A Legacy in 20th-Century Medicine: Robert Allan Phillips and the Taming of Cholera

Stephen J. Savarino

United States Naval Medical Research Center, Silver Spring, Maryland

The legacy of Captain Robert Allan Phillips (1906–1976) was to establish effective, evidence-based rehydration methods for the treatment of cholera. As a Navy Lieutenant at the Rockefeller Institute for Medical Research (New York, New York) during World War II, Phillips developed a field method for the rapid assessment of fluid loss in wounded servicemen. After the war, he championed the establishment of United States Naval Medical Research Unit (NAMRU)–3 (Cairo; 1946) and NAMRU-2 (Taipei; 1955), serving at the helm of both units. Phillips embarked on cholera studies during the 1947 Egyptian cholera epidemic and brought them to maturity at NAMRU-2 (1958–1965), elucidating the pathophysiologic derangements induced by cholera and developing highly efficacious methods of intravenous rehydration. His conception of a simpler cholera treatment was realized in the late 1960s with the development of glucose-based oral rehydration therapy, a monumental breakthrough to which many other investigators made vital contributions. Today, these simple advances have been integrated into everyday medical practice across the globe, saving millions of lives annually.

A person's true wealth is the good he or she does in the world.
—Muhammad

It is a curious commentary on human nature that the ravages of war often foster major advances in medical science and practice. The tumult of World War II set the stage for a major achievement of 20th-century medicine: the development of intravenous and oral rehydration therapy for cholera and related diarrheal illnesses. Captain Robert Allan Phillips, through brilliance, preparedness, and serendipity, became a central figure in this public-health triumph.

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Reprints or correpondence: Dr. Stephen J. Savarino, Naval Medical Research Center, 503 Robert Grant Ave., Silver Spring, MD 20910-7500 (savarinos@nmrc.navy.mil).

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EARLY YEARS

Robert Allan Phillips was born in Clear Lake, Iowa, on 16 July 1906. His father and uncle were partners in one of the few medical practices in the area, operating a clinic and small hospital that adjoined Phillips' boyhood home. During World War I, Phillips' father volunteered for duty in Europe as an Army Medical Corps officer. He later served for years as the mayor of Clear Lake. A studious youngster, Phillips received his bachelor of science degree from the State University of Iowa (Iowa City) in 1927, before graduating from the Washington University School of Medicine (St. Louis, MO) in 1929. During the 3 years that Phillips spent in St. Louis, which included a 1-year surgical internship at Barnes Hospital, he published his first scientific paper on the effect of ergosterol on blood coagulation [1].

Phillips was awarded a National Research Council Fellowship at Harvard Medical School (Boston, MA) in 1930. He joined the Physiology Department, which

was directed by the eminent chairman Walter B. Cannon, and engaged in studies of the autonomic nervous system, intestinal and renal physiology, and carbohydrate metabolism. He received further surgical training at Yale University School of Medicine (New Haven, CT) before becoming an instructor in physiology at Stanford University (Stanford, CA). From 1936 to 1940, Phillips served as Assistant Professor in Physiology at Cornell Medical College (New York, NY). Working at these institutions, and influenced by leading physiologists of his day, Phillips developed a reputation as a careful, innovative experimentalist.

WORLD WAR II SERVICE

As the United States prepared for World War II, Dr. Phillips was commissioned a lieutenant in the US Naval Reserve in August 1940. In December 1940, he was assigned to the Rockefeller Institute for Medical Research (New York, NY), where he joined the laboratory of Donald D. Van Slyke, a renowned leader in clinical chemistry whose laboratory would perform war-related research on shock and blood substitutes.

