11

Parasites and Their Diseases

Introduction

In the first section of this chapter, we survey and briefly describe the parasites important to humans and the diseases they engender. In Section 11.2, we detail the life cycle of the parasites responsible for malaria. While there are four species of mosquitoes involved, the biggest threat is from *P. falciparum*. Next, we have a look at the complex interactions between parasites and their human hosts with an eye on potential lines of control of parasitic diseases. And in the last section, we introduce a mathematical model for malaria. The exercises invite the reader to use the model to explore some epidemiological scenarios for malaria.

11.1 Protozoan Parasites Cause Important Human Diseases

Parasitic protozoa are a major cause of infectious disease worldwide. Parasite infections account for a higher incidence of morbidity and mortality than diseases produced by any other group of organisms. According to the World Health Organization, over 300 *million people worldwide are affected by malaria alone and between* 1 *and* 1.5 *million people die from it every year.*

Protozoans are classified according to their mode of locomotion.

As noted in Chapter 4, *parasitism* describes a symbiotic relationship between two organisms in which one, the *parasite*, is benefited and the other, the *host*, is usually harmed by the interaction. The parasite is *obligate* if it can live only in association with a host. In contrast, *faculative* parasites are free-living organisms that are capable of becoming parasitic under favorable circumstances.

Parasites are typically small organisms, most of these members of several protozoan families and helminth (worm) families. Recall that protozoans are single-celled "animals" whose cell possesses a nucleus. Protozoan parasites, to which we will restrict ourselves here, are therefore quite small, being on the order of 10 to 40 micrometers (μm) in size; bacteria are typically 1 to 10 μm. Like viruses and bacteria,

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protozoan parasites are called *microparasites*, while those of the helminthic phyla are *macroparasites*. What microparasites have in common is the ability to increase their numbers by a prodigious amount within the host. And if the parasite does live within the body of the host, it is termed an *endoparasite*; an *ectoparasite* lives on the body surface of its host, the tick being an example of the latter.

A primary way of recognizing and differentiating protozoan species is whether they are motile, and if so, by what means. All methods of single-cell locomotion are represented: via pseudopodia, cilia, and flagella. One phylum, Sporozoa, are not motile.

The *amoeboids* move by streaming cytoplasm in the direction of motion, forming a *pseudopod* extension of the cell. The remainder of the cell then pulls itself along in that direction. In addition to movement, this technique is used by the microorganism to feed. In what is called *phagocytosis*, the pseudopodia surround and engulf particles of food. The amoeboids largely constitute the subphylum *Sarcodina*.

The most widespread pathogenic disease caused by this group of organisms is *amebiasis* or *amebic dysentery*, which results from an infection of the protozoan *Entamoeba histolytica*. Infection occurs when cysts on fecally contaminated food or hands are ingested. The cyst is resistant to the gastric environment of the host and passes into the small intestine, where it decysts and multiplies. *E. histolytica* thrives best in oxygen free environments and does not possess mitochondria. The cycle of infection is completed when the organisms encyst for mitosis and are passed out of the gut with feces.

The *ciliates* move by means of *cilia*, which are short, hairlike projections emanating over most of the surface of the organism. As mentioned in Chapter 7, the beating of the cilia is synchronized in order that directed motion result.

The ciliates largely make up the subphylum *Ciliophora* and are the most complex of the protozoans. Ciliates have special organelles for processing food; food vacuoles move along a gullet from which digestible nutrients are absorbed by the cytoplasm. At the end of the gullet, the indigestible residue is eliminated at an anal pore. Ciliates also have two types of nuclei. The *macronucleus* controls metabolism, while the *micronucleus* controls reproduction. Two ciliates may even exchange genetic material in a process called *conjugation*.

Only one ciliophoran, *Balantidium coli*, infects humans. The *trophozoite*, or motile stage, of the organism inhabits the *caecum* and nearby regions of the intestinal tract of its host. This is at the upper end of the colon, where the small intestine empties. *B. coli* is the largest known protozoan parasite of humans, measuring between 50 and 130 μm. The organism is also unique among protozoan parasites in that it contains two prominent *contractile vacuoles* used for the control of osmosis. Depending on their environment, protozoans can gain water via osmosis. The excess water is forced into the vacuole, which consequently expands in size. At some point, the water is expelled outside the cell through a temporary opening in the plasma membrane, and at this time the vacuole rapidly contracts.

B. coli typically reproduce asexually by fission. However, conjugation also occurs in this species.

Transmission of the disease *balantidiosis* from one host to another is accomplished by the cyst stage of the organism. Encystation usually occurs in the large intestine of the host and is expelled with the feces. Decystation occurs in the small intestine of the newly infected host.

The *flagellates* possess one or more long, slender, whiplike protrusions from one end of their bodies used for locomotion. (The word *flagellum* is Latin for whip.) Flagellates belong to the phylum *Zoomastigina* (in some classification systems).

