Appendix B

HOW DO WE KNOW WHAT WE KNOW: THE EVIDENCE BEHIND THE EVIDENCE

The approach of this report is to give the best evidence and advice available at this time and also to indicate where more evidence is needed. The report relies on evidence reports, consensus conferences, and governmental recommendations that have been developed through a process that reviews and evaluates all evidence in a structured, unbiased, and comprehensive manner.

It is important for clinicians and consumers to understand the origins of this evidence and advice. In fact, the evidence presented in this report has been collected and analyzed in many different ways. Some common study designs include cross-sectional longitudinal studies and randomized clinical trials. These terms, along with others that are commonly used in research, are defined in the box below.

Research Terms and Study Designs

- **Clinical trial (intervention; controlled trial):** A special kind of experimental study that tests the effectiveness of a substance or behavior (drug, diet, exercise) using consenting human subjects. The conditions of the study—selection of treatment groups, nature of interventions, management during follow-up, etc.—are specified by the investigator for the purpose of making unbiased comparisons.
- **Double-blinded:** Neither the participants nor the researchers know who receives the intervention versus the placebo.
- **Placebo:** An inert or innocuous substance used especially in controlled experiments testing the efficacy of another substance.
- **Randomized:** The study participants have been assigned to receive the active intervention or placebo randomly.
- **Observational study:** A study in which the practice or factor being studied is observed in a group of participants who have voluntarily chosen to follow or not follow this practice, i.e., they are not randomly assigned.
- **Cross-sectional study:** Study participants are observed and measurements are made at one point in time.
- **Longitudinal study:** Study participants are observed and measurements made at multiple points in time.
- **Meta-analysis:** A technique in which results from several studies are combined to produce an estimate of the effect of the factor being studied.

(Fletcher et al. 1988, MedlinePlus 2004.)

The endpoints being measured in the various studies often differ. For example, although fractures due to osteoporosis are a serious threat late in life, they are not common in younger individuals. So most studies of young people focus on how much bone mass is accumulated or how much calcium is retained when the body is put under the influence of a factor such as physical activity, calcium, or vitamin D.

Since fractures are more common in older individuals, they are commonly used as an endpoint of interest in studies of this age cohort and often are studied in older populations. A common approach is to compare two groups of people with different rates of fractures to determine which characteristics of the group with low fracture rates are protective of bone health, and/or which factors in the high-fracture group put them at risk. These "observational studies" make very important contributions by generating hypotheses about risky versus protective behaviors and lifestyle practices. The Study of Osteoporotic Fractures, which began in 1987 (see box below), has followed a group of 9,904 White women age 65 and older over a period of years to collect a variety of information as they age (Cummings et al. 1995). This study is the largest and one of the most important contributors to knowledge about the risk of fracture in older women. See Table 8-1 in Chapter 8 for risk factors that were derived from the Study of Osteoporotic Fractures. In 1997, a similar study, called Mr. OS, was launched to address the gaps in knowledge about osteoporosis and fractures in men.

Observational studies have some biases, including the fact that participants are selecting what they do. As a result, these studies can only determine that certain factors (e.g., behaviors, conditions, nutrients) are associated with lower or higher risks, not that the factor causes the change in risks. To get around this problem, some factors can be tested in an even stronger experimental design call the "double-blinded randomized clinical trial" (sometimes also referred to as "controlled" or "intervention" trials). In these studies, two or more groups of individuals are randomly assigned to receive an active intervention—such as calcium supplements—or a placebo (a pill or procedure that appears the same as the active intervention, but does not contain the active treatment). In this design, neither the participants nor the scientists conducting the study know who is receiving the active substance or the placebo. When the groups are large enough, all the other characteristics of the individuals in the study can be balanced similarly across the groups, thus eliminating, or at least reducing, the chances of various biases. This makes it possible to determine the effect of the intervention much more clearly. For this reason, this type of study has been called the "gold standard" for evidence. Drugs approved by the Food and Drug Administration for the treatment of osteoporosis and the prevention of fractures go through the rigorous testing of randomized clinical trials. Lifestyle factors and behaviors are sometimes tested using this design as well. Sometimes there are gaps in the evidence because large, well-designed studies have not yet been carried out in all different age and ethnic groups and in both men and women. Nevertheless, judgments can be made by expert groups to provide the best possible advice based on consideration of all available evidence. When developing guidelines for individuals about the diagnosis, prevention, or treatment of a disease or condition like osteoporosis and fractures, these experts rate the "strength" of the evidence using a variety of factors such as the design (e.g., was it a randomized controlled clinical trial, an

observational study, or a report of a single case?), study size, and characteristics of the study population (e.g., gender, age, severity of illness). Sometimes they combine results from several studies using a technique called "meta-analysis."