Van Slyke assigned Phillips to develop a deployable method of measuring the specific gravity of blood and plasma, because established methods were impracticable for use in the field [2]. Phillips discovered that copper sulfate solutions worked quite well for this application, and he developed methods to calculate various blood indices and to estimate intravascular fluid deficits on the basis of changes in the specific gravity of blood [3, 4]. The copper sulfate method (figure 1), also known as the Phillips–Van Slyke test, was adopted by the US and British armed services and proved invaluable in the field management of hemorrhage, burns, and shock during the war [2, 5, 6]. The test was later adapted by the Red Cross and, for many years, served as the method of choice for screening the hemoglobin levels of prospective blood donors [7].

In 1944, Phillips was detailed to the Cairo, Egypt, unit of the United States of America (USA) Typhus Commission, the mission of which was to perform research and develop control measures against typhus fever, a serious hazard for Allied forces in North Africa [8]. In Cairo, Phillips upgraded clinical chemistry capabilities at the Commission laboratory and conducted biochemical and physiological studies of patients with typhus on the unit's research ward at the Abbassia Fever Hospital (Cairo). In May 1945, Phillips was temporarily assigned to the newly liberated concentration camp at Dachau, Germany, where horrid conditions had promoted the spread of typhus fever. He established a laboratory at Dachau to support the clinical care of persons with typhus [9].

Phillips was profoundly affected by these overseas-duty assignments. From a military standpoint, he recognized the importance of such opportunities for the study of diseases in situ

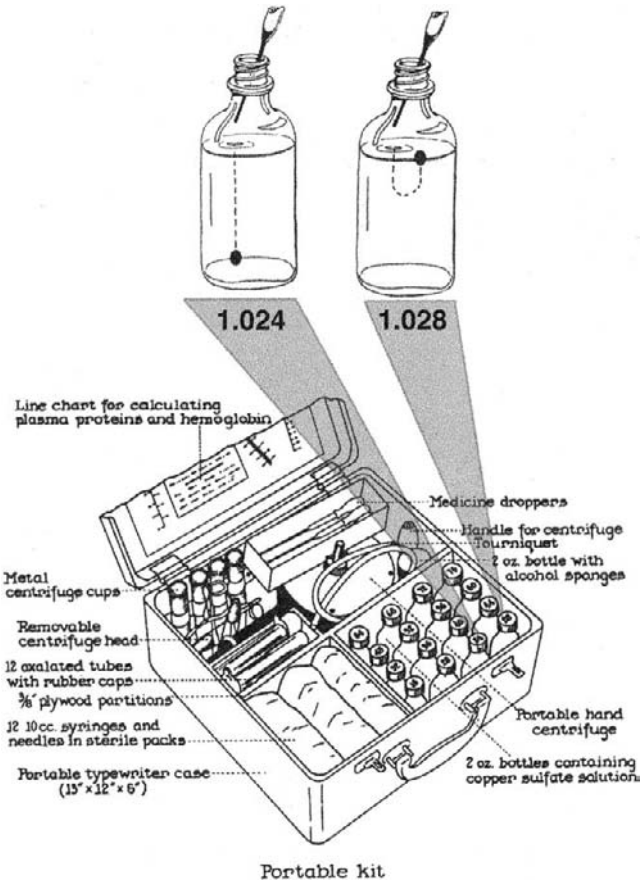

Figure 1. The copper sulfate test kit shown here was packaged for use in the field during World War II (adapted from [4]). The test was widely adopted by the US and British armed services for assessment of intravascular fluid deficits in wounded combatants during the war, and it was later used by Robert Allan Phillips in his studies of cholera. Blood (or plasma) specific gravity is determined by releasing drops of fluid into a graded series of copper sulfate solutions covering a defined range of specific gravities. Specific gravity of the body fluid is equivalent to that of the solution in which the drop neither rises nor falls (interpolated in the figure as 1.026).

that may threaten combatants. Moreover, he acutely realized the broader value of international scientific cooperation.

