PART II:
WHAT SKILLFUL STATITICIANS HAVE DISCOVERED

Having read Chapters 2 and 3, we understand why crucial questions must be asked whenever we encounter medical advice brought to us by an observational study or controlled experiment. Unless the answers to these questions are satisfactory, we are better off ignoring the counsel offered us. Even a single unsatisfactory response means that we cannot trust what we are being told.

But we are not alone. Many researchers and publishers are quite aware of the potential problems noted in the previous chapters. In fact, not so long ago, in an attempt to make published studies more trustworthy, the editors of some medical journals adopted a 22-item checklist of their own. Their *Consolidated Standards of Reporting Trials (CONSORT)* statement is designed to ferret out incompetent and fraudulent research associated with clinical trials, along with the often sleazy reporting of results.[1] Even more important has been the creation of the *Cochrane Collaboration* by a group of researchers who were tired of the fact that the vast majority even of published randomized controlled trials produced misleading results, which made them worse than worthless. Founded in 1993, this not-for-profit independent organization now involves over 11,500 volunteers in more than 90 countries who rigorously review (published and unpublished) health-related

randomized controlled trials as well as some observational studies. By now, over 3,000 of their *systematic reviews* can be accessed at the online Cochrane Library; they embody the current consensus on many health-related questions—derived after a comprehensive search to identify all relevant similar studies, asking the kinds of questions noted earlier in this book, and discarding the results of all studies that fail to satisfy these quality criteria. Over time, these reviews are updated and, if necessitated by superior evidence, withdrawn.[2]

The six chapters of Part II offer numerous illustrations of how this systematic-questioning approach has provided answers to a host of puzzling questions. In fact, as we peruse Chapters 4–9 and follow the work of the Cochrane collaborators and others, we are applying our newly-won skills *under supervision*. Later on, Chapters 10 and 11 will guide us, respectively, to health-related sources in print and on the Internet where we can practice statistical thinking on our own.

And note: The material found in Part II is equivalent to a random-access memory. The chapters can be read in any order. The claims examined within chapters can be read in any order. We are free to select whatever issues we find most interesting and ignore the rest.

CHAPTER 4
EXAMINING CLAIMS ABOUT PRESCRIPTION DRUGS

Preview

When your doctor prescribes a drug to relieve your anxiety, calm your stomach, control your pain, save you from leukemia, or treat an infection in your lungs, the last thing you want to worry about is heart trouble. But over one hundred commonly used drugs carry an admittedly small risk of inducing potentially dangerous reactions that can cause a patient's heart to beat out of control or, in some cases, stop altogether, resulting in sudden death.

Not so long ago, the Duke University Medical Center and the FDA joined forces to develop early warning signals for such reactions. One goal was to identify drugs that can lead to the rare but lethal heart-rhythm irregularity, called *torsades de pointes,* which is French for "twisting peaks" after the pattern on an electrocardiogram that reveals the problem. This type of heart rhythm produces essentially no effective cardiac output. An affected person feels lightheaded, dizzy, is short of breath and aware of the heart fluttering. But if an episode lasts more than about 10 seconds, it produces collapse with unconsciousness, sometimes associated with seizure activity due to brain hypoxia. If the rhythm doesn't terminate within a minute or two, death is the result; if it does terminate, the patient will generally recover consciousness quite quickly.

Such runaway heart beats were shown to be caused by the allergy pill Seldane and the heartburn remedy Propulsid, which were withdrawn from the market. But these *torsades* can also be caused by several widely used antibiotics (like Biaxin, Erythrocin, and Zagam), by most antipsychotics (like Haldol, Mellaril, Orap, Serentil, and Thorazine), by narcotic-dependence and pain-control drugs (like Dolophine, Methadose, and Orlaam), and by all sorts of other drugs (like Betapace, Cardioquin, Cordarone, Corvert, Norpace, Pacerone, Procan, Quinaglute, and Tikosyn) which, paradoxically, are supposed to control heart-rhythm disturbances!

