# Chapter 5

# CONSERVING THE FIGHTING STRENGTH: MILESTONES OF OPERATIONAL MILITARY PREVENTIVE MEDICINE RESEARCH

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## INTRODUCTION

Science, sanitation, technology, and medicine are entwined inextricably with the conduct of war, and, to a remarkable degree, the events and consequences of war have shaped human history.[1] Infectious diseases, for example, have consistently determined the rise and fall of armies, nations, and societies.[2,3] It is not surprising therefore that the benefits of military preventive medicine research extend far beyond the military exigencies that spawn that research. Given that fundamental understanding, this chapter limits its scope to military infectious diseases research conducted in direct support of military operations—either by investigators in the field or with materials collected there. The chapter does not reiterate the most often recounted military medical research achievements (eg, the Reed commission in Cuba; see Chapter 2, The Historical Impact of Preventive Medicine in War) nor provide an exhaustive account of research accomplishments with military operational relevance. Rather, it introduces readers to relatively unheralded efforts that established precedents, set standards, or elucidated principles of military operational preventive medicine research.

The latter half of the 19th century marked the beginning of the era of "scientific" military preventive medicine.[4] Pasteur developed the germ theory, which is the foundation of modern microbiology, immunology, public health, and preventive medicine. Koch devised methods of culturing and staining bacteria and developed tuberculin as immune therapy for tuberculosis.[5] Between 1870 and 1890, the bacterial etiologies of tuberculosis, leprosy, anthrax, gonorrhea, cerebrospinal meningitis, typhoid fever, pneumococcal pneumonia, diphtheria, tetanus, brucellosis, and relapsing fever were elucidated; Laveran described the link between plasmodium and malaria; Manson documented for the first time that insects transmit diseases; Finlay hypothesized that yellow fever was transmitted by a single species of mosquito; and Lister developed a system of "antiseptic" surgery that employed chemical and physical barriers to surgical wound contamination.[4]

In 1883, Baron Kanehiro Takaki of the Japanese Navy medical bureau suspected that beriberi resulted from "a wrong method of diet."[6] To test his hypothesis, he arranged for two ships to sail identical 9-month-long voyages during which one crew ate usual rations—raw fish and polished white rice—while the other ate a high-protein, low-carbohydrate diet. The former suffered high rates of beriberi, but the latter had few cases. By 1890, through nutritional intervention alone, beriberi was eliminated as a threat to the Japanese navy.[6] (Approximately 50 years later, vitamin $B_1$ [thiamin] was isolated from rice hulls, and its deficiency in diets was shown to cause beriberi.) Takaki's classic intervention trial foreshadowed an era of militarily focused, scientifically rigorous preventive medicine research conducted in the field.

## ARMY SURGEON GENERAL STERNBERG

In 1893, George Miller Sternberg was appointed Army Surgeon General. For operational preventive medical research, there could not have been a more propitious time or man for this appointment. While serving as an Army physician, Sternberg became a pioneer in the emerging fields of bacteriology and immunology. He was the first in the world to recognize and describe the pneumococcus and the first in the United States to document plasmodium in a malaria patient. He did exhaustive research into methods and effects of disinfection.[7] He wrote the definitive bacteriology textbook of the time, and his investigations of yellow fever—in the laboratory and in the midst of multiple epidemics—disproved a succession of claims of bacteriologists around the world regarding the disease's etiology. Finally, Sternberg was the first to conduct virus neutralization assays, which remain a keystone of infectious disease research. Yet Sternberg was not one-dimensional. His scientific achievements were matched by remarkable and diverse military accomplishments. He was a skillful and courageous combat surgeon during the Civil War and the Indian wars, and he served in a variety of clinical and public health staff and leadership positions during peacetime.[8]

Thus at a time of exploding knowledge and expanding opportunities, the Army had a Surgeon General who was distinguished as a researcher, scientific innovator, and military officer. He understood the needs and concerns of commanders and soldiers, he knew the importance of basing military medical practices on sound scientific principles, and he perceived the long-term benefits of military medical research. Early in his tenure as Surgeon General, he equipped laboratories and encouraged medical staffs at Army hospitals to con-

duct research, and he developed an aggressive, multidisciplinary, and scientifically robust central research program. Of all of Sternberg's contributions, however, the following are seminal with regard to military research in operational preventive medicine.

### Army Medical School

In 1893, Sternberg founded the Army Medical School, the first graduate school of preventive medicine and public health in the United States. Since its founding, the faculty and staff of the Army Medical School (later renamed the Army Medical Service Graduate School and now the Walter Reed Army Institute of Research [WRAIR]) have provided medical research support to the military services and many of the research efforts described in this chapter were conducted by officers from this institute.

### Outbreak Investigation Teams

As Surgeon General, Sternberg pioneered the use of multidisciplinary specialist teams to investigate diseases that significantly threatened military operations. For example, in 1898 Sternberg commissioned the Reed-Vaughn-Shakespeare Board to determine the causes of the high rates of typhoid fever in Army training camps. Major Walter Reed of the Army Medical School led the team. Vaughn and Shakespeare were commissioned as majors in the US Volunteers for the specific purpose of serving on the board. The board's findings regarding asymptomatic carriage and modes of transmission of typhoid fever provided landmark insights into its epidemiology, pathophysiology, and methods of control.

### Overseas Research Laboratories

Sternberg wanted to establish overseas laboratories so that military scientists on these research boards could work with local experts in the natural settings of tropical diseases of military operational concern. His first research board worked in the Philippines and established a laboratory there. Many officers who served on that board—including Simmons, Strong, Siler, Craig, and Vedder—became Army, national, and world leaders in the fields of tropical diseases, public health, and military preventive medicine.

Sternberg sent his second research board to Cuba,[9] where it also established a laboratory infrastructure. The board's primary mission was to determine the cause, modes of transmission, and means of prevention of yellow fever. The success of the Walter Reed Yellow Fever Commission is legendary. However, a major part of its success is attributable to collaborations with nonmilitary scientists such as Dr. Carlos Finlay, a renowned Cuban physician who developed the theory of yellow fever transmission by stegomyia mosquitoes. Dr. Finlay actively supported the definitive experiments of Reed in Cuba and thus enabled the preeminent military medical research achievement in US history.

Strong central and overseas laboratories staffed with world-class investigators do not ensure successful military preventive medicine research support. Research effort must be focused on operationally significant and militarily relevant problems. Thus, operational military preventive medicine research should begin and end in the field—where real-world problems occur and their effects are most keenly felt. In turn, individual care providers in field settings can play significant roles in military preventive medicine research programs.

