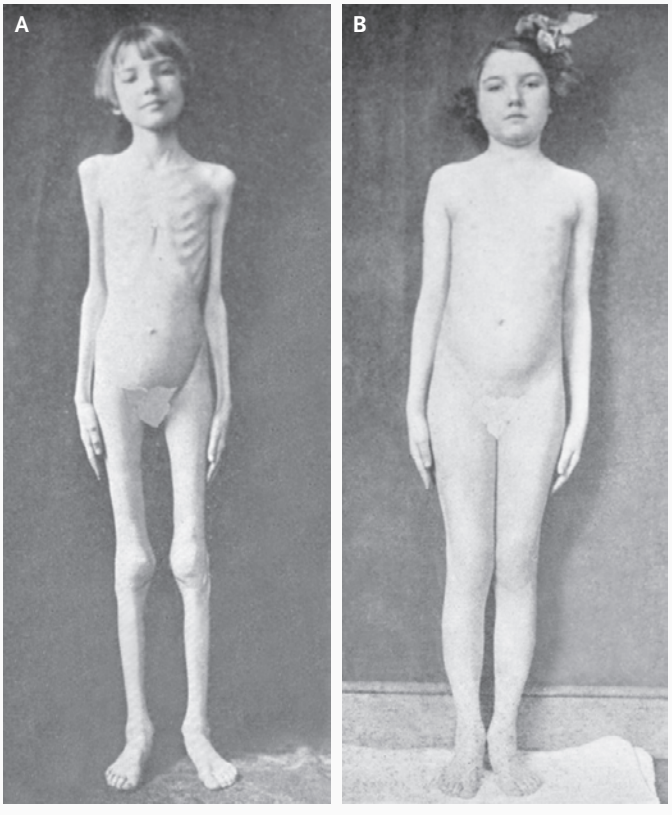

Figure 1. Effects of Insulin Therapy.

These photographs from 1922, in a case described by Geyelin,[11] show a young girl with insulin-deficient diabetes before treatment with insulin (Panel A) and after treatment (Panel B).

single-chain precursor proinsulin[13] was important not only for our understanding of the biochemistry of insulin but also because it applies to other peptide hormones that are transcribed as single-chain precursors. Insulin was the first hormone to be cloned[14] and then produced for therapeutic use by means of recombinant DNA technology, which provided an unlimited supply of this important molecule and laid the foundation for the biotechnology industry. Figure 2 shows the structure of insulin.

The development of the radioimmunoassay for insulin by Rosalyn Yalow and Solomon Berson in 1959 permitted the quantitative measurement of pancreatic beta-cell function in animals and humans and established the radioimmunoassay as a powerful tool for measuring proteins, metabolites, and other chemicals present in very low concentrations.[15] Much of our current understanding of diabetes has resulted from the ability to measure serum insulin levels.

PATHOGENESIS OF DIABETES

INSULIN RESISTANCE AND INSULIN DEFICIENCY

Over the past two centuries, we have learned that diabetes is a complex, heterogeneous disorder. Type 1 diabetes occurs predominantly in young people and is due to selective autoimmune destruction of the pancreatic beta cell, leading to insulin deficiency. Type 2 diabetes is much more common, and the vast majority of people with this disorder are overweight. The increase in body weight in the general population, a result of high-fat, high-calorie diets and a sedentary lifestyle, is the most important factor associated with the increased prevalence of type 2 diabetes. Older adults are most likely to have type 2 diabetes, although the age at onset has been falling in recent years, and type 2 diabetes is now common among teenagers and young adults.

Harold Himsworth first proposed in 1936 that many patients with diabetes have insulin resistance rather than insulin deficiency.[16] We now know that insulin resistance is essential in the pathogenesis of type 2 diabetes and that the disease results from both insulin resistance and impaired beta-cell function.[17] A clinical phenotype widely called the metabolic syndrome, which includes insulin resistance, upper-body obesity, hypertension, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol,[18] identifies persons at high risk for glucose intolerance and diabetes. Such persons are also at high risk for cardiovascular disease and should be targeted for preventive strategies.

