Tropical Diseases in Travelers

EDITED BY

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WILEY-BLACKWELL
A John Wiley & Sons, Ltd., Publication
Tropical Diseases in Travelers
Dedicated with love

to my wife Carmela and our children, Miriam, Aviad, and Naama
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It is with great pleasure that I write this preface to a new and valuable book, *Tropical Diseases in Travelers*, edited by Professor Eli Schwartz. Professor Schwartz has assembled a diverse, international, and very talented team of contributors to address an important, yet underappreciated, concept in tropical and travel medicine. The clinical presentations of infectious disease may be different in the non-immune, infrequently exposed traveler than the immune and multiply exposed inhabitant in a tropical environment.

The classic descriptions of the great tropical diseases began to appear in the 1800s as the Western powers began their imperial era in the Indian subcontinent, China, Southeast Asia, and, finally, in Sub-Saharan Africa. Suddenly, soldiers, businessmen, missionaries, and settlers needed to run the Western empires became casualties of infectious diseases of the tropics. Even in those early days, clinicians recognized that clinical presentations in otherwise healthy, non-immune, well-nourished adults were different from those seen in the native populations. The reasons for this difference included the size and frequency of the infectious inoculum, the lack of any prior immunity from past exposures or maternal immunity, and the fact that local populations often had a complex background of malnutrition, multiple co-infections, and far advanced diseases.

Symptoms in travelers are caused by far fewer organisms, leading to acute presentations with exuberant immune reactions in the non-immune. Symptoms in local populations may be manifest after years of multiple infections, with a large organism burden, organ system damage from years of inflammation, and chronic disability. Finally, the genetic background of travelers is distinctly different than the local population that have co-evolved with infections, such as malaria.

Acute and chronic schistosomiasis are excellent examples. The acute syndrome can be seen following a single exposure to fresh water and is caused by only a few adult worms, leading to an immune-mediated acute syndrome (Katayama fever). In travelers, subsequent clinical disease is often related to sporadic ectopic egg deposition that leads to catastrophic neurologic involvement, dermatologic presentations, or other bizarre syndromes. Chronic schistosomiasis occurs after years of exposure, the presence of hundreds of adult worms, and the near continuous deposition of eggs into the portal circulation leading to cirrhosis and portal hypertension. These are two very different diseases that occur in the local population or the returning traveler.

This book also includes historically important diseases such as typhoid fever, which used to be more common in the developed world, and leptospirosis, which has a cosmopolitan distribution, but is more commonly encountered in the developing world. Providers of travel medicine may be the first to encounter these patients.

Information on how tropical diseases present in travelers has never before been captured in a single, easy-to-access publication. Professor Schwartz, as book editor and co-author of numerous chapters, is eminently qualified for this task. He has been an original thinker in travel medicine, always pushing the discipline to question dogma and to consider new approaches. The other contributors are also all experts in their field.

Travel medicine is a relatively new discipline that has focused on the pre-travel aspect of traveler needs. This new book is the first to summarize the knowledge of post-travel presentations in the otherwise non-immune and non-endemic population. With such focus, this book will be useful to all practitioners, including primary care and infectious disease clinicians, who encounter the post-travel patient.

*Tropical Diseases in Travelers* is presented in four sections. Following a useful general introduction is a detailed discussion of multiple viral, bacterial, and parasitic infections. The third clinically relevant section on the syndromic approach to patients will be useful in evaluating
returning travelers with symptoms. The book concludes with two helpful appendixes.

In the globally connected world of the twenty-first century, the lines of travel and tropical medicine are blurred. Immigrants and refugees, displaced and discarded in their own world, may turn up at your first-world doorstep as tropical medicine patients, whereas soldiers and humanitarian workers may present with clinical presentations in the developing world, confusing those used to caring for local populations. The same infectious agent can lead to dramatically different diseases, depending on the background immunity of the host, access to timely care, and the pathogen load in the body. This book will help us all to see the differences.

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Acknowledgments

I would like to begin by thanking the publisher, Blackwell-Wiley, for recognizing the value of a special volume on tropical diseases in travelers and for helping to bring this book to fruition. Special thanks go to Robin Bonner and Eleanor Umali of Aptara, for their dedication to the book’s production and their commitment to meeting our target date for publication.

My gratitude goes to all of the contributors for their efforts and for sharing their experience and expertise to produce such high-quality chapters. My special thanks to Nancy Piper-Jenks for her invaluable assistance during the writing of this book. I would also like to thank my colleagues at the Center of Geographic Medicine and at the Department of Medicine C, at Sheba Medical Center, Tel Hashomer, for engaging in constant dialogue with me over the years concerning these topics and for their support during the writing of Tropical Diseases in Travelers.

I end with our ancient verse: “Much have I learnt from my masters, more from my colleagues, but the most from my own students” [Talmud of Babylon, Tractate Taanit, 6]. By the same token, I would like to thank all of my teachers and colleagues, in Israel and abroad, from whom I have learned a great deal. However, a special thanks is dedicated to my patients, from whom I have learned the most.
Tropical Diseases in Travelers—General Aspects
Introduction

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The explosion of global travel during recent decades has been well documented, and it has become common to see travelers from the developed world venturing to more and more remote corners of our planet. Exotic travel exposes people to exotic diseases, which they subsequently take with them to other places. The SARS (severe acute respiratory syndrome) epidemic illustrates how one person, who journeyed from an endemic area of China to Hong Kong, was able to infect several people at a hotel, who themselves became infected transporters of SARS, allowing its worldwide spread. A more recent example is the Chikungunya outbreak that began in the regions of the Indian Ocean and spread to Africa and India. Travelers then carried the disease into Europe, thus causing its documented autochthonous outbreak in Italy. Therefore, tropical diseases are no longer confined to the tropics.

