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Article *in* JAMA The Journal of the American Medical Association · June 1984

DOI: 10.1001/jama.251.18.2387 · Source: PubMed

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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 (pommidoro) 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.[12] 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.[1]

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.

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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 placebos 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 our 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.[17] 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.[18] 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.[19] The obvious conclusion was that starch blockers have no role in the treatment of obesity.[20] 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 indeed 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 1'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?"

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