ESTABLISHMENT OF NAVAL MEDICAL RESEARCH UNIT (NAMRU)–3 AND THE FIRST ENCOUNTER WITH CHOLERA

As the war in Europe ended in May 1945, the USA Typhus Commission planned to dissolve the Cairo unit. Together with a group of the Cairo unit's other officers, Phillips saw the wisdom of maintaining a permanent medical research laboratory in Cairo. With informal encouragement from the Egyptian Ministry of Health, Phillips returned to Washington, D.C., where he persuaded the US Navy to take up this charge. The US Navy, the Egyptian government, and the USA Typhus Com-

mission soon made an arrangement whereby US NAMRU–3 was established and occupied the Commission's facilities. Meanwhile, Phillips had resigned his Navy commission and had briefly served as Chief of Physiology at the A. I. DuPont Institute in Wilmington, Delaware, only to be called back to duty in late 1946 with a Regular Navy commission and orders to take command of NAMRU-3 in June 1947.

In addition to using his knowledge of science and administration, the launching of NAMRU-3 just after the war tested Commander Phillips' political mettle. He had to consolidate support from the Navy Bureau of Medicine and Surgery (BUMED) in the face of many other military priorities. The Egyptian government's ratification of a final agreement regarding NAMRU-3 was delayed by larger issues, not the least of which was the expression of US support for changes in immigration policy in Palestine that preceded the establishment of Israel [10]. Phillips' handling of events during the first 6 months of his tenure allayed misgivings on both sides about the merits of this new cooperative research venture and inexorably altered his own scientific path.

Cholera, an ancient scourge of the Indian subcontinent, had established a more pervasive reign of terror in successive pandemics that spread across the globe beginning early in the 19th century [11]. Egypt had been stricken by several major epidemics; the last cholera epidemic of a serious nature occurred in 1902 and claimed 35,000 lives in <3 months [12]. In 1947, prevailing concepts regarding the pathogenesis and treatment of cholera were misguided, and case-fatality rates for persons with cholera gravis typically exceeded 60%. Remarkably perceptive studies by O'Shaughnessy [13], Latta [14], and others had portended the efficacy of intravenous rehydration therapy for cholera as early as 1831. Acceptance of these findings and their further development were long stymied by erroneous concepts of the disease process. As suggested by Cosnett [15, p. 770], "the idea was much ahead of contemporary knowledge of physiological chemistry and microbiology." When a cholera outbreak occurred in Egypt on 21 September 1947, the same could not be said. Commander Phillips unknowingly had been preparing for this chance encounter for most of his professional life.

The appearance of cholera in lower Egypt caught the country by surprise. In addition to instituting cordons around affected areas, the Ministry of Health hoped to stem the epidemic by mass vaccination with the killed parenteral cholera vaccine. Having a very limited vaccine stockpile, the Ministry turned to NAMRU-3 for assistance [10]. Phillips quickly orchestrated a massive airlift of vaccine from the United States, and NAMRU-3 aided the Egyptian government in its vaccination campaign. An outpouring of assistance followed from around the world, coordinated by the World Health Organization. Despite the Egyptian government's best efforts to combat the outbreak, it caused some 30,000 cases of cholera and 20,000 deaths during the ensuing 3 months; the high case-fatality rate was not atypical for the time [11].

At the Abbassia Fever Hospital, Commander Phillips swiftly improvised a clinical study of cholera. Under his direction, a team of Navy personnel and Egyptian hospital staff undertook the study and treatment of a series of adult patients with cholera who were admitted with severe shock. Analyses indicated that the stool of these patients with cholera was isotonic with blood and contained an excess of bicarbonate (which accounted for the sometimes profound acidosis), but had minimal amounts of protein [16, 17]. Guided by the copper sulfate method, fluid replacement and maintenance was achieved with intravenous infusion of isotonic saline supplemented with potassium. With use of the Van Slyke manometric method to measure serum levels of carbon dioxide, base deficits were calculated and corrected by periodic intravenous infusion of a concentrated solution of sodium bicarbonate that was concocted from local supplies.

