From a pump handle to oral rehydration therapy: a model of translational research

Stanley G. Schultz

University of Texas Medical School, Houston, Texas

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Schultz SG. From a pump handle to oral rehydration therapy: a model of translational research. Adv Physiol Educ 31: 288–293, 2007; doi:10.1152/advan.00068.2007.—Few afflictions have attracted as much attention and impacted on as many societal and biomedical areas as cholera. Dr. John Snow’s studies launched the field of epidemiology, were early applications of medical cartography, and promoted the use of statistical methods in medicine. The finding that cholera was due to the ingestion of contaminated water lent to the demise of the prevalent “miasmatic theory of contagion,” set the platform for the “germ theory of disease,” and promoted the growth of public health concerns for water purification and sanitation. More recent attention to this disease led to the notion of “secretory diarrhea” and the translation of basic principles to the development of oral rehydration therapy and its “spin-offs” (Gatorade and Pedilyte). cholera; John Snow; miasma; germ theory; sodium-coupled sugar absorption; diarrhea; small intestine

THROUGHOUT ITS BRIEF RECORDED HISTORY, humankind has been visited by a number of afflictions that have grown to the levels of global pandemics and have ravaged millions of lives (10). Among them is cholera, a disease characterized by severe abdominal cramps, vomiting, profuse watery diarrhea [the Greek entymology of the word “cholera” is “like a roof gutter” (2)], and, in its most severe presentation, circulatory collapse and death. Because of these somewhat nonspecific characteristics, the precise history of cholera is uncertain. There is evidence for cholera epidemics in India as far back as 400 BCE and convincing reports of sporadic outbreaks in that subcontinent between the 15th and 19th centuries (2, 10). But, as discussed by Longmate (10) and others (2), there is little debate that the first pandemic of the disease, now referred to as Asiatic cholera, can be traced to an outbreak in August 1817 in Jessore (Jashahor), Bangladesh, a community just 70 miles from Calcutta, India, and equally distant from Dhaka, Bangladesh. Unlike previous epidemics, this outbreak soon expanded beyond national boundaries and began its ineluctable march to the southwest, spreading like an army of death beyond the borders of India into the Middle East and Russia and, by 1831, threatening every Western European capital. And, like an army, the spreading scourge paused from time to time, as if to reenergize, only to resume its deadly, devastating march. By 1832, it leapt across the Atlantic Ocean and invaded “fortress America,” following the “Indian Wars” and the “Gold Rush” as far as the west coast and claiming as many as 150,000 lives (1% of the total population of the United States at that time or the equivalent of 3 million lives today) (24).

In the words of medical historian Charles Rosenberg (18), “Cholera was the classic epidemic of the nineteenth century as plague had been of the fourteenth.” The differences, of course, are that population densities were higher and trade, people, armies, and information flowed faster in the 19th century than in the 14th century, whereas, during that period, the art of medicine became less barbaric but remained equally impotent (11, 18).

Longmate chose the title King Cholera: a Biography of a Disease (10) for the title of his informative and engaging monograph, because he likened the disease to a “. . . mad monarch who, during his reign, ravaged the world.” The word “ravage” is not being used lightly. German poet Heinrich Heine writes of the epidemic that struck on the day of the celebration of the Midcarême, March 29, 1832, in Paris, France, where he was visiting at the time (7):

That night the balls were more crowded than ever; hilarious laughter all but drowned the loudest music; one grew hot in the chahut, a fairly unequivocal dance, and gulped all kinds of ices and other cold drinks—when suddenly the merriest of the harlequins felt a chill in his legs, took off his mask and to the amazement of all revealed a violet-blue face. It was soon discovered that this was no joke; the laughter died and several wagon-loads of people were driven directly from the ball to the Hoˆtel Dieu, the main hospital, where they arrived in their gaudy fancy dress and promptly died too!

Later in this essay, describing the riots in the streets of Paris, Heine writes “It was as if the end of the world had come!” It is estimated that in Moscow, Russia, thousands were afflicted and many succumbed (10). Physician/author Anton Chekhov’s brilliant writing career was interrupted by his being named “cholera doctor” in charge of more than 25 villages, 4 factories, and 1 monastery in the neighborhood of Moscow during a dreadful outbreak in 1892. He writes, in a letter dated August 16, 1892, to a dear friend, Russian journalist/editor Aleksei Suvorin (5):

The treatment of cholera requires of the doctor deliberation before all things—this is, one has to devote to each patient five to ten hours or even longer. As I mean to employ Kantani’s treatment—that is, cysters of tannin and subcutaneous injection of a solution of common salt—my position will be worse than foolish; while I am busying myself over one patient, a dozen can fall ill and die.

