

A Pill for All by the Year 2000?¹

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INTRODUCTION

Multiple new ways to prevent disease and promote wellness have been discovered in the past 25 years, many of which recommend that we take a pill. The implications of this increasing interest in pills to promote healthiness and to improve the quality and quantity of life have received surprisingly little attention from the public health community, but have not gone unnoticed by the public (Fig. 1).

About 50 years ago the U.S. Public Health Service began to talk about promoting health, replacing an exclusive focus on preventing disease. A 1941 article in *Fortune* magazine [1] described the multiple tasks of public health and preventive medicine, noting that the entire 1941 U.S. prevention budget was only 34 million dollars. This was 1% of the national budget on health care; the percentage seems sadly familiar.

Health promotion apparently began in earnest during the Second World War when the U.S. Public Health Service promoted an emphasis on individual effort to be as healthy as possible, in order to be ready should we be needed in the trenches or on the home front. Thus, war provided a patriotic incentive for the concept that the individual should make proactive choices for healthy behaviors in order to maximize ability and capacity.

After the War, personal responsibility for health was the theme of increasing public education and awareness campaigns led by volunteer organizations and the public health sector. The shift from a public health preoccupied with infectious diseases following the introduction of immunizations and antibiotics to one also committed to chronic diseases played a role in increasing the focus

on each individual's responsibility for his or her own health.

In the past 10 years, we have seen a proliferation of mass marketing of health promotion—including prescription and nonprescription medications—directly to the public. Today most U.S. magazines and many newspapers include full-page advertisements discussing diseases about which men and women need to ask their doctor or pharmacist. The direct-to-public advertising typically contains two pages of color—and one page of black and white fine print, unlikely to be read by most readers, which contains contraindications and warnings. Since 1997, when the FDA relaxed the rules about prescription drug advertising on television and radio, the drug industry spent more on direct appeals to the public than it spent on advertising in medical journals [2]. According to Nancy Dickey, President of the American Medical Association, as quoted in the *Wall Street Journal* [3], “Consumer education leads to some oversimplification. There’s a difference between an educated patient and a patient who has been sold a medication. . . .”

Pills for health represents a paradigm shift in health promotion. This shift has been facilitated by managed care. As health maintenance plans allow less and less time to talk to a patient, it is faster and easier to prescribe a pill. Dr. Dickey noted [3] that advertisements may convince patients to ask for drugs they don’t need, which consumes the already limited time the physician could otherwise have used for education or prevention.

PILLS VERSUS A HEALTHY DIET

Today’s public health education can be illustrated by the food pyramid (which has not changed, although the foods move around in it periodically). The public health message to help individuals toward a more healthy diet has been coupled with important policy changes such as food labeling.

The problem with the desirable focus on a healthy diet can be observed in any typical California “natural food store,” where there are more pills than fresh fruits