Even the anti-anginal drug Vascor, the anti-cancer (leukemia) drug Trisenox, the anti-malaria drugs Aralen and Halfan, the anti-nausea and sedative drugs Inapsine and Motilium, and the anti-pneumonia drugs Nebu-Pent and Pentam have been linked to the dangerous side effect. Other types of side effects are just as common, which should motivate us to learn all we can about the process that brings prescription drugs to the market and, even more importantly, about the ones that we consume ourselves.[1]

CHAPTER 5
SCRUTINIZING OVER-THE-COUNTER MEDICATIONS

Preview

Over-the-counter drugs can be purchased as easily as a bottle of bubble bath or a loaf of bread, but that doesn't mean they are harmless. Yet that's exactly what many people think. Why else, they ask, would such drugs be available without a prescription? Surely, someone must have tested them, must be monitoring them, and would quickly let us know if something were awry. But don't be so sure.

Consider the story of *phenylpropanolamine* or PPA, a synthetic ingredient found in all sorts of appetite suppressants, such as Dexatrim and Thinz, and also in commonly used cough or cold remedies, such as Comtrex, Contac, Coricidin, Dimetapp, and Triaminic. For decades, millions of Americans have used all sorts of products containing PPA, but recently researchers were intrigued by numerous reports describing the occurrence of *intracranial hemorrhage* after the ingestion of phenylpropanolamine products, often after their first use. The victims were mostly adolescent girls or young women between the ages of 17 and 45 years. In response to the concern aroused by these reports, the researchers collaborated with the FDA and manufacturers to undertake the *Hemorrhagic Stroke Project*, involving 702 patients and 1,376 control subjects. By late 2000, the results were in.

For women, the *odds ratio* for the association between the use of appetite suppressants containing PPA and the risk of a hemorrhagic stroke was 16.58 (with a p-value of 0.02). Rough translation: They were about 16 times more likely to get a stroke when taking such pills as when not taking them and there was only a 2% chance that this finding was a mere fluke. The corresponding ratio for the association between the first use of cough or cold remedies that contained PPA and such stroke was 3.13 (but with a p-value of 0.08). Thus, taking the drugs made a stroke 3 times more likely, but this finding had an 8% chance of being a fluke (which would make us reject the finding under the 5% rule discussed in Chapter 3). More likely than not, however, the 16.58 odds ratio measured a real phenomenon. The odds ratio being a close approximation of relative risk, this result strongly suggested that phenylpropanolamine in appetite suppressants was indeed an independent risk factor for hemorrhagic stroke in women.[1]

This chapter will show why we should not be surprised that over-the-counter drugs are far from 100% safe.

CHAPTER 6
ASSESSING MEDICAL DEVICES AND PROCEDURES

Preview

Of all forms of cancer, lung cancer is the deadliest. If you have particular reasons to fear the disease—considering your family history or long exposure to tobacco smoke, perhaps—you would wish for a screening test that can find such cancer early before it becomes untreatable. A recent study published in *The New England Journal of Medicine* seemed to provide plenty of hope by suggesting that a kind of three-dimensional chest X-ray, called *spiral computed tomography (CT) screening*, could detect most lung cancers while they were still localized and potentially curable. Before long, a Lung Cancer Alliance advertising campaign featured sports celebrities urging us all to make "the right call" and get screened.

The authors of the study had used CT scans to examine 31,567 asymptomatic persons for lung cancer, which resulted in a cancer diagnosis in 484 participants. Of these, 412 had clinical stage I lung cancer, and their 10-year survival rate was 88%. In fact, among the 302 participants with clinical stage I cancer who underwent surgical resection within 1 month after diagnosis, the 10-year survival rate was 92%. In contrast, the corresponding survival rate for U.S. lung cancer patients in general was an abysmal 10%. Concluded the authors enthusiastically: "Annual spiral CT screening can detect lung cancer that is curable."[1]

Yet a few months later, another study, published in an equally prestigious journal, *The Journal of the American Medical Association,* came to diametrically opposite conclusions, arguing that spiral CT screening didn't save lives and that asymptomatic individuals, therefore, should *not* be screened prior to a further clarification of the procedure's potential benefits and risks. The authors of the *JAMA* study had given annual CT scans to 3,246 asymptomatic current or former smokers for a number of years and treated detected nodules. Their screening diagnosed 144 individuals with lung cancer, 109 of these had a lung resection, and 38 died, but there was no evidence of a decline in the number of lung cancer deaths with screening as opposed to no screening. The reason: While CT screening increased the rate of lung cancer diagnosis 3-fold and the likelihood of a thoracic resection 10-fold, it did not reduce the risk of death from lung cancer because screening itself was positively harmful. Lung cancer is not an inexorably progressive disease. It encompasses a broad spectrum of disorders: some tumors rapidly progress to death, some advance more slowly, and others—so-called "indolent" ones—are too lazy, laid-back, lethargic, sluggish, and slothful to progress at all; they may even regress and disappear over time. CT screening