The flagella of these organisms enable them to swim and thus thrive in liquid media, which can include blood, lymph, and cerebrospinal fluid. With an elongate, torpedo-like shape, they are adapted to swim with reduced resistance. A flagellum achieves locomotion by beating in a regular rhythm. A series of bends propagates in wavelike fashion along the length of the flagellum, starting at its attachment point and proceeding to the free end. This movement is fueled by ATP.

The fine structure seen in cross-sections of flagella and cilia are identical; thus flagella may be considered as elongated cilia.

Several clinically important diseases are attributed to the flagellates. Those infecting the intestine or other spaces within the body (lumen) are *Giardia lamblia* and *Trichomonas vaginalis*. The former causes *giardiasis*, which is acquired by the ingestion of cysts, usually from contaminated water. Decystation occurs in the duodenum, and trophozoites colonize the upper small intestine, where they may swim freely or attach to the submucosal epithelium. The free trophozoites encyst as they move downstream, and mitosis takes place during the encystment. The cysts are passed in the stool. Man is the primary host, although beavers, pigs, and monkeys are also infected and serve as reservoirs (see below).

Trichomoniasis is the disease caused by *T. vaginalis*. The organism colonizes the vagina of women and the urethra and sometimes prostate of men. Infection occurs primarily via sexual contact, although nonvenereal infections are possible. The organism divides by binary fission, which is favored under low acidity (pH $>$ 5.9; normal pH is 3.5–4.5). *T. vaginalis* does not encyst.

Those diseases in which flagellates inhabits the blood are *African trypanosomiasis* (sleeping sickness) and *leishmaniasis*. Sleeping sickness is caused by *Trypanosoma brucei gambiense*, mainly affecting Western and Central Africa, and *Trypanosoma brucei rhodesiense*, which is restricted to the Eastern third of the continent. *Trypanosoma* are the first protozoans we have discussed whose life cycle takes place in more than one host, with the consequential problem of transmission between hosts. Actually, this sort of life cycle is the rule rather than the exception, and we digress for a moment to discuss some of its general characteristics.

The host harboring the adult or reproductive stage of the parasite is called the *definitive host*. An *intermediate host* serves as a temporary but essential environment for the development or metamorphosis of the parasite short of sexual maturity. A *vector* is an organism that transmits the parasite to the definitive host. This is usually an intermediate host. Infected animals that serve as sources of the parasite for later transmission to humans are *reservoir hosts*. The reservoir host shares the same stage of the parasite as humans but is often better able to tolerate the infection.

Returning to trypanosomiasis, mammals, including cattle and humans, are the definitive hosts for the organism. Thus from a human being's point of view, cattle are reservoir hosts. The intermediate host and vector is the *tsetse fly*. Humans acquire the parasite when an infected fly takes a blood meal. The infective stage of the parasite makes its way to the salivary gland of the fly. As the fly bites, saliva serves to dilate the blood vessels and to prevent coagulation of the blood. At the same time, the parasite is transmitted with the saliva. Conversely, an infected human transmits a stage of the organism to any biting fly within the extracted blood.

Leishmaniasis is caused by any of the three subspecies *Leishmania donovani*, *L. tropica*, and *L. braziliensis*. These organisms are also multihost parasites, whose intermediate host and vector is the *sandfly*. Transmission of the parasite to the host is unique. The parasites, many hundreds of them, reside in the gut of the fly and are deposited in the skin of the victim when the sandfly feeds. Macrophages of the host quickly engulf the intruders. But remarkably, macrophages are the target cells of infection by the parasite! The invading parasite encases itself in a vacuole within the macrophage, where it lives and reproduces. Later, a biting sandfly will be infected via the blood of its meal.

The last group of protozoan parasites, the *sporozoans*, are essentially immotile, and every species of the group is parasitic. In humans, they give rise to such diseases as *malaria*, *babesiosis*, *toxoplasmosis*, and *Pneumocystis carinii pneumonia* (PCP), among others. While most members of the group are multihost, the agent causing PCP, *Pneumocystis carinii*, is an exception. In place of locomotor devices, members of this group possess structures known as the *apical complex*. This is a collection of readily identifiable organelles (microscopically) located beneath the plasma membrane at the anterior end of the organism. It is thought that the function of the complex is to secrete proteins facilitating the parasite's incorporation into the host cell.

