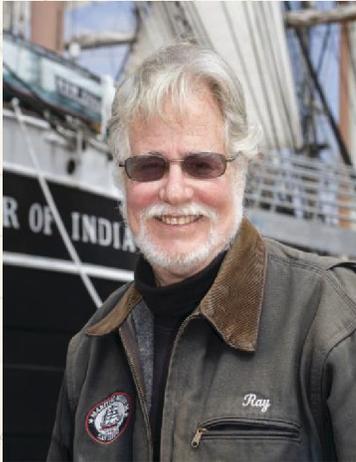


Dear Shipmates:



Raymond Ashley
Ph.D., K.C. I., President /CEO
Maritime Museum of San Diego

As I'm sure many do, I try not to look at the news too much, and also as many do with mixed success. One of the most prominent subjects you see in the news concerns the urgent search for medications and vaccines for coronavirus and the rigorous time-consuming trials necessary to ensure that they are safe and effective, *maddingly* time consuming in the midst of an emerging crisis taking an ever-larger toll. The constant background refrain grows ever louder: "why not just try everything, *anything* you think might work?"

That was once the norm after all.

Until the very first clinical trial in history.

The Dawn of Clinical Medicine

Large scale epidemics were once the common experience of humanity, but as the world was not always so closely and immediately connected as it is now many of these afflictions were more localized, hemmed in by "disease gradients" which served as barriers to vectors of contagion and prevented their emergence as pandemics. Among the most effective of these disease gradients were the oceans, until people learned how to cross even the widest of them with sailing ships, which in turn elevated the spread of a wide spectrum of epidemic disease to world changing potential. *Now* the disease gradient we live with daily has shrunk from the width of an ocean to a bare six feet of social distancing.

One epidemic disease however, was a consequence of seafaring, not the result of it: scurvy. Today, we think of scurvy as vitamin C deficiency, but until the role of vitamins became understood in the 1930's, there was no way to distinguish what effects were the result of the lack of any specific nutrient. Consequently, even though vitamin C deficiency produced the quickest and most horrific symptoms, scurvy as it once existed could be the cause of any of several dietary deficiencies or multiples of them, making isolation of cause extremely difficult. Also complicating isolation of cause, was that while we tend to think of citrus fruits as the primary sources of vitamin C and other vitamins, these nutrients can be found in lots of foods to degrees which vary over time and freshness. Thus, one could be consuming oranges, lemons, and limes and avoid scurvy at some times but not at others.

Scurvy was a serious and devastating disease which might typically begin to appear among a ship's crew after only six weeks at sea, sometimes less, and ultimately limited the time a ship might spend under way, how far it could sail with adequate strength, or if, due to the weakened state of its crew, the ship made its destination at all. To cite one of the most extreme examples, in 1740, eight men-of-war under the command of Commodore George Anson departed England for the Pacific to attack Spanish possessions and capture the Manila galleon. Though successful in fulfilling the mission, only the flagship HMS *Centurion* completed the voyage, bringing home to England just 145 of the 1,939 men who set out, most of those lost having died of scurvy. As an interesting aside, because children are less susceptible to vita-

min deficiency, especially vitamin C deficiency, by the time HMS *Centurion* fought and captured the galleon *Nuestra Senora Covadonga*, her crew was composed almost entirely of children – the original company of “lost boys.” The Spanish squadron sent out in pursuit of Anson’s expedition was itself destroyed by storms off Cape Horn – and by scurvy.

Such experiences imparted enormous urgency for European sea powers to determine a cause and remedy for the disease. The first maritime state to do so might well win the international contest for seaborne empire. The problem, however, was not only a flawed understanding of disease itself, but lack of a systematic as opposed to anecdotal method for isolating cause and cure.

During most of the eighteenth century, formal medicine favored theories of disease based on the ancient Galenic “balance” system of diagnosis, in which health was defined as a proper balance of “humors” within the body (blood, phlegm, black bile, yellow bile). Towards the end of the period, the most accepted variant of this approach was the system of Hermann Boerhaave (1668-1738) of Leyden. Commonly referred to as the “solidist” system, disease in various forms emerged as a consequence of blocked or unbalanced nervous and cardiovascular solid tissues (“fibers” or tubes) that could upset their capacity to sustain humoral balance through the circulation or flow of blood, nerve fluids, sweat, saliva, mucus, urine, excreta, etc. Various medicines and combinations of them could be prescribed to augment circulation or reestablish a proper balance of fluids, or to achieve balance by purging the body of unwanted fluids. Phlebotomy (bleeding) remained an important technique among these.

Thus, cures for scurvy tended to extrapolate from this understanding to a variety of “let’s try *this*” approaches and anecdotal reporting of the results. For instance, salt water was believed to unblock pores and promote free “insensible perspiration,” – along with various dietary supplements. Likewise bleeding to restore humoral balance was observed to work, especially if reinforced with a better dietary regimen. Purgatives, such as “Ward’s Drop and Pill” which produced violent intestinal reactions, also worked to restore balance, so it seemed, and promote recovery in those it did not kill outright. In the latter half of the century, notions of humoral balance began to be influenced by discovery of the acid to base spectrum present in many foods, and especially citrus fruits which had been widely known since medieval times to prevent scurvy (citrus fruits spoiled and rapidly lost any antiscorbutic value when carried to sea, otherwise scurvy would never have been a problem). Believing that it must be the acidic quality of citrus which restored the “acid-base” balance and prevented scurvy, popular eighteenth-century cures included ingestion of hydrochloric acid and sulphuric acid, with side effects we can well imagine.