The term tropical diseases is not limited to ailments acquired from a particular tropical geographic area of the world. Indeed, tropical diseases such as yellow fever and malaria were once a very important cause of morbidity and mortality in regions as far north as Boston, USA. Instead, we are referring to diseases acquired in the developing world, where public health standards are lower and hygiene and sanitation are not customary. For this reason, we are encountering numerous infectious diseases that were at one point endemic worldwide and had been controlled or eradicated in industrialized countries during the twentieth century.

As physicians who encounter returning travelers with various tropical diseases, we see a clear picture of these so-called “exotic diseases” presenting in a unique fashion in travelers. In fact, these diseases tend to manifest very differently in nonimmune travelers than in indigenous populations of the tropics. Teachbooks focusing on tropical diseases understandably limit their descriptions to the classical presentation of such tropical diseases, with descriptions of these diseases in indigenous populations, not in travelers.

The significant distinctions between travelers to developing countries and local residents are apparent through differences in the types of infections commonly seen in the two populations, as well as in the clinical presentations and management of these diseases.

Epidemiologically, these distinctions reflect differences in the likelihood of exposure to the infections, as well as intensity of exposure, which is typically higher among indigenous populations. For example, melioidosis (caused by the gram-negative soil- and water-associated bacterium Burkholderia pseudomallei) is a common cause of community-acquired sepsis in northern Thailand, yet the disease is rarely seen in travelers. The same is true for trypanosomiasis (sleeping sickness), filarial infections, and cholera, which are rarely seen in travelers.

Outbreaks of yellow fever are commonly reported among local residents in endemic regions, but are virtually never seen in travelers—in this case, most likely because of their high uptake of the efficacious yellow fever vaccine.

Disparate background immunity also affects the way in which some diseases manifest. For example, malaria in adult populations in endemic countries may not cause life-threatening disease, whereas in traveler populations, even low-grade parasitemia may cause a severe and life-threatening condition.

In many developing countries, hepatitis A is not viewed as an important problem because most children are infected at a young age, when infection is mild and often unrecognized. Older children and adults are therefore immune to the disease. However, the virus regularly contaminates food and water and poses a significant threat to nonimmune travelers who enter the area.

Clinical manifestations are also often different. These manifestations may be based on previous immunity and/or other not-yet-defined immunological causes. Excellent examples are the manifestations of infection with the various species of schistosome worms. This disease,
which is one of the most common infections in the tropics, is a leading cause of morbidity due to late and chronic stages of infection (i.e., hematuria, urinary retention, in *Schistosoma hematobium* infection, and portal hypertension with *S. mansoni*). These manifestations, however, are rarely seen in travelers. They most commonly present with acute schistosomiasis, which occurs several weeks after exposure and leads to Katayama syndrome, a hypersensitivity reaction to the helminth antigen. Katayama syndrome is in fact the principal presentation of schistosomiasis in travelers, causing significant morbidity, whereas among local residents, it is virtually nonexistent, and therefore barely discussed in tropical disease textbooks.

Malaria is another example, in that it always presents as a significant febrile disease among nonimmune travelers and yet it can often occur without fever among local populations.

Methods of diagnosis may differ. For example, in endemic countries, diagnosing helminth infections among the indigenous population is done by finding ova in the stool. Serology is usually inadequate because it cannot differentiate between current and past infection and, therefore, will almost always be positive.

In the case of travelers, however, the situation is the contrary; due to low worm burden, ova are infrequently found in stool. Moreover, because travelers can present with illness during the helminthic migration phase, detection of ova in stool is biologically unlikely. Therefore, the most important diagnostic tools in travelers are serological methods.

There are also variations in treatment. There are common misconceptions that the best available treatments and most knowledgeable approaches to the treatment of tropical diseases are found in endemic countries. In tropical countries, the most accessible drugs are low-cost medicine, rather than the best available. Thus, malaria may still be treated in local populations with older drugs to which resistance has developed; however, for the non-immune traveler, this treatment may be fatal.

As another example, we have shown that the most effective (albeit expensive) treatment of *Leishmania braziliensis* is liposomal amphotericin B; yet, antimonials, which are older and more toxic drugs, are used in endemic countries because of their lower costs. Thus, choosing the correct drug and dosage should be tailored to nonimmune travelers.

The study of tropical diseases in travelers offers the advantage of exploring the natural history of these diseases in a clearer light. First of all, these tropical diseases present in nonimmune travelers, resulting in a more accurate picture of their natural history. In addition, there are generally fewer confounders or additional infections (e.g., malnutrition, HIV, or other tropical disease infections) that might impact the natural history of the disease.

The fact that there is usually more thorough patient follow-up in industrialized countries offers an opportunity for further assessment of the outcomes of infectious diseases over the long term. For example, assessing the efficacy of malaria prophylaxis for *Plasmodium vivax* infection can hardly be done in an endemic area because late infection cannot be differentiated from re-infection. However, there are opportunities for long-term follow-up in travelers who return to nonendemic countries. Indeed, observing returning travelers from vivax endemic areas has allowed us to conclude that current malaria prophylaxis is actually inadequate for vivax prevention.

