making old drugs new again

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MEDICINE AND SOCIETY

Debra Malina, Ph.D., Editor

Why Is There No Generic Insulin? Historical Origins of a Modern Problem

Jeremy A. Greene, M.D., Ph.D., and Kevin R. Riggs, M.D., M.P.H.

Although the exact development costs of any particular drug are never disclosed, economists estimate the average investment for an innovative drug that is brought to market at more than $1 billion and rising.[1,2] These high costs of pharmaceutical research and development are often invoked to justify the high price tags of new medications. Although the price point of effective new drugs — from hepatitis cures to new agents for heart failure — may initially be out of reach for many patients, market laws predict that drugs with strong demand should become more accessible after market exclusivity ends and generic competition begins. Since 1984, when the Drug Price Competition and Patent Term Restoration Act was passed, pharmaceutical innovation and access have been balanced on that premise: innovative drugs are rewarded with high prices during their window of patent protection, and generic competition reduces prices thereafter.[3,4]

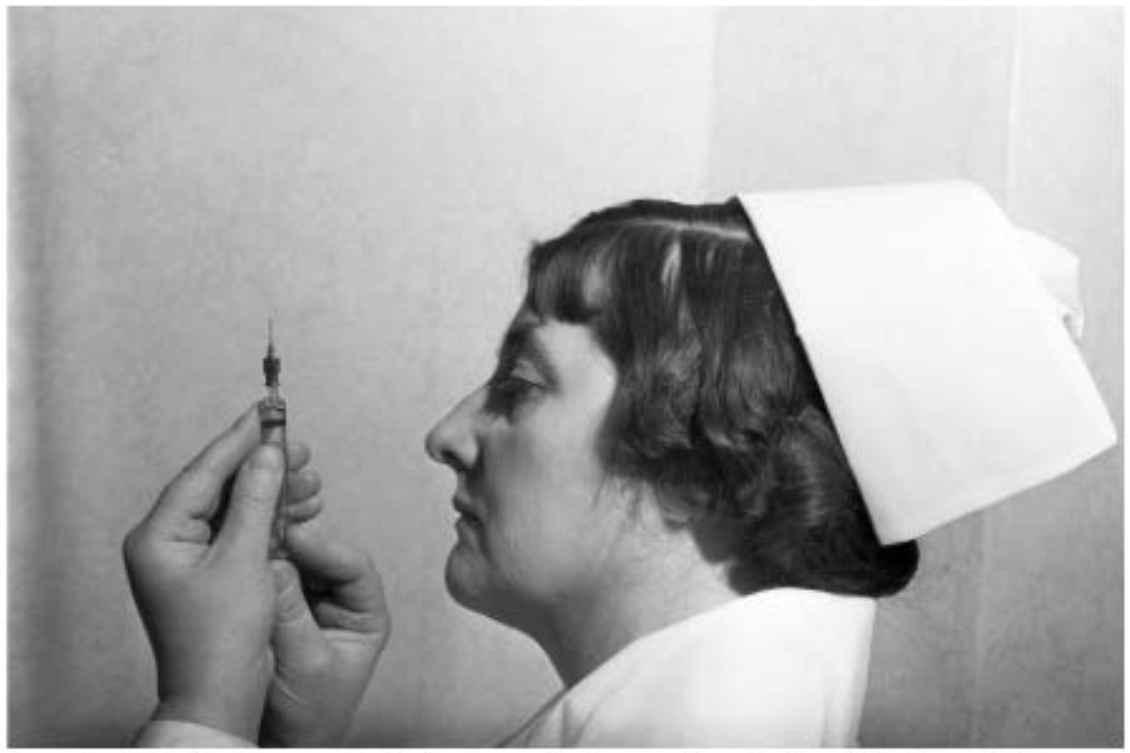
What happens when this expectation is not met for a drug that is essential for managing a disease with enormous public health significance? When insulin was discovered in 1921, it was hailed as one of the first "wonder drugs" of the 20th century, capable of transforming a fatal affliction into a manageable chronic condition.[5] Today, there are 21 million people living with diabetes in the United States alone, 6 million of whom take insulin.[6] And yet insulin is available only in brand-name forms — out-of-pocket costs for uninsured patients range from $120 to $400 per month. Whereas many other essential medications are available as $4 generics, no similarly low-priced versions of insulin are available. For many patients — especially those without insurance — the price of insulin is still too high to pay, and the consequences are disastrous for individual and systemic management of diabetes.[7]

The conundrum of why a medication discovered almost 100 years ago is still not available as a low-priced generic agent has historical origins — and implications for contemporary policy and practice.