Malaria is caused by four members of the genus *Plasmodium*: *P. vivax*, *P. falciparum*, *P. malariae*, and *P. ovale*. Malaria is one of the most prevalent and debilitating diseases afflicting humans. The World Health Organization estimates that each year 300–500 million cases of malaria occur worldwide and more than two million people die of malaria. *P. falciparum* (malignant tertian malaria) and *P. malariae* (quartan malaria) are the most common species of malarial parasite and are found in Asia and Africa. *P. vivax* (benign tertian malaria) predominates in Latin America, India, and Pakistan, whereas *P. ovale* (ovale tertian malaria) is almost exclusively found in Africa. The vector for malaria is the female mosquito of the genus *Anopheles*. The life cycle of the parasite proceeds through several stages, each of which is attended to by a different form of the organism. In the next section we will examine the life cycle in detail.

Babesiosis is a disease of recent appearance. It is caused by the protozoan *Babesia microti*, which is a natural parasite of the meadow vole and other rodents. The intermediate host and vector of the disease is the deer tick, *Ixodes dammini*. As is familiar by now, the parasite is injected into the definitive host through the saliva of an infected tick when it takes a blood meal. In the host, the organism lodges in erythrocytes (red blood cells), where it multiplies. In turn, the tick acquires the parasite by ingesting the blood of an infected host. Since the mortality rate for ticks

is high, it is likely that an infected tick will not live to pass on the parasite. Therefore, the parasite has adapted to colonize the offspring of an infected female tick, thereby greatly increasing its chance of transmission to a definitive host. This is achieved when a form of the parasite invades the ovarian tissues of the tick. As a result, the newly hatched eggs are already infected.

Toxoplasmosis has worldwide distribution and a surprisingly high infection rate. In the United States, 50% of the population is seropositive to the causative organism, *Toxoplasma gondii*, meaning that they have been immunologically exposed to it. Normally infection is asymptomatic, but it does pose a serious threat in immunosuppressed individuals and pregnant females. As we will shortly see, cats are the definitive host. For this reason, women should avoid contact with litterbox filler during a pregnancy. With the spread of AIDS, toxoplasmosis has become much more serious.

The principal means for acquiring toxoplasmosis is by eating inadequately cooked meat or by contact with feral or domestic cats. A form of the organism, called an *oocyst*, is passed in large numbers with the feces of an infected cat to the soil. There they may be ingested by cattle, sheep, pigs, rodents, or even humans directly. The cycle of infection is completed when a cat eats an infected animal such as a mouse. In the intermediate host, the organism develops into a form called *pseudocysts* that may persist for years in muscle and especially nerve tissue. Eating undercooked meat containing pseudocysts can also result in infection.

The disease PCP has vaulted into prominence coincident with the increasing incidence of AIDS. Of the opportunistic diseases associated with AIDS, PCP is the most common cause of death, affecting an estimated 60% of AIDS patients in the United States. The disease is caused by *Pneumocystis carinii*, which is an extracellular

Table 11.1.1. Parasite summary.

Disease	Parasite	Host multiplicity	Infection path	Infection site
amebiasis	*E. histolytica*	unihost	contaminated food	intestine
balantidiosis	*B. coli*	unihost	contaminated food	intestine
giardiasis	*G. lamblia*	unihost	contaminated water	intestine
trichomoniasis	*T. vaginalis*	unihost	sexually transmitted	sex organs
trypanosomiasis	*T. brucei gambiense*, *T. brucei rhodesiense*	multihost	vector (tsetse fly)	blood
leishmaniasis	*L. donovani/tropica*, *L. braziliensis*	multihost	vector (sandfly)	blood
malaria	*P. vivax/falciparum*, *P. malariae/ovale*	multihost	vector (mosquito)	blood
babesiosis	*B. microti*	multihost	vector (tick)	blood
toxoplasmosis	*T. gondii*	multihost	contaminated soil	nerve tissue
PCP	*P. carinii*	unihost	aerosol	lungs

parasite found in the interstitial tissues of the lungs and within the alveoli. The mode of transmission from one human to another is thought to be via inhalation of cysts from the air.

We summarize the above in Table 11.1.1.

11.2 The Life Cycle of the Malaria Parasite

The life cycle of P. falciparum (*see Figure* 11.2.1) *is typical of that of many protozoan parasites. As we will see, it is quite complicated, much too complicated to be supported by the relatively meager genome of a virus or bacterium.*