On the basis of sound physiological principles and basic biochemical analyses, Phillips and colleagues saved all but 3 of the 40 patients studied; the 3 patients who died had been admitted in extremis [16]. Although this was a small series, the 7.5% mortality rate in the face of severe illness was extraordinary even when compared with the results obtained by treatment with hypertonic saline infusions, as described earlier in the century by Sir Leonard Rogers [18, 19].

In 1947, Egypt awarded Commander Phillips the Egyptian Gold Cholera Medal for his actions. The consequent elevation in public standing of the fledgling NAMRU-3 prompted Egypt to formally recognize NAMRU-3 in June 1948, one year after Phillips' arrival. Likewise, the observations of then Navy Surgeon General Rear Admiral Clifford Swanson (figure 2) during his October 1947 visit convinced him of the command's value to the United States.

Having established NAMRU-3 on a strong foundation, Commander Phillips returned to BUMED in Washington, D.C., in 1952. Unfortunately, the findings of his 1947 studies had little immediate impact on the treatment of cholera on the Indian subcontinent, to where disease activity had temporarily receded. Publication of his work as part of a symposium in a local journal [20] seems to have contributed to the paucity of international attention.

RECOMMISSIONING OF NAMRU-2 IN TAIPEI AND THE ADVENT OF THE SEVENTH CHOLERA PANDEMIC

In Washington, D.C., Phillips engaged in the management of Navy medical research. Encouraged by the success of NAMRU-3, he sought another strategic location where Navy overseas

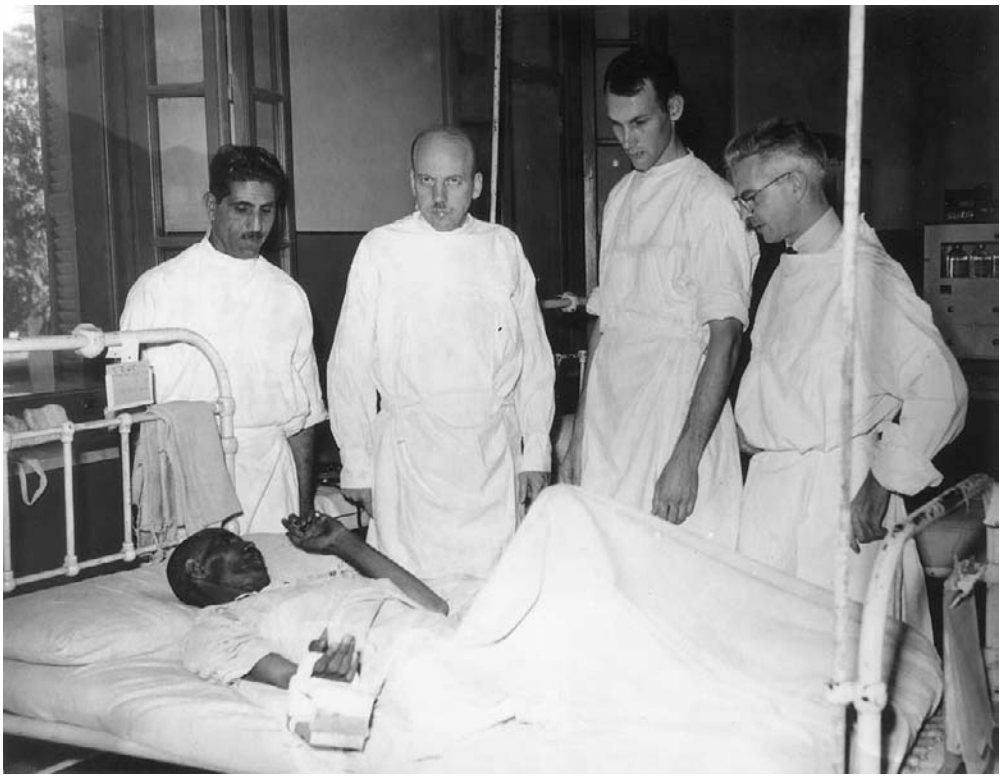

Figure 2. Standing at the bedside of a patient with cholera at the Abbassia Fever Hospital (Cairo) in 1947 are *(left* to *right)* the head nurse of the Naval Medical Research Unit–3 research ward, Emam Effendi; Navy Surgeon General Rear Admiral Clifford Swanson; Lieutenant (junior grade) Moulton Johnson; and Commander Robert A. Phillips (official photograph of the US Navy; kindly provided by Charles Knight).