GENETIC FACTORS

Genetic factors play an important role in the development of diabetes. Type 1 and type 2 diabetes are polygenic disorders, and multiple genes and environmental factors contribute to the development of the disease. A few forms of diabetes (e.g., maturity-onset diabetes of the young and neonatal diabetes) are single-gene disorders that affect the pancreatic beta cell[19,20] but account for only 1 to 2% of cases. In type 1 diabetes, alleles at the human leukocyte antigen locus on the short arm of chromosome 6 appear to explain up to 50% of the cases of familial clustering.[21,22] In contrast, a predominant genetic susceptibility lo-

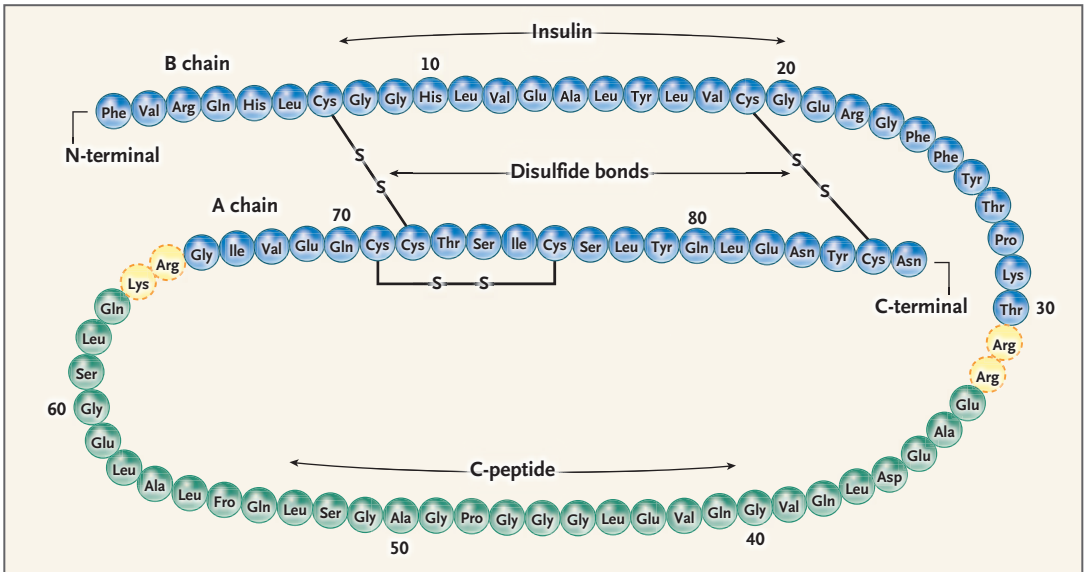

Figure 2. The Structure of Human Proinsulin.

Proinsulin is converted to insulin by proteolytic converting enzymes that remove the connecting peptide (C-peptide) and the lysine-arginine (Lys-Arg) and arginine-arginine (Arg-Arg) sequences of dibasic amino acids, leaving the mature insulin molecule, which consists of A and B chains connected by disulfide bonds.

cus for type 2 diabetes has not been found. Genetic studies have identified over 40 genetic variants that increase the risk of type 2 diabetes, but in the aggregate these variants account for only about 10% of the heritability of the disorder.[23,24] Individually, persons with these variants have an increased risk of diabetes of 10 to 15%, as compared with persons without the variants. The multiplicity of genes that contribute to the risk of type 2 diabetes makes it difficult to determine this risk precisely or to develop selective preventive or therapeutic strategies based on the genetic profile.

PREVENTION AND TREATMENT OF DIABETES

The approach to the prevention and treatment of diabetes has been transformed since the discovery of insulin, which led to the rapid development of a widely available and lifesaving new treatment and initiated a series of advances that have fundamentally enhanced the daily lives of patients with diabetes and dramatically extended their life expectancy. Many advances have resulted from important clinical trials that were reported in the *Journal* and elsewhere.[25-49] Some highlights of these studies include the use of biosynthetic human insulin, which has virtually eliminated local reactions at the injection site; insulin syringes and needles that are small and convenient to use and have reduced the pain of injections; home glucose monitoring,[25] which together with measurements of glycated hemoglobin,[26] allows therapy to be altered on the basis of accurate assessments of glucose control; and insulin pumps[27] driven by computer algorithms[28] that adjust insulin doses on the basis of the continuous measurement of glucose levels to achieve glucose concentrations within the physiologic range (Fig. 3). Preventive strategies and treatments for diabetic complications have undergone impressive improvements. The beneficial effects of angiotensin-receptor blockade, angiotensin-converting–enzyme inhibition, and protein restriction in preventing diabetic nephropathy have been shown.[29-34] Advances in kidney transplantation have extended the lives of patients with advanced diabetic kidney disease, and laser photocoagulation has preserved the vision of millions of patients with diabetic retinopathy.[35] Advances in islet-cell and pancreas transplantation have also been impressive.[36,37] Recent evidence exemplified by the results of two randomized, controlled clinical trials reported this past spring in the *Journal* suggests that bariatric surgery to induce weight loss in patients with

Figure 3. Milestones in Diabetes Diagnosis and Management.

