The Tomato Effect

Rejection of Highly Efficacious Therapies

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THE TOMATO (Lycopersicon esculentum) is a New World plant, originally found in Peru and carried back to Spain from whence it quickly spread to Italy (pomodoro) and France, where it was known as the pomme d'amour and thought to have aphrodisiac properties (this is the first recorded confusion between the placebo effect and the tomato effect—described herein). By 1560, the tomato was becoming a staple of the continental European diet.

Of interest is that while this exotic fruit from South America (along with other novel products such as potatoes, corn, beans, cocoa, and tobacco) was revolutionizing European eating habits, at the same time it was ignored or actively shunned in North America. During the 18th century, tomatoes were not even cultivated in North America. Not until the 1800s did North Americans accept the tomato as edible; commercial cultivation of tomatoes was rare until the 20th century, although in the past eight decades the tomato has grown to become our largest commercial crop.

The reason tomatoes were not accepted until relatively recently in North America is simple: they were poisonous. Everyone knew they were poisonous, at least everyone in North America. It was obvious. Tomatoes belong to the nightshade (Solanaceae) family. The word "nightshade" is usually preceded by the word "deadly," and for good reason. The leaves and fruit of several plants in this family, for example, belladonna and mandrake, can cause death if ingested in sufficient quantity. The fact that the French and Italians were eating tomatoes in increasing quantities without seeming harm did not encourage colonial Americans to try them. It simply did not make sense to eat poisonous food. Not until 1820, when Robert Gibbon Johnson ate a tomato on the steps of the courthouse in Salem, NJ, and survived, did the people of America begin, grudgingly, we suspect, to consume tomatoes.

The previous paragraphs are meant to explain the derivation of the term "tomato effect." The tomato effect in medicine occurs when an efficacious treatment for a certain disease is ignored or rejected because it does not "make sense" in the light of accepted theories of disease mechanism and drug action. The tomato was ignored because it was clearly poisonous; it would have been foolish to eat one. In analogous fashion, there have been many therapies in the history of medicine that, while later proved highly efficacious, were at one time rejected because they did not make sense. The purpose of this article is to expand on this concept by describing three examples, all from the field of rheumatology. We contend that the tomato effect is in its own way every bit as influential in shaping modern therapeutics as the placebo effect. While the placebo effect has contributed to the enthusiastic and widespread acceptance of therapies later shown to be useless or harmful, the tomato effect has stimulated the rejection or nonrecognition of highly efficacious therapies. Recognition of the reality of the tomato effect, while not preventing future errors, may at least help us better understand our mistakes.

Colchicine

The use of colchicine for the specific treatment of acute gout attacks dates back to the fifth century. Colchicum is an extract from the corm of Colchicum autumnale, a crocuslike plant found along the eastern shores of the Mediterranean. In the fifth and sixth centuries, Christian and later Moslem physicians in Constantinople demonstrated a fair knowledge of the clinical pharmacology of such extracts—formulation, indications, dosages, and toxicity. Most medical writers of this period recommended the concomitant administration of aromatic spices to prevent the well-recognized gastrointestinal (GI) tract side effects of colchicum. During the next six centuries there were frequent references to the use of colchicum in both acute and chronic gout. Students of the medical school at Salerno, Italy, the first such school in western Europe, continued to learn how to use colchicum to treat gout during the so-called Dark Ages. After the 13th century...
centuries later.

The success of l’eau medicinale d’Husson stimulated considerable activity within the medical community. For a time the sale of this patent medicine was banned in Paris. In 1814, James Watt discovered that the active ingredient was colchicum. At about this same time the kings of England and France were both successfully treated with colchicum, which conferred regal if not scientific patronage on this treatment. The last major medical holdout was Trouseau, the French skeptic famed for his statement that we should use new remedies quickly before they lose their efficacy. Apparently he attributed the success of colchicum to the placebo effect. This is the second recorded confusion between the placebo effect and the tomato effect.

One final point about colchicum. While this treatment fell victim to the return of the holistic concepts of Hippocrates and Galen during the Renaissance, it should also be noted that the discovery of colchicum in all probability stemmed from these very same concepts. Extracts of plant bulbs and roots were frequently used by classical physicians to induce diarrhea and/or vomiting, thereby purging the body of excesses of particular humors. That one of these extracts, colchicum, had a specific therapeutic effect for a specific disease was recognized about the time when Hippocratic and Galenic thought began to be challenged by other medical systems, particularly those of the great Arabic civilization.

