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FEVER: BEYOND MALARIA

I confess myself unable to differentiate certain cases of malarial remittent from typhoid fever, without the blood examination.

—William Osler, 1892

In 1844, in *Zeitschrift für rationelle mediz,* a treatise exhorting physicians to apply scientific thought and methods to medicine, Jacob Henle wrote:

> Only in medicine are there causes that have hundreds of consequences or that can, on arbitrary occasions, remain entirely without effect. Only in medicine can the same effect flow from the most varied possible sources. One need only glance at the chapters on etiology in handbooks or monographs. For almost every disease, after a specific cause or the admission that such a cause is not yet known, one finds the same horde of harmful influences—poor housing and clothing, liquor and sex, hunger and anxiety. This is just as scientific as if a physicist were to teach that bodies fall because boards or beams are removed, because ropes or cables break, or because of openings, and so forth.[1]

Over a century and a half later, Henle's eloquent description of the problem of confounding causes with effects remains applicable to the case of fevers in Africa. Despite scientific advances in the understanding of specific febrile illnesses, the treatment of fever continues to be based on empirical symptoms rather than laboratory diagnosis—with consequences that are often fatal to individuals and devastating for whole societies.

In tropical Africa, malaria exerts a heavy burden by sickening up to half of the population in highly endemic areas each year. Most malaria attacks manifest as a brief but debilitating fever, but the more severe forms of the disease account for most of the deaths. In severe malaria, parasite-infected red blood cells stick to

each other, to uninfected cells, and to the lining of blood vessels. This clumping reduces the number of red blood cells available to deliver oxygen to vital organs and occludes blood vessels. In the worst cases, red blood cells stick within the brain and, in the case of pregnant women, the placenta. *Plasmodium falciparum,* the parasite form that causes severe malaria, produces these effects through a specific and deadly mechanism. Red blood cells are converted from oxygen couriers for the host into parasite factories. Channels created on the red cell's surface serve as ports for nutrients, and many blood cell proteins are digested to provide fodder for the developing merozoites. New parasite proteins are mounted on the outside of the red blood cells, forming unsightly knobs that can be seen with an electron microscope. A key component of these knobs is a recently described protein called PfEMP1 (*Plasmodium falciparum* erythrocyte membrane protein 1), which is encoded by *var* genes, so named because of their ability to shuffle, ensuring that the precise nature of PfEMP1 varies constantly. Each strain of *P. falciparum* boasts about sixty different *var* genes, providing a large repertoire of potential cassettes that can be used to vary the part of PfEMP1 that is recognized by the host immune system. Although some iterations of PfEMP1 are probably more effective, and therefore more deadly, than others, by and large the variable regions are interspersed with the functional regions so that the structure of these proteins changes only ever so slightly but strategically. This variation allows the parasite to prevent the immune system from learning how to identify and remove infected cells. It also makes it difficult to make vaccines that protect against severe malaria.

Mounting proteins on the host cell membrane is an extremely effective tactic. Even more ingenious is endowing these knob proteins with the ability to make the infected cell sticky. Unlike normal red blood cells, PfEMP1-coated red blood cells fail to slip through capillary blood vessels. They stick to the sides of capillaries and to each other, providing a cozy cocoon for forms of the parasite that do not live in cells, including the sexual forms, gametocytes, which are sucked up with blood by mosquitoes in order to infect new hosts. The infected patient's blood vessels are soon dotted with sticky clumps, known as rosettes. Uninfected red cells become trapped in rosettes made by infected ones, making it easier for newly emerged parasites to find a target host cell without being destroyed by armies of protective white blood cells. The formation of rosettes ultimately leads to blood vessel clogging, and, depending on their location, convulsions, potentially fatal coma, or organ failure in the same manner that internal blood clots cause strokes. As more blood cells are pulled from circulation or ruptured by escaping parasites, patients become acutely anemic; not enough oxygen is conveyed to the body's cells, leading to further complications. Four of the many *Plasmodium* species can cause disease in humans, but only *P. falciparum,* the

predominantly African species, produces the deadly PfEMP1. PfEMP1 has preferred binding sites on human cells, and variation in the distribution and location of host proteins could account for some of the interindividual variation in the predisposition to severe malaria. Severe malaria is therefore a syndrome with a very specific cause: a protein produced by the pathogen. The action of this protein and many other virulence factors, most of which remain unknown, make it vital that *falciparum* malaria is diagnosed promptly and treated appropriately.