## HOOKWORM ANEMIA

In 1899, First Lieutenant Bailey K. Ashford commanded a small Army hospital in Ponce, Puerto Rico. While caring for hurricane victims, he was struck by the high prevalence of anemia with severe asthenia among the local, and particularly the poorest, civilians. He began systematically to examine the blood and stools of "tropical anemia" patients, and soon he noted that the most severely ill patients invariably had eosinophilia and hookworm. More importantly, however, patients whom he treated with thymol, an anthelminthic drug, rapidly increased their red blood cell counts and improved their states of general health. He concluded that hookworm caused tropical anemia and that both could be cured with anthelminthic therapy. In April 1900 in the *New York Medical Journal*, Ashford published his clinical, laboratory, and therapeutic observations and proposed his etiologic theory. The report and theory were largely ignored.

Although discouraged, Ashford asked to be reassigned to Puerto Rico so he could continue his studies and advocate for enhanced treatment and prevention of tropical anemia. In 1903, almost 4 years after publication of his initial observations, the Puerto Rico Anemia Commission was established (with a budget of $5,000). Under its auspices,

**Fig. 5-1.** As a young medical officer in Puerto Rico, Lieutenant Bailey K. Ashford, US Army, discovered that hookworm infestations caused a virulent anemia syndrome that was hyperendemic among local field workers. His subsequent clinical and public health activities inspired worldwide campaigns to diagnose, treat, and prevent hookworm anemia. Reproduced from Ashford. *A Soldier in Science*. New York: William Morrow (Harper Collins); 1934.

Ashford and colleagues established a model clinic in the town of Utuado. As the clinic's reputation grew, however, patients from throughout the island—as many as 1,200 in a day—sought care from Ashford and his staff. During the commission's 7-year existence, more than 300,000 patients were evaluated, treated, and counseled regarding prevention (Figure 5-1).[10]

The success of the Puerto Rico Anemia Commission motivated philanthropist John D. Rockefeller to form the Rockefeller Sanitary Commission to diagnose, treat, and prevent hookworm anemia in the southern United States. The Rockefeller Commission's success in the United States spawned the Rockefeller International Health Commission, which became the renowned Rockefeller Foundation.[10] Untold lives have been saved and countless more improved as a direct result of the dedication and persistence, as well as the skilled field research, of a junior Army medical officer.

## WATER PURIFICATION

In 1909, the Secretary of War appointed a board of officers to investigate and make recommendations regarding water supplies for permanent military installations. In 1910, Major Carl Darnall, a physician assigned to the Chemistry Laboratory of the Army Medical School, began work on a system that used anhydrous chlorine gas to purify water in large quantities. By 1911, Darnall had constructed a prototype apparatus that was small, light (less than 200 lbs), effective, and reliable in laboratory tests. Before it could be accepted for military use, however, Darnall had to test the system's efficacy and reliability under field conditions. Darnall installed his apparatus next to the mechanical filter at the pump house at Fort Myer, Va. For 2 weeks, the systems worked side by side on the same "turbid, at times muddy"[11(p791)] Potomac River water. To explore its range of capabilities, the source water was at times deliberately contaminated with fresh horse manure or drawn downstream from a sewer drainpipe. The trials documented that Darnall's system was simple and inexpensive to install and operate—and was as efficient as other systems and more reliable. The board recommended that the system be used "at a

military post with polluted water and no satisfactory purification system."[11(p796)]

Two years later, Major William Lyster, another Army physician, developed a field water system that used calcium hypochlorite for disinfection. To this day, chlorinated drinking water is stored in canvas bags, referred to as "lyster bags," that hang from tripods and tree limbs throughout military encampments.

Research and development of military water systems eventually became the responsibility of the Corps of Engineers.[12] But early in the 20th century, two Army physicians developed principles and systems for providing safe drinking water to soldiers and their families in the field and in garrison.

## HEMOLYTIC STREPTOCOCCUS AND ACUTE RHEUMATIC FEVER

At the beginning of World War II, streptococcal infections and their acute and late sequelae were considered important childhood diseases but not significant military threats. In addition, there was remarkably little understanding of the natural history or pathophysiology of streptococcal infections, of the relationships between streptococcal infections and acute rheumatic fever, or of the capabilities of antibiotics such as sulfadiazine and penicillin to eradicate carriage, prevent clinical sequelae, or interrupt epidemics.

In 1943, there were rheumatic fever outbreaks at several military bases, particularly in the Rocky Mountain region. At the peak of epidemic activity at one installation, the rheumatic fever attack rate exceeded 10 per 100 persons per year.[13] The following year, prospective studies were conducted at Camp Carson, Colo. The investigators concluded that "if rheumatic fever is to be prevented, hemolytic streptococcal infections must be prevented.…The most urgent studies for the future should be directed toward…preventing hemolytic streptococcal infection and determining the manner in which hemolytic streptococci cause the rheumatic state."[14(p268)] For the next 6 years, though, fears of selecting for and disseminating resistant streptococcal strains precluded studies of penicillin prophylaxis in military populations.

In October 1948, representatives of the Armed Forces Epidemiological Board (AFEB) visited Camp Carson and Lowry Field in Colorado and Fort Francis E. Warren in Wyoming to select a site for long-term studies of streptococcal disease and rheumatic fever. The team chose Fort Warren because of the "high incidence of these diseases and the extreme [medical and command] interest...."[14(p276)] A letter to the site visit team from Colonel John C.B. Elliott, the post's commanding officer, attested to his commitment: "I am determined to solve this problem if it is humanly possible.…I will throw every resource I can to the assistance of this unit if it will come in here and work with us."[14(p279)]

In January 1949, the Streptococcal Disease Laboratory began operations at Fort Warren, an Army (but soon to be an Air Force) technical training base. Dr. Charles Rammelkamp, the laboratory's director, and Army physicians First Lieutenant William Brink, First Lieutenant Floyd Denny, and First Lieutenant Lewis Wannamaker formed the initial professional staff. Army, Air Force, and local civilian personnel provided technical and administrative support. In a series of classic studies, the Laboratory demonstrated that penicillin G was the drug of choice for treating streptococcal pharyngitis, that rheumatic fever could be prevented by the treatment of acute streptococcal infections with penicillin,[15] that treatment lasting 10 days was more effective than shorter courses for eradicating the streptococcus, and that antibiotic therapy within 9 days of onset of acute pharyngitis was effective in preventing rheumatic fever.

The Laboratory also assessed the feasibility and determined the most efficient and effective regimens of mass penicillin prophylaxis to prevent or interrupt epidemics. In early studies, men were given oral, procaine, or benzathine penicillin in various dosages and schedules. The studies documented that complete eradication of streptococcal carriage depended on the penicillin dosage and the period of treatment. In other studies, airmen were given various doses of benzathine penicillin as prophylaxis against streptococcal infections. There was a strong correlation between the dose of benzathine penicillin and the duration of protection from subsequent streptococcal infections.