THE ORIGINS OF INSULIN

In a widely celebrated tale of biomedical serendipity, insulin was discovered in 1921 by an unlikely scientific team at the University of Toronto, led by a young orthopedic surgeon without laboratory training, Frederick Banting, and a medical student, Charles Best. After improving their technique of extracting the active insulin (initially termed isletin) from whole animal pancreas, they produced enough to treat the first patient, Leonard Thompson, in 1922. A patent was not filed until later, however, in part because academic medicine viewed the patenting of biomedical research products with some distaste. When the team applied for a U.S. patent in January 1923 (which they later sold to the university for $1), they stated that their goal was not profit, but ensuring the speedy and safe availability of their discovery to the public.[8] The patent, they wrote to their university's president, was a form of publication: "When the details of the method of preparation are published anyone would be free to prepare the extract, but no one could secure a profitable monopoly."[9]

Patenting insulin also provided a means to control the quality of a product by controlling who could manufacture it.[10] After attempting to manufacture insulin in a production facility on the university campus, the researchers realized they lacked the expertise needed to produce enough drug for North American markets. In 1923, they teamed up with Eli Lilly, an established pharmaceutical company with experience producing glandular extracts.[9] Lilly was allowed to take out U.S. patents for any manufacturing-



A nurse in 1938 checks the amount of insulin in a needle. For many decades, the only insulin available to

Understanding Insulin Sticker-Shock

Published on December 22nd, 2014 | *by Craig Idlebrook*

Mary Clark, a realtor in Cincinnati, has grown accustomed recently to being the center of attention at the pharmacy. An independent contractor, Clark has had trouble finding affordable health insurance that covers the costs of the insulin she needs to control her Type 1 diabetes. Since 2012, she's noticed the price she must pay out-of-pocket has increased steeply; it's been a big enough leap that even the pharmacists pause in their work when filling her order. "Everyone was just stunned and they would just stand and stare at me," Clark says.

She knows many other people with diabetes that are in the same situation, especially those who use long-acting insulin like Lantus. She says she can't afford pump therapy and she has cut out all other expenses, including doctor's visits and dental care, to keep up with the cost of insulin.

"We do without everything. There will be diabetics who will go without insulin and they can't," Clark says. "You won't make it."

FierceBiotech
THE BIOTECH INDUSTRY'S DAILY MONITOR

Topics: Biosimilars

Merck takes aim at Sanofi with a Lantus biosimilar of its own

February 10, 2014 | By Damian Garde

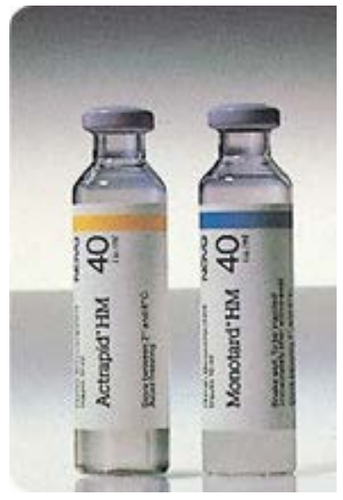
Sanofi ($SNY) and its top-selling Lantus may have bought some time last month with a legal wrench in Eli Lilly's ($LLY) spokes, but now Merck ($MRK) has bulldozed its way into the conversation with plans to kick off late-stage studies for its own knockoff of the blockbuster drug, further complicating an already heated fight.