The severe malaria that was presumed to have killed fourteen-year-old Emeka is the cause of almost two million deaths each year, mostly very young children in Africa.[2] Typically, the central nervous system is involved, causing convulsions, and severe malaria is often fatal, even when patients are taken to the hospital. The shocking truth is that the optimal way to intervene in this deadly course is not known. As many as 15 to 20 percent of patients admitted to the hospital with severe malaria die, even if they are given antimalarials and supportive care. Patients in a *P. falciparum*–endemic area with fever who also show anemia and convulsions or impaired consciousness are presumed to have severe malaria.[3] Diagnosis depends on a combination of clinical examination and relatively simple laboratory testing. The syndrome is defined by both a lowered hemoglobin level and an elevated parasite count, making it one of many conditions common in Africa in which definition of the disease assumes a laboratory diagnosis even though one is rarely implemented. The syndrome's inordinately high parasite counts can readily be determined by microscopy, while hemoglobin levels can be estimated with the most rudimentary of centrifuges or with a more recently devised portable testing system. Fortunately, many secondary care and some primary care institutions can perform these tests, since these patients urgently need transfusion. However, some facilities lack the capacity to screen blood, so transfusions carry the risk of transmitting an even more deadly disease such as HIV or hepatitis.

That so many of these patients do not survive is attributed to the poor response of the severe malaria syndrome to available therapies, which do not affect the deadly cascade of blood clumping and central nervous system damage. This attribution in turn depends on the presumption that clinical diagnosis of severe malaria is reliable. In many parts of Africa, *falciparum* malaria is so highly endemic that many patients with these symptoms do have the syndrome. But the symptoms of severe malaria resemble those of life-threatening systemic bacterial infections, which respond well to timely medical intervention. Blood is a nutritious medium, and a wide variety of organisms will thrive there. Although malaria parasites have the edge of an injecting vector, the mosquito, bacteria, viruses, and other parasites also can cause bloodstream infections. Many of these infections are treatable, provided they are identified in time.

Recent reports from multiple African sites have observed that clinical diagnosis of severe malaria is often imprecise. Doctors in a teaching hospital in Kumasi, Ghana, found that the clinical signs and symptoms were insufficient to distinguish patients with severe malaria from those with life-threatening bacteremia. According to Jennifer A. Evans and her co-workers, 182 of 251 patients (72.5%) were shown to have malaria, but 11.1 percent of patients—who without laboratory workup would have been diagnosed as having malaria—were negative for malaria parasites and actually had a bacterial bloodstream infection, that is, bacteremia. The other twenty-three patients (9.2%) were infected with both plasmodia and bacteria. Indeed, the severe presentation of many children with bloodstream infections arose from misdiagnosis at an earlier stage in their illness. In 2000, 42 percent of all illnesses and 32 percent of all deaths in Tanzania were attributed to malaria, but when clinical scientists attempted to verify malaria diagnoses in the laboratory, only 46 percent of patients diagnosed with malaria actually had the disease. Doctors in Kilifi, Kenya, like their colleagues in Ghana and Tanzania, noticed a high mortality rate among children admitted with high fever. When they processed blood cultures in the lab for every child admitted between August 1998 and July 2002, much to their surprise they found that bacteremia was a leading cause of death in children, responsible for one in three infant deaths and a quarter of deaths in older children. The most common bacteria identified were *Streptococcus pneumoniae* and *Haemophilus influenzae,* both of which also cause respiratory and ear infections, as well as nontyphoidal *Salmonella,* that is, those strains that do not produce typhoid fever. In a fourth example from Malawi, clinical signs alone had an acceptable predictive accuracy for bloodstream infections caused by *Mycobacterium tuberculosis* or *Streptococcus pneumoniae,* but they were unable to differentiate bacteremia caused by nontyphoidal *Salmonella* from malaria. In 2007, a group in Tanzania found that severe infections in young children were more commonly bacterial than malarial and that severe bacterial bloodstream infections were a leading cause of death at the Muhimbili National Hospital in Dar es Salaam.[4]