medical research could expand. A few visits to Taipei, Taiwan, convinced him that it was a suitable location for such a venture. NAMRU-2 was originally commissioned at the Rockefeller Institute during World War II, under the leadership of Captain Thomas Rivers, was forward-deployed to the Pacific during the latter part of the war, and was deactivated in June 1946 [21]. With this historical precedent, BUMED developed plans to recommission NAMRU-2 in Taipei. After an agreement was reached with the Taiwanese government in 1955, Captain Phillips reported as the first commanding officer of NAMRU-2 Taipei, a post he held for the next 10 years.

In 1958, when classical cholera erupted in Bangkok, Thailand, for the first time in a decade, the unit deftly responded to the Taiwanese government's call for assistance. With outbreaks of classical cholera occurring annually in Thailand during the next few years, and with the emergence of El Tor cholera from Sulawesi, Indonesia, in 1961 ushering in the seventh pandemic, cholera became a centerpiece of NAMRU-2's research agenda. In a report from Egypt 10 years earlier, Phillips and colleagues admitted that, although their studies partially clarified the disease state associated with cholera, "the development of this state was not investigated, and until it is, the disease process, as opposed to the disease state will not be understood" [17, p. 13]. To this task, Phillips set to work with his assembled research team, which was dubbed the "Order of the Perforated Pad," in reference to the customized army cot devised by Raymond Watten to simplify the management of persons with purging cholera (figure 3). During the next several years, countries throughout the Far East that had populations stricken with cholera called upon NAMRU-2 for assistance (figure 4). In what evolved into a systematized response to an outbreak, a mobile research team carried all needed equipment and materials to the afflicted area by military transport. The team rapidly indoctrinated local caregivers regarding proper cholera treatment. The NAMRU-2 team then typically gained permission to establish a research ward and perform clinical studies that fit into a broader program of cholera research.

At the Chulalongkorn University Medical School in Bangkok, Phillips' team, including Raymond Watten, Francis Morgan, Quentin Blackwell, Boonam Vanikiati, and others, performed complete balance studies of patients with cholera, measuring the volume and electrolyte content of all output and input during the course of illness, while proscribing oral intake during the early treatment period. Phillips had wanted to do this in Cairo, but he was deterred by a staff hesitant to withhold drink from patients. An accurate, dynamic understanding of the physiologic derangements of cholera emerged that substantiated and greatly extended observations made during the Cairo

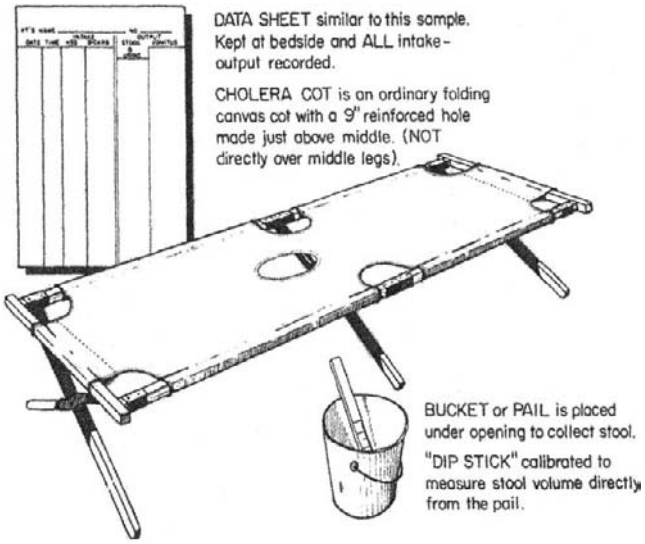

Figure 3. The Watten cholera cot, the design of which was improvised from a standard Army cot by Raymond Watten in 1958, provides a simple means for collecting and measuring all stool output (official illustration of the US Navy; kindly provided by Charles Knight).

epidemic. On the basis of these studies, Phillips' group further refined their evidence-based approach to management with fluids [22–25].