detects them all, 10 times as many cancers as regular chest X-rays do, but many of these clearly do *not* destine people to die. Yet these people are treated, whether they really need it or not, and as numerous unnecessary surgeries remove parts of lungs, 5% of affected patients die within a month. Another 20–44% experience serious complications. Biopsies and other diagnostic procedures that are performed in response to findings on a screening CT constitute another potential harm.[2]

When we think about it, we can see the problem with the two studies just noted. The first of these focused on the *survival rate* (the number alive after a specified time, such as 10 years, following diagnosis, divided by the number of diagnoses). Let us take, say, 1,000 persons considered at risk for lung cancer and *not* screen them. Following months of coughing and unexplained weight loss, some 200 of them might be diagnosed with lung cancer at age 60 and only 20 of these might be alive at age 70, making for a 10-year survival rate of 20/200 or 10%. This is the usual situation found in the U.S. population in general. But routine CT screening might diagnose the same 200 persons as early as age 50 and, even without treatment, they could be around at age 60, making for a 10-year survival rate of 200/200 or 100%! Even if most them died by age 70, the impressive survival rate associated with CT screening would falsely imply that such screening was a great help. In fact, by advancing the time of diagnosis, early CT screening creates a "lead-in bias," a mirage that draws our attention away from the ultimate outcome, which in this case is an identical rate of death.

The second study focused on the *mortality rate* (the number of deaths divided by the number studied) and compared the rates without screening or with it. In the above example, in the absence of screening, some 200 of 1,000 individuals would become symptomatic at age 60 and 180 of these would die by age 70, making for a mortality rate of 180/1,000 or 18%. With screening of all 1,000 individuals, on the other hand, all sorts of additional diagnoses would be made even at age 50, involving not only the 200 individuals noted above, but, say, an additional 400 who would never become symptomatic and would never die of lung cancer—a situation called "overdiagnosis." True enough, the biopsies and surgeries that follow on the heels of early diagnosis could easily save 20 of the 180 otherwise destined to die by age 70. But these procedures could simultaneously be killing 20 of the 400 who would never have become symptomatic at all. Altogether, the mortality rate with screening would remain at 18%!

Widespread CT screening could thus easily and dramatically increase statistical measures of *survival*, while having no effect whatsoever on measures of *mortality*! Many thoughtful observers, therefore, have quite properly concluded that *observational studies* of CT screening, such as those noted above, tell us little indeed. Only *controlled experiments*, such as the clinical trials recently initiated by European researchers and the U.S. National

Cancer Institute, will tell us whether the enthusiasm for routine CT screening is justified. [By 2009, preliminary results of the ongoing Italian *DANTE trial*, which randomized about 2,500 heavy smokers (all men; aged 60–75) to annual CT scanning or to no imaging, had shown no mortality difference between the screening and control groups. The American trial, known as the *U.S. National Lung Screening Trial*, randomized 50,000 smokers to annual screening with either chest X-rays or low-dose CT, but the results will not be in for years.] In the meantime, the American College of Chest Physicians has published new guidelines on lung cancer screening. Because CT screening is likely to detect a huge number of tiny and indolent tumors, but the end effect on mortality of such early detection and treatment is unknown, the guidelines do not recommend such screening until there is proof that the procedure actually saves lives.[3]

CHAPTER 7
APPRAISING THE VALUE OF LIFESTYLE ADVICE

Preview

Some researchers predict that human beings will soon live to be 120 or even 150 years old. But they do not attribute this likely event to future medical advances alone. Better drugs, fancier medical devices, and new surgical procedures will help, but the most important factor here, they predict, will be *lifestyle changes* that smart people will adopt. Following a healthy diet, getting regular exercise, sleeping enough, controlling body weight, reducing stress, avoiding tobacco smoke—these are the kinds of things that will lower our risk for disease and increase our ability to function independently for many more years than is currently the case.