The study of infectious diseases in travelers may also elucidate the natural history of many cosmopolitan diseases, such as leptospirosis, that are seen less frequently these days in industrialized countries. Sporadic cases and outbreaks do occur in industrialized countries, although they tend to be missed by clinicians. The understanding of diseases in travelers can contribute to the clinician’s knowledge and awareness of disease when it occurs at home.

Practicing travel medicine may also help in managing patients who have not traveled, such as those with diarrheal diseases. The evaluation of patients with diarrheal diseases in the travel clinic is a large part of everyday practice and can teach non-travel-medicine practitioners about differential diagnosis and methods of detection and management, so that lengthy and expensive evaluations may not be necessary.

Travel medicine is a relatively new discipline and is a subspecialty that has continued to evolve over recent years. A number of textbooks that focus on pretravel health issues and the prevention of illness in travelers are now available.

This book is a first attempt at drawing together knowledge accumulated in recent years in the area of “post-travel”—those issues concerning the manifestation of tropical diseases and their diagnosis and treatment in travelers. The traveler, as a sentinel, has given us the opportunity to observe these diseases from another perspective. This knowledge can help us to understand better the morbidity and mortality of these diseases and, more important, to appropriately evaluate and treat the traveler who may be ill upon returning home.
The Art of Travel Medicine a Century Ago

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In a lecture given about one hundred years ago, Sir Patrick Manson addressed an issue that remains highly relevant today. The title of his lecture was “Diagnosis of Fever in Patients from the Tropics.”

As a reminder, Dr. Patrick Manson (1844–1922) was a British parasitologist (born in Scotland) and founder of the field of tropical medicine. He was the first to discover (1877–1879) that filariasis (Filaria bancrofti) is a mosquito-borne disease; transmission of a disease by an insect was a revolutionary idea at the time. He hypothesized that malaria could also be transmitted by mosquitoes, which was subsequently proven to be correct through the research of Sir Ronald Ross in India.

In 1890, Dr. Manson settled in London, where he organized the London School of Tropical Medicine (1899). He was knighted in 1903 and continued to practice medicine until his death. His fieldwork in several tropical regions of the world led him to his pioneer observations on tropical diseases, which were then also used to treat colonists and soldiers who encountered infectious diseases unknown in the temperate European climate. His book Tropical Diseases (1898) became the classic textbook on this subject.

The British Empire at this time ruled over a vast and expansive domain, encompassing about a quarter of Earth’s total land area; as was often said, “The sun never sets on the British Empire.” From a medical point of view, this meant that repatriating soldiers or other British officials back to the UK took several weeks, which is a long period of time, exceeding the incubation time of many diseases.

Dr. Manson’s lecture (Appendix, this chapter), which was published in the British Medical Journal in 1909 [1], may shed some light on the common diseases among travelers of that time, as well as highlight some of the changes that have occurred both in the tropics and in industrialized countries since then (Table 2.1). The major points that I would like to highlight include the following.

### The common mistakes among clinicians who see the returned traveler from the tropics

The most important mistake, according to Manson, was the overdiagnosis of “tropical disease” among those who returned to the UK. He called on the diagnostician to “disabuse his mind” of thinking that any fever occurring in a patient from the tropics must be a tropical fever. He was concerned that cosmopolitan diseases, which were the common diseases of his time, would be ignored by physicians. The significant mundane diseases of his time were tuberculosis, syphilis, typhoid, sepsis, and malignant diseases.

In our era, there are two major changes. First and foremost is that the ordinary infectious diseases that Manson mentioned no longer occur routinely in industrialized countries, which corresponds to the changes in epidemiology of diseases throughout the twentieth century. Although, at the beginning of the twentieth century, infectious diseases continued to be the leading cause of morbidity and mortality, with improved hygienic conditions, followed by the introduction of vaccines and antibiotics, there was a progressive decline of infectious diseases [2]. The current situation is that cardiovascular and malignant diseases are the major causes of mortality, whereas infectious diseases account for only about 5% of mortality, in contrast to the current situation in developing countries, where infectious diseases are still the major cause of death (Figures 2.1a and 2.1b) [3].
The second development, which followed the first, is that the principal question of differential diagnosis in returning travelers today is not between tropical infectious diseases and ordinary infectious diseases but rather between tropical infectious diseases and chronic, often incurable Western diseases. Our role in dealing with the health of returning travelers therefore is to re-emphasize to physicians who practice medicine in the industrialized world that infectious diseases still exist in the world. Travelers returning from endemic areas may carry with them an infectious disease that could be either life-threatening, or associated with intolerable symptoms, and which, in either case, may have the potential of a simple and rapid cure. An example of the latter is a returned traveler with a few weeks of diarrhea. A Western physician may tend to think about chronic conditions such as inflammatory bowel disease or malignancy and may fail to consider the possibility of parasitic infections such as giardiasis that can be cured within a few days of treatment.

The importance of malaria

One of the issues that appears to be constant throughout this period of a century is the importance of malaria. Malaria was the commonest of all tropical febrile infections in Manson’s time. This remains unchanged in our era and in almost all case series of febrile ill returned travelers, malaria is the leading cause (see Chapter 3).

However, he stated that “there is no disease so easily and so surely recognized as malaria.” He made this statement in spite of the fact that a laboratory diagnosis of malaria was not easily made as compared to this day and age. A malaria diagnosis one hundred years ago was based on one of three options, in the following order of importance:

One was the \textit{periodic character of fever}, demonstrating a rise in fever every 2–3 days.

The second option was the result of a \textit{therapeutic trial} of quinine, a successful trial showing a response within 48–72 hours.