Working in collaboration with the NAMRU-2 team at Chulalongkorn in 1959, Eugene Gangarosa of the Walter Reed Army Institute of Research (Washington, D.C.) observed the normal histologic appearance of intestinal capsule biopsy specimens obtained from patients with cholera [26], and Robert Gordon of the US National Institutes of Health (Bethesda, MD) confirmed the integrity of the gut mucosa by demonstrating intestinal impermeability to large molecules [27]. These studies convincingly refuted the long-standing view promoted by Virchow that denudation of the intestinal epithelia was the principal feature of cholera pathology [11]. Taken together with the dearth of protein in cholera stool [17] and the rapid, dramatic recovery of properly resuscitated patients, these findings suggested that a localized biochemical defect leads to the massive fluid efflux in cholera. In fact, in the same year De [28] and Dutta [29] first demonstrated that *Vibrio cholerae* elaborated an enterotoxin capable of causing such intestinal fluid secretions in rabbits; the highly potent cholera toxin was purified a decade later by Richard Finkelstein [30].

In October 1961 and for several years thereafter, annual outbreaks of El Tor cholera occurred in The Philippines, prompting NAMRU-2 to establish an outpost at San Lazaro Hospital in Manila. The intravenous treatment methods used by the Navy proved highly efficacious in this setting, and further simplification of these procedures was developed [31]. Phillips came to realize, however, that intravenous rehydration was impracticable for mass application because of its costliness and dependence on patient hospitalization. With Craig Wallace, Quentin Blackwell, and others, he undertook oral fluid replacement studies in June 1962. Applying the same meticulous balance techniques, they assessed water and ion clearances after oral administration of fluids of varying electrolyte composition and tonicity, and, for the first time, showed in adult patients with cholera that oral glucose stimulated the absorption of sodium [32, 33]. These findings built upon prior animal tissue studies showed that glucose enhances the intestinal transport of sodium and water [34–36], although Phillips later claimed that he had no foreknowledge of these seminal studies when he initiated this line of clinical research [37]. Foreshadowing the breakthrough that occurred several years later, Phillips stated, "We have further evidence which suggests that by incorporation of glucose in an oral solution that one may be able to develop an oral treatment regimen which in the average case might completely eliminate the requirements for intravenous fluids" [32, p. 712].

In 1963, Phillips and Craig Wallace undertook a clinical trial to assess the efficacy of oral rehydration with glucose electrolyte solutions (C. K. Wallace, personal communication). Uncharacteristically, Phillips insisted on doing the study without laboratory support as a proof of its simplicity. Treatment consisted of an oral solution of high sodium concentration supplemented with glucose, along with continued administration of intravenous fluids to ensure adequate hydration. Oral absorption of sodium and water was demonstrated; however, to the investigators' alarm, 5 of 40 patients who were receiving this treatment died of pulmonary edema. In retrospect, it appeared that the combination of oral and intravenous fluids was excessive in some cases, causing circulatory overload and congestive heart failure [37, 38]. These dispiriting results caused Phillips to seriously question the feasibility of oral rehydration therapy. Despite his own skepticism, he saw his therapeutic concept of an oral cocktail realized several years later, largely because those around him had a sustained belief in the scientific framework that he and others had advanced.