There certainly is plenty of evidence that apart from plain luck, as embedded in our genes, what we do for ourselves can be more important than what medicine has to offer us. One recent study, for example, followed 6,500 middle-aged and elderly persons for 20 years. Compared to physically active and non-smoking individuals, the physically inactive were 40% and smokers were 56% more likely to end up in a nursing home. More impressive by far than such a single study can ever be is the comprehensive 500-page report on cancer prevention released in 2007 by the World Cancer Research Fund and the American Institute for Cancer Research. This study reviewed 7,000 research reports from a worldwide pool of 500,000 written since records began in the 1960s. It concluded that there was a strong (and presumably causal) link between *obesity and five types of cancer*, ranging from (post-menopausal) breast cancer to cancers of the colon, endometrium (womb), esophagus, kidney, and pancreas. Excess fat apparently affects the hormonal balance in the body. And some fat cells release hormones, such as estrogen, which increases the risk of breast cancer, while other fat cells, such as those around the waist, encourage the body to produce growth hormones, which increase other types of cancer risks. Thus, keeping slim is one of the best ways of preventing cancer.

True enough, lifestyle changes, like New Year's resolutions, are easier said than done. Breaking old, bad habits and adopting new, healthy ones, can be terribly difficult. Still, the authors of that landmark study had a number of suggestions for us, most notably with respect to diet and exercise: achieving a body mass index within the normal range (18.5–24.9); exercising between 30 and 60 minutes a day; severely limiting the consumption of alcohol, red meat, processed meats, and salt; drinking water rather than sugary drinks; eating plenty of fruit, vegetables, and fiber; breastfeeding exclusively for the first six months after birth; and forgetting all about fighting cancer with dietary supplements.[1]

CHAPTER 8
INVESTIGATING FOODS WE ARE TOLD TO EAT

Preview

The Greek physician Hippocrates (460–377 B.C.), who laid the foundations of scientific medicine and is traditionally (and, perhaps, inaccurately) considered the author of the oath of ethical behavior sworn by new physicians, supposedly said this: "Let thy food be thy medicine."

There are many today who agree wholeheartedly. If we just eat the right kinds of foods, they argue, we can forget about drugs. Crucial hidden substances contained in properly selected foods—antioxidants, carotenoids, enzymes, minerals, omega-3 fatty acids, phytohormones, vitamins, and thousands of other "healing nutrients"—can keep us healthy, happy, and energized. And if we *are* sick, these same substances can provide amazing health benefits and defeat virtually every symptom or disease, we are told. Thousands of nutritionists stand ready to point the way, to show us which *regular foods* can reduce our blood pressure, lower cholesterol, clean out clogged arteries, and save us from heart disease; can boost our energy, restore fading memory, relieve arthritic pain and keep the effects of aging at bay; can even help us lose weight, prevent diabetes, and defeat cancer.[1]

Thus, we are told that *spinach* can cure cataracts (the clouding of the lens that leads to vision loss) and stave off age-related macular degeneration (damage to the central area of the retina). We are told that *coconuts* contribute to the optimal functioning of the immune system and can keep the common cold and flu at bay. We are told that *asparagus* can save us from kidney stones, that *avocados* cure migraines, that *blueberries and blackberries* clear up "brain fog" and fend off Alzheimer's, and that *cranberries* act as an antibiotic and cure urinary tract infections. A host of foods, ranging from *berries, nuts, and whole grains* to *fish and shellfish* (notably anchovies, caviar, Atlantic herring or mackerel, mussels, canned or wild salmon, sardines, scallops, Rainbow trout, and tuna) are said to remove cholesterol from arteries, prevent blood clots, reverse inflammation, and ultimately prevent coronary heart disease. Meanwhile, *pistachio nuts, soybeans, and sunflower seeds* are said to alleviate diabetes, *Brazil nuts, cinnamon, and yams* to lessen menopausal symptoms, while *plums* cure anemia and *parsley* the gum disease gingivitis. And *cruciferous vegetables* (like broccoli, Brussels sprouts, cabbage, cauliflower, kale, or watercress), we are told, fight off cancer, while certain food *combinations*—tomatoes *plus* broccoli; apples and oranges *plus* blueberries; the spice turmeric *plus* yellow onions; or tomatoes *plus* olive oil—have an even more powerful synergistic cancer-fighting effect than any of these alone.