Photographs of the saccharometer and the early insulin preparation are from the Science Museum collection at the Science & Society Picture Library.

type 2 diabetes is much more effective than either standard or intensive medical therapy alone in lowering glucose levels and even in achieving disease remission.[38,39] Advances in technology have thus profoundly improved our ability to monitor diabetic control (from urine testing to home glucose meters to continuous glucose monitoring) and to treat this disease and its complications (laser therapy for diabetic retinopathy, kidney transplantation for diabetic renal disease, and bariatric surgery to induce disease remission).

Diabetes care has been at the forefront of efforts to develop team-based approaches to patient care that involve physicians, nurses, nutritionists, social workers, podiatrists, and others and in developing models of care delivery for chronic illness. Using such an approach, the Diabetes Prevention Program showed that physical activity and weight loss can reduce the risk of diabetes in predisposed persons by 58%.[40] Major effects are also seen after treatment with metformin[40] or pioglitazone.[41] The Diabetes Control and Complications Trial showed that improved glucose control reduces microvascular complications in type 1 diabetes,[42] and the United Kingdom Prospective Diabetes Study showed the same for type 2 diabetes.[43] Intensive insulin therapy to prevent hyperglycemia improves outcomes in critically ill patients.[44,45]

The effect of diabetes treatment on cardiovascular outcomes and mortality is a critical issue. The Steno-2 Study showed that a multifactorial intervention aimed at improving control of glucose levels, lipid levels, and blood pressure led to a 50% reduction in cardiovascular mortality among patients with type 2 diabetes.[46,47] Among patients with type 1 diabetes, improved glucose control leads to a reduction in macrovascular disease, an effect that becomes apparent only many years after the improvement has been achieved.[48] The recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed that aggressive glycemic control of type 2 diabetes reduced the risk of nonfatal myocardial infarction but increased overall mortality.[49] The reasons for these differences between studies are not clear, but in type 2 diabetes, multiple factors increase the predisposition to cardiovascular disease. Indeed, treatment of hyperlipidemia and hypertension appears to be more effective in reducing cardiovascular events than does treatment to lower glucose levels. As a result of these and other findings, the treatments available for patients with diabetes have improved dramatically, particularly over the past 30 to 40 years.

PREVALENCE OF DIABETES — A WORLDWIDE EPIDEMIC

Unfortunately, the improvement in outcomes for individual patients with diabetes has not resulted in similar improvements from the public health perspective. The worldwide prevalence of diabetes has continued to increase dramatically. The difficulty in applying the principles of diabetes care from the individual patient to the population reflects the unique challenges of implementing research findings and effecting behavioral change. Figure 4 shows the number and percentage of persons in the U.S. population with diagnosed diabetes between 1980 and 2010 (http://www.cdc.gov/diabetes/statistics/prevalence_national.htm). During this period, the number of diagnosed cases of diabetes increased from 5.6 million to 20.9 million, representing 2.5% and 6.9% of the population, respectively. Nearly 27% of persons over 65 years of age have diabetes. If current trends continue, 1 in 3 U.S. adults could have diabetes by 2050. The American Diabetes Association estimated that the cost of diagnosed diabetes in the United States was $174 billion in 2007,[50] and efforts to prevent and treat diabetes threaten to overwhelm health systems throughout the world.

FUTURE CHALLENGES

Given the surge in the prevalence of diabetes, timely prevention of this disease at the population level is essential. Opportunities abound for the implementation of preventive public policies. Rigorous scientific methods will be needed to evaluate the effects of policy and legislative initiatives to eliminate trans fat from the diet; require restaurants to provide the caloric content of items on their menus; reduce the availability of high-calorie, high-fat foods in school cafeterias; and impose a tax on sugar-sweetened beverages. Lifestyle modification will undoubtedly play a key role in the ultimate solution to the problem of diabetes, but the necessary modifications have not been easy to implement, and more definitive solutions will depend on the ability of basic science to point prevention and treatment in new directions. Advances in basic immunology — in particular, the transformation of primitive stem cells into pancreatic beta cells — offer promise for the preven-