THE PAKISTAN–SOUTHEAST ASIA TREATY ORGANIZATION (SEATO) CHOLERA RESEARCH LABORATORY AND ORAL REHYDRATION THERAPY FOR CHOLERA

An outspoken advocate for international cooperation on cholera research, Phillips was named to succeed Fred Soper and Abram Benenson as the third Director of the Pakistan-SEATO Cholera Research Laboratory (PS-CRL) in Dacca, East Pakistan, upon his retirement from the Navy in 1965. Established in 1961, as cholera began to capture growing US and international interest, the PS-CRL became an important center for cholera research. In 1979, it was reorganized as the International Centre

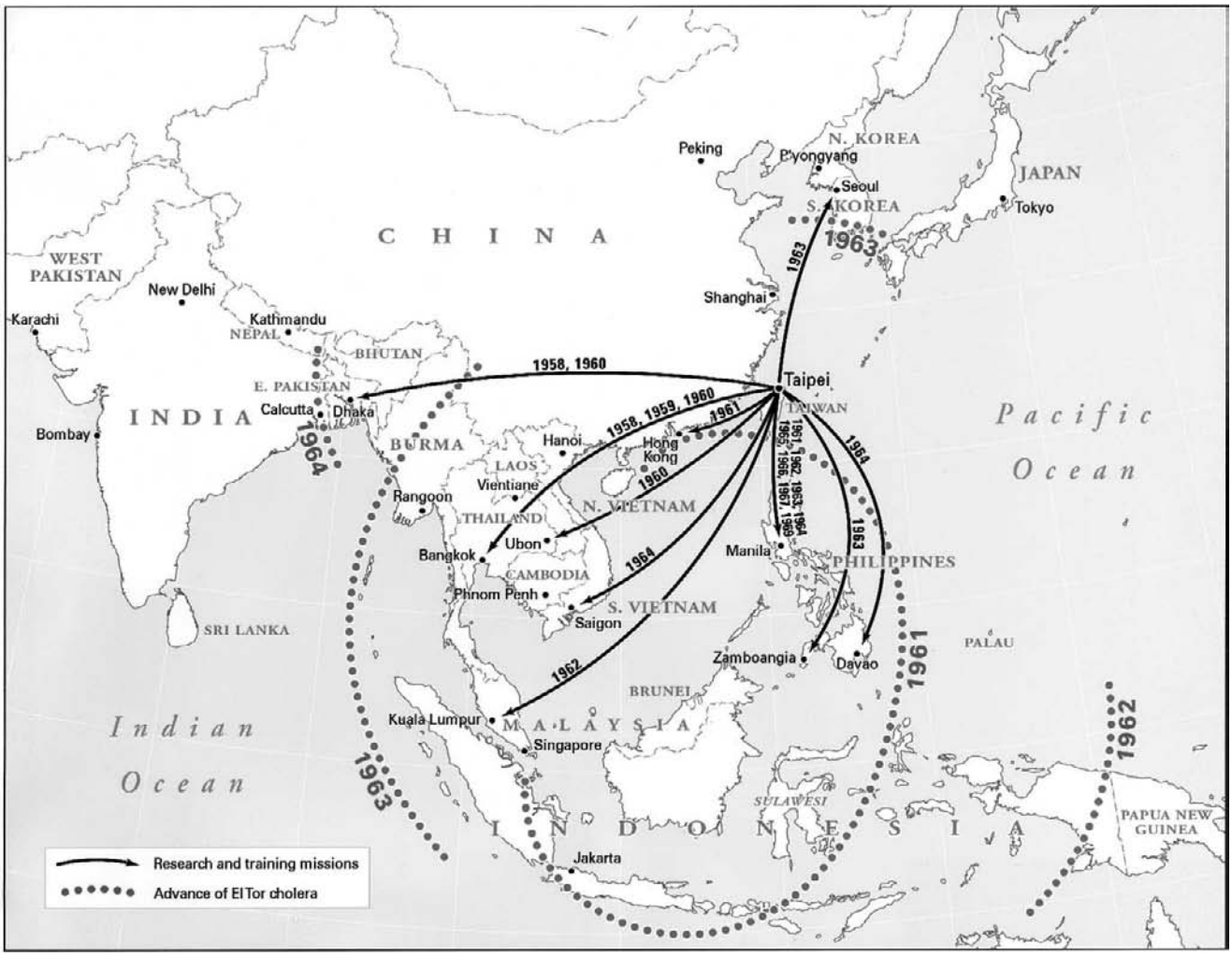

Figure 4. Year(s) and destination(s) of the many cholera research, training, and advisory missions conducted by Naval Medical Research Unit–2 medical scientists throughout the Far East during the decade beginning in 1958.