More specifically, tomatoes are said to be the weapon of choice against prostate and pancreatic cancer, cruciferous vegetables against lung cancer, garlic against stomach cancer, broccoli and flaxseed against breast cancer, basil against bladder cancer, mustard greens against colon cancer, green tea against liver cancer, onions against esophageal, oral cavity, ovarian, and throat cancers ….the list goes on. And if that isn't enough, we are urged to remember that *maple syrup* and *red wine* can stave off the aging process and make us live longer as well.

But can we believe all this good news? Unfortunately, all too many authors who dispense nutrition advice adopt the cloak of scientific authority while misunderstanding the most basic aspects of science. The claim that apples cure cancer, for example, can be traced to researchers who placed cancer cells taken from rats into a dish and killed them with high concentrations of antioxidant procyanidins taken from apples. But the response of the human body metabolizing diluted amounts of this "cancer killer" would be different and would also vary from person to person. Likewise, the claim that broccoli cures breast cancer can be traced to a laboratory study in which cancer cells sitting in glass dishes had trouble dividing and growing after being inundated with the antioxidant sulforaphane found in cruciferous vegetables.

The very fact that food advice changes over time, just like the weather, should make us suspicious. Remember cheese or eggs? At one point, they were said to be really bad for us, contributing to heart disease; more recently, they have been treated as our best friends. Assuming we are not lactose intolerant or allergic to it, cheese is now good for us and fatty cheese is to be preferred over low-fat or nonfat cheese because the latter, we are told, increases insulin output and the risk for diabetes, while the former slows the stomach emptying time, along with insulin production, which keeps the blood sugar level steady, prevents diabetes, and is ultimately good for the heart. Eggs, too, were once shunned for fear that cholesterol in the yolk promotes heart disease. But now even the American Heart Association okays the consumption of 4 eggs per week (if poached or soft-boiled and not fried or scrambled, because cholesterol exposed to heat and oxygen turns into a harmful substance). Eggs are praised for providing the highest-quality protein, along with all needed vitamins (except C), crucial minerals (like iron, selenium, and zinc), and unsaturated healthy fat—all that for a mere 75 calories that provide great energy lasting for hours.[2]

Even when nutritional advice comes to us from highly respected sources, it pays to be cautious. Consider the argument that eating plenty of fatty, omega-3-containing fish will save us from cancer. In 2005, the *Journal of the National Cancer Institute* published results from the 1-million-person *European Prospective Investigation into Cancer and Nutrition* or EPIC trial: Those who consumed less than 0.5oz of fish per day had a 40% higher relative risk of colon cancer than those who ate more than 1.75oz of fish per day. But the trial did not differentiate fatty fish from other types of fish, which makes it impossible to

assess the above argument! And a 2006 systematic review in the *Journal of the American Medical Association* of 38 similar studies published between 1966 and 2005 concluded: "A large body of literature spanning numerous cohorts from many countries and with different demographic characteristics does not provide evidence to suggest a significant association between omega-3 fatty acids and cancer incidence. Dietary supplementation with omega-3 fatty acids is unlikely to prevent cancer."[3]

What about omega-3 fatty acids and heart disease? As Harvard's Dr. Dariush Mozaffarian put it: "Among all the things in our food supply….fish is one of the most important foods you can choose for cardiovascular health." He and others suggest that eating fish twice a week reduces the risk of coronary death by over a third, presumably because fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—protect against stroke, atrial fibrillation, high blood pressure, and congestive heart failure by lowering triglycerides, preventing blood clots, and inhibiting the growth of arterial plaque. (These researchers also argue that associated dangers from toxins found in fish—notably mercury, polychlorinated biphenyls or PCBs, and dioxins that are suspected of causing neurological damage and cancer—are relatively minor and can be reduced further by consuming a variety of fish instead of a single type.)[4]

But, once again, these conclusions are far from certain. As noted in the Institute of Medicine's, *Seafood Choices: Balancing Benefits and Risks*, the claimed cardio-protective effect of fatty acids comes from observational studies, not from controlled experiments. Therefore, proof is lacking. Dr. Mozaffarian's observed 36% risk reduction in coronary death might have come from omega-3 fatty acids in fish, but it could just as well have been caused by substances that haven't even been discovered, or the fact that people who ate more fish therefore ate less red meat, or that fish eaters are systematically different from other people, because they happen to be the type of persons who eat more fruits and vegetables, exercise more, or never smoke. Thus the observed risk reduction might be explainable by any one of these confounding factors and have nothing to do with those fatty acids at all.