The elegantly designed and flawlessly executed studies of the Streptococcal Disease Laboratory produced much of the fundamental knowledge that underlies current treatment, prevention, and prophylaxis practices around the world. In recognition of its achievements, in 1954 the Laboratory received the Lasker Award from the American Public Health Association. The citation in part reads: "The success achieved is due in great measure to…keen awareness of the advantages afforded by military populations in epidemiological analyses. The collaboration of the medical departments of all three services in the work of the Laboratory, with minor

exceptions, has been exemplary."[14(p303)]

The Laboratory formally closed in September 1955. Ironically, there was an outbreak of streptococcal pharyngitis among Air Force trainees at the renamed Warren Air Force Base the following spring. In the midst of the outbreak, Captain John Davis of the base hospital and Dr. Willard Schmidt of Western Reserve University—a veteran of the Streptococcal Disease Laboratory—gave a single injection of benzathine penicillin to each of 2,214 trainees at the start of their training. Trainees with histories of allergies (483) were exempted from penicillin treatment and served as controls. During the first 2 weeks of follow-up, there were no cases of streptococcal pharyngitis in the treated group and 19 in the controls. Three cases "broke through" in the treated group during the third week, but there was still a significant protective effect. By the fourth week and thereafter, streptococcal pharyngitis rates in the two groups were comparable.[16] It was fitting that the real-world effectiveness of mass benzathine penicillin prophylaxis was demonstrated during an outbreak of streptococcal disease at Warren Air Force Base.

With the exception of Reed's Yellow Fever Commission, the legacy of the Streptococcal Disease Laboratory may be preeminent in the annals of operational military preventive medicine research. Today's military scientists and research managers would do well to study and emulate the methods and practices of the Streptococcal Disease Laboratory.

## TROPICAL SKIN DISEASES

During the Vietnam War, skin diseases were the leading cause of clinic visits and the third leading cause of hospitalizations among soldiers, behind gastrointestinal and respiratory illnesses and ahead of malaria.[17]

In 1968, two US Navy physicians, Lieutenant Michael McMillan and Lieutenant Robert Hurwitz, were assigned to the hospital at Quang Tri Combat Base in the northernmost province of South Vietnam. Between October and December, they conducted a prospective study of 50 Marines who were evacuated from the field or otherwise hospitalized for disabling skin diseases ("jungle rot"). Patient histories indicated that most serious lesions developed at sites of minor scratches, mosquito bites, or leech attachments. Most cultures yielded group A beta hemolytic streptococci or *Staphylococcus aureus* or both. In every case, wound debridement and systemic penicillin therapy resulted in rapid healing and return to duty. The Navy physicians concluded that care and cleaning of minor wounds could prevent serious secondary infections, and they recommended the early use of systemic antibiotics to treat "tropical pyoderma."[18]

At about the same time at the southernmost end of Vietnam, infantrymen of the Army's 9th Infantry Division were exposed almost continuously, particularly during the rainy season, to rice paddy or swamp water during combat operations in the Mekong delta. In 1968, the WRAIR deployed a specially trained Field Dermatology Research Team led by Captain Alfred Allen.[17] The team was augmented by David Taplin, a civilian consultant from the University of Miami School of Medicine, who had conducted studies of skin diseases in the Florida Everglades (Figure 5-2).[19]

The team established its field laboratory in the Mekong delta, and between October 1968 and September 1969, it surveyed men of the 9th Division immediately on their return from combat operations (eg, patrols, reconnaissances in force). The investigators examined each soldier and recorded the location, size, and diagnosis of each skin lesion; suspicious lesions were cultured for bacteria and fungi. The team found that during the rainy season, skin diseases reduced the combat strength of rifle companies by as much as a third and that, even in the dry season, skin diseases accounted for nearly 80% of lost field-duty days in typical infantry battalions.[20] The surveys also revealed that bacterial and fungal infections were more prevalent and much more severe in combat troops than in support troops; that in combat troops, 20% of the fungal and most of the bacterial infections occurred in the area of the sock and boot; that the incidence of pyoderma was 2.5 times higher among white as compared to non-white infantrymen; and that group A beta hemolytic streptococci were responsible for as much as 90% of the most serious and disabling ulcerative pyodermas. The team also verified the effectiveness of early, systemic antibiotic treatment of bacterial pyodermas of infantrymen.[21] Based on these findings, the research team recommended the early and aggressive use of penicillin and griseofulvin, limitation of exposures to wet terrain during combat operations when possible, and mandatory removal of wet footwear during periods of "stand-down" from combat operations.

The presence of the research team in the Division area, combined with an aggressive education program, raised awareness among Division personnel regarding the nature and importance of skin infections. In turn, commanders became focused on

**Fig. 5-2.** In the Mekong delta region of South Vietnam and in other regions during rainy seasons, skin infections associated with continuous water immersion were leading causes of combat manpower losses. Studies conducted among front-line units in combat zones led to practical and effective treatments and preventive interventions. Photograph: Courtesy of the Walter Reed Army Institute of Research, Silver Spring, Maryland.

prevention, soldiers reported skin lesions earlier, and medics made more timely and accurate diagnoses. The result was more effective treatment. By the end of the tour of the research team, the 9th Division was losing fewer man-days each week than they had lost each day before the team's arrival.

In retrospect, the "jungle rot" of the Marines in the north was similar in etiology and pathogenesis to the "jungle sores" of infantrymen in the Mekong delta. In both settings, field studies led to preventive practices that decreased morbidity and conserved combat strength.

## PLAGUE

Plague was known to be endemic in Vietnam since at least the start of the 20th century. Beginning in 1962, however, there was a countrywide epidemic that most significantly affected the large coastal cities. In the 5 years from 1962 through 1966, nearly 13,000 cases of plague were recorded among Vietnamese civilians.[22] As the United States expanded its presence in Vietnam in the mid-1960s, plague was considered a significant operational threat—particularly at logistical bases adjacent to foci of the civilian epidemic. To counter the threat, all US servicemembers before departing for Vietnam were immunized with a killed plague vaccine of unproven efficacy.

In 1964, WRAIR deployed a multidisciplinary team to study the plague epidemic and to document its effects on deployed US forces. In initial studies, the team trapped and examined more than 13,000 small mammals to document the distribution and concentration of the plague bacillus in its known natural hosts. Three species of rodents were identified as major plague reservoirs: *Rattus norvegicus*, *R exulans*, and *Suncus murinus*. Specimens of all three had antibodies to *Yersinia pestis*, plague's causative organism, as well as infestations

with Oriental rat fleas (*Xenopsylla cheopis)*, the classic vector of bubonic plague. Even though rats infected with *Y pestis* and fleas competent to transmit plague to humans infested Vietnamese cities and nearby US base camps, US servicemembers were spared. The research question was clear: Were environmental and personal protective measures preventing exposures of troops to infected rats and fleas or was the vaccine providing immunologic protection? Lieutenant Colonel Dan Cavanaugh and colleagues from WRAIR conducted studies to elucidate the answer.