Last, diagnosis was made with the use of a \textit{microscope}. To have a reliable microscopic test, the patient could not be under quinine treatment, but just as important, the microscopist “should know his business.” According to Manson, extensive training was needed to make an accurate diagnosis and to avoid “comic” mistakes.

Currently, in travelers with malaria who present usually within a few days after the onset of their fever, the synchronous pattern of the fever with a periodicity of 2–3 days (tertian malaria) is rarely seen (see Chapter 21). Thus, diagnosis must be based on the malaria smear. The lack of experience of microscopists continues to be an important issue, particularly because most laboratory technicians have not seen many cases of malaria. Therefore, there are ongoing attempts to find easier, friendlier methods for
malaria diagnosis. In recent years the antigen-detection rapid test has become a helpful tool, although it cannot replace malaria smears (see Chapter 22). Further development of the polymerase chain reaction (PCR) method for commercial use may significantly improve our ability to diagnose malaria and more accurately identify the malaria species.

However, the most common and the most important problem we encounter these days in malaria diagnosis in industrialized countries is the lack of physician awareness of the risk of malaria exposure in returning travelers and their failure to consider malaria as a potential cause of fever. The mortality rate from malaria in Western countries is high, reaching about 2–3% of all falciparum cases, and about 10–15% among patients with severe malaria. An important factor in this poor outcome is the delay of diagnosis by physicians [4].

Malaria was a common disease in Dr. Manson’s time, but it seemed to be, as it currently is in the hyperendemic countries, a “background” disease. Therefore, another important message he wanted to convey was not to miss other diagnoses due to a self-proclaimed malaria diagnosis. As he described at that time, when the patient came in and told the doctor that he had malaria, the reason for his visit was principally to get treatment for his own diagnosis. Under the name of “malaria fever,” the patient might in fact have tuberculosis, endocarditis, a liver abscess, or other illnesses. This is not the case today with returning travelers, but this situation reminds us of scenarios in endemic countries (mainly in Sub-Saharan Africa), where many illnesses are attributed to malaria without a thorough examination and definitive diagnosis, thus missing many other treatable diseases [5].

The incubation time

Although Dr. Manson did not mention the term “incubation period” directly, he clearly mentioned several diseases that were not relevant to the practitioner seeing the returning patient. The two major examples he gave were dengue fever and yellow fever; these diseases “need not to be considered.” These diseases belong to the flaviviruses and were well known at that time. Yellow fever was a major killer during the period (e.g., it was one of the major foes during the Panama Canal construction). However, these viral infections have short incubation periods of about 1 week. Transportation during that era was mainly by sea, which meant that the travel time from most areas in the British empire back to London was lengthy, eliminating diseases with short incubation times. (Around the world even in 80 days was an illusion, as illustrated by the classic science fiction novel written by Jules Verne, who lived during the same period.)

Table 2.1 Comparison of the status of diseases during Manson period and our time.

<table>
<thead>
<tr>
<th>Travel-related diseases in the 1900s</th>
<th>Status of diseases in 1900s</th>
<th>Status of the diseases in the 2000s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria—leading cause</td>
<td>Common</td>
<td>Malaria—leading cause</td>
</tr>
<tr>
<td>Hepatitis</td>
<td></td>
<td>Hepatitis is almost never seen in travelers owing to vaccine</td>
</tr>
<tr>
<td>Liver abscess</td>
<td></td>
<td>Liver abscess—occasionally seen</td>
</tr>
<tr>
<td>Brucellosis</td>
<td></td>
<td>Brucellosis—rarely seen</td>
</tr>
<tr>
<td>Viral hepatitis (Kala-Azar)</td>
<td>Less common</td>
<td>Seen as co-infection in HIV patients</td>
</tr>
<tr>
<td>Trypanosoma</td>
<td></td>
<td>Rarely seen</td>
</tr>
<tr>
<td>Filariasis</td>
<td></td>
<td>Rarely seen, and mainly from recreational activities in developed countries</td>
</tr>
<tr>
<td>Relapsing fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dengue fever</td>
<td>Not seen</td>
<td>Very common</td>
</tr>
<tr>
<td>Yellow fever</td>
<td></td>
<td>Very rare owing to vaccine effect</td>
</tr>
<tr>
<td>Typhoid, tuberculosis, septicemia</td>
<td>Cosmopolitan</td>
<td>Cosmopolitan diseases, but rarely seen</td>
</tr>
<tr>
<td>Endocarditis, sepsis</td>
<td></td>
<td>Not a common cause for fever</td>
</tr>
</tbody>
</table>
One of the major changes that began during the second part of the twentieth century was the public aviation service, which today enables us to circumnavigate the globe within 36 hours (Figure 2.2). The idea corresponding to this change, that “the world has become a global village,” assumes medical significance in that the incubation time is no longer a barrier in transmitting disease from one side of the globe to the other. Add to this the fact that traveling outside country borders is no longer confined to a select group of people but instead has become a popular trend (approximately 900 million travelers annually), and the public health significance is obvious.

In relation to the diseases mentioned above, dengue is widespread worldwide and has become the most prevalent arbovirus. For travelers, it is a major threat and is seen very often. According to the GeoSentinel data, dengue is now the second most common disease in returning travelers and is the first cause of fever outside Sub-Saharan Africa (see Chapter 7).

Yellow fever is rarely seen in travelers, but this is a result of another change that has occurred since Dr. Manson’s time—the development of a highly effective vaccine, which has dramatically changed the morbidity map of the disease.