CHAPTER 9
CHECKING UP ON DIETARY SUPPLEMENTS

Preview

Sometimes the pamphlets that land in our mailbox bring news that seems just too good to be true. One of them may tell us about scary *free radicals*—oxygen atoms or molecules with a single unpaired electron on their outer ring—that course through our blood stream, cause oxidative damage to our cells (a cellular version of rust on a car) and, ultimately, bring us not only wrinkled skin, but cancer and chronic degenerative diseases, like Alzheimer's and heart disease. But don't despair, the pamphlet says, the existence of those radicals may be inevitable—given that it is linked not only to pollution and smoking, but to perfectly normal body metabolism and exposure to sunlight—but the dreadful consequences can be avoided with the help of *antioxidants*. They are molecules capable of slowing or preventing the harmful oxidation just referred to and they do so by mopping up free radicals before they have a chance to destroy cell membranes and genetic material buried deep within cells. To be sure, our body makes its own antioxidants, such as superoxide dismutase and other enzymes, and, through a diet rich in fruits and vegetables, we can get more antioxidants still, in the form of vitamins (like A, C, and E) or carotenoids (like beta-carotene and lycopene) or minerals (like selenium and zinc) or thousands of flavonoids, to name just a few. But the best source of these free radical hunters, our pamphlet says, comes from easily available over-the-counter *supplements*, which, of course, the creators of that pamphlet are more than willing to supply.

The power of antioxidants to hunt down free radicals, we are told, is measured on a special "oxygen radical absorbance capacity" or ORAC scale. Per 100 grams, for example, blueberries give us 2,400 ORAC units, grapes 750, kiwi fruit 602, onions 450, and eggplant 390. But to have a fighting chance against oxidative stress, our body needs at least 5,000 units per day, easily supplied by a single 400 mg dose of *Q-Vida*, a highly potent cutting-edge antioxidant derived from the Argentinean quebracho tree! Such treatment, we are told, neutralizes all the free radicals, prevents oxidative cell damage, and thereby assures us of cardiovascular health (no more damage to arterial blood vessels), vigorous brain function (no more age-related cognitive decline as brain cells die), elastic body tissues (no more damage to precious collagen), and more. In short, antioxidants are the key to health and youth. With their help, we feel younger, we look younger, and we live longer.[1]

Not to be outdone, another pamphlet urges us to consume *Essential 7*, an even more

powerful supplement. "If you consume two servings a day, your body's cells will receive up to 1.2 million ORAC units of anti-aging, anti-oxidant protection per month so that you stay young 20 to 40 years longer," it says. This massive dose of sheer goodness, we are told, will support our brain health; increase our energy and help us recover from exertion faster; balance our blood sugar and manage diabetes; inhibit cancer; lower our blood pressure, maintain healthy cholesterol levels, and prevent heart disease; help us lose weight, burn fat, and build a lean body mass; help us control stress, sleep better, relieve mood swings, and fight depression; decrease problems of menopause; give us healthier hair and skin; protect our vision; enhance our immune system, decrease thyroid problems; prevent kidney stones and osteoporosis; inhibit ulcer pain, and more.[2]

Could one ask for more? Surveys show that a majority of people take such claims on faith. But consider what happens when we pay a bit more attention to scientific evidence. Then we come across information that causes us to doubt that antioxidants are a veritable "fountain of youth." For one thing, the ORAC scale that allegedly measures how antioxidants can quench radicals, although useful in a laboratory setting—that is, in an artificial environment outside a living organism—does not predict the effects of antioxidants on humans who consume relevant foods or supplements. While *in vitro* and animal research have consistently shown antioxidant health benefits, human trials have not.[3]

In fact, we know that supplementation with potent doses of particular antioxidants—vitamin A, C, E, beta-carotene, selenium or any one of thousands of flavonoids—can achieve nothing or even do more harm than good. One systematic review of 67 randomized trials of antioxidant supplements found no evidence that they prolong life, along with strong evidence that they might shorten it. The review included almost 250,000 subjects, some healthy, others subject to various diseases. The 19 strongest studies (double-blind, with good randomization and follow-up) concluded that large doses of antioxidant pills *increased* the risk of death: 16% for vitamin A, 7% for beta carotene, and 4% for vitamin E, regardless of whether the tested subjects were ill or healthy. Concluded the authors: "Beta carotene, vitamin A and vitamin E, given singly or combined with other antioxidant supplements, significantly increase mortality." The effects of vitamin C and selenium were unclear.[4] (Interestingly, some studies have now shown that small doses of vitamin C get rid of free radicals, while large doses aid in their formation.)