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DRUG-FREE AMERICA

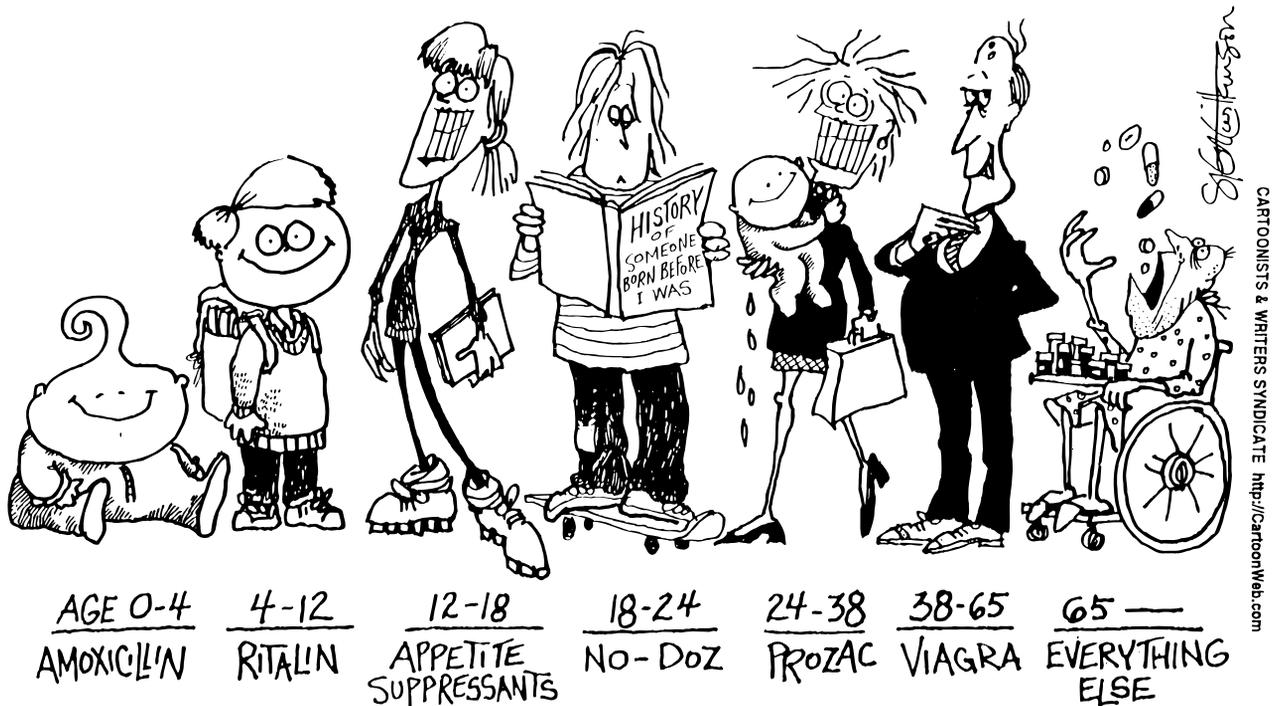


FIG. 1. Reproduced by permission of the publisher and courtesy of Signe Wilkinson/CWS.

and vegetables. Pills are where the money is. Although the health claims that can be made on nutraceuticals are limited, little booklets that tell you what these pills will prevent or cure are available in close proximity. These books do not always make excessive claims, but tend to be selective in the studies cited.

For example, one monograph on the benefits of β -carotene supplements describes the epidemiologic studies showing less cancer or heart disease in people who consume more β -carotene-rich foods—and fails to mention the clinical trials reporting that β -carotene supplements are not associated with reduced cancer risk. They rarely quote a Finnish study of more than 25,000 smokers who were randomly assigned to tablets of vitamin E, β -carotene, or placebo: more lung cancer was seen in men assigned to β -carotene than in the control group, and vitamin E, while not harmful, was also not associated with benefit [4].

The promotion of β -carotene for health was based on its role as an antioxidant, but β -carotene has many other biologically interesting effects, which could have been lost in processing. Perhaps that is the reason why β -carotene is not beneficial as a supplement. Or perhaps we are giving the wrong dose or the wrong isomer. It

is possible that the pill has not replicated another more important beneficial nutrient in β -carotene-rich food or that β -carotene is biologically available only in the context of the total food. For example, lycopene, a more powerful antioxidant than β -carotene, illustrates the value of food versus an isolated antioxidant. If you eat lycopene-rich tomatoes by themselves, you cannot absorb lycopene. For lycopene absorption, the tomatoes must be eaten with fat, such as olive oil or cheese. (Pizza is a health food?)

There is also concern that high-dose supplements may interfere with the action of medications. In two studies reviewed elsewhere [5], probucol, a powerful antioxidant and lipid-lowering medication, significantly reduced restenosis after angioplasty. The addition of vitamins C and E, and β -carotene, completely eliminated probucol's beneficial effect on coronary arteries.

These epidemiologic studies suggest that food, not pills, is the preventative of choice. Supplements make expensive urine, and they may be harmful. So why do we not just recommend the foods that these nutrients come from? What a creative idea, but not sexy enough

or financially rewarding enough to have captured much of the public's attention.

In a few instances, however, the scientific literature does support the concept that diet alone may not be sufficient. In a recent paper on the prevention of heart disease, Omenn et al. [6] discuss the relation of circulating folate levels and hyperhomocysteinemia and note that the bioavailability of folic acid from the usual conjugated folates in the diet is one-half that found in supplements and that 14 intervention studies showed substantial decreases in the average level of hyperhomocysteinemia after the administration of from 650 to 10,000 μg of supplemental folic acid. These data can be interpreted to mean that an amount of folic acid not easily obtained by diet is necessary to reduce the risk of heart disease [7]. One wonders if this would be true in populations consuming a nonatherogenic diet?