Chekhov was referring to the Italian physician/scientist Arnaldo Catani, who, during an outbreak of cholera in 1884 in Naples, Italy, used hypodermoclysis (subcutaneous infusion) of solutions of sodium chloride as a reasonably effective therapy (24).

The Mid-19th Century: Epidemiology and Pathogenesis

Despite its terrible toll, how this scourge was spread remained a mystery for many centuries. One popular notion was
that disease was due to inhalation of impure, fouled, or contaminated air: the “miasmic theory” (“to infect from the fog”) (9, 10). One can trace this theory back to the ancient beliefs that humans are made up of four elements: namely, air, fire, earth, and water. Health depended on a homeostatic balance of these elements; imbalance, on the other hand, was the ultimate cause of disease. The inhalation of “foul” air could adversely alter that balance. Hippocrates, in his treatise *On Airs, Waters and Places*, emphasized the importance of considering air quality in the differential diagnosis of disease and, on his advice, bonfires were lit to purify the air during the plagues that struck Athens, Greece, in the 5th century BCE (1). This notion gained circumstantial support from the innumerable observations that disease was prevalent in slums laden with foul garbage and in foul-smelling prisons and that rotting food (or corpses) were odiferous. By the 19th century, the miasmic theory had become dogma. In addition to many noted physicians, Florence Nightingale, the nurse famous during the Crimean war, was an uncompromising advocate of this notion. She proclaimed that scarlet fever, measles, and smallpox were spread by odors arising from drains beneath dwellings and rigorously promoted hygiene and fresh air on that account (9, 25).

One Victorian physician who was skeptical of this mode of disease transmission was Dr. John Snow, who ranks high among the fathers of modern medicine. His main accomplishments, which were not fully appreciated during his brief lifetime, not only anticipated the “germ theory of disease,” generally credited to Pasteur, but also gave birth to the sciences of epidemiology and statistical medicine and promoted the expansion of public health by water sanitation (25).

John Snow was born in York, UK, in 1813. After attending a private school, where he excelled in mathematics, he joined the medical profession at the age of only 14 years by the common route of the day, namely, apprenticing himself to a surgeon. At about that time, he became a vegetarian, a teetotaler, an active advocate of temperance, and only drank water that he himself distilled. According to his closest biographer (17) “…he lived on anchorite’s fare, clothed plainly, kept no company, and found every amusement in his science books, his experiments, and simple exercise (swimming and hiking alone); he remained a bachelor throughout his life.” He completed his apprenticeship and became qualified to practice medicine in 1838; he obtained his MD degree from the University of London in 1844.

But for the invasions of London by cholera during the period of 1831–1854, Snow would be relegated in the history of medicine to being one of the forefathers of anesthesiology. That was the focus of his medical practice and research from the time he received his doctoral degree until his death in 1858 at the age of 45 years old, presumably from a cerebral vascular accident; indeed, it was the income from his anesthesiology practice that afforded him the time to investigate the epidemiology of cholera. Soon after the discovery of the anesthetic properties of ether and, later, chloroform, Snow became an authority on their use to relieve pain and was the first to develop an inhaler for the consistent delivery of these volatile agents. He played a significant role in overcoming the skepticism and fear of these agents on the part of many in the medical community and administered chloroform, on his handkerchief, to Queen Victoria in 1853 on the occasion of the birth of Prince Leopold and again in 1857 at the birth of Princess Beatrice (25).

Because of his interest and research in inhalation anesthetics and pulmonary physiology, Snow was dubious about the miasmic mode of transmission of cholera. It was clear to him that the problem resided in the intestine, not in the lung, and he was among the earliest to argue that death was due to a “thickening of the blood” (24) secondary to the watery diarrhea. He hypothesized that the problem might arise from the consumption of water that was contaminated by the evacuations of cholera patients. He gathered observations strongly suggestive of that link during an outbreak in 1849 and put forth his hypothesis that year in a self-financed, 31-page publication entitled *On the Mode of Transmission of Cholera* (23). His argument, however, fell on deaf ears. His conclusion was based on circumstantial evidence and was too weak to loosen the tight grip of the miasmic dogma!