The key turned out to be another disease: murine typhus. Like plague, murine typhus occurs when its etiologic agent (*Rickettsia mooseri*) is transmitted to humans by fleas living on infected rats. Their modes of transmission are similar, but murine typhus—unlike plague—was relatively common among US forces, particularly support personnel in rear areas.[23]

To assess the relative sizes of reservoirs of plague and murine typhus, the WRAIR team trapped 49 rats on US bases at Cam Ranh Bay, Cu Chi, and Ton Son Nhut. Eight (17%) rats had antibodies to *Y pestis* and ten (20%) to *R mooseri*.[24] Next, the team retrieved the stored serum samples of 58 soldiers who had been hospitalized with clinically diagnosed and serologically confirmed murine typhus. The titers to *Y pestis* of 7 (12%) of the 58 confirmed murine typhus patients rose during their hospitalizations. The findings documented that typhus patients were frequently exposed to rat fleas infected with both *R mooseri* and *Y pestis*. Since no coinfected patients developed clinical manifestations of plague, the investigators concluded that the plague vaccine had conferred immunologic protection against flea-transmitted *Y pestis*.

The team's findings were consistent with the experience of US forces in Vietnam. During the entire war, there were only four cases of plague (three of whom had been immunized).[24] After the war, the team's findings helped inform plague vaccination policies in a variety of military and civilian settings.[25]

In retrospect, the legacy of the plague research team may lie more in its methods than its findings. It demonstrated that stored biological materials, particularly those linked to unique military or clinical circumstances, could yield significant, and unpredictable, military medical research benefits. Also, the team's ingenious use of specimens collected for studies of one disease to investigate an epidemiologically similar disease of greater military operational concern exemplified attributes essential to successful field research, especially in combat environments: focus on the military mission, ingenuity, resourcefulness, and technical excellence.

## MENINGOCOCCAL MENINGITIS

In general, progress in military preventive medicine research has occurred over generations, with each advancing to the limits of the knowledge and technology of the day. The campaign against meningococcal disease, particularly in the setting of military training, exemplifies the value of patience, persistence, and focus across generations. For most of the 20th century, military researchers have led efforts to combat meningococcal meningitis in military trainee populations by developing and proving the efficacy of such interventions as acute respiratory disease wards, sulfa drugs for epidemic interdiction and chemoprophylaxis, and vaccines. This effort spanned 65 years and involved both Army and Navy researchers. The benefits have been felt by military recruits and the commanders who depend on them, but civilian populations have perhaps benefited the most.

In November 1917, during the mobilization for World War I, there was an outbreak of cerebrospinal meningitis among recruits at Camp Jackson, SC.[26] For 8 months, Major William Herrick, chief of the medical service at the camp hospital, systematically tracked the physical and laboratory results of 265 patients with meningitis. He documented fevers, malaise, and respiratory symptoms an average of 48 hours before the first signs of meningitis, and he recovered meningococci from the blood of patients before they had meningeal signs. He concluded that meningococcal disease was primarily a systemic infection, meningitis was a manifestation of secondary infection of the central nervous system, and the spread of meningococci from the nasopharynx to the meninges occurred by bloodborne rather than direct invasion. Special wards were established at Army basic training camps so that trainees with febrile respiratory illnesses could be removed from their units and systematically monitored to detect early signs of meningitis. For decades, the "ARD ward" (acute respiratory disease ward) was a cornerstone of recruit medicine.

In June 1941, Drs. John Dingle, Lewis Thomas, and Allan Morton reported that meningococci were eradicated from the nasopharynges of patients who were treated with sulfadiazine.[27] The findings suggested a potential use of sulfadiazine for epidemic

control. In the midst of a meningitis outbreak at a naval training center in the winter of 1942 to 1943, Lieutenant Francis Cheever, Lieutenant Commander B.B. Breese, and their colleagues from the Naval Medical School, Bethesda, Md, studied the effects of sulfadiazine on meningococcal carriage. Men from a single barracks were divided into two groups: one group received sulfadiazine for 3 days and the other remained untreated. By the fourth day, carriage prevalence had increased among the controls, but all 161 carriers who were treated were negative.[28] The study demonstrated the potential value of mass sulfadiazine treatment to prevent or interrupt meningococcal outbreaks.

That same winter, Colonel Dwight Kuhns and colleagues tested the effects of mass sulfadiazine treatment during meningitis outbreaks at two Army training camps. More than 15,000 soldiers were given 2- or 3-day courses of sulfadiazine. Meningitis rates and carriage prevalences declined and remained low among those who were treated, in extreme contrast to the controls (2 cases among 15,000 given prophylaxis and 40 cases among 19,000 controls).

Kuhns and colleagues concluded that mass sulfadiazine chemoprophylaxis was safe and effective under the following conditions: first, all individuals in a closed group should be treated simultaneously; second, all personnel who later joined the group should be treated before they were incorporated; and third, once treated, the group should be protected from reinfection from outside sources.[29] These principles continue to guide the use of mass antibiotic chemoprophylaxis to control meningococcal and other militarily important communicable diseases.

In 1943, Dr. John Phair, Captain Emanuel Schoenbach, and Dr. Charlotte Root conducted meningococcal carriage studies among soldiers at Fort Meade, Md. While verifying sulfadiazine's effect on nasopharyngeal carriage, they warned that "care must be exercised in the prophylactic employment of the sulfonamides as its widespread and injudicious use might…lead to…infections with sulfonamide resistant meningococci."[30(p153)] The warning was prescient. Mass sulfadiazine chemoprophylaxis was a mainstay of military preventive medicine practice from its first widespread use in 1943 until the emergence of significant sulfa resistance 2 decades later.

In March 1963, there was an outbreak of meningococcal meningitis among recruits at the US Naval Training Center, San Diego. The epidemic continued despite sulfadiazine treatment of all trainees and cadre. An investigation was conducted by a Navy preventive medicine team that was augmented by Dr. Carl Silverman of the Public Health Service and Dr. Harry Feldman, chairman of the Committee on Meningococcal Infections of the Armed Forces Epidemiological Board. In a defining study, Commander Jack Millar supervised the administration of sulfadiazine to trainees of two companies with a combined carriage prevalence of 57%. When therapy was completed, carriage prevalence remained at 49%, and the predominant carriage strains were sulfonamide-resistant group B meningococci.[31]

**Fig. 5-3.** In response to recruit camp meningitis outbreaks caused by antibiotic resistant strains of *Neisseria meningitidis*, Doctor Malcolm Artenstein led a team of military investigators in the development of vaccines against the most dangerous meningococcal serogroups. Photograph: Courtesy of the Walter Reed Army Institute of Research, Silver Spring, Maryland.