for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) [38]. The inaugural recipient of the Gates Award for Global Health in 2001, the ICDDR,B has endured as an acclaimed center for the study of diarrheal diseases, nutrition, and demography [39].

The most consequential work that originated from the PS-CRL under Phillips' leadership from 1965–1971 was furtherance of the scientific basis for and application of glucose-based oral rehydration therapy for cholera. [40–42]. This work included the first successful clinical trial reported by David Nalin, Richard Cash, Rafiqul Islam, Majid Molla, and Phillips [43], which demonstrated that an oral glucose-electrolyte solution, when regulated to match fluid losses, greatly diminished the requirement for intravenous fluid therapy in the early phases of cholera. In tandem with the PS-CRL group, Nathaniel Pierce and colleagues at the Johns Hopkins University International Centre for Medical Research and Training in Calcutta, India, performed a complementary research program [44, 45]. Impelled by their parallel successes, researchers at both centers undertook trials that demonstrated the efficacy of oral rehydration therapy at rural outposts [46] capped by a robust proof of its effectiveness among refugees with cholera who were fleeing war in Bangladesh [47]. Although Phillips' confidence in the prospects of glucose-based oral rehydration therapy had been so thoroughly shaken by the discouraging Philippine trial that he apparently slowed the progression of early field trials at PS-CRL, the overwhelmingly positive evidence that accrued from these studies won back his enthusiasm. Extensive subsequent research on cholera and other dehydrating diarrheal diseases and policy initiatives have established glucose-based oral rehydration therapy as the cornerstone of treatment for cholera and related illnesses, with intravenous therapy reserved for the most severe cases.

Phillips retired as director of PS-CRL in 1971 at the age of 65 years and returned to Taipei, where his family had continued

to live during his tenure in Dacca. He remained active in research, although his most productive years had passed. His health gradually declined, and he died on 19 September 1976.

PERSPECTIVE

For his development of the copper sulfate method and, later, his landmark cholera work, Phillips received numerous decorations. In 1967, he became the only career military officer to receive the Albert Lasker Medical Research Award, the nation's preeminent medical prize, "in recognition of his enormous contributions to the understanding of the mechanism of death in cholera, and the development of a life-saving method of treating it" [48, p. 147].

Twenty-five years after his death, Dr. Phillips' impact on military medical research remains in evidence. The US Navy maintains laboratories in Cairo; Jakarta, Indonesia (the current location of NAMRU-2); and Lima, Peru (established in 1983). The mission of these laboratories remains the study and control of regionally important infectious diseases. No one was more directly responsible for establishing this network than was Phillips, whose vision of international scientific cooperation helped advance the cause of military medicine and general public health alike. During his career, Phillips mentored a generation of military and civilian medical scientists, many of whom have made important contributions of their own to the advancement of knowledge about diarrheal diseases and related areas.

With the close of the 20th century, one can assess with further perspective Captain Phillips' specific achievements in cholera research. Astounding advances in medicine during the past century ranged from the consolidation of the germ theory of disease to the dawning of genomic medicine, but few advances have so profoundly impacted public health as have those fostered by Phillips and his colleagues. Today, oral and intravenous fluid therapy for diarrhea and dehydration are part of everyday medical practice. Intravenous rehydration therapy has reduced the mortality rate associated with cholera accompanied by severe dehydration and shock to <1%, and it continues to be the mainstay of therapy for such patients. In global terms, oral rehydration therapy is responsible for saving the lives of millions of children annually who would otherwise die of diarrhea and dehydration, regardless of etiology.

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