In 1853–1854, another serious outbreak of cholera visited London, which resulted in more than 50,000 deaths. This gave Snow the opportunity to strengthen his hypothesis. In 1853, he tabulated the incidence of deaths from cholera in subdistricts of South London that obtained their water from the upper Thames, before the river reached the sewer drains of London, and compared that with the incidence of deaths in subdistricts that obtained their water from the lower Thames, after contamination by London’s wastes. The incidence of deaths in the “cleaner” water was significantly lower than that in the “contaminated” water. However, statistical reasoning was still in its infancy at that time, and Snow’s careful tabulations remained unconvincing (25).

Snow’s argument was, however, dramatically augmented by his celebrated mapping of the homes in the Golden Square district of Soho (not far from his home), in which cholera resulted in an unusually high incidence of deaths. His now famous 1854 map (Fig. 1) (9, 24) clearly indicated that the deaths were largely confined to residences that clustered around a pump situated on Broad Street, whose water was later found to be contaminated by sewerage seeping from a nearby cracked drain; indeed, 500 deaths occurred within 250 yards of that pump. Homes that neighbored other pumps were largely spared except for those that had drinking water transported to them from the Broad Street pump. Interestingly, there were no outbreaks in a nearby prison that reeked of filth but drew its water from a distant site—so much for the miasmic theory!

On September 7, 1854, he requested permission from the Board of Guardians of that parish to have the Broad Street pump handle removed, a request that they greeted with considerable skepticism. But, having no other recourse, it was granted. The handle was removed the next day, and the incidence of cholera in the area plummeted.

Snow published these findings in the second edition of *On the Mode of Transmission of Cholera* (23), which appeared in 1855. He further noted the following:

A very important point with respect to this pump-well is that the water passed with almost everybody as being perfectly pure and it did in fact contain less impurity than water from other pumps in the same parish which had no share in the propagation of cholera. We must conclude from this outbreak that the quantity of morbid matter which is sufficient to produce cholera is inconceivably small, and that the shallow pump-wells in a town cannot be looked upon with too much suspicion whatever their local reputation might be.
However, as hard as they tried, he and others who he consulted could not identify the “invisible agent” responsible for the disease in the incriminated pump’s water. This proved to be a weakness in his hypothesis that believers in the miasmic theory clung to; Snow’s theory was never fully accepted during his lifetime, and it was even subject to ridicule (10, 25). He lost £200 on his book, which must rank among the most influential in the history of public health and medicine [the purchasing power of £200 in 1850 is approximately equal to £16,000, or $30,000 (USD) today].

Ironically, during the very same year that Snow was carrying out his Broad Street pump studies, Italian microscopist Filippo Pacini observed comma-shaped particles, or “vibriones,” in the stool and intestines of victims of a cholera outbreak in Naples but not in the stool of individuals who were not afflicted; he speculated that these particles might be the causative agents (9, 24, 25). Unfortunately, Pacini’s observations, which were published in the Italian journal *Gazetta Medica Italiana Toscana* (1854), went unnoticed. Three decades elapsed before Robert Koch, the discoverer of the bacteria responsible for causing tuberculosis (*Mycobacterium tuberculosis*) and one of the founders of modern microbiology, rediscovered that the “invisible culprit” in the water was the comma-shaped bacterium (“Kommabacillus”) *Vibrio cholerae*. By that time, the germ theory of disease was gaining favor, and Koch’s findings were rapidly accepted. However, justice was ultimately done; in 1965, Pacini was officially acknowledged as the discoverer of the vibrio that is now called *Vibrio cholerae pacini*.

**The Mid-20th Century: Pathophysiology and Therapy**

By the 1960s, it was clear that *Vibrio cholerae* does not invade and destroy the small intestinal mucosa leading to denudation, as was once suggested (13, 24). Instead, it colonizes on the surface of the mucosa, multiplies many-fold, and secretes a toxin that elicits a massive intestinal secretion of an isotonic fluid whose composition resembles blood serum except that it is high in bicarbonate (14, 16, 12). Death is the result of dehydration and circulatory collapse complicated by metabolic acidosis and can occur within hours of the onset of symptoms. Indeed, one of the terrifying aspects of the disease is that an individual in the pink of health in the morning might turn into a shriveled corpse by the evening.

Ever since the pioneering insights of O’Shaughnessy and Latta in 1832 (24), treatment has focused on replacing lost fluid by the intravenous administration of saline solutions containing bicarbonate or lactate. This therapy is, however, very expensive, supplies of sterile intravenous fluids are limited and can be rapidly exhausted in the event of a massive outbreak, and professional supervision and sterile precautions are necessary. Thus, while intravenous replacement therapy is very effective in the hospital setting, it was clear that it is “hardly feasible in
large scale epidemics over wide and remote areas of underdeveloped countries" (24).