The following year, 85 cases of meningitis occurred among military personnel at Fort Ord, Calif. When the fiancée of a trainee died of meningitis soon after they spent a day together, hysteria spread, the post was quarantined, and basic training was suspended.[32] In December 1964, Lieutenant Colonel Joseph Cataldo, deputy surgeon of the Special Warfare Center at Fort Bragg, NC, led a team that provided either sulfadiazine or sulfadiazine plus penicillin to 21,000 trainees, cadre, family members, and civilians who worked on post. Of 5,689 soldiers who gave samples for culture after

completing the therapy, 207 (3.6%) were carriers of sulfa-resistant meningococci. Approximately 3 weeks later, sulfa-resistant strains were the predominant carriage strains in both the sulfadiazine and the sulfadiazine-plus-penicillin treatment groups.[33]

The Cataldo team's experience reinforced findings of Dr. Ross Gauld and colleagues from WRAIR earlier in the year. Gauld's team documented that sulfa-resistant group B meningococci consistently emerged as the predominant carriage strains in serial cohorts of Fort Ord trainees. They concluded that "control demands the development of … a satisfactory immunizing agent."[34(p71)]

In response to the sulfa-resistance crisis, Dr. Malcolm Artenstein (Figure 5-3), a renowned virologist at WRAIR, with Captain Irving Goldschneider and Captain Emil Gottschlich, initiated studies of determinants of immunity against meningococci. They documented that immunity was serogroup-specific, so separate vaccines would have to be developed against each of the five epidemiologically significant serogroups: A, B, C, Y, and W-135. By 1968, they had produced a candidate vaccine against serogroup C meningococci, which caused the most cases at that time. In 1969 and 1970, they conducted large, controlled vaccine efficacy studies at Army basic training camps throughout the country. The results were compelling: only two cases of group C disease occurred among more than 28,000 recruit volunteers who received the experimental vaccine; 73 cases of group C disease occurred among nearly 115,000 unvaccinated controls. In these classic studies, the vaccine efficacy against group-homologous disease was 89.5%.[35] Since the fall of 1971, group C meningococcal vaccine has been given to all new Army and Navy trainees.[36,37]

Through the remainder of the 1970s, vaccines were developed against serogroups A, Y, and W135. Since the fall of 1982, recruits in all the services have received the tetravalent (serogroups A, C, Y, W135) meningococcal vaccine before the start of their basic training.[38] There have been few cases and no reported outbreaks of meningococcal disease by vaccine-homologous serogroups in immunized military populations.

Since their development, meningococcal vaccines have saved the lives of hundreds of military trainees. But the number of lives saved at recruit camps is small compared to the number of those—mainly children—who have been protected during epidemics around the world. It was recently estimated that 60 million to 80 million doses of meningococcal vaccine are required annually for worldwide epidemic control.[39]

## LEPTOSPIROSIS ("FORT BRAGG FEVER")

In July 1942, soldiers at Fort Bragg, NC, began to seek medical care for an unknown but distinctive acute febrile illness. The syndrome included spiking fevers, chills, frontal headaches, and lumbar and periorbital pain. The defining feature, however, was a pretibial rash that appeared approximately 4 days after the initial onset of symptoms. Between late July and early September, 40 soldiers presented with the syndrome. Lieutenant Colonel Worth B. Daniels and Captain H. Arthur Grennan, physicians at the post hospital, led the investigation of what seemed a new disease. To assist the investigation, the Army Surgeon General appointed a special commission consisting of Dr. Paul Topping (National Microbiological Institute, National Institutes of Health), Dr. John Paul (Yale University School of Medicine), and Major Cornelius Philip.[32] Despite intensive epidemiologic, clinical, and laboratory investigations (including analyses of mosquitoes and flies and inoculations of patient fluids into humans, monkeys, chicken eggs, and rodents), the etiology could not be determined. The syndrome became known as "pretibial" or "Fort Bragg" fever.[40] Outbreaks of the illness recurred, and investigations into its etiology continued through the next 2 summers.

In 1943, First Lieutenant (later Captain) Hugh Tatlock was assigned to the Fort Bragg laboratory of the Commission on Acute Respiratory Diseases of the Armed Forces Epidemiological Board. In August 1944, Dr. Tatlock injected the fresh blood of a soldier with pretibial fever into laboratory animals. Eventually, the filtered plasma of a febrile guinea pig yielded a "virus" that was immunologically distinct from rickettsiae and viruses[41] that were known at the time to cause similar illnesses. Tatlock thought he had discovered the viral etiology of the new disease.

In 1951, Major William Gochenour and his colleagues at the Army Medical Service Graduate School in Washington, DC, decided to reexamine the sera of soldiers who had been diagnosed with Fort Bragg fever during the outbreak of 1944, including the patient from whom Tatlock had recovered the "new virus." Serum pairs were tested against antigens from a collection of strains of leptospirosis. Convalescent specimens had high titers of antibodies reactive with antigens of *Leptospira autumnalis*, a well-known cause of febrile illnesses in Japan. Additional studies confirmed that Fort

**Fig. 5-4.** Epidemiologic investigations documented that leptospirosis was a consistent threat to participants in jungle training during rainy seasons in Panama. Controlled studies among US-based units that deployed to jungle training during a rainy season demonstrated the clear effectiveness of doxycycline chemoprophylaxis. Photograph: Courtesy of Colonel Jerome J. Karwacki, Medical Corps, US Army.

Bragg fever was a leptospiral rather than a viral illness. The Fort Bragg strain of leptospirosis was eventually designated *L interogans*, serogroup *autumnalis*, serovar *fort-bragg*.[42] Thus, patient sera collected at Fort Bragg 8 years previously enabled military scientists in laboratories in Washington, DC, to link Fort Bragg fever to a strain of leptospirosis that was previously undocumented in the United States.[43]

But the book was not closed on leptospirosis. In 1981, epidemiologists from WRAIR investigated an outbreak of acute febrile illnesses among soldiers who had recently returned from jungle training in Panama (Figure 5-4). The team documented that leptospirosis caused the outbreak. Active surveillance of other units training in Panama revealed recurrent high attack rates of leptospirosis during the rainy season (September through December). In collaboration with the command surgeons of deploying airborne and ranger units, Lieutenant Colonels Ernest Takafuji and James Kirkpatrick and colleagues from WRAIR traveled to the Jungle Operations Training Center at Fort Sherman, Panama, to conduct a randomized, double-blinded, placebo-controlled field study of the effectiveness of doxycycline as prophylaxis against leptospirosis. The results demonstrated an unequivocal preventive effect.[44] In March 1983, the AFEB recommended that all soldiers attending Panama jungle training during the rainy season receive doxycycline prophylaxis.[45] In August 1983, the AFEB's recommendation became Army policy.[46]

Dr. Daniels, who described Fort Bragg fever, commented that "the disease was described by Army clinicians, studied by Army medical personnel with the assistance of Army consigned consultants, transmitted to animals by an Army research worker, and finally proved as to etiology by an Army veterinarian and others."[32(p83)] He could have added that Army epidemiologists characterized its military importance, and Army physicians developed, tested, and fielded a safe, inexpensive, and highly efficacious preventive measure.

The success of military preventive medicine with regard to leptospirosis required transfers of information, insights, and precious clinical materials from field sites to central laboratories, among investigators of various specialties, and across generations. The overall experience stands as a model of effective operational military preventive medicine research.