Perhaps this type of result is not really surprising. Under normal circumstances, we never consume just one particular nutrient that is contained in one particular food. Nor do we consume just one type of food in isolation. More likely than not, if antioxidants do have any of the promised health benefits, they work synergistically and must be consumed by us in the form of a whole food or set of foods. Consider the 38 different antioxidants contained in the thyme plant: [5]

4-Terpineol, alanine, anethole, apigenin, ascorbic acid, beta carotene, caffeic acid, camphene, carvacrol, chlorogenic acid, chryoeriol, eriodictyol, eugenol, ferulic acid, gallic acid, gamma-terpinene isochlorogenic acid, isoeugenol, isothymonin, kaempferol, labiatic acid, lauric acid, linalyl acetate, luteolin, methionine, myrcene, myristic acid, naringenin, oleanolic acid, p-coumoric acid, p-hydroxy-benzoic acid, palmitic acid, rosmarinic acid, selenium, tannin, thymol, tryptophan, ursolic acid, vanillic acid

Then ask yourself how easy it would be to identify, say, the *one* antioxidant among them, if it exists, that has anti-cancer properties. A next to impossible task.

Or consider flavonoids of which over 6,000 have been identified so far. They perform many functions in plants: protecting them from environmental stresses, deterring with bitter taste fruit-eating animals that could harm seeds, attracting with sweet taste insects and birds during pollination, and more. And these flavonoids are ubiquitous throughout every plant; we can find them in the tender leaves of the tea plant, in the fruits of the apple tree, in the root bulbs of an onion, in every fruit and vegetable. Table 9.1 provides examples.

Table 9.1 Flavonoids in Fruits and Vegetables [6]

Flavonoid	Where Found
Anthocyanins	Blackberries, black currants, black grapes, blueberries, cherries, plums, red cabbage, rhubarb, strawberries
Flavanols	Apples, apricots, beans (green or white), blackberries, blueberries, broccoli, cherries, chocolate, cider, grapes, kale, leeks, peaches, red wine, tea (black or green), tomatoes, yellow onions
Flavanones	Citrus fruits and juices (grapefruit, lemon, orange)
Flavones	Capsicum pepper, celery, parsley, thyme
Isoflavones	Legumes, miso, soy foods (beans, flour, milk), tofu
Hydroxybenzoic acids	Blackberries, black currants, raspberries, strawberries
Hydroxycinnamic acids	Apples, artichokes, blueberries, cherries, kiwis, pears, plums, potatoes
Proanthocyanidins	Apples, avocados, bananas, beans (black, pinto, kidney), beer, chocolate, cider, cinnamon, cranberry juice, curry, grapes, Indian squash, kiwis, mangos, nectarines, nuts, pears, peaches, plums, red wine, tea

Conventional medical practitioners conclude: Even if flavonoids and all the other antioxidants did have healing qualities, rather than isolate a few of them into a powerful supplement (and possibly isolating the wrong ones), we would be wiser to stick with the real deal and just consume the foods identified in Table 9.1. More likely than not, this approach will save us from the harm that excessive supplementation might bring.

We should note, however, that the advocates of complementary and alternative medicine (CAM) who urge us to heal ourselves with dietary supplements (and all sorts of unconventional procedures as well) do not take kindly to criticism coming their way from the conventional medical establishment. For example, CAM advocates reject the notion, presumably supported by the above-named systematic review, that antioxidant supplements are ticking time bombs.[7] As they put it, this idea was backed up by "a meta-analysis of 67 studies that showed a link between the use of three types of antioxidant supplements (vitamin A, beta carotene, and vitamin E) and a slight risk of early death. Impressive, as long as you ignore the more than 400 antioxidant supplement studies in which no deaths were recorded. And these studies *were* ignored-every one of them conveniently excluded from the meta-analysis." Unfortunately for the CAM advocates, the excluded studies were ignored for a very good reason; they were methodologically flawed and totally worthless.