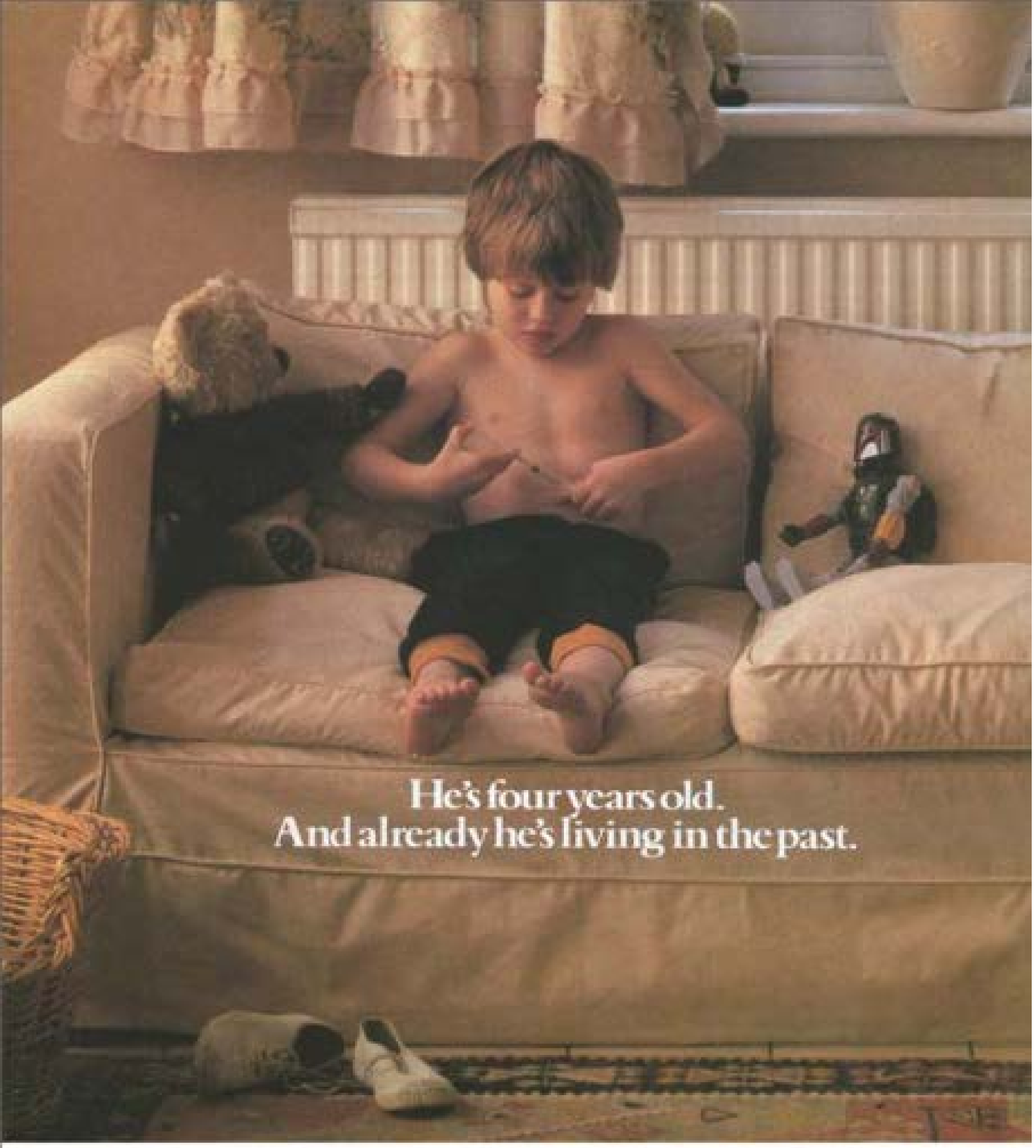
Under an expanded agreement with Samsung Bioepis, a joint venture between the South Korean giant and Biogen Idec ($BIIB), Merck plans to develop MK-1293, an insulin glargine candidate that, much like Lantus, provides long-acting relief for patients with Types 1 and 2 diabetes. The pair said it plans to get started on Phase III trials for MK-1293 soon, but a Merck spokeswoman declined to provide a more detailed timeline of the drug's development path.

Merck's entré further complicates the battle over Lantus, a drug whose sales grew 20% last year to bring in about $7.8 billion for Sanofi. The French drugmaker's patent doesn't expire until 2015, but the promise of a blockbuster biosimilar has competitors queuing up to take a shot. Eli Lilly appeared to be first in line as it raced to the FDA with its Lantus generic, but Sanofi's January patent infringement suit triggered a 30-month FDA delay that will likely put off Lilly's launch well into 2016. And that could be the break Sanofi needs to polish up Lantus' successor, the promising U300, and pull off a seamless transition.

making old drugs new:
Novo insulins in the 20th c.

1920s 1940s 1960s 1980s 2000s





In 1982 a new form of insulin was launched on the U.K. market.

Humulin. It's outstandingly pure.[1] And it's a less immunogenic form of insulin than that which comes from the pancreas of pigs and cattle.[2]

Hence it produces fewer antibodies.[2] Basically, Humulin uses genetic engineering and the techniques of recombinant DNA technology as the method of manufacture.