## JAPANESE B ENCEPHALITIS

Japanese encephalitis (JE), a mosquito-transmitted viral disease, is the predominant cause of outbreak-associated encephalitis in the world. Japanese B virus, the causative agent of JE, is enzootic in domestic animals throughout the southwest Pacific and southeast Asia. In endemic regions, there are seasonal increases in JE incidence and occasional large outbreaks.[47]

In July 1945, there were several cases of encephalitis among inhabitants of Heanza Shima, a small island close to Okinawa. A few days later, four cases were reported among residents of the main island. Naval Medical Research Unit 2 in Guam confirmed the diagnosis of Japanese B viral encephalitis and sent a team to assist medical officials from the US Military Government of Okinawa in an investigation.

Through July and August, cases of encephalitis continued to occur among the indigenous populations of Okinawa (91 cases) and two nearby islands (36 cases). Although more than 80% of cases were among children (nearly a third of all cases were fatal), the US occupation forces were not spared. Between July and September 1945, 38 Americans developed illnesses compatible with viral infections of the brain, 12 developed severe manifestations of encephalitis, and 2 died. Autopsy examinations of brain tissue and assays of convalescent sera implicated Japanese B virus as the cause. Lieutenant Colonel Albert Sabin of the Army Epidemiology Board joined the investigation.[48]

Sabin and colleagues observed that all cases of encephalitis among Americans occurred among the relatively few who were stationed in the northern part of the island. Factors that increased the risk for an outbreak included unsuccessful attempts to eradicate mosquito-breeding sites, particularly in the north because of its rough terrain, and the fact that for military reasons, most civilians and their domestic animals had been moved from the south to the north of the island before the outbreak. Also, serosurveys revealed that prevalences of virus-neutralizing antibodies increased with age among Okinawan residents (10 years or younger: 0%; 11 to 19 years: 55%; 20 years or older: 90%) and that indigenous domestic animals, including horses, goats, and cows, had serologic evidence of prior infections. Finally, there was a large outbreak of malaria in the island's northern provinces coincident with the encephalitis outbreak.

Sabin and local military public health officials concluded that there was an imminent and significant JE risk to American forces on Okinawa, particularly those deployed near foci of the civilian outbreak. The urgency of the public health situation, as well as the military operational circumstances, precluded a controlled study of the safety and efficacy of an inactivated mouse brain extract vaccine, the only product available for immediate use. Without delay, programs of aggressive mosquito control and mass vaccination were initiated. By the end of the summer, more than 60,000 personnel stationed in the north of the island had been immunized with remarkably few serious side effects.[48] The outbreak subsided coincident with the immunization campaign, but because there were no unimmunized controls, the independent effects of the vaccine could not reliably be determined.

Only a few years after World War II, US forces were again engaged in a JE-endemic theater. In 1946, Sabin and colleagues reported four cases of JE among American soldiers in southern Korea.[49] In 1949, Army physicians helped South Korean health officials investigate a large JE outbreak that included more than 5,500 cases, of which more than 40% were fatal. During the investigation, cattle, sheep, horses, and swine were found to have high prevalences of antibodies to Japanese B virus. Thus, by 1950, JE was known to be entrenched on the Korean peninsula,[50] and it soon showed that it could have an effect on military operations. During the summer of 1950, there was an outbreak among US forces that included an estimated 300 cases—of which at least 19 were fatal—among personnel who were defending the Pusan perimeter. At the peak of the outbreak, 10 cases per day—as many as 20 in a single night—were admitted to an Army evacuation hospital that was already overwhelmed with combat casualties.[51]

Approximately a decade later, Japanese B virus again attacked US forces but this time in southeast Asia. Between April and September 1969, Army physicians Captain W. Bruce Ketel and Lieutenant Colonel Andre J. Ognibene described the clinical courses of 57 patients with encephalitis who were evaluated at the 93d Evacuation Hospital in Long Binh, South Vietnam. Virus isolation and serologic studies implicated Japanese B virus as the principal cause. The authors estimated that during the outbreak as many as 10,000 US servicemembers may have been infected, most with mild or no symptoms. The authors asserted the need for a safe and effective vaccine.[52]

In 1984 and 1985, Lieutenant Colonel Charles Hoke and colleagues from the Armed Forces Research Institute of Medical Sciences in Bangkok,

Thailand, conducted a randomized, blinded, placebo-controlled trial of a highly purified, inactivated JE vaccine made from whole virus derived from mouse brain. Between November 1984 and March 1985, more than 60,000 children living in an endemic area of northern Thailand received either JE vaccine or placebo (tetanus toxoid). The vaccine's observed protective effect was 91%.[53] And in 1994, Major Jeffery Gambel and colleagues used sera routinely collected and stored in the Department of Defense Serum Repository to document persistence of antibodies to Japanese B virus up to 3 years after a primary immunizing series.[54]

Today, US forces are protected against JE, a persistent and widespread threat to military operations in the strategically critical Asia-Pacific region. Field studies during outbreaks in World War II, Korea, and Vietnam made clear the military importance of JE and the need for a safe and effective vaccine. Hoke's study among children in Thailand validated Sternberg's concept of 90 years earlier that military preventive medicine research, especially during peacetime, is often best conducted in *nonmilitary* settings of high disease risk. Finally, Gambel's study was the first to employ routinely archived serial serum specimens of active duty soldiers for the explicit purpose of military operational preventive medicine research.

## MALARIA

Following World War I, Germany conducted intensive research to develop synthetic alternatives to quinine for preventing and treating malaria. In 1933, their efforts were rewarded with the discovery of quinacrine hydrochloride (Atabrine). When the United States and its allies lost access to natural sources of quinine at the beginning of World War II, quinacrine became, and remained throughout the war, the mainstay of Allied malaria prevention efforts.[55]

During World War II, there were more than 115,000 cases of malaria annually among US soldiers;[56] most were caused by South Pacific strains of *Plasmodium vivax* notorious for their propensity to relapse.[57] During the war, the malaria chemotherapy research program of the National Research Council supported the synthesis and testing of more than 14,000 candidate antimalarial compounds. Of approximately 80 that were tested against human malaria strains, the most promising was chloroquine, a member of the 4-aminoquinoline class.[58] In July 1945, the Board for Coordination of Malaria Studies of the National Research Council recommended a trial of the chemoprophylactic effects of chloroquine among troops in the Pacific. In August 1945, Major John Maier, on a leave of absence from the Rockefeller Foundation, began a study of weekly chloroquine (compared to daily quinacrine) among Army engineers operating on the Bataan Peninsula in the Philippines. Unfortunately from a medical research perspective, the war ended and units began demobilizing within weeks of the study's commencement.[59]

In the aftermath of World War II, Colonel John Elmendorf, commandant of the Army School of Malariology, Fort Clayton, Canal Zone, studied the long-term effects of various methods of malaria control in small towns in Panama.[60] Elmendorf and colleagues documented that weekly chloroquine was well tolerated and effective against *P falciparum* and erythrocytic forms of *P malariae* and *P vivax*. Elmendorf had to terminate his studies prematurely when the Army School of Malariology closed in December 1946.[61]