After a long and frustrating history, it is now appreciated that we need clinical trials of foods, not just pills. Recent exciting studies of diet changes show health benefits without pills. One excellent example is the Dietary Approaches to Stop Hypertension (DASH) study [8], a double-blind placebo-controlled study of men and women who had "mild hypertension" of the type sometimes ignored by doctors. Subjects were randomly assigned to placebo, to increased fruits and vegetables alone, or to increased fruits and vegetables plus decreased saturated fat (mainly decreased dairy products). Over the 8-week intervention, the placebo group had no change in systolic or diastolic blood pressure; there was an intermediate fall in blood pressure in the group assigned to increased fruits and vegetables and a dramatic fall in blood pressure in the group assigned to more fruits and vegetables plus fewer dairy products. This was accomplished without weight loss (and without any significant change in sodium intake, based on urine sodium analyses). The observed magnitude of blood pressure change would be expected to reduce the stroke rate by 27%. This approach, as opposed to pills, has the potential to shift the population distribution of blood pressure downward, potentially reducing the number of individuals who would need antihypertensive pills. Had this observation been based on a medication, full-page advertisements by the sponsors would have followed. In this case, DASH had 15 minutes of media attention and was soon forgotten.

HORMONE DEFICIENCIES

Preoccupation with health-promoting supplements is not limited to nutraceuticals. "Hormone deficiency" is another hot topic. A popular position states that "Estrogen is a must for every woman over 50." (The postmenopausal female has been pictured on the cover of *Newsweek* as a dead tree with only a few leaves left on it.)

Until recently, the major rationale for long-term estrogen use was the prevention of heart disease, the most common cause of death among older women [9]. The medical community has not yet recovered from its disbelief when the first large randomized double-blind placebo-controlled clinical trial, Heart and Estrogen/Progestin Replacement Study (HERS) [10], showed no reduction in the risk of a new coronary event when women with documented coronary heart disease were treated with Prempro. In fact, hormone therapy in HERS women was associated with a significantly increased risk of coronary heart disease during the first year of treatment.

Estrogen therapy is not entirely innocuous in other respects. Reanalyses of data from 51 studies confirmed a 30% increased risk of breast cancer among women who took postmenopausal estrogen for more than 5 years [11]. Women assigned to the estrogen plus progestin regimen in HERS experienced the same increased risk reported in the reanalysis, although the difference was not statistically significant [10].

Older women's health is a major issue because the number of elderly women is increasing worldwide. In the United States, as in much of the world, women live one-half their adult lives after the menopause. And there is significant scope for improving the health of older women. So many old women equals an ideal pharmaceutical market. Industry will continue to develop new and improved prevention pills for older women. Some of these new medications designed to promote health are very exciting, but at the same time raise critical questions about who should get what pill, what will the risk-benefit ratios be, and can any country afford to treat all healthy older women in an effort to prevent conditions they may never get (or not get until they are in their 80's)?

For example, the decision not to treat (nearly) all postmenopausal women will be very difficult if the new medications called selective estrogen receptor modulators (SERMs) are as promising as they seem. One commercially available SERM, Evista, appears to prevent fractures and breast cancer [12]. Assuming there are no major postmarketing surprises, how will we decide who should have this pill? And who will pay for it?

Although most interest in hormones and health has focused on postmenopausal "estrogen-deficient" women, the male decrease in testosterone and DHEAS levels—often beginning by age 35 [13]—also has attracted increasing attention. Testosterone replacement is now possible by injection, pills, or patches. Should asymptomatic men with testosterone levels that are "a little low" be treated with a little testosterone? Most of us would probably say no and cite concerns about prostate cancer. But an article in my son's exercise magazine called "My month on DHEA" was written by a

man about 30 years of age who said he “felt a lot better” while taking this over-the-counter hormone.