PART III:
WHERE TO PRACTICE OUR OWN STATISTICAL THINKING

Chapter 10: Reading Printed Materials
Chapter 11: Surfing the Internet

Having studied the chapters of Part I, we understand why crucial questions must be asked whenever someone urges us to heed the results of the latest observational study or controlled experiment. All we have to do is take the List of Eight (Chapter 2, *Observational Studies*) or the List of Twelve (Chapter 3, *Controlled Experiments*) and begin asking those questions. Unless the answers are satisfactory, we are better off ignoring the advice that is coming our way. Even a single unsatisfactory answer means that we cannot trust what is being offered us.

The six chapters of Part II have, in turn, illustrated how productive this approach can be. By asking similar types of questions, the Cochrane collaborators and other serious researchers have managed to separate truth from fantasy with respect to thousands of medical questions just like those raised in Chapters 4–9. But there is no need for us to wait passively until someone approaches us with another bit of "breakthrough medical news" or until trustworthy researchers have assessed its validity for us. We can also take an active role and *search* for relevant information about our health. When we do, the same smart questions should be asked. Chapters 10 and 11 guide us, respectively, to health-related sources in print and on the Internet that we can seek out. Having found them, we can practice *statistical thinking* on our own, assess the validity of what we find, and then make the right decisions about our health.

CHAPTER 11
SURFING THE INTERNET

Preview

Picture this: A member of your family has just been diagnosed with cancer. At your workplace, a colleague tries his best to abate your panic. He has just read, he says, he cannot remember where, about a treatment involving *mistletoe*. Yes, mistletoe, he says, incredible as it sounds, the very plant we all know so well from Christmastime. Over 30 different extracts, he says, are for sale in every European country right now, quite legally too, and Germany's social insurance system even pays for it! So it must be good.

That evening, of course, you race to your computer and start googling. Your mind is spinning. You picture the scene, many decades ago, when you sat under a mistletoe twig and stole your very first kiss, but your hands type what seems to be the most promising term for your Google search, *mistletoe and cancer*. And there you are: In precisely 0.19 seconds, your computer has surfed the Internet and offers you 322,000 websites to peruse, all of which mention or promote mistletoe as a treatment for the dreadful disease. In no time at all, you learn that mistletoe *(viscum album)* can be turned into an extract with which cancer patients can inject themselves. One preparation, called ISCADOR and produced by Weleda, is the original mistletoe medicine for cancer that was first marketed in Switzerland way back in 1917. Nowadays in Europe, you are told, mistletoe is a key component in everybody's cancer therapy. Oncologists use it in addition to conventional therapies, such as chemotherapy, radiation, and surgery.

You also learn about Rudolf Steiner who developed *anthroposophy* a century ago, an approach to healthcare based on assumed associations among four postulated dimensions of the human body (physical body, etheric body, astral body, and ego) on the one hand and plants, minerals, and the cosmos on the other. Anthroposophic drugs, like mistletoe, are based on ancient alchemistic and homeopathic notions and are to be used partly as adjuncts to and partly as substitutes for conventional medicine. Steiner's intuition that mistletoe might help treat cancer is based on the fact that mistletoe is a parasitic growth that eventually kills its host. So why not make cancer cells the host?

You learn more that that! Some 1,000 *in vitro* studies allege to have shown that the main constituents of mistletoe (alkaloids, lectins, and viscotoxins) produce anti-cancer activity, but also enhance the proliferation of some cancers. Similarly inconsistent results appear in clinical studies. Many are methodologically weak and cannot possibly pass our questioning test, but

nevertheless report positive results. And the most rigorous randomized controlled studies say the mistletoe treatment is no good. They also list a wide range of serious adverse effects: local reactions at the site of injection (subcutaneous inflammation mimicking metastatic malignancy), anaphylaxis, dyspnoea, haemorrhagic colitis, herpes simplex, herpes zoster, joint pain, kidney failure, lymphangitis, paraesthesias, sarcoidosis, ulceration, and vertigo.

Are you confused, once again? As this chapter will show, there are foolish and smart ways to surf the Internet. Try searching for "mistletoe and cancer + emedicine" and, in 0.28 seconds, you get a mere 1,430 hits. There is a reason for that.[1]

NOTES

PART II: WHAT SKILLFUL STATISTICIANS HAVE DISCOVERED

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Chapter 6: Assessing Medical Devices and Procedures

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Chapter 11: Surfing the Internet

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