Which means it can be produced economically and in large quantities for years to come.

In spite of this, however, many young diabetics like Matthew are still being prescribed purified pork insulin.

Why? We don't really know. But what we do know is that the future is likely to see all patients on human insulin.

So why shouldn't they be prescribed it now? After all, it's available in a variety of formulations to suit differing needs.

Humulin

Human Insulin (crb)

THE HUMAN WAY TO TREAT DIABETES

the use and abuse of history in present-day pharmaceutical policy

other old drugs made new

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Perspective

Incentives for Drug Development — The Curious Case of Colchicine

Aaron S. Kesselheim, M.D., J.D., and Daniel H. Solomon, M.D., M.P.H.

N Engl J Med 2010; 362:2045-2047 | June 3, 2010 | DOI: 10.1056/NEJMp1003126

In July 2009, the Food and Drug Administration (FDA) officially announced what physicians have long known — that the drug colchicine can effectively treat acute flares of gouty arthritis. The plant from which colchicine is derived was first used as a therapeutic agent for gout more than 3000 years ago in ancient Greece, and the tablet form has been widely available as a generic prescription drug in the United States since the 19th century. On the basis of evidence that had built up over the years, numerous consensus guidelines recommended colchicine as an effective second-line treatment for gout — for example, in patients who had adverse effects from nonsteroidal antiinflammatory drugs.[1]

It came as a surprise to many patients and physicians that the FDA not only approved the new version of colchicine (Colcrys) but also granted the manufacturer, Philadelphia-based URL Pharma, 3 years of market exclusivity for this ancient drug. The possibility of such an exclusivity period arose because colchicine, despite its longevity, had never been officially approved by the FDA for a particular indication. The 1938 Food, Drug, and Cosmetic Act required that all new drugs be approved by the FDA for safety before being introduced on the market, but it allowed drugs that were already on the market to remain available. Starting in the 1960s, the FDA began to evaluate the safety and efficacy of older drugs, looking first at drugs that might pose the greatest threat to public health or that appeared to lack effectiveness. Colchicine was one of a number of drugs that the FDA never formally evaluated, although the agency did review and approve a combination pill containing colchicine and probenecid (Col-Probenecid, Watson Laboratories) for use in gout.

Mother Jones

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Here's Why Your Asthma Inhaler Costs So Damn Much

—By ***Kevin Drum*** | Wed Oct. 16, 2013 12:58 PM EDT

Dr. Russell Saunders is pissed off:

> As I'm sure comes as no surprise, I prescribe a lot of medications....One medication I prescribe with great frequency is albuterol, a bronchodilator. Asthma is a very common childhood illness, and one that primary care providers can often manage without consulting subspecialists.
>
> ....So I prescribe a lot of albuterol [inhalers]. Or rather, I would if they existed. Unfortunately, albuterol inhalers per se are not currently on the market. What my patients really get are prescriptions for Proventil or Ventolin or Proair. There are, at this time, precisely zero generic albuterol [inhalers] on the market.
>
> The reason why there are none on the market and thus patients (or their insurance companies, if they are blessed with good coverage) are forced to pay for the name brands is contained in this horrifying and infuriating article about pharmaceutical pricing in the *New York Times*. If it does not make your blood boil, then I congratulate you for having a more even temperament than I.