As the population has aged, “anti-aging” has become the new buzz word for health promotion. There is even a medical journal with this title. In our local newspaper there are regular advertisements for anti-aging pills, including human growth hormone, DHEA, testosterone, pregnenolone, and melatonin—all recommended to restore or exceed youthful levels. What would a youthful level of pregnenolone do for you? Self-medication with “natural” hormones is probably more excessive in California than in other parts of this country, but there are many seniors all over the country who are medicating themselves with “natural” hormones that can be purchased without a prescription.

SANITY AND SEX PILLS

Mood-elevating drugs are another category of potential pills for all. One book review from *The New Republic* [14] refers to the wave of pharmacotherapy for “cosmetic mental attitudes.” Prozac has been called plastic surgery for the personality. For everyone who has been upset that his or her grant was not funded, paper was not accepted, or child did not get into Harvard, there are now pills for coping. These pills can perform miracles for the truly depressed. This is good. But should they be used for ordinary, appropriate sadness, even grief? If we can make people feel good all the time with pharmacology, what will be the price to pay?

I recall a 1969 advertisement in a prominent medical journal which essentially recommended the treatment of all unhappy housewives, offering a daytime sedative for everyday situational distress. The text of another advertisement from this era (showing a male physician taking a woman’s pulse) read “Whatever the diagnosis: Librium!” Some of us are worried that this philosophy is coming back.

It must be admitted that the introduction of some of these new pills has yielded nonmedicinal benefits. The availability of effective medication for depression helped to destigmatize mental illness, just as the availability of Viagra brought the high frequency of erectile dysfunction out of the closet. At the same time, Viagra highlights issues of appropriate and cost-effective therapy, as illustrated by the well-publicized request by a 70-year-old man for 30 pills, as a 1-week supply.

ROSE’S RULES

No thoughts on prevention pills would be complete without recalling some of Rose’s Rules for Prevention (Table 1) [15]. One of the late Geoffrey Rose’s many pithy observations was that appropriate recommendations for health can be made without clinical trials only when the recommendation is for a return to the “evolutionary norm”—such as not smoking, exercising more,

TABLE 1

Rose’s Rules of Primary Prevention^a

1. No trial is necessary when the intervention follows the evolutionary norm (e.g., exercise, low-fat diet, not smoking).
2. When the risk of the disease is low, then a small risk of intervention may be too large.
3. A randomized controlled trial is necessary to establish a risk–benefit ratio when the intervention is a drug.

^a Reproduced, by permission of the publisher, from Ref. [15].

and eating less animal fat and less salt and more fruits, vegetables, and fiber. A pill is not a return to the evolutionary norm. Rose also pointed out that most people who receive preventive treatment will not benefit, because most people will not get the disease they are trying to prevent. It follows that the lower the individual’s risk of the disease to be prevented, the more unacceptable is any small increased risk. This last is Rose’s prevention paradox.

Do not misunderstand me. I do not want to go back to the days before medicine. I am worrying about preventive medication for almost everyone.

THE HIGH-RISK STRATEGY

Because pill prevention for everyone is not affordable nor necessarily safe, many prevention practitioners believe that it is more logical to provide pills for prevention only to the high-risk group. This is *not* as simple a solution as it appears. How do we define high risk? There is a cost of screening that even the United States may not be able to afford. There is also the problem of labeling. It has been said that screening makes happy people into patients; an individual labeled with hypercholesterolemia may become hypochondriacal. Alternatively, someone labeled with a good cholesterol may go soon and often to a fast-food restaurant for a high-salt saturated-fat meal—not realizing this is *not* a healthy diet for overall health, independent of blood cholesterol levels.

Recently it has been suggested by a respected physician–scientist that the screening process should be extended to include the genotype [16]. In the not-too-distant future, we will each have a complete genotype on a credit card; one swipe and, theoretically, we and our health care provider will know which pills we should take. I am not certain this advance will have a favorable impact on the public health, but we need to be prepared: respected scientists are eagerly anticipating extending—and possibly restricting—the screening process to include the genotype.

One big recent change in the high-risk screening approach has been persuading the public to demand that doctors do what preventionists [17] say they should do. Now that we have data to show benefit, we have been

making the public aware of their risk status. When physicians were slow to treat mild hypertension or to measure their patients' cholesterol, industry and government joined forces in an effective public education program. The Hypertension Detection and Follow-up Program led to the "Know your blood pressure" campaign and the Lipid Research Clinic Coronary Primary Prevention Trial led to the "Know your cholesterol" campaign. Recently, we have added the "Know your blood sugar" campaign and the "Ask your doctor about osteoporosis" campaign.