Meanwhile, in another world of investigation, basic scientists were focusing their attention on the mechanisms of sugar and ion transport by the mammalian small intestine, subjects yet in their embryonic stage. By 1962, it was known that 1) sugar accumulation by small intestinal cells, in vitro, was abolished if sodium was excluded from the bathing medium; 2) sugar accumulation was abolished by digitals glycosides (e.g., ouabain), which were known to inhibit the sodium-potassium pump; and 3) fluid absorption is greater in the presence of glucose than in its absence (22). The interpretation of these findings was, however, controversial. Was the requirement for intracellular and/or extracellular sodium? Is sugar accumulation directly dependent on a functional sodium-potassium pump? Do the digitalis glycosides directly inhibit sugar accumulation? Does glucose facilitate fluid absorption because of its nutritional value?

To answer these questions, a method was required that would allow rapid (near instantaneous) measurement of sodium absorption rates by the epithelium and the ability to separately perfuse the lumen-facing (mucosal) and blood-facing (serosal) sides of the epithelium.

In 1962, I modified the "short-circuit technique" introduced by the great Danish physiologist Hans Ussing for the study of sodium transport by frog skin to study mammalian epithelia. Using this technique, we (20–22) found that the electrical potential difference across the rabbit small intestine and the "short-circuit current" (i.e., the external current needed to null the spontaneous electrical potential difference) were instantaneous measures of the rate of sodium absorption by the tissue. We (20–22) also found that the addition of sugars or amino acids to the solution bathing the mucosal (luminal) surface of the tissue resulted in an immediate, concentration-dependent increase in the rate of sodium absorption and that this could be prevented by the addition of digitalis glycosides to the solution bathing the serosal (blood), but not the mucosal (lumen), surface of the tissue. Furthermore, this effect was independent of whether or not the sugar or amino acid was metabolized by the cells (20–22).

Based on these and others' findings, in 1964, we (20) proposed a double-membrane model for coupled sodium and sugar and/or amino acid absorption by the small intestine (Fig. 2). The essential features of this model are that sugars and/or amino acids enter the cell across the apical or mucosal membrane tightly coupled to sodium and energized by the electrochemical potential difference for sodium across that barrier. Sodium is then actively extruded from the cell, across the basolateral membrane, by the classic, ATP-dependent, ouabain-inhibitable, sodium-potassium pump found in virtually all animal cells. It is this pump that establishes the driving force for the entry processes. This model for sodium-coupled solute transport has been validated for the small intestine and renal proximal tubule of all animals throughout the phylogenetic scale. Furthermore, during the past two decades, the three transporters [C1, C2, and (?)] postulated in this model (Fig. 2) have acquired their molecular identities: the Na-coupled glucose transporter (C1), first cloned and sequenced by Ernst Wright and coworkers, is referred to as Na-coupled glucose transporter (SGLT1) (cf. Ref. 26); the basolateral membrane sugar-facilitated transporter (?) is glucose transport 2 (GLUT2) (cf. Ref. 16); and transporter C2 is the well-characterized, ubiquitous Na-K-ATPase.

Inasmuch as by the early 1960s it was well established that water flow is secondary to and driven by solute flow (22), our model could readily explain the observation that fluid absorption is increased by glucose. We now know that for every glucose molecule absorbed, two sodium ions and two countercations (mainly chloride) must also be absorbed (16, 26); thus, glucose augments total solute (and, therefore, water) absorption approximately fourfold.

Finally, by the late 1960s, it was clear that cholera is not the result of malabsorption due to epithelial desquamation, or to “poisoning” of the sodium pump, as was postulated by Phillips (15), but is due, rather, to hypersecretion by otherwise-normal villus crypt cells in response to elevated intracellular cAMP (6). The cells responsible for sodium-coupled solute absorption, which appear to be congregated on the upper half of the intestinal villus, are also perfectly intact (cf. Refs. 13 and 24). In short, as concluded by Norris et al. (14), cholera (and other so-called secretory diarrheas) is due to a perfectly normal, reversible, secretory process that has gone out of control under the influence of the cholera toxin. When intestinal fluid secretion overwhelms the maximum capacity for fluid absorption, the result is net fluid loss, or diarrhea.