Some remedies were more empirical still and emerged, not from medical theory, but more rudimentary assumptions. Many captains observed that victims of scurvy were extremely lethargic, and assumed that the lethargy

was itself the cause rather than the consequence of the disease. Their remedy, was to require incessant labor of patients in pumping bilges, working aloft, exposure to the elements, and when all else failed, dancing until the patient dropped. Unfortunately, these activities tended to drain what little of the vitamin remained in their system. Finally, there was the most empirical cure of all and one of the most popular. Observing that scurvy occurred mainly at sea and that many patients recovered quickly upon return to land, captains and surgeons sometimes buried their ill men up to their necks in boxes of dirt and ballast tailings, literally immersing them “in the land” as it were to bring on the desired result.

As we know now, none of these things had the slightest chance of working, but ALL of them were reported to work because some of the patients who were subjected to them recovered and among those patients and surgeons who witnessed the recovery, that anecdotal evidence provided the only explanation needed. And so, with protocol informed by anecdotal evidence in support of prevailing theory, scurvy continued to ravage the crews of ships and determine the outcome of great events. During the naval intensive Seven Years War (1759-1763) for instance, British seaman and marines killed in battle at sea numbered slightly over 1500. Seaman and marines lost to disease, mostly scurvy, numbered 133,708 - more than *twice* the strength of the entire Royal Navy of 1759. When that world war concluded there was no reason to believe that this kind of attrition would not go on forever, in every war and on every ocean of the world.

But what no one quite realized at that time was that something unlikely and profound had already happened; something that western medicine had never seen before, and which would change everything.

In 1747, during the same War of Austrian Succession that saw Anson's squadron nearly destroyed by scurvy, naval surgeon James Lind found himself posted to the 50-gun HMS *Salisbury* during a ten-week patrol in the English Channel. After only four weeks (a very early onset, possibly exacerbated by recent massive crop failures and an associated lack of fresh provisions throughout Britain and in all of her ships at sea), Lind began to see patients presenting with symptoms of scurvy. The weather had been foul so there was no opportunity to open hatches and gun ports to promote ventilation, which was thought to be a serious precursor to scurvy. On the other hand, the water supply was “fresh and sweet,” which should have offset the bad ventilation. These countering tendencies bewildered Lind and provoked him to undertake a remarkable and unprecedented experiment.

He isolated twelve of the victims “as similar as I could have them” in the same part of the ship and placed them on diets that were identical except for a few critical factors. The common fare included gruel with sugar for breakfast, either fresh mutton broth or pudding for dinner, and for supper barley and raisins, rice, currants, etc. There were six variations upon this basic regimen, each tested by two men for a period of fourteen days. The daily variations were:

1. One quart of (hard) cider.
2. Twenty-five “guts” (drops) of *elixir vitriol* (sulfuric acid) three times per day and gargle with same.
3. Two spoonful of vinegar three times per day before meals, as well as gargle and addition of vinegar to their food to acidulate it.
4. A “course” of half a pint of sea water per day.
5. An “electuary” (paste), the size of a nutmeg made up of garlic, mustard seed, balsam of Peru (resin from the tree *Myroxylon pèveirae*), dried radish root, and gum myrrh. They were to drink barley-water acidulated with tamarinds, and were occasionally given cremor tartar (potassium hydrogen tartarate) as a mild laxative. (The electuary was a pain reliever prescribed by another surgeon).
6. Two oranges and one lemon for six days: the extent of the supply.

Within six days, the two seamen who had consumed the oranges and lemons had recovered. This was not surprising; most people knew that was the best remedy if such things were available (and there certainly weren't many to be had on HMS *Salisbury*). The seamen consuming the oranges and lemons, the prevailing “standard of care,” were effectively the *control* group, at that time a completely novel concept. What was surprising was that none of the other things worked at all, even though every one of them was reported to be effective anecdotally. Those twelve sailors in HMS *Salisbury* constituted the first clinical trial in medical history. Interestingly, to this day, vitamin C remains among the most popular placebos used in modern double-blind clinical trials.

Two hundred and seventy-three years later, we anxiously tune in or log on daily seeking news of progress toward a cure for coronavirus, and every day there seems to be a new candidate promoted as the thing which will solve the problem, solve it quickly, and solve it without the interminable delays attending a true clinical trial. Because above all things, we just want this to be over.

We are all the crew of HMS *Salisbury* now.
... which is where I'll pick this up next week.

Stay below and stay safe!

Raymond E. Isley



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At *Star of India* Wharf | 1492 N. Harbor Dr., San Diego, CA 92101-3309 | sdmaritime.org