The fine line between public education and public anxiety has been noted recently by Dave Barry, who wrote "Television has become infested with commercials for drugs that we're supposed to ask our doctors about. Usually the announcer says something scary like, 'If you're one of the 337 million people who suffer from parabolical distabulation of the frenulum, ask your doctor about Varvacron.' . . . At that point, you're thinking, 'Gosh, I better get some Varvacron!' Then the announcer tells you the side effects [18]."

The high-risk approach has almost certainly saved lives and preserved health. Nevertheless, the high-risk approach has serious problems for public health promotion. One obvious problem is cost: we cannot afford to screen everyone for everything. Screening for blood pressure, cholesterol, and even glucose could be affordable in affluent countries, but treating everyone to healthy levels is expensive, and even if it were free, it would not necessarily follow. It is even more expensive to test for other common "screenable" diseases such as osteoporosis: the only good way to diagnose low bone density, the strongest risk factor for osteoporotic fractures, is a bone scan. Even in European countries with money and socialized medicine, only 30% of all women can have a fully paid bone scan [19]. So, it is not going to be easy to screen everyone.

Another problem with the high-risk approach is that most disease does not occur in the high-risk group, because most people are not in the high-risk group. Only a population-based strategy has the potential to shift the entire distribution of risk factors in a healthier direction. For example, as reviewed by Whelton et al. [20], blood pressure treatment cannot control the risk of blood pressure-related cardiovascular disease for three reasons: (1) not all patients who visit a health care provider after their hypertension is detected will have their blood pressure treated and controlled, (2) even those who are treated well are likely to have a higher risk of cardiovascular disease than their untreated counterparts, and (3) treatment of persons with hypertension has no effect on the cardiovascular disease risk among persons with normotensive blood pressure "in the normal range"—who account for 30–40% of the total population burden of blood pressure-related cardiovascular disease.

Finally, a pill is too easy: it circumvents the clinician's need to look at and listen to the whole patient. It is much easier to give a pill, and the patient expects it. The health management organizations must also expect it; a pill is much more compatible with the 10-minute "encounter" than counseling. The cover of a little book by Poulter et al. [21] illustrates this point. As shown in Fig. 2, the physician is giving his hypertensive patient a prescription, but has not noticed that his patient is very overweight and is smoking and drinking.

As shown in Table 2, based on the National Ambulatory Medical Care Survey in the United States, less than half of the surveyed patients reported receiving any counseling on diet or exercise [22]. According to this survey, physical activity, diet, and weight control were more often promoted by cardiologists than by generalists, internists, or family medicine doctors. Then, the horse is out of the barn: most people do not have a cardiologist until *after* they have heart disease.

The effectiveness of counseling is limited by the amount of time available to spend by the health care provider and by his/her ability as a counselor. In a recent (unpublished) survey, physicians were asked what