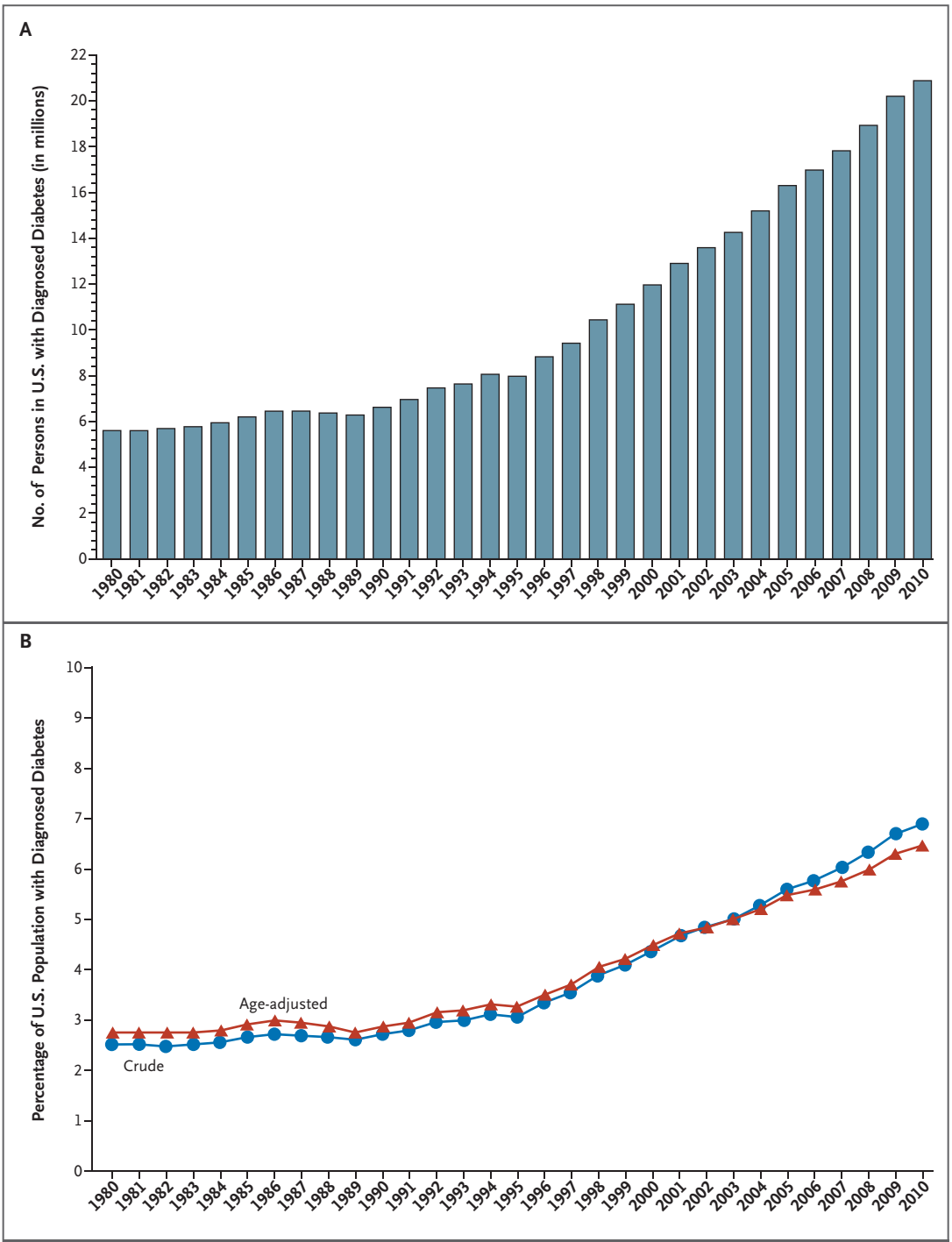

Figure 4. Number of Persons and Percentages of the Population with Diagnosed Diabetes in the United States, 1980–2010.

Panel A shows the number of cases of diagnosed diabetes between 1980 and 2010 among U.S. adults 18 to 79 years of age. During this period the number increased from 5.6 million to 20.9 million. Panel B shows the crude and age-adjusted percentages of the U.S. population with diagnosed diabetes for this same period of time. Data are from the Centers for Disease Control and Prevention (http://cdc.gov/diabetes/statistics/prevalence_national.html).

tion and treatment of autoimmunity in patients with type 1 diabetes. Advances in the identification of diabetes-susceptibility genes should clarify the relative role of insulin resistance and beta-cell dysfunction and identify molecular pathways and new drug targets, leading to more effective approaches to the prevention and treatment of type 2 diabetes. Although the challenges are still substantial, if we build on past accomplishments, there is every reason for optimism that another breakthrough as dramatic as the discovery of insulin will occur in the foreseeable future, with a similarly dramatic impact.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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