Blood culture by first principles, which is still the most common approach used in the African laboratories that provide this service, is challenging but possible on a small budget, provided that a skilled and dedicated microbiologist performs the procedure. Because blood culture directly informs treatment for the most deadly infections, the expense, time, and effort that must be invested is worthwhile. Culturing pathogens from blood specimens is fraught with technical difficulties for laboratories in developing countries. Blood is a supremely nutritious medium, and some organisms that infect blood are very demanding to culture outside the body. First, blood must be collected from the patient, taking care to avoid contamination of the sample from the patient's skin or the

environment. A liquid broth culture is prepared by adding 3–5ml of blood to media in large bottles. Some patients are too ill to spare enough blood for the test. Blood culture bottles are expensive and, because of their large size, difficult to ship, an important consideration in a continent where virtually all laboratory materials are imported from abroad.

If bacteria grow in the primary culture medium, the causative organism is subcultured on plates of solid media, isolated, and identified. To recover some of the most common isolates from children, including *Streptococcus pneumoniae,* clean blood must be added to media as a supplement. Many African laboratories are forced to use expired human blood obtained from blood banks. If the blood contains antibodies against the causative organism being cultured, growth will be inhibited; if the blood donor had recently taken antimicrobials before donating the sample, these too might inhibit target organisms. Western laboratories use commercially available sheep or horse blood. There is little incentive for companies to produce blood culture bottles or sheep blood in many parts of Africa because so few institutions use the products. Many more things can go wrong in this process, making the isolation rate of many diagnostic laboratories low and sometimes confounded by contamination. When common, but fastidious, organisms such as *Strep. pneumoniae* are missed, physicians lose confidence in the laboratory. Thus diagnostic development must be implemented to the highest standards of quality. Western laboratories overcome many of the difficulties associated with blood culture by using automated systems. Although these are costly, because of the challenges associated with blood culture by traditional methods, they are cost effective, particularly if many specimens must be processed. This is true even in Africa, and automated systems, though few and far between, are the best option for reference laboratories and large hospitals and have even been used successfully in rural hospitals.[5] In the Kilifi, Kenya, and 2007 Dar es Salaam studies, basic blood culture conditions were close to ideal, and a very high yield of bacterial cultures was reported, although in both cases the authors observe that it is likely that some cases were missed. Accurate results from blood cultures can improve cure rates considerably. Given the case-fatality rates for bacteremia, particularly in young children, investment in at least some form of blood culture is justified by the results.

Parsing "Typhomalaria"

In addition to septicemia, Lyme disease and a number of viral infections, including influenza, produce symptoms that are similar to malaria.[6] In 1989, I was diagnosed with typhoid fever after four medical consultations. In parts of Africa

that are hyperendemic for malaria, such as Nigeria, typhoid and other bacterial infections are commonly suspected only when malaria medicines do not work. Typhoid fever is caused by the human-adapted Typhi variety of the bacterium *Salmonella enteritidis.* People become infected with the organism by ingesting contaminated food or water. Most non-Typhi *Salmonella* cause uncomplicated diarrhea, but typhoid fever, sometimes called enteric fever, is a systemic illness characterized by a fever that is clinically indistinguishable from malaria. A few other *Salmonella* serovars, Paratyphi A, B and C, can also produce an enteric fever, but it is sometimes milder than that caused by the typhoid bacillus. The typhoid bacillus is the worst of its cousins: prolonged infection can result in death from intestinal perforation.