Following World War II, military malaria research flagged[62] as the threats to US forces waned. However, in 1950 when Korean forces from the north invaded the south, the United States again faced the challenge of deploying a large nonimmune force to a malaria-endemic theater. Through the summer of 1950, US servicemembers intermingled with multitudes of civilian refugees who poured into the collapsing beachhead at Pusan.[63] Conditions favored the rampant transmission of malaria, as housing, sanitation, and mosquito control failed. In July, the Army Surgeon General directed that troops in Korea receive weekly chloroquine prophylaxis. Because of limited supplies, however, the routine use of chloroquine ceased in October 1950, as the seasonal risk passed, and then resumed the following April. Still, in 1950 there were remarkably few cases of malaria among troops who complied with the prescribed prophylaxis regimen.[55]

With the start of routine troop rotations in the spring of 1951, however, the Korean malaria situation abruptly worsened. Vivax malaria emerged among thousands of servicemembers who had stopped their chemoprophylaxis[64] while en route to their homes or new duty assignments throughout the United States.[65] An answer was needed.

Of the thousands of compounds screened during World War II, only the 8-aminoquinolines displayed activity against exoerythrocytic ("tissue") forms of malaria. Primaquine, an 8-aminoquinoline synthesized at Columbia University, had the best

margin between its minimal effective and maximal tolerated doses. In the 1940s, studies among inmate volunteers at federal penitentiaries documented that primaquine plus either chloroquine or quinine cured infections with prototypical strains of vivax malaria.[55] Unfortunately, when the Korean War began, primaquine was still experimental, and there had not been trials of its efficacy against strains of Korean origin. Clearly, in the summer of 1951, there was an urgent need for research and policy regarding the use of primaquine.

In August 1951, the Army Surgeon General established an expert mission to assess the feasibility of using mass primaquine therapy among returning Korean War veterans. The mission concluded that all troops leaving Korea should receive 15 mg of primaquine daily for 2 weeks—the maximum dose considered at the time to be safe without medical supervision. Before the policy could be promulgated, however, its feasibility and safety under real-world conditions had to be assessed.

In September 1951, Dr. Alf Alving of the University of Chicago, Major John Arnold, and Major Donald Robinson conducted studies of mass primaquine treatment without direct medical supervision aboard troop ships. On 18 September, in Sasebo, Japan, 1,493 servicemembers boarded the *USNS Sergeant Sylvester Antolak* destined for Seattle, Wash. The men were divided into two groups: one group received 15 mg of primaquine daily and the other received placebo. The voyage was rougher than usual for the season, but, remarkably, seasickness affected exactly the same number of men in each group. More importantly perhaps, there were no signs of toxicity associated with the primaquine, and, specifically, there was no evidence of hemolysis among black troops (approximately 17% of the total).[64] Shortly after the *Antolak* sailed, 2,060 servicemembers bound for the United States boarded the *USNS Marine Phoenix*. The men had taken daily primaquine for variable periods while awaiting embarkation, but once aboard, they were divided into two groups: one continued daily primaquine and the other took placebo. Again there were no significant differences in either seasickness or tolerance of the treatments between the groups.[64] The shipboard trials of Alving and colleagues documented the feasibility, tolerability, and safety of mass primaquine therapy even under the conditions of long and rough sea voyages. In short order, the Armed Forces Medical Policy Council advised the Services to begin routine primaquine therapy for all personnel leaving Korea.[66] The policy was instituted in December 1951.

As the malaria epidemic emerged among Korean War veterans, Alving and collaborators from the Army, Navy, Public Health Service, and civilian academic institutions conducted studies at Forts Breckenridge (Ky), Meade (Md), Dix (NJ), and Benning (Ga) and at Camp LeJeune (NC). Among hundreds of Korean War veterans with malaria, the investigators assessed the therapeutic and toxic effects of various regimens of primaquine plus chloroquine. Of numerous important findings, the studies revealed that 40% to 50% of vivax malaria of Korean origin relapsed after treatment with chloroquine alone;[63,67,68] that adding to chloroquine either 10 mg of primaquine daily for 14 days[67] or 15 mg of primaquine daily for 7 days[68] cured most cases; that 20 mg of primaquine daily for 7 days produced severe hemolysis in one black patient of 14 who were treated with the regimen;[67] and, finally, that 15 mg of primaquine daily for 14 days plus chloroquine was the treatment of choice for radical cure of Korean vivax malaria.[63] By the end of 1951, due in great part to the expeditious and incisive studies of Alving and his collaborators, the Services had safe and effective malaria control[66] and treatment[69] programs. In fact, much of current practice regarding the use of primaquine derives from studies conducted during the Korean War.

The military's experience in Korea helped foster unprecedented optimism regarding malaria's prevention, control, and even eradication. In 1960, however, the euphoria turned to apprehension with the first report of chloroquine-resistant *P falciparum.* Two American geophysicists working in Colombia, South America, were the first reported cases.[70] In short order, resistant falciparum strains were documented in other countries of South America and in southeast Asia. Years later, Brigadier General William Tigertt, commandant of WRAIR, recalled the "incredulity with which such reports were received by public health workers"[71(p605)] in southeast Asia. Major General Joe Blumberg, commanding general of the Army Medical Research and Development Command, recounted that "no organized effort to deal with resistant *P falciparum* was begun until, as has repeatedly happened in the past, it was fully recognized to be a problem of grave military importance."[62(p730)]

In August 1962, a US Marine captain stationed in Nha Trang, Vietnam, developed falciparum malaria despite weekly chloroquine prophylaxis. In November, he was transferred to the Navy Hospital at Great Lakes, Ill, after his infection had withstood three courses of escalating dosages of chloroquine. At Great Lakes, Captain Robin Powell and col-

leagues (including Dr. Alving) unequivocally documented the chloroquine resistance of the captain's Vietnam-acquired strain.[72] In 1964, Major Llewellyn Legters, Preventive Medicine Officer at the Army Special Warfare Center at Fort Bragg, NC, and colleagues reported three cases of chloroquine-resistant falciparum malaria among recent returnees from Vietnam.[73] The authors emphasized the urgent need for drugs that would "prevent infections with drug resistant strains of *P falciparum*."[73(p175)]

Several years before significant US involvement in Vietnam, Lieutenant Colonel Stefan Vivona of WRAIR had conducted a study of more than 50,000 participants that demonstrated that weekly chloroquine plus primaquine (45 mg) formulated in a single tablet was a safe and feasible method of providing malaria chemoprophylaxis under field conditions.[74] In 1962, the weekly C-P tablet became the Army standard regimen for malaria chemoprophylaxis,[75] and it was the prescribed method of malaria control in the early years of US operations in Vietnam.