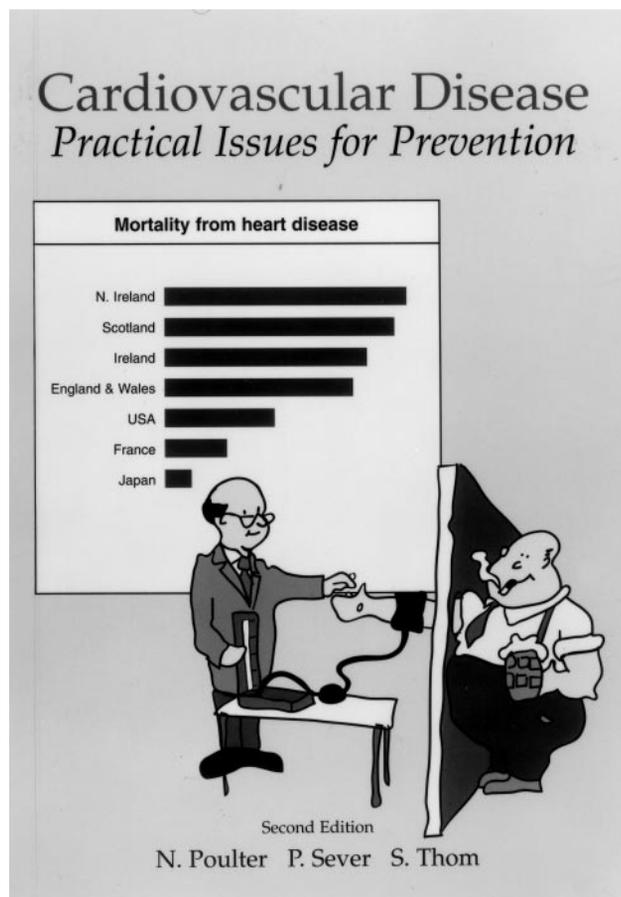


FIG. 2. Reproduced, by permission, from Ref. [21].

TABLE 2

Number and Percentage of Persons Who Attended General Medical/Gynecologic Visits That Included Counseling for Prevention of Cardiovascular Disease, by Selected Characteristics—United States, National Ambulatory Medical Care Survey, 1995 [21]

Characteristic	Estimated No. of visits ^a	Subject of counseling					
		Physical activity		Diet		Wt reduction	
		%	(95% CI) ^b	%	(95% CI)	%	(95% CI)
Age group (years)							
20–34	6.9	18.9	(±6.4%)	20.1	(±6.6%)	7.9 ^c	(±4.4%)
35–49	10.3	15.9	(±4.9%)	17.7	(±5.1%)	10.5	(±4.1%)
50–64	9.8	23.8	(±5.9%)	29.5	(±6.3%)	15.1	(±4.9%)
≥65	13.0	18.2	(±4.6%)	23.2	(±5.0%)	8.0	(±3.2%)
Sex							
Men	11.8	23.0	(±5.3%)	26.6	(±5.5%)	12.0	(±4.1%)
Women	28.2	17.5	(±3.1%)	21.2	(±3.3%)	9.7	(±2.4%)
Race/ethnicity ^d							
White, non-Hispanic	34.4	19.7	(±2.9%)	23.1	(±3.1%)	10.3	(±2.2%)
Black, non-Hispanic	3.7	13.0 ^c	(±7.8%)	21.5	(±9.2%)	10.9 ^c	(±7.0%)
Hispanic	1.9	19.9 ^c	(±12.6%)	20.3 ^c	(±12.7%)	11.9 ^c	(±10.2%)
Region ^e							
Northeast	9.4	20.2	(±5.6%)	23.2	(±5.9%)	10.2	(±4.3%)
Midwest	9.7	22.3	(±5.8%)	25.7	(±6.0%)	14.4	(±4.8%)
South	12.6	14.3	(±4.2%)	15.7	(±4.4%)	5.8	(±2.8%)
West	8.3	21.4	(±6.1%)	29.7	(±6.8%)	12.9	(±5.0%)
Total	40.0	19.1	(±2.7%)	22.8	(±2.9%)	10.4	(±2.1%)

^a In millions.

^b Confidence interval.

^c Estimates should be interpreted with caution because the relative standard error is ≥30%.

^d Numbers for other racial/ethnic groups were too small for meaningful analysis.

^e Northeast—Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; Midwest—Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; South—Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia; and West—Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, Oregon, Utah, Washington, and Wyoming.

they most wanted to know about the treatment of hyperlipidemia; the most commonly identified need, by far, was how to get patients to improve their lifestyle. (The second most commonly identified need was how to get patients to take their pills.) These physicians recognized compliance as a far more problematical issue than the choice of drug regimens.

As Martha Hull noted in her 1997 presidential address to The American Heart Association [23], the gap between what we know and what we do is large. “Closing the gap calls for translation of research not only from the bench to the bedside, but from the hospital to the ambulatory care center and into the home and community. While we anticipate the role of genetics in prevention and treatment, we must tap all available talent to improve health behavior in the information age. This will require the same support, commitment, and enthusiasm given to biomedical research.”

EXERCISE: AN EXAMPLE

One of the Year 2000's health objectives was to increase to at least 50% the number of primary care physicians who routinely assess and counsel their patients

regarding physical activity [24]. The Preventive Services Task Force says that all doctors should counsel patients with regard to regular physical activity [25].