The vigilance needed for the clinician who sees these patients

In Western medicine, we are taught that we should try to find one disease that will explain or encompass all of the patient’s symptoms. In tropical medicine, we should be alert to the possibility of multiple infections. The “zoo phenomenon,” which refers to a patient’s acquiring several pathogens, is not uncommon, especially in dealing with intestinal infections. Additionally, febrile infections can be caused by simultaneous infections (see Chapter 37).

Manson urges his audience not to fall into the trap of limiting findings to one diagnosis, and if there is just one diagnosis, to be sure that it fully explains the case. During this time, he stated, “In tropical disease, malaria is apt to complicate everything, so that multiple infection is rather the rule rather than the exception.” In our time, that might be the rule in the malaria-endemic countries, but it is not the rule among travelers. However, vigilance is needed, and whenever the course of the disease does not correspond with the specific diagnosis, a search for another pathogen should be made.

The shrinking world, a process that has progressed rapidly since the time of Manson, has led to the border crossing of many diseases. Thus, physicians now must be familiar with many diseases, irrespective of their geographic locations and incubation time. In addition, there is a substantial increase in the number of travelers, who are mostly short-term travelers, not the long-term expatriates as seen by Manson, and therefore not immune to diseases from outside of their own environment. These conditions of the twenty-first century have shed new light on and revealed new aspects of the old tropical diseases. Physicians in the West are thus further challenged to understand and manage this vast array of travel and tropical diseases.

References

Appendix: "Diagnosis of Fever in Patients from the Tropics," by Sir Patrick Manson (1909) [1]

An Address
ON THE
DIAGNOSIS OF FEVER IN PATIENTS FROM THE TROPICS.
DELIVERED AT A MEETING OF THE WESTMINSTER DIVISION OF THE METROPOLITAN COUNTY BRANCH.

SIR PATRICK MASON, K.C.M.G., M.D., L.L.D., F.R.S.

I HAVE twenty minutes in which to speak about certain points which have to be attended to in attempting the diagnosis of fevers in patients coming from the tropics. The time is very short. I shall not waste it, therefore, in preliminaries, but proceed at once to my subject.

Sources of Fallacy.

The first point I shall urge is a very important one. It is the necessity for the diagnostician to dismiss from his mind the very natural idea that because a fever has been contracted in or is occurring in a patient from the tropics it must necessarily be a tropical fever, symptomatic of some infection or condition peculiar to the tropics. This in my experience is one of the commonest and most misleading diagnostic fallacies. It so happens that my line of practice lies in great measure among patients from the tropics; but I am bound to say that half the patients from the tropics sent to me for an opinion or who come to me under the idea that they are suffering from tropical disease are not so suffering, although very likely they have fallen sick in the tropics or soon after return from the tropics. When you have dealings with a Sterlin man you are apt to be obsessed with the preconceived idea of the national reputation for omniscience, forgetting that, in the main, Sterlin men are very like other men, having the same physical, moral, and mental attributes. Just so, and perhaps even more so, in our contemplation of热带 diseases. The portion of a human's attributes that of other men, the remainder portion of disease in and from the tropics is ordinary disease; the other portion special. Therefore when you encounter a fever in a patient from the tropics, think first and last (unless the diagnosis be glaringly obvious) of a tropical fever. Think first of and carefully test for those great and pandemic conditions—beriberi, dysentery, yellow, epidemic, malignant disease, and sepsis. If the soul and nature of the disease are not at these possibilities, make it an invariable rule to go over all the organs systematically, one after the other, beginning at the center and ending at the sides of the foot. I could tell many a story illustrative of the wisdom and necessity for this precaution—as obvious when stated as pointedly, but, like so many other obvious things, so frequently overlooked or ignored. This is the first and perhaps the most important point I would make.

The next and equally obvious point I would impress on you is not to be misled by the diagnosis of malaria which in many instances is nearly sure to volunteer. Patients' statements in this respect are apt to be very positive and corresponding cases of tropical fever are apt also to be very positive. If you are not satisfied with the idea of your patient having malarial fever, insist on his going to a suitable diagnostician. And if you treat him on your own diagnosis, I have seen many cases of toil, distress, and discomfort, of liver tumors, of pyrexia, of syphilis overlooked for this reason. It should be an axiom with us never, without a thorough and independent examination, to accept another man's diagnosis, least of all a patient's diagnosis.

Having excluded as far as we can these sources of falacy, then, and only then, you may conclude that the fever, for we suppose, you are trying to diagnose is probably tropical. Now consider. There may be tropical conditions that are rather remote from the tropics and are likely to be brought to this country and are associated with fever. Of course, we may safely exclude such acute and short-lived as yellow fever, dengue, and so forth; these need not be considered.

Tropical Fevers.

Let me enumerate what I might designate the important tropical fevers in the approximate order of the frequency with which they present themselves in practice here. First of all, of course, comes malaria; next, perhaps, hepatitis and liver abscess; then Malariaeana or Mala fever; next, and at a long interval, hiva-ausa, trypano- somiasis and sleeping sickness, relapsing fever, syphilis, and probably other infections about which we so yet know nothing, but only suspect their existence. Each of the fevers I have mentioned has some features by which it may be recognised, or, at all events, suspected.
Tests of Malaria.

Manuscript our first duty is to recognize or to exclude the occurrence of them all—namely, malaria. Fortunately, this is easily done. Provided we set about it in the proper way and have a little time allowed as there is no disease so easily and so surely recognizable as malaria, for of this infection we have not one or two, but three absolutely pathognomonic tests. I am in the habit of describing these tests as, first, the clinical test of periodicity: secondly, the therapeutical test of the action of quinine; and thirdly, the microscopical test, the determination of the presence or absence of the malaria parasite or of its product, malarial pigment, in the blood.