The ease of typhoid transmission in many parts of the world and the significant fatality rates associated with the infection make early and accurate diagnosis imperative. The only reliable means of diagnosing typhoid fever is by culturing the organisms—that is, by growing and then identifying them. A culture is produced by spreading bacteria, or a specimen containing them, onto a Petri dish containing nutrients and a gelling agent called agar. To grow *Salmonella,* nutrients for growth and chemicals, which inhibit many other bacteria, are added to the agar. Indicators are also added, which produce different colors with different bacteria. The plate is incubated at human body temperature (37°C). The next day, if bacteria are present, they will be visible to the naked eye. Each bacterium laid down the night before will produce a small circular colony a few millimeters in diameter. If the colonies have an appearance consistent with that of *Salmonella* and test positive in confirmatory tests, the laboratory technician then screens for capsule, gooey carbohydrate material on the outside of the bacteria, and flagella, the whiplike structures that bacteria use to move. If the capsule and flagella types are those of Typhi and the patient has a febrile illness, then a diagnosis of typhoid fever can be made. It is possible to test the bacterial culture for susceptibility to different antibiotics. Such susceptibility testing can provide the patient's prescriber with valuable information about which drugs can be used to clear the infection.

Culture is slow and is difficult in poorly equipped laboratories. And the results are not always definitive for typhoid fever. At certain stages of the illness, patients who actually have typhoid may be culture-negative: 75 percent of those infected are culture-positive in the first ten days, but by twenty-one days, the proportion of infections that can be identified by blood culture falls to about 30 percent.[7] In the case of my own probable typhoid infection, at the time I was tested I had been ill for at least a month, so I probably would have been culture-negative. As it is, culture was never attempted on my behalf. To overcome the limitations of culture, serological methods, such as those used in my case, which

detect antityphoidal antibodies in blood, have become prominent for diagnosing typhoid and related infections.

The pioneer in serological diagnosis of typhoid was Georges-Fernand-Isidor Widal. In 1896, he developed the classic test that bears his name after observing that a clumping reaction occurs when serum (blood from which the blood cells have been removed) from people who have, or have had, typhoid is mixed with *S.* Typhi. The clumping reaction is indicative of an immune system that has learned to fight the typhoid bacillus. In the Widal test, the serum is serially diluted, or titered, to determine the greatest dilution that can still produce a clumping reaction. The more dilute the titer, the more antityphoid antibody in the serum of the patient, and therefore the greater opportunity the patient's body has had to respond to typhoid bacteria. A presumptive diagnosis of typhoid is made when antibody titer is shown to rise over two successive and appropriately spaced tests. Three-quarters of typhoid patients will show a twofold to threefold increase in the second of two titers measured during the first week of infection.

Although the theoretical basis for the Widal test is sound and has become the basis for other diagnostic protocols, the Widal test itself is insufficiently sensitive and problematic. Like all diagnostic tests, the Widal test is most reliable when performed by a properly trained technician and the reagents have been appropriately stored. Serological reagents are notoriously unrobust. Different *Salmonella* Typhi bacteria have different capsule and flagella types. Each type must be tested, making the test rather complex to set up and perform, and therefore prone to error. Unlike blood cultures, the Widal test provides no opportunity to determine antimicrobial susceptibility, which is becoming increasingly important as drug resistance becomes more common. The Widal test is nonspecific. It is possible to get a significant titer for one or more of the typhoid antigens, and consequently a false-positive result, when a patient does not have typhoid fever but instead has dysentery, malaria, tuberculosis, hepatitis, cirrhosis, tularemia, rheumatoid arthritis, immunological disorders, infectious mononucleosis, or a recent vaccination against typhoid or cholera. As many of these conditions are common in Africa, depending on a single Widal test for the diagnosis of *Salmonella* infection is highly unreliable. When a negative result is obtained, the patient may not have typhoid, may be a typhoid carrier, may have a low-grade infection, or may be a poor responder—if they are not the victim of a test error from damaged reagents.[8] In my own case, described in chapter 1, the combination of early malaria chemotherapy failure, a single Widal test, and the signs and symptoms of my disease and recovery following chloramphenicol therapy—not to mention the wisdom of my nurse-mother—suggest that I had typhoid fever, but I might have had one of many other bacterial infections.