It is important to remember that the scientific knowledge that fuels recommendations and public policy is built on the contributions of not only dedicated scientists, but also thousands of volunteers—men, women, and children—who decide to participate.

The Human Side of Research

It is often easy to forget that clinical research depends upon the willing participation of real people. Several important studies in the area of osteoporosis and bone health demonstrate the "human" side of research.

Camp Calcium

Camp Calcium is a unique study supported by the National Institutes of Health and conducted by the Department of Foods and Nutrition at Purdue University. Since 1990, Camp Calcium has brought together teenagers to participate in a 6-week camp in which their dietary intake of calcium is strictly controlled. Researchers also checked participants' waste and blood samples each day. The dietary calcium in the foods was varied to determine how much calcium teenagers can absorb during their most active growing period. Due to the higher incidence of osteoporosis in females, the first six camps (1990, 1993, 1996, 1997, 1999, and 2000) included only girls, with each camp designed to provide insight into a specific factor, as described below:

- Comparison of calcium metabolism in adolescents versus young adults (Wastney et al. 1996).
- Establishment of calcium requirements for teenage girls. The Food and Nutrition Board of the National Academy of Sciences used research from Camp Calcium in setting such requirements (Wastney et al. 2003).
- Effect of maturation on calcium metabolism in teenage girls.
- Effect of race on calcium metabolism (Bryant et al. 2003).
- Effect of high and low levels of sodium on calcium retention in two races (Palacios et al. 2004).
- Determination of whether higher calcium intakes can negate the negative influences of sodium.

The 2001 camp was the first to include males, with the goal of establishing calcium requirements for teenage boys.

Participants in Camp Calcium hardly think of themselves as participating in a serious and important study. The camp itself is designed to be fun, consisting of mini-sports camps led by Purdue University athletic department staff and athletes, along with field trips, movies, nutrition and health classes, and other educational opportunities. The interaction of the young people with the scientists through the camp may inspire a few to choose a career in science. Participants also get the satisfaction of knowing that they are helping in the development of important scientific findings that will have a significant impact on the health of future generations.

The Study of Osteoporotic Fractures

The SOF study began in 1986, when women over age 65 living in four different communities (Baltimore, MD; Portland, OR; Minneapolis, MN; and the Monongahela Valley outside of Pittsburgh, PA) were invited to participate in a study designed to determine the long-term impact of physical activity on osteoporotic fractures and other more general health measures, including mortality. The study has generated important findings, including recently released data indicating that women who become or stay physically active after age 65 were only half as likely as those who are sedentary to die from cardiovascular disease, cancer, or other causes during a 7-year follow-up period (Gregg et al. 2003).

These findings would not have been possible, however, were it not for the dedication of the nearly 10,000 women who signed up for SOF, many of whom are still alive and actively participating today. For as long as 17 years, the "women of SOF" have attended clinic visits, filled out questionnaires/postcards, and received home visits or phone calls from SOF staff, all with the purpose of allowing researchers to track their health status and activity levels and to conduct blood and other tests. Many who have relocated to other parts of the country still participate by filling out and sending in their questionnaires and/or by scheduling visits to the SOF clinic when they are visiting home.

Many do so out of a sense that what they are doing is important, if not for themselves, then for others. As an 87-year-old who was the 15th person to enter the SOF study noted, "I am happy to be involved in a study that will help others." Many also find participation itself to be a rewarding experience, not only because it inspires them to become more physically active, but also because the clinic visits and other activities make them feel important and appreciated. A 78-year-old participant has had such a good experience with SOF that she has joined two other studies at the same clinic.

The organizers of SOF make a concerted effort to make participants feel appreciated. For example, they provide lunches during clinic visits and give participants a framed certificate documenting their participation. These efforts have paid off, as participants routinely make sacrifices to attend their clinic visits. One participant drives over 150 miles each way to attend. Others routinely come in despite facing a variety of health problems and/or mobility limitations that confine them to a wheelchair or that require them to use a walker. Sons and daughters of participants routinely go to great lengths to help their mothers participate; one son even flew from Chicago to Pittsburgh to pick up his mother in a nursing home and take her to the SOF clinic. Participants make these sacrifices because being in SOF means something to them; one participant even left instructions that her participation in SOF be mentioned in her obituary.

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