(mis)remembering Kefauver:
the FDAA Amendments of 1962

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Perspective

History of Medicine

Reform, Regulation, and Pharmaceuticals — The Kefauver–Harris Amendments at 50

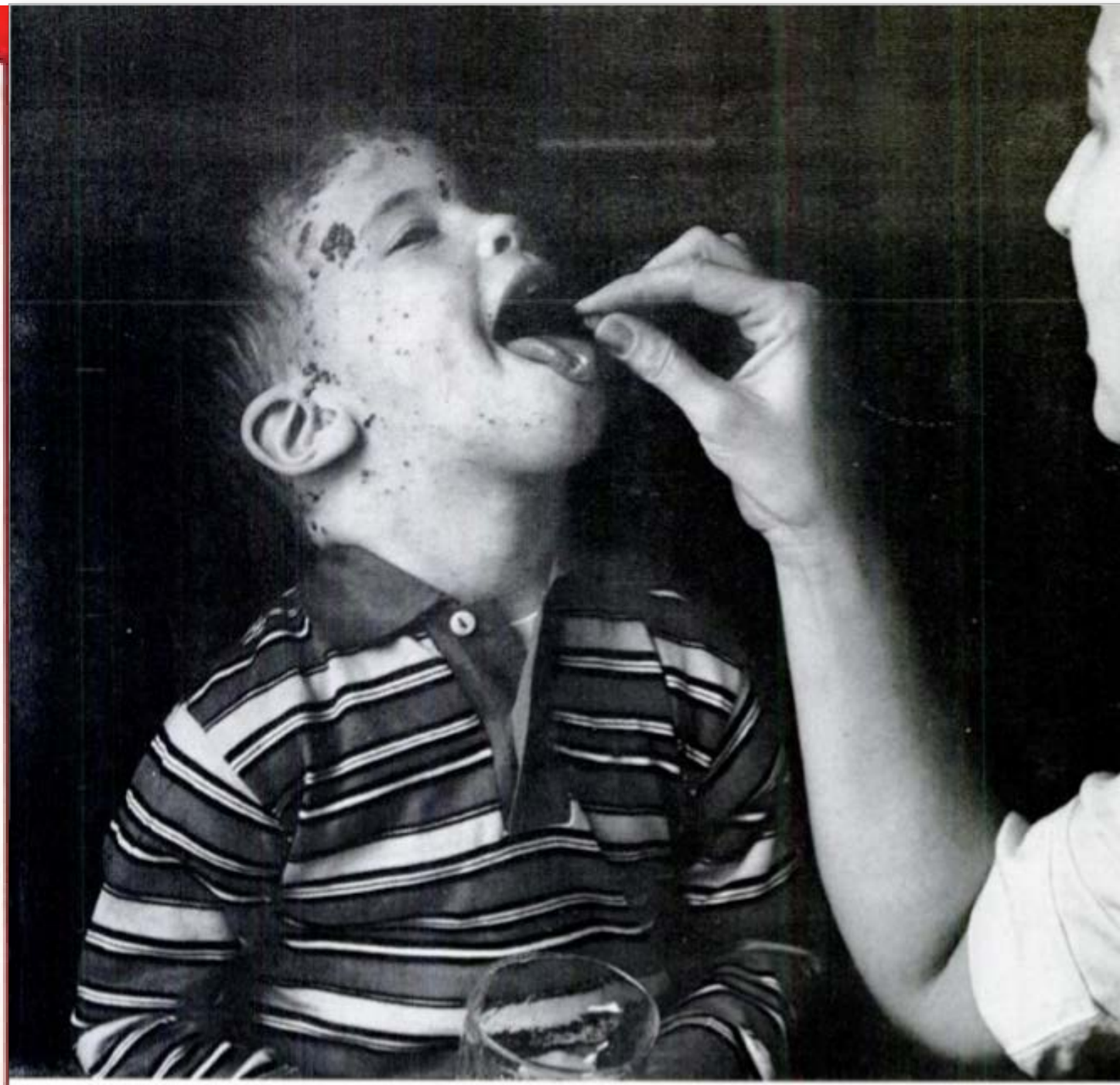
Jeremy A. Greene, M.D., Ph.D., and Scott H. Podolsky, M.D.

N Engl J Med 2012; 367:1481-1483 | October 18, 2012 | DOI: 10.1056/NEJMp1210007

Fifty years ago this month, President John F. Kennedy signed into law the Kefauver–Harris Amendments to the Federal Food, Drug, and Cosmetic Act (see photo). With the stroke of a pen, a threadbare Food and Drug Administration (FDA) was given the authority to require proof of efficacy (rather than just safety) before approving a new drug — a move that laid the groundwork for the phased system of clinical trials that has since served as the infrastructure for the production of knowledge about therapeutics in this country. We often remember the Kefauver–Harris Amendments for the thalidomide scandal

President John F. Kennedy Signing the

consumerist critique of pharmaceutical marketin



FOUR-YEAR-OLD JIMMY PORTER RECEIVES A PILL FROM MOTHER. DRUGS AND DOCTORS COST PORTERS (FIVE CHILDREN) A TENTH OF THEIR INCOME LAST YEAR

BIG PILL BILL TO SWALLOW

The wonder-drug makers get handsome profits from their captive consumers

MARKETING 7 - Pricing (Drugs)

MARKETING 7 - Pricing (drugs)