Culture, with all its attendant shortfalls, remains the gold standard for typhoid diagnosis. When the Widal test is properly performed and the results carefully evaluated, it is of some value in the diagnosis of *Salmonella* infection. Unfortunately, patients screened by the Widal test in many parts of Africa are rarely tested more than once, because testing is costly relative to medicine and access to laboratories is limited. Because of the confounding from other antigens, Widal tests are most useful when they detect a rise in titers over time. A properly performed Widal test would evaluate *Salmonella* somatic (O) and flagellar (H) antigen levels in blood at initial presentation and then a few days later. A fourfold increase in titers measured over a week apart, but particularly the somatic O titer, is diagnostic for typhoid fever. About 85 percent of typhoid patients exhibit such a rise in titers across the first month of infection. In my own case, and in those of the few others who get tested, however, a diagnosis is based on a single test reading.

The test is not misused in this way from lack of knowledge. As Michael O. Ibadin and A. Ogbimi explain, "In most tropical countries, saddled with enormous burden from the disease, recourse is often made to other methods because modern facilities are lacking. Thus despite acknowledged shortcomings the single Widal test on serum samples collected during active phase of the illness is commonly used in these countries, including Nigeria."[9] Hypothesizing that cross-reactivity from malaria was a potential cause of overdiagnosis of typhoid, they demonstrated that agglutination reactions with several of the Widal antigens, particularly anti-D agglutination, were significantly greater in patients with malaria parasitemia than in controls. Patients with malaria are more likely to generate a single false-positive Widal test result.

Distinguishing malaria and typhoid is an old problem. During the late nineteenth century, Sir William Osler, a renowned physician and one of the most knowledgeable typhoid specialists of his time, was concerned about the high rates of typhoid fever in the United States as well as by the failure of many doctors of his time to distinguish malaria from typhoid.[10] Many of his contemporaries made a diagnosis of "typhomalaria" because of their inability to delineate these two infections. Although he did not have access to diagnostic tools that could unequivocally differentiate these two fevers, Osler knew that by observing the trends in temperature charts it was possible to distinguish the ups and downs of benign (non-*falciparum*) malaria from the smooth waves of typhoid fever. Osler proposed that a single consultation with a patient was an insufficient basis for a diagnosis. Clinical monitoring of patients is impossible in many parts of present-day Africa, where physicians and hospital beds are few and death from fever can come swiftly. Nor would temperature charts distinguish typhoid fever

from the *falciparum* malaria that is most common in Africa. But the high level of background noise from confounding infections endemic in the region compromises the Widal test. To make matters worse, at the other end of the spectrum researchers in Cameroon blame the Widal test for large-scale and long-standing *over*diagnosis of typhoid fever.[11]

At the Korle-Bu Teaching Hospital, in Accra, Ghana, where diagnostic capabilities exceed what is available in most of Africa, physicians concluded that the Widal test adds little to clinical diagnosis:

> From the foregoing [data] it is recommended that typhoid fever should be diagnosed by culture of blood samples. The Widal test is non-specific, poorly standardized and often confusing and difficult to interpret. In our opinion, the Widal test should not be used in isolation as a diagnostic procedure for *S. typhi,* but as an additional aid. If culture facilities are not available a strong clinical suspicion, rather than the Widal test, warrants therapeutic intervention.[12]

A standard test that cannot return a result that is any more accurate than "strong clinical suspicion" is difficult to justify and may contribute to the perception that laboratory testing is not cost effective. Why does the uninformative Widal test remain the mainstay for laboratory diagnosis of typhoid fever in Africa? As diagnostic tests go, it is relatively inexpensive even though it is prone to error. It requires no sophisticated equipment and can be performed by a minimally trained technician. But mere convenience is not enough to advocate the routine use of a test, even when there is no alternative. Zurich-based medical microbiologist Eric Böttger observes that funds expended on Widal tests, which yield equivocal results, could be funneled into malaria diagnosis because clinical signs combined with a negative malaria test are almost as predictive as a positive Widal test for typhoid fever, or at least bacterial infection, in highly endemic areas. The Widal test may be inexpensive, but it is cost ineffective.