This confluence of findings suggested that increasing total solute absorption by adding solutes that are absorbed by sodium-coupled mechanisms (sugars and/or amino acids) to the fluid in the small intestinal lumen, thereby increasing fluid absorption, might reduce or even overcome the cholera toxin-induced secretory response. This prediction was confirmed by studies on rabbit (14) and canine (4) small intestines challenged with cholera toxin. In 1968, Hirschhorn et al. (8) carried out the first carefully controlled study showing that intestinal perfusion of cholera patients with saline solutions containing glucose strikingly reduced fluid loss. Later, Nalin and Cash (12) demonstrated that oral or intragastric saline solutions containing both glucose and glycine were more effective in reducing fluid loss by cholera patients than solutions that contained either glucose or glycine alone. Thus, the ability of sodium-coupled solute absorption to promote water absorption
in humans afflicted with cholera, under carefully controlled conditions, was clearly demonstrated.

These compelling findings, however, did not convince the medical establishment, who remained skeptical that such a simple therapy could substitute for traditional intravenous fluid replacement in severely stricken patients under epidemic conditions in the field (19, 24). There were legitimate concerns over whether vomiting patients would be able to retain sufficient amounts of the ingested fluid. Also, there were lingering memories of a study in which 5 of 30 patients died following a regimen consisting of orally and intravenously administered fluids. The oral fluid (19, 24) erroneously contained a large concentration (400 mM) of glucose in addition to isotonic saline and was very hypertonic with respect to plasma; the disastrous results left a lasting impression on Phillips, the director of the program, whose skepticism became somewhat of a barrier to the further exploration of the usefulness of oral rehydration therapy (ORT) (16, 24).

This conundrum was resolved, serendipitously, in 1971, when, during the “Bangladesh War of Liberation,” millions of refugees from East Pakistan (now Bangladesh) sought refuge in squalid camps in India. Cholera ran rampant throughout these refugees, and supplies of sterile intravenous fluids were nearing exhaustion. One camp, under the supervision of a pediatric gastroenterologist, Dilip Mahalanabis (19, 24), decided to preserve intravenous fluids for those in overt shock and urged the others to consume as much of a homemade glucose-containing electrolyte solution as they could. Because thirst is stimulated by dehydration, patients avidly consumed oral rehydration solutions in amounts necessary to replenish and maintain body fluids. The outcome was dramatic. The fatality rate of those who were treated by ORT was only 3%, much lower than the 18% rate for those who received intravenous replacement fluid.

By 1975, ORT employing solutions of salt and sugar was established as a safe, inexpensive alternative to intravenous rehydration in all ages and regardless of the etiology of the diarrhea, leading *Lancet* (9a) to opine that “The discovery that sodium transport and glucose transport are coupled in the small intestine so that glucose accelerates absorption of solute and water was potentially the most important medical advance this century.”

In this respect, it is of interest that Susruta, the father of Ayurvedic medicine in India (circa 1000–500 BCE), recommended drinking a “... profuse quantity of tepid water in which rock salt and molasses have been dissolved ...” for the treatment of diarrhea (3). And, there are many reports of occasional salutary use of oral glucose-saline solutions in cholera (2). But, lacking a sound scientific foundation and well-controlled studies, these sporadic reports did not “take hold.” There are few more telling examples in the history of medicine where the credibility provided by a firm basic science foundation played a greater role in translational research.

The Future

It must be emphasized that diarrhea is not a disease; rather, it is a nonspecific symptom that may accompany many diseases. ORT does not cure any disease! It simply provides an effective, safe, and inexpensive way to replace fluid lost by diarrhea and maintain normal fluid balance once losses are replenished. It staves off the lethal consequences of severe hypovolemia, namely, circulatory collapse or shock.

Regrettably, it is estimated that millions of lives are still lost annually as a result of diarrheal disease that might have been saved using ORT; children under the age of 5 years old account for close to 2 million those deaths. Clearly, it is society’s responsibility to educate its populace as to the efficacy of ORT, produce sufficient amounts of packets of oral rehydration salts, and ensure the distribution of these packets to all those in need. It is up to policy makers at all levels of government and the private sector to ensure that the “fruits of the laboratory bench are fully translated to meet human needs at the bedside.”

A danger that many that live in “developing countries” face is that the availability of a cheap, safe, and effective treatment for water loss will delay or forestall efforts on the parts of economically pressed countries to develop water purification and sanitation capabilities. Such effective preventive measures would make cholera and other water-borne diseases as uncommon in the developing countries as they are in industrialized nations.

GRANTS

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REFERENCES