Gold

The discovery of the efficacy of gold therapy for rheumatoid arthritis was somewhat analogous to the discovery of colchicum treatments for gout. From 1900 until 1940, the preponderant theory of the pathogenesis of rheumatoid arthritis was that it either represented a direct infection of the joints or was a reaction to a chronic infection at another site in the body. Indeed, “chronic infectious arthritis” was a synonym for rheumatoid arthritis. The popular therapies for rheumatoid arthritis evolved directly from that theory. In 1931, Cecil wrote that “the most important single factor in the treatment of rheumatoid arthritis is the removal of foci of infection.” This meant tonsillectomy, adenoidectomy, and extraction of teeth, along with other procedures as indicated. “This demands very thorough investigation—there is no use in halfway measures.” Osler’s Modern Medicine is quoted as stating. Other popular therapies included vaccination with killed streptococci and typhoid bacilli.

The use of gold in the treatment of rheumatoid arthritis evolved directly from this infectious theory. At the end of the 19th century, Koch described the inhibition of the growth of tubercle bacillus in vitro by the salts of several heavy metals, including gold. This finding led to trials of these compounds in patients with tuberculosis, syphilis, and other chronic infectious diseases, including rheumatoid arthritis. The first reported trial of gold salts for treatment of rheumatoid arthritis was in 1927, and this was followed by a series of reports both in Europe and the United States noting favorable results with this agent. In 1945, the first double-blind, placebo-controlled trial of gold therapy produced dramatic results favoring gold therapy. Unfortunately, this favorable report coincided with the discrediting of the “infectious” theory of rheumatoid arthritis on which the rationale of gold therapy was based. All “activist” therapy based on the infectious theory was disparaged. Gold rapidly devolved from a scientific to a magical treatment. Without the support of the infectious theory, gold shots became uncomfortably reminiscent of alchemy. The next 20 years witnessed the decreasing popularity of gold therapy in the face of increasing evidence of its effectiveness. While some medical centers continued to inject gold, many ceased using it altogether during the 1950s and early 1960s. Therefore, one textbook of medicine published in 1956 does not mention gold as a therapy for rheumatoid arthritis, while the 1960 edition of the same textbook notes that “it is still being used in many medical centers.” A 1966 textbook mentions the popularity of gold compounds in the past tense. Gold started to regain its former popularity only when the medical community accepted both the evidence of gold’s efficacy and medicine’s ignorance of gold’s mechanism.
of action. The fact that gold now has an unknown mechanism of action—is a truly idiopathic medicine—is no longer an impediment to its use, because rheumatoid arthritis has become an idiopathic disease.

Aspirin

Extracts of the bark of the willow tree (Latin and salix) have been used off and on for almost three millennia for the relief of pain and fever. After the commercial production of sodium salicylate and acetylsalicylic acid started in the late 1800s, high-dose salicylate therapy (12 to 24 aspirin per day) became the treatment of choice for acute rheumatic fever. High-dose salicylate therapy is also recognized today as the initial treatment of choice for rheumatoid arthritis, but this has been the case only since the mid-1950s. At the end of the 19th century there appeared several reports showing that high-dose salicylate therapy was highly efficacious in relieving the pain, swelling, stiffness, and malaise of rheumatoid arthritis. Coincident with the discovery of the efficacy of high doses of salicylates in the treatment of rheumatoid arthritis, however, came the acceptance of the infectious theory of the disease. It did not make sense that aspirin, a pain and fever medicine, could have any real effect on a chronic infectious process. Thus, from 1900 to 1950, every major textbook of medicine and every article on the treatment of rheumatoid arthritis that we reviewed either did not mention aspirin treatment or made brief mention that low doses (eight aspirin or fewer daily) given intermittently could be a helpful adjunct in controlling pain. The only mention of high-dose aspirin therapy was in the context of a warning that one needed to watch patients carefully because of their tendency to become addicted to high doses of salicylates. By the early 1950s the infectious theory was discarded, and rheumatoid arthritis was seen as a chronic inflammatory disease of unknown origin. In this same period, experiments in rats showed aspirin to possess substantial anti-inflammatory properties in addition to analgesia and antipyresis. Starting in the mid-1950s, most textbooks and review articles recommended aspirin in doses as high as could be tolerated by patients with rheumatoid arthritis. Therefore, high doses of aspirin for rheumatoid arthritis became an accepted treatment some 70 years after the initial studies demonstrating its efficacy.

