The Pol-e-Pill Finally Arrives

James A. Levine[1] and Ronald M. Davis[2]

The global obesity epidemic affects billions of people (1), and, in its wake, a worldwide epidemic of type 2 diabetes has followed (2,3). Obesity is not only associated with diabetes, of course, but also with the other partners in the X-gang: hypertension, hyperlipidemia, and cardiovascular disease (4). As exemplified in an original article in this issue of *Diabetes* (5), the link between diabetes and obesity continues to be scrutinized in detail. In the wake of this metabolic catastrophe, the ill effects of joint pain, degenerative arthritis, and sleep apnea ensue (6). A ripple of despair similarly washes over the oncology community, who now realize that the global tragedy of obesity claims cancer lives too (7–10). "But how about us?" the immunologists (11) and vascular (4) specialists cry; obesity dulls the body's response to infection, impairs wound healing, and, consequently, diminishes reproductive capacity (12).

All of this is important, but none of it matters to Keith Mitchell, who expresses his frustration to his impotent physician, "Doc, I've tried every diet on earth. Why can't you help me?" (13). Keith returns home bereft of hope to later apologize to his children, with whom he is too tired to play (14), and to his wife, whom he feels ill adept to love.

Obesity touches every aspect of society, from the economic viability of nations (15) to the look of defeat reflected in the eyes of Keith's daughter as she gazes upon her broken father (16). The obesity epidemic accounted for 27% of the increase in health care spending in the U.S. between 1987 and 2001 (17). Is it any surprise that we in the medical community feel despair at our incapacity to provide scalable real-world solutions to the 300 trillion excess calories stored in the human fuel reserve and its associated torrent of disease? (An average person with a BMI of 22 kg/m^2 has 13 kg of fat mass, and an average person with a BMI of 33 kg/m^2 has 36 kg of fat mass. The difference is 20,000 g or 180,000 kcal. With 1.5 billion [1,500,000,000] people in the world with obesity, the excess stored calories approximate 270,000,000,000,000 kcal.)

The notion of a polypill to prevent X-gang disease has been touted for a decade (18–24). The most popular variant of this concept is a tablet that people take as early as childhood to prevent the onset of metabolic diseases and even obesity itself. If such a tablet were available, clinically effective, safe, and affordable, we would run out of ink (or toner cartridges) prescribing it. Prescribing such a polypill would become the mandate of thousands of health care professionals worldwide. We would all sleep better at night, knowing that Keith was.

What would be the mode of action of such a polypill? A polypill might function via several pathways such as through molecular targets (e.g., the insulin/insulin-receptor pathways) (25), on specific tissues such as muscle and adipose (26), and/or through neuronal (26) and humeral effectors (27). Because the discovery path for a single pill with such broad-ranging targets is prolonged and exhaustive (28), a polypill that contains multiple, preexisting chemicals is a more logical approach for preventing metabolic disease and obesity.

The problem with a broadly functioning, chemically complex polypill is that side effects and multiple interactions with other medications are likely to result once global deployment has been achieved. However, like crossing the road, we must consider the benefit-to-risk ratio. Understanding that more than 5% of the U.S. population has diabetes and, for the first time in history, at least one or two of Keith's daughter's friends will develop type 2 diabetes (2,3), what safety profile should we tolerate? A few deaths sacrificed for the salvation of the many is the burden long born by federal agencies such as the Food and Drug Administration (29).

With the magnitude of obesity-associated health problems and the impact of obesity on health care costs, cogent arguments for urgent implementation of an effective polypill are easy proffered. It is therefore with delight, at the dawn of a new year, that we are able to announce the release to market of an effective Pol-e-pill. The Pol-e-pill, discovered two centuries ago (30), has been independently tested at multiple centers across the world and has been the focus of numerous publications and government reports (31–37). The Pol-e-pill's mode of action affects multiple molecular targets and it is efficacious at squelching the gang of four (diabetes, hypertension, hyperlipidemia, and cardiovascular disease) (38–41), positively affecting multiple other obesity-associated comorbidities and, when prescribed at a high enough dose, decreasing body weight (35,42–45).

The Pol-e-pill has an excellent dose-response curve (46) and a superb safety profile. At low doses, the Pol-e-pill is essentially free of side effects (although in the unwell, the low-dose Pol-e-pill needs to be carefully monitored). However, at supra-optimal doses, the Pol-e-pill does have an increased incidence of adverse effects, which can be ameliorated by decreasing the dose (47). Better still, the Pol-e-pill is not constrained through any active patents, and so its cost is low. The Pol-e-pill can be potentially prescribed across the world today.

So, it is finally here—Keith's dream—an effective "prescribe-able " solution for preventing and treating diabetes,

From the [1]Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; and the [2]Center for Health Promotion and Disease Prevention, Henry Ford Health System, Detroit, Michigan.
Corresponding author: James A. Levine, levine.james@mayo.edu.
Received 24 January 2008 and accepted 27 January 2008.
R.M.D. is president of the American Medical Association.
DOI: 10.2337/db08-0108
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obesity, and most obesity-assisted complications. The dose-response effects, safety profile, and low cost render the Pol-e-pill amenable to worldwide prescription. Check the cartridge in your Pharma-labeled pen and the toner level in your printer—Keith is on his way.

The Pol-e-pill is exercise. Prescribe it. The package insert, with details on indications and contraindications, benefits and risks, dosage and administration, supporting evidence, and additional resources for clinicians and patients, is available at http://exerciseismedicine.org/. We urge physicians to prescribe exercise just as they would a more costly tablet.

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