In late 1965, US force strength and cases of malaria (more than 98% *P falciparum*[76]) began to increase rapidly in Vietnam. Major Taras Nowosiwsky, Preventive Medicine Officer, Office of the Surgeon, US Army Vietnam, tracked malaria experience among US troops through a longitudinal system that "provided a continuous flow of information on the whereabouts of individual units each night by area of bivouac."[77(p462)] He documented few cases among troops who remained in base camps, but in five separate outbreaks during combat operations in endemic areas, he estimated that the average attack rate of *P falciparum* malaria was 10 per 1,000 men per day.[77]

In 1963, the Army launched the Antimalarial Drug Development Program to develop drugs to prevent or treat chloroquine-resistant *P falciparum* malaria. During the next 10 years, 27 of more than 200,000 compounds received Food and Drug Administration approval for advanced clinical testing in humans.[78] One drug tested early in the program was 4,4′ diaminodiphenylsulfone (Dapsone), which was found to prevent patient infections with chloroquine-resistant strains of *P falciparum*.[79] In 1966, Major Robert J.T. Joy, chief of the Army Medical Research Team in Vietnam, conducted controlled studies of the chemoprophylactic effects of Dapsone (plus weekly C-P) among soldiers of the Army's 1st Cavalry Division and 25th Infantry Division during combat operations in Vietnam's Central Highlands, an area of known high malaria risk. All study participants continued weekly C-P chemoprophylaxis to which they added either daily Dapsone (25 mg) or placebo. Joy's studies documented significantly lower malaria attack rates in units that supplemented weekly C-P with Dapsone.[80,81] Despite uncontrollable differences among the units in the nature and intensities of their malaria exposures (eg, times, locations, and characteristics of combat operations) and in levels of compliance with prescribed chemoprophylactic regimens, Joy's findings were pivotal to the revision of Army malaria control policy. In July 1966, the Surgeon General directed that Dapsone be added to weekly C-P prophylaxis when troops in Vietnam were at high risk of exposure to drug-resistant *P falciparum* (as determined by the US Army Vietnam preventive medicine officer).[82]

Just as during the Korean War, malaria (mostly caused by *P vivax*) emerged in large numbers among returning Vietnam veterans in the late 1960s. In response, Army clinical investigators studied the responsiveness of *P vivax* of Vietnamese origin to the standard suppressive dose of chloroquine (300 mg) plus primaquine (45 mg). Of 42 patients with acute vivax malaria who were treated with a single C-P tablet, all had prompt clinical responses, and none had documented parasitic or clinical relapses.[83] To assess compliance with prescribed terminal prophylaxis regimens, Colonel O'Neill Barrett and colleagues surveyed 671 recent Vietnam returnees. Most respondents (70%) admitted failure to take terminal chemoprophylaxis as prescribed, and 25% reported taking no prophylaxis at all. Rank and personal experiences with malaria were not significant correlates of compliance.[76] Together, the studies documented that noncompliance, rather than drug refractoriness, accounted for most malaria cases among returning servicemembers.

The malaria experiences of the military services in World War II, Korea, and Vietnam have been replayed many times on smaller scales. For example, in December 1992, the United States deployed forces to Somalia to provide security and humanitarian assistance. Between December 1992 and May 1993, 48 cases of malaria occurred among deployed US servicemembers; most (85%) were caused by *P falciparum*. Risk factors were noncompliance with prescribed chemoprophylaxis and failure to use personal protective measures against arthropods.[84] Vivax malaria emerged in significant numbers after soldiers and Marines returned to the United States.[85] Beginning in May 1993, Lieutenant Colonel Bonnie Smoak and colleagues from WRAIR investigated an outbreak of malaria among recent Somalia returnees from the Army's 10th Mountain Division at Fort Drum, NY. Following initial clinical attacks, 60 soldiers received standard curative

courses of primaquine: 15 mg daily for 14 days. Twenty-six (43%) of the sixty cases relapsed and required a second treatment course, and eight of them relapsed a second time. Higher doses of primaquine (30 mg daily for 14 days) were needed to achieve radical cures in these refractory cases. The experience suggested that primaquine-resistant *P vivax* strains were endemic at least focally in Somalia.[86]

At the turn of the century, Spanish-born American philosopher George Santayana wrote: "Progress, far from consisting in change, depends on retentiveness… when experience is not retained, as among savages, infancy is perpetual."[87(ch12)] Nearly 60 years later, Brigadier General William Tigertt reflected that "malaria can never be regarded with complacency and always must remain high on the military medical research priorities list. If we and those to follow us fail to recognize this, we and they deserve to be classified as savages in the sense the word was used by Santayana."[88(p82)]

## SUMMARY

Nearly a century ago, Sternberg realized that there were medical threats unique to military service that were unlikely to be addressed by nonmilitary medical investigators. Thus, as Surgeon General, he established institutions (eg, central and overseas research laboratories) and procedures (eg, deployable multispecialty research teams, military-civilian collaboration mechanisms) to ensure that state-of-the-art research capabilities could be applied to and integrated with military operations worldwide. The field preventive medicine research successes recounted in this chapter attest to the value of the system and the procedures he established. Common characteristics of those successes include investigator selflessness, military operational relevance, medical command support, field command support, and collaboration with nonmilitary colleagues.

The preventive medicine researchers discussed in this chapter focused their studies on operationally critical aspects of militarily relevant questions. Their research agendas were not driven by their personal professional interests or the nonmilitary research priorities of others. Still, many military researchers gained professional prominence, acclaim, and respect for their studies that focused on military problems.

Military medical researchers require support (eg, administrative, logistical, monetary, technical) from parent institutions before, during, and after the field phase of studies. While the scope, level, and duration of necessary support are easily and often underestimated, the successful research programs described here were generally well supported. In addition, properly archived biological specimens often have provided the keys to success of military preventive medicine research programs. It is sobering, however, to note that gaps and inconsistencies in levels of support—generally due to shortsighted shifts in priorities, agendas, and budgets—frequently threatened the ultimately successful outcomes of even the most productive and widely acclaimed military research programs.

Operational preventive medicine research requires the sincere and dedicated support of the field (nonmedical) chain of command. Without exception, field commanders and their subordinate leaders provided access and support to the successful research programs discussed in this chapter.

The most successful military research programs consistently involved close collaborations with nonmilitary subject matter experts. Through the years, various mechanisms have been used to link military investigators with their civilian scientific and technical counterparts. For example, during war and other national emergencies, nonmilitary researchers have often been drafted into or volunteered for military medical service. Also, nonmilitary institutions (eg, academic centers, proprietary and nonprofit research and service organizations) have often collaborated with military research institutes on studies of mutual interest.

If necessity is the mother of invention, then military operations, particularly during combat, indeed provide fertile opportunities for military preventive medicine research. In turn, the military preventive medicine research successes of the past, such as those reviewed in this chapter, should challenge, motivate, and guide future military medical researchers and their leaders.

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