There are other indications of malarial infection, such as leucopenia with relative increase of the large mononuclear leucocytes, enlargement of the spleen, and anemia. These are only of relative value. Their absence is strong evidence against malaria, but their presence, seeing that they occur in other tropical diseases, does not prove the presence of malaria. They are not absolutely diagnostic in the same sense as are the three tests I have just mentioned, and need not be further considered.

The most important clinical test of malaria is periodicity—the periodic recurrence of the fevers and other phenomena. Practically all fevers, whether malarial or not, exhibit a periodicity. In tuberculosis, in typhoid, in sepsis, and in so forth, there is a regular evening rise and morning fall of temperature, often quite as marked as in malaria. There is very definite quotidian periodicity. Quotidian periodicity is therefore not peculiar to, is not a diagnostic mark of malaria. We do meet with quotidian malarial fevers, especially in malarial countries. But quotidian periodicity, if taken alone, does not justify a diagnosis of malaria. So far from doing so, it is actually misleading. It is perhaps the most frequent cause of erroneous diagnosis in tropical practice. This you can readily understand. A patient from India, for example, comes to you with a story that every afternoon he has a shivering fit followed by a rise of temperature to 105°, and this goes on after some hours by a very slight sweat. He may mention no other symptoms. You may be in a hurry. You jump for malaria, and you prescribe quinine. This patient does not improve. You make a careful physical examination and find no tuberculosis, or of liver abscess, or of some other form of visceral disease.

Quotidian periodicity, therefore, should be absolutely excluded before the disease is diagnosed as malaria. The periodicity characteristic of malaria, and absolutely distinctive and exclusive of infection, is a review of previous periodicity. These you find in no other condition, and are diagnostic of malaria. The only circumstance in which quotidian periodicity may be a help in diagnosis is when the recurring fever sets in very late in the night, say after midnight or before 02 or 03 clock during the day. Such a time for the commencement of a daily fever is almost peculiar to malaria.

Malaria, it is well known, has usually been applied to all fevers of the type of the leucoma, except those of the malaria, but all those we are dealing with malaria not. But in using this test we must be sure that the quinine is given properly, and that it is absorbed. Very often the quinine is given in a subcutaneous dose, but in some insidious form, as in coated pill, dusty tablet, or soluble sulphate. In cachectic conditions of the stomach given in any of these forms the drug may not be measured, much less seen, and cannot therefore be regarded as efficiently acting for malaria.

When it is of importance that we should be certain of its action, quinine should be given in solution, or, in highly cachectic or irritable conditions of the stomach, intramuscularly in doses of 7 to 10 grains. If no improvement is made on a fever by quinine given in this way, do not blame the drug; revise the diagnosis.

Even more reliable than the clinical or the therapeutical test of malaria is the microscopical test. If the malaria parasite or its product—haematozoa, or malarial, as it is usually called—is found in the blood, diagnosis is easy. The parasite of malaria is necessarily present at one time or another in the course of all malarial infections; it is always present in the visceral blood, nearly always in the peripheral blood, and, given certain conditions, can be readily demonstrated, ever so, to secure these conditions. In the first place the patient should be under the influence of quinine; in the second place the person who searches for the parasite must know the business. Even a small dose of quinine—say, perhaps, quite insufficient to check the fever—may cause the parasites to disappear temporarily from the peripheral circulation. The possession of a microscope, and even skill in other departments of microscopy, do not always imply ability to recognize the malaria parasite. To do so absolutely requires experience—special experience—and long training. It is not a difficult matter, but, as with everything else, you must know how to set about it, and be familiar with the fallacies. It would be a comical list were 1 to enumerate all the various objects that have been brought to me as specimens of the malaria parasite.

I would warn you, therefore, to be careful about accepting a diagnosis of malaria from an inexpert microscopist, but I would encourage you to have absolute confidence in the positive diagnosis, and in ninety-nine cases out of a hundred in the negative diagnosis of malaria from an experienced and conscientious microscopist.

Liver Abscesses.

Assuming that we have to deal with a tropical fever and that by one or all of the tests I have enumerated we have excluded malaria, the question comes to be, which of the several tropical fevers I have mentioned are we dealing with?

In the case of liver abscesses? The first and all-important question we put is—has the patient had dysentery or diarrhea?. If so, there is to say the least strong presumption in favour of such diagnosis. We search, therefore, for local signs, for enlargement of the hepatic area, especially upwards, for local pain, oedema, or even softness. We inquire as to anaemia, progressive emaciation, for irritability and depression of mind; we look for a mouth complaint; we inspect the stools, look for slime or other indications of a former or an existing dysentery; we inquire for a dorsal or right shoulder pain, for shoulder pain, and we make a count for the white corpuscles in the blood—a leucopenia being against, a leucocyte being in favour of, liver abscess. Usually symptoms are casuistically suggestive we explore the liver under chloroform, being prepared to operate at once if abscess is discovered.
Mediterranean Fever.

We may respect Mediterranean fever, more especially if the patient has come from Malta, although this disease is by no means unknown elsewhere—as in India, China, and even in Central Africa. The point in favour of a Mediterranean fever diagnosis is an indolent type of the fever, often preceded by headache, with the common rheumatic pains of the joints, and the absence of indications of other diseases.