Limited physical activity is the behavior we know the least about changing, and it may be the only common health-related attribute that is not at least partly correctable with a pill. In a recent clinical trial, exercise plus a National Cholesterol Education Step 2 diet significantly reduced LDL cholesterol among both men and women, but there was no significant improvement in the diet-only group, compared with the controls [26]. The pharmaceutical industry is not marketing physical activity, and public health professionals have not partnered as effectively as we should with the makers of workout videos, treadmills, gyms, and exercise-appropriate clothes and shoes.

Data showing that counseling is useful and feasible comes from the Physician-Based Assessment and Counseling for Exercise (PACE) study [27]. This clinical trial was based on two premises: that physicians can be helped to improve their exercise counseling and that education is not enough because even sedentary people

know that they should exercise. Behavioral intervention must accomplish more than teaching people what they already know. In PACE, counseling was provided in less than 5 minutes by 70% of providers, and most patients reported following the recommendations given [28].

PACE trained physicians to fill out an activity level assessment that asked the patient whether he or she was interested in exercising. If the patient said no, the doctor said, "Well, I think you should think about it. We'll talk about it next time." No time was wasted on the patient who said no, but a seed was planted. Effort was focused on the patient who said, "I've been thinking about it, but I don't have time, doc." Physicians were given easy-to-use materials including a diary for the patient. In the program evaluation, some doctors' offices offered this intervention, others did not; physicians and office staff followed 212 sedentary primary care patients using this protocol. The intervention patients received PACE counseling and a 2-week booster call; they were assessed before and 4 to 6 weeks after the office visit. The intervention group did better on number of minutes walked per week by report or by Caltrac (an activity monitor used to validate self-reported exercise) [29].

The PACE study showed that we can effectively change patient behavior, if we get the right message to the right patient. Instead of being frustrated by talking to patients who are not even in the contemplative stage of behavior change, we should focus on the ones who might change.

Peer pressure is with us. The more people who are exercising, the more normal it looks. When I grew up, if an adult was seen running down the streets of San Francisco, a policeman would have assumed he had stolen something and would have arrested him. Now, running is an acceptable behavior.

QUESTIONS OF COSTS AND PRIORITIES

One of the important questions raised by the new paradigm of universal pill use is: "When is an unhealthy behavior a response to social ills?" Some would say that drug use and smoking and a sedentary TV addiction are symptoms of a depressed, unhappy, disaffiliated child or adult, and public health should work on societal ills. I agree that the big solutions will require political will and know-how by legislators who have been educated by an articulate public health team. But an emphasis on societal ills does not make individual health promotion unimportant, only much more difficult. Public education about healthy behaviors should not be restricted to the educated and affluent. We do have strategies other than pills. There are published, documented methods to help with issues of smoking cessation, healthy diet, physical activity, alcohol, and seat

belts. There are complementary public health policy methods, including food labels and fortification, tobacco taxes, alcohol taxes, drunk driving laws, and seat belt laws.

Is a pill for all ever appropriate? Should everyone get vitamins, minerals, estrogen replacement, testosterone replacement, DHEAS replacement, growth hormone replacement, mood elevators, etc.? Would people feel better and be kinder and gentler—maybe not shooting each other so often—if everyone was on a mood-enhancing pill? Probably none of us would advocate universal health-promoting medication, but we might all recommend medication to delay deterioration. How different is this from health promotion? What can be achieved by taking pills without making other lifestyle changes versus making lifestyle changes without medication?

And can society afford to pay for drugs when patients are not impaired (yet), but want to improve their life or their longevity? The latter is called enhancement by the policy gurus. A recently completed 2-year study by the Hastings Center in Garrison, New York, called the Prospects of Technologies Aimed at the Enhancement of Human Capacities [30], concluded that insurers (and society) can pay for treatments but not enhancements. The treatment versus enhancement distinction reopens the question of the high-risk group; as Peter Coy put it [31] "How bad does your sexual function—or your memory, or obesity—have to be before you're considered impaired?"

With the really remarkable new drugs in development at the present time, we are on a very slippery slope in that we may soon believe that a pill, or a handful of pills, will be the answer. The issues raised above deserve more attention before "we let the genie of universal preventive prescription escape from the bottle" [32] and before we give up the last semblance of healthy behaviors based on our evolutionary norm. I do not think that would be healthy.

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