Other Tomatoes

The aforementioned discussion represents our attempt to show that colchicum, gold, and high-dose aspirin were tomatoes—efficacious medicines that were ignored or rejected for a time because their presumed mode of action did not fit the prevailing concepts of disease pathogenesis. These therapies simply did not make sense. In many cases, in rejecting these tomatoes, physicians of the time turned to various placebo trials that did make sense. Therefore, purgatives were the preponderant therapy for gout for six centuries and removal of foci of infections the major treatment for rheumatoid arthritis in the first half of the 20th century.

The status of tomatoes, like placebos, changes when they are recognized for what they are. For this reason it is difficult to identify present-day tomatoes. It would seem, however, that modern medicine is particularly vulnerable to the tomato effect. Pharmaceutical companies have increasingly turned to theoretical over practical arguments for using their drugs. Therefore, we are asked to use a new arthritis drug because it stops monocytes from crawling through a filter, a new antidepressant because it blocks re-uptake of serotonin but not norepinephrine into rat synaptosomes, a new antihypertensive because it blocks angiotensin generation, or an oral diabetes drug because it increases insulin receptors on monocytes. What gets lost in such discussions are the only three issues that matter in picking a therapy: Does it help? How toxic is it? How much does it cost? In this atmosphere we are at risk for rejecting a safe, inexpensive, effective therapy in favor of an alternative treatment perhaps less efficacious and more toxic, which is more interesting in terms of our latest views of disease pathogenesis. Such an attitude also increases the risk that we use a medication to "normalize" a laboratory value—blood glucose, uric acid, or cholesterol—regardless of whether it improves the patient's state of health and even if it increases risks for morbidity and mortality.

We will conclude this discussion by providing two examples of modern therapies amenable to the tomato effect. One may very well be a tomato; the other is probably not, but in both we can trace the dynamics that allow us to make the mistake of rejecting an efficacious treatment.

Our first example is ergoloid mesylates (Hydergine), a combination of three ergot alkaloids marketed for the treatment of mild to moderate dementia. This drug was originally introduced as a peripheral and cerebral vasodilator, its presumed mechanism of action in improving memory and modifying behavior in elderly demented patients. During the 1960s several articles appeared reporting no effect of ergoloid mesylates on cerebral blood flow. Because of these reports the use of ergoloid mesylates fell into disrepute, especially in academic medicine. This occurred despite the publication of more than 20 double-blind, placebo-controlled trials showing that ergoloid mesylate administration was indeed associated with substantial improvements in objective measurements of memory and behavior. The problem was that it seemingly did not work the way it was supposed to work; so it was rejected. We still do not know how it works. Somehow, what became important was that the drug was proved in laboratory experiments not to increase blood flow to the brain.

The other contemporary example is the use of starch blockers for obesity. A recent article reported that these agents do not increase fecal caloric content. The obvious conclusion was that starch blockers have no role in the treatment of obesity. Here we have all the elements necessary for the tomato effect. A therapy (starch blockers) is claimed to cause weight loss. It is rejected because it does not increase fecal caloric excretion. What if it does in fact cause weight loss? We may never know.

There is no reason to think that starch blockers are effective. The point of the example is to demonstrate how a drug can be rejected for reasons other than a directly demonstrated lack of efficacy. The example brings up another risk factor for the
tomato effect. If a treatment bypasses the medical establishment and is sold directly to the public, whether starch blockers, megavitamins, or l'eau d'Husson, the temptation in the medical community is to accept uncritically the first bad news that comes along.

We cannot progress in medicine without a theoretical structure. Structure by necessity limits our peripheral vision while allowing us to focus on a particular path. The benefit of such a structure far outweighs the detriment. However, we can reduce the detriment by asking, almost in ritual fashion, certain questions. Before we accept a treatment we should ask "Is this a placebo?" and before we reject a treatment we should ask "Is this a tomato?"