A reliable, single-point spot test for typhoid fever would have inestimable value, not only in Africa but also in Asia, where typhoid fever is highly endemic. Unfortunately, sensitive and suitable methods of testing for typhoid that could be used in remote, resource-constrained parts of the world do not yet exist. Only a few attempts have been made to replace currently available but highly problematic tests. Returning from a meeting of typhoid researchers in November 2005, Gordon "Doog" Dougan, a microbiologist who has devoted his life to the study of typhoid pathogenesis and vaccine development, described typhoid diagnosis as "an absolute mess. It's in the dark ages."[13] His frustration is well founded. He is developing vaccines for which field testing will be problematic if it is impossible to say who has and who does not have typhoid.

Salmonella Typhi's disease cycle and progression are among the more complex for bacteria. There are reasonably effective vaccines in use and in development. It is more complicated to develop a typhoid vaccine than a diagnostic test, ruling out scientific roadblocks as the principal reason why the disease poses such a formidable diagnostic challenge. In fact, after the threat from typhoid in Europe and North America waned with improved sanitation, the impetus to develop new tests diminished. Widal's outdated test, which represented the cutting edge of infectious disease diagnosis almost a century ago, has yet to be replaced. By contrast, cancer and HIV testing have evolved considerably in the last three decades, becoming more specific, more sensitive, and simpler to execute. Similar strides in typhoid fever diagnosis have not been made, or even attempted, even though more people are infected with this disease each year than with HIV. Current scientific technology has not yet been rigorously applied to typhoid fever diagnosis. Molecular technologies for the detection of specific bacterial antigens in urine seem promising, but much needs to be done before such tests are available, particularly in African clinics.

In 2008, the Ugandan Ministry of Health noticed an unusually high rate of hospital admissions due to intestinal perforations. A collaborative investigation by the Ministry of Health and the U.S. Centers for Disease Control uncovered an epidemic of typhoid fever. Typically, 2–3 percent of patients with untreated typhoid fever will succumb to perforations of the small intestine, but in this epidemic, an estimated 50 percent suffered this life-threatening condition, which requires emergency surgery. The reason for the unusually high rate of complications is still under investigation, but the scientists that investigated the epidemic agree that it is due to one of three possibilities: an extraordinarily virulent strain of Typhi bacteria, underreporting of mild infections, or delays in treatment.[14] The last two possibilities would arise directly from diagnostic shortfalls.

Typhoid may be one of the more prevalent and serious infectious diseases that are often confounded with malaria, but many other bacterial infections are commonly misdiagnosed as malaria. Existing diagnostics for bacterial bloodstream infections are too slow, too expensive, or too unreliable. The absence of cheap and easily applicable tests for invasive bacterial infections is undermining the introduction of routine rapid diagnostics for malaria as well. In several pilot studies, it was found that health workers were consistently prescribing antimalarials for patients who tested negatively for malaria parasitemia. Perhaps they did not trust the new tests, many of which needed to be evaluated further at the time, but they also had no diagnostic protocol for febrile patients who do not have malaria. Ideally, multiplex diagnostic tests would allow point-of-care diagnosis of malaria and its most common confounders. But simple and reliable tests for many common bacterial and viral diseases have yet to be developed. The

technology to develop them does exist. For example, a rapid diagnostic test for *Yersinia pestis,* the causative agent of plague, was developed and tested in Madagascar and successfully applied in an Algerian epidemic.[15] Similar methods could be used to design blood tests for other bacteria.