Apart from the symptoms mentioned the evidence for this fever is principally of a negative nature. The fever may assume all sorts of characters. Often it is indolent in type, but so often is it a distressing insidious and quiet illness, often of a low continued type, often a nulity of all of these. The serum test is reliable under ideal conditions, but my experience of it in London is the reverse of favorable. When I employ it I usually send the blood to two different laboratories; as often as not I get "positive" from one and "negative" from the other. So I do not trust it here, although, where fresh cultures are obtainable, it is quite as trustworthy as the corresponding test for typhoid, and even more delicate.

Kala-azar.

We have a patient from India, from China, from the Sudan, or from North Africa. He has a chronic fever, his spleen reaches near his umbilicus, and his liver is very much enlarged. He has been ill for months; he is anaemic; his tongue is clean and the papilla and digestion are good; he has taken graters by the pound, and is able to eat as much as before; and yet he just seems to get worse and worse. He is suffering from kala-azar—the disease produced by the Leishmania. To make sure of the diagnosis we first draw the fever chart—a fever chart; very likely we note that there are two distinct rises of temperature in the twenty-four hours. We examine the blood; there is a very marked leucopenia, more marked even than in malaria, and there is a relative increase in the large mononuclears. Possibly, though this is not likely, we may find a Leishmania body or two, if we search long enough, in the white blood cells of the patient. In the presence of such a fever and such a history we are entitled to puncture the spleen or liver or the Leishmania body in the jujube or fragments of pulp as obtained. Such a procedure is not dangerous but extremely painful, aspictically, and with a dry needle and syringe. I say "dry needle and syringe," for if a trace of moisture be present in these it will, by condensation, distort the parasites, that, though present, they may be hard to recognize. Of course, one must be familiar with the techniques for their demonstration, and the details of the structure of the parasite, for it is exceedingly minute and might be mistaken for a minute yellowish, flat, or platelet.

Trypanosomiasis.

The patient comes from the tropics. He complains of intense physical and mental weakness, headache perhaps, tenderness of the limbs when he is moved about. You suspect trypanosomiasis. You stripe him and inspect his skin. You see great patches of erythema, many inches in diameter, usually having a ring appearance and looking slightly yellowish; you palpate the spleen in his neck, axilla, or groin, and you find that some or all of them are enlarged—perhaps from the point of view of the roentgenologist, the spleen, as a rule, is enormously enlarged. That patient is almost surely the subject of trypanosomiasis, and may die of sleeping sickness. Examine his blood with a sixth objective, examining it especially during one of the recurrent attacks of fever, and you are almost sure to find the trypanosome. It will not be found in every field of the microscope, and you may have to return to the host several times, but in the end you are almost sure to find it. If you fail to find it in the blood, procure with a hypodermic needle one of the enlarged cervical glands, and examine the lymph so obtained; in it you have even a better chance of finding the parasite. The blood count is very similar to that of malaria.

Relapsing Fever.

The patient comes from India, from tropical Africa, from North Africa, or even from Siberia. He tells you that he has attacks of fever, perhaps violent fever, regularly about once a fortnight. He has been ill from three to five or six days, that he relapses nearly every day, that he is quite free from the interests, he may have had three or four or even eight or nine attacks. What are they? The blood is negative for malaria; there is no marked leucopenia. Examine the blood during one of the fever paroxysms, and probably you will find the aphyrocyte of relapsing fever. In the African variety it takes some looking for. If you find its diagnosis is established. Such cases I have seen more than once in recent years in London. They were imported from Africa, from Siberia, and from India.

Elephantoid Fever.

Another patient may tell you he has attacks of violent fever coming on at irregular intervals of weeks, months, or years, that the attacks last for two or three days, and may be attended with severe rigor, delirium, high temperature, and be followed by profuse sweating. If he comes from the West Indies, particularly from Barbados, he will call this disease "fever and ague," but it is not fever and ague as we understand it. It is not malaria but elephantoid fever for the most part, and if we inquire as to the occurrence of inflammation of the skin, serous, or scrotal lymphangitis, we are sure to find that such is the case. The patient is almost certainly the subject of elephantoid fever, and in or has been the subject of filarial infection.

The possibility of those various and very different infections should always be present in the diagnosis.

Filaria.

I began with a word of warning; I shall conclude with another word of warning, and it is this: Do not infer that because you have found in your patient’s blood or elsewhere the microorganism of one disease, that you have also infected the patient with another disease. The complete and full expression of the case. In tropical disease malaria is apt to complicate everything, and multiple infection of patients is the rule, not the exception.

When you find the malaria parasite the patient has certainly got malaria, but that does not mean that he has not other infections. I have sometimes been "caught" in consequence of ignoring this obvious precaution. I was asked to see a patient just returned from Portuguese West Africa. He was suffering from fever and dysentery. He had dysentery severe enough, and his spleen was enormously enlarged. He had taken much quinine; as it seemed to irritate his bowels I stopped it. At my first visit he had no fever. I found nothing in his blood. I left instructions that if I were to see him four days later I should have an attack of fever.
Some days afterwards I was sent for; his temperature being over 100°. I took a slip of his blood, hoping to find in it the parasite of malaria. Judge, however, of my horror when, instead of the malaria parasite, there was an unmistakable trypanosome staring me in the face! After a few days the fever disappeared, and, with the fever, the trypanosomes also.

A fortnight later there was again a return of fever, and I again examined the blood, expecting to find the trypanosomes. I found no trypanosomes, but I found plenty of tertian malaria parasites. And so the case went on, every now and again a fever spell with trypanosomes in the blood, and every now and again a fever spell with malaria parasites in the blood. By the persistent use of arseny and of quinine both, leishmania were finally expelled from the circulation. The patient is now, I believe, quite well.

Last year I had in hospital a patient from an African colony who carried with him the malaria parasite, the trypanosomes, the Plasmodium falciparum, the flagellates. Besides an assortment of intestinal parasites, including Ascariis lumbricoides, Trichuris trichiura, and Entamoeba duodenalis—a veritable menagerie, which, as long as it remained with us, we appreciated very highly at the Tropical School. He could always supply us with a subject for demonstration or for a clinical lecture.

I fear my exposition of the subject has been very sketchy and inadequate; it is necessarily so in consequence of the time limit imposed on me. I trust, however, I have given you the leading points for reliable diagnosis.
**Epidemiology of Post-Travel Illnesses**

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**Introduction**

Disease surveillance is a prerequisite for the assessment of health risks and the evaluation of established preventive measures. It enables us to identify changing epidemiological patterns and groups of high-risk travelers possibly requiring modifications and optimal targeting of existing intervention concepts or the introduction of novel strategies. Moreover, information on the epidemiology of specific infections also provides guidance for differential diagnoses in ill returned travelers, facilitating the assessment and quantification of disease risks.

International travel is becoming increasingly popular. The current estimate of 846 million international arrivals represents an average growth of 4.2% between 1995 and 2006, with Sub-Saharan Africa being one of the major contributors to this rise. The leading travel destination is Europe, with more than 460 million travelers, followed by Asia, the Americas, the Middle East, and Africa. With regard to long-term prospects, the number of international travelers is expected to reach nearly 1.6 billion by the year 2020 (Figure 3.1) [1].

Undoubtedly, travel is related to enhanced health risks, most notably when travelers visit areas where the communicable disease burden is high, sanitation is poor, and the quality of medical care is limited. Each year, about 50 million people travel from industrialized to developing countries [2]. About 20–70% of international travelers report travel-related illnesses, usually dependent on destination and other travel conditions, including season, itinerary, duration, and purpose of travel [3, 4]. However, the majority of health problems reported by travelers are mild conditions, such as diarrhea, respiratory infections, and skin disorders [5].

Traveling to endemic countries has become increasingly popular for all age groups. In recent years, the numbers of senior, pregnant, and pediatric travelers have steadily increased. In a population that visited a travel clinic prior to travel, 14% were above 55 years of age [6]. According to an airport survey, 30% of US travelers were 50 years of age or older. Elderly people represent a growing group of travelers with a considerable rate of comorbidity [7]. Also, Stauffer et al. estimated that 4% of overseas travelers are infants and children [8]. This is confirmed by an Israeli study reporting a proportion of more than 5% for the age group below 18 years of age [9]. This varying demography of travelers increasingly needs to be taken into consideration in dealing with post-travel illness.

This lack of surveillance data for imported cases of infectious diseases prompted the establishment of various travel-related surveillance systems.

The GeoSentinel Surveillance Network started in 1995 through a collaborative agreement between the International Society of Travel Medicine (ISTM) and the Centers for Disease Control and Prevention (CDC) and consists of specialized travel/tropical medicine clinics on six continents recording information on ill travelers [10]. The main aims of the GeoSentinel Surveillance Network are to monitor global trends in disease occurrence among travelers and to ascertain risk factors and morbidity in groups of travelers categorized by travel purpose and type of travel.

A few years later, in 1999, the European Network on Imported Infectious Disease Surveillance (TropNetEurop) was founded, serving as an European electronic network...
of 37 clinical sites related to importation of the major tropical diseases. For the first time, these novel sentinel surveillance systems allow the identification of temporal and geographic trends in infectious disease occurrence in traveling populations worldwide. Through the global surveillance of infectious diseases in travelers, refugees, and immigrants, valuable persuasive science-based information about important aspects of post-travel morbidity is generated to guide post-travel diagnosis, develop adequate pretravel prevention strategies, and hopefully lead to travelers’ improved health. This chapter summarizes results of available systematic studies investigating the epidemiology of post-travel illnesses, including data on the above-mentioned large-scale surveillance systems. In-depth epidemiology of specific diseases, however, is covered in the specific chapters.

Methods of investigations for post-travel morbidity

Generally, two different categories of post-travel disease epidemiology data exist.

Disease attack rate

Attack rates of specific diseases is calculated by dividing the number of ill travelers (numerator) by the number of all people who traveled to the same destination during the same observation period (denominator). Data of this kind, however, are rare.

Population-based risk

Only a few studies have supplied such specific population-based risk figures, which provide a useful pretravel tool for travelers for assessment and rating of disease-specific geographic risks. The data are limited to selected traveling population groups and/or geographic areas, such as Israeli travelers in Bolivia contracting cutaneous leishmaniasis (attack rate, 1 in 300 travelers) [11] or sufferers from myiasis in the Amazon basin (attack rate 1 in 190 travelers) [12]. In a recent survey, the rabies exposure risk among long-term travelers was estimated to be 2.66 per 1000 travelers per month [13].

Serosurveys

Serosurveys performed pre- and post-travel may likewise provide estimates of disease attack rates. This approach has been used, for instance, to evaluate the incidence of dengue fever in populations traveling to selected geographic regions. Dutch travelers to Asia (with a median stay of 1 month) had a seroconversion rate of 2.9% [14]. An Israeli survey performed among travelers who had spent at least 3 months in a tropical area observed a seroconversion rate of 6.7% [15]. A survey of tuberculin