Diagnosis and surveillance are better in South Asia, where vaccines have been piloted, than they are in Africa. In the last decade, the introduction of a new Vi vaccine in many parts of Asia has led to a significant fall in the number of typhoid fevers. Unfortunately, this drop was followed by a rise in the number of enteric fevers caused by *Salmonella* Paratyphi.[16] The distinction is important: Typhi serovar causes typhoid fever, and Paratyphi serovar causes paratyphoid fever. Collectively, these systemic diseases are referred to as enteric fever. Although paratyphoid fever is reputed to be less lethal than typhoid, it still is a critical illness. There are some indications that Paratyphi strains currently circulating in Asia are just as virulent as Typhi. It is not clear whether the apparent rise in paratyphoid fever is due to better case detection or to a true resurgence of the disease to fill the niche recently vacated by typhoid fever. Had a similar event been seen in Africa, where typhoid fever is rarely differentiated from paratyphoid or other infectious fevers, it is likely that the vaccine would have been deemed ineffective. Without appropriate diagnostic tests, the number of enteric fevers would seem to have remained unchanged after vaccination. (Even more likely, enteric fevers would have been entirely overlooked by clinically diagnosed "malaria"). The rationale for vaccination would not have been evident and its cost would have been regarded as unjustified. This observation could have resulted in the withdrawal of an effective intervention and would have blinded health policymakers to the need for a paratyphoid vaccine. Indeed, one of the reasons why typhoid vaccines are not used routinely in Africa is because diagnostic shortfalls mean that their value has never been estimated.[17]

A few people infected with Typhi have no symptoms but carry the infectious bacteria in their gall bladders. These carriers shed the bacterium and can infect others. The best-known typhoid carrier was "Typhoid Mary" Mallon, a food preparer who infected forty-seven people in New York City between 1900 and 1915.[18] Mary was repeatedly asked to pursue an alternate career, and her refusal to do so eventually led to her incarceration on public health grounds after the deaths of three people she had infected. The prospects faced by food handlers are much less bleak today. Carriers can be treated and the bacillus eradicated. Since they are asymptomatic, however, carriers must be identified through laboratory testing. Many countries require or recommend that food handlers be tested for the typhoid bacillus, particularly if they are working in highly endemic areas. In Kumasi, Ghana, 2.3 percent of food handlers tested by one research group were identified as typhoid carriers. Similar rates are found in The Gambia,[19] but most

African food handlers have never been tested. Eating food prepared in restaurants or by street vendors is commonplace; so is communal cooking in family compounds. As long as testing is unavailable, hundreds of incognizant people are at risk of contracting typhoid. A good many are likely to be misdiagnosed as having malaria. Clearly, reliable and practicable diagnoses for typhoid fever and typhoid carriers need to be developed and applied. The technology exists to develop them, but they presumably are a low priority.

In addition to developing and deploying typhoid diagnostics and vaccines in Africa, priority should be placed on tests and vaccines for nontyphoidal salmonellosis. The spread of multiresistant strains of nontyphoidal *Salmonella* in Africa has made the need for a vaccine more pressing. Enteric fevers caused by *Salmonella* not belonging to the highly virulent Typhi and Paratypi sero-vars are generally rare. Most people with nontyphoidal *Salmonella* infections do not suffer more than a mild to moderate, self-resolving diarrhea. Malnutrition, the AIDS epidemic, and possibly malaria endemicity, however, have made some patients, notably African children, vulnerable to diseases that resemble typhoid but are caused by its less virulent cousins. This "new" illness is increasingly being documented in laboratories in Kenya and Malawi and presents yet another diagnostic challenge.[20] Before vaccines that protect against one or more deadly forms of *Salmonella* are effectively piloted, adequate monitoring protocols must be developed and implemented. These protocols will also be valuable in diagnosing the disease, identifying outbreaks, and caring for patients. In truth, they should have been in place years ago.