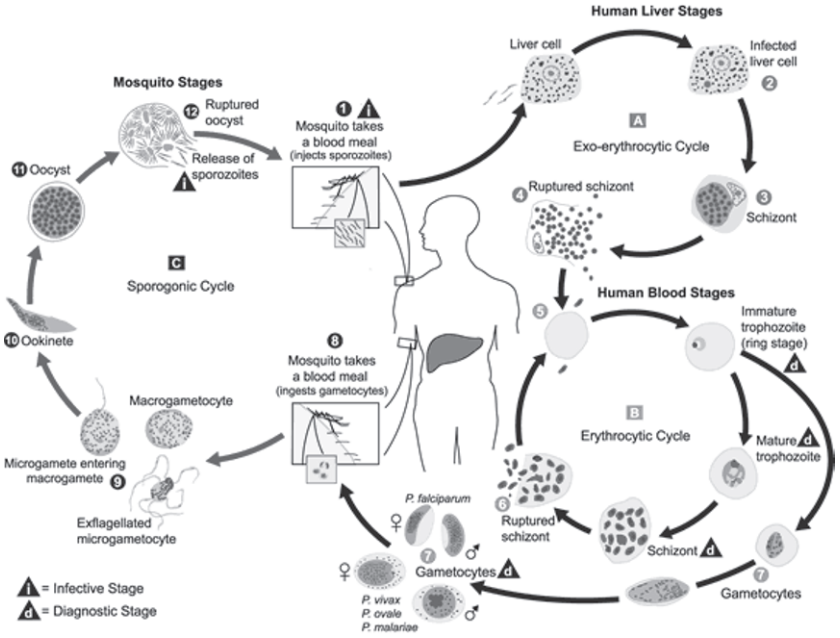

Fig. 11.2.1. Life cycle of the malaria parasite *P. falciparum*.

Of course, the complication of their life cycle confers survival advantages. For example, if some natural disaster befell mosquitoes, the intermediate host, the pool of human infectees, would serve as a reservoir for the restoration of the parasite. A simple life cycle, such as that of the variola virus, which is responsible for smallpox, is vulnerable to eradication.

Although the need for living in an intermediate host does present the opportunity to attack the parasite at that source, eliminating the mosquito has proved impossible. In like fashion, with many stages to their life cycle, there are just as many opportunities for a drug against the organism, but in reality these stages have come to exist as a way

for the parasite to thwart the host's immune system. The time the organism spends floating free in the bloodstream, where an opportunity for a vaccine exists, is brief.

Plasmodia have evolved a complicated life cycle with many specialized forms.

Infection begins in humans with the bite of an infected female *Anopheles* mosquito. The male *Anopheles* lacks the mouth parts for penetrating human skin and instead feeds on plant juices. The parasite is in a slender, elongated form between 10 and 55 μm in length called a *sporozoite*. This form lasts only about one hour in the circulating blood. The parasite makes its way to the liver, where it enters a parenchymal (functional) cell of the liver. Here the sporozoite undergoes development into the *exoerythrocytic schizont* form of the organism and feeds on the cell's cytoplasm. The sporozoites of *P. vivax* and *P. ovale* are capable of becoming *hypnozoites*. This form remains dormant in the *hepatocyte (liver cell)* for anywhere between several months and up to four years. Upon emergence from their hibernation, the normal life cycle is resumed. This is the first of the parasite's two asexual reproduction cycles in man. The second is within a blood cell.

After one to two weeks and several cell divisions, each schizont ruptures, giving rise to thousands of *merozoites*, which enter the bloodstream. Merozoites are about 2.5 μm in length. In the bloodstream, they invade red blood cells, initiating the *erythrocytic schizogonic phase* of the infection. This is the stage responsible for the symptoms of fevers and chills experienced by victims of malaria. The attack upon red blood cells is mediated by surface antigens. For example, *P. vivax* requires the red blood cell surface to present the so-called *Duffy* blood group antigen for recognition. However, nearly all West Africans lack this antigen and are resistant to vivax malaria.

Inside the erythrocyte, the merozoite grows to the *early trophozoite*, or ring stage. This stage feeds on hemoglobin and develops into the mature, or *late trophozoite*, stage. These trophozoites reproduce by multiple fission events into schizonts. And once again, schizonts produce a new generation of merozoites, each of which is capable of infecting a new erythrocyte.

However, these second-generation merozoites may transform into the gametocyte stage of the parasite instead; *microgametocytes* are the male gametocytes, and *macrogametocytes* are female. Despite their names, the two are approximately the same size. Up to this point in the life cycle, reproduction has been asexual, but that will change in the next stage.

The sexual phase of development takes place in the mosquito. Gametocytes are ingested by the mosquito with a blood meal and conveyed to its gut. The gametocytes are unaffected by the insect's digestive juices and are, in fact, released from the erythrocyte as it is digested. Then the microgametocyte undergoes a maturation process, accompanied by cell division, called *exflagellation*, in which six to eight *microgametes* are formed. Each is equipped with flagella, with which microgametes seek out their counterpart, *macrogametes*. Of course, macrogametes have derived from macrogametocytes according to a separate development. The gametes fuse, giving rise to a diploid zygote.

Within 12 to 24 hours, the zygote elongates into a motile wormlike form known as an *ookinete*. Ookinetes penetrate the wall of the gut, where the next phase of development takes place. It changes to a round shape and further develops into a form called an *oocyst*. It is from the oocysts that the sporozoites will arise.

To begin this last phase of the life cycle, an oocyst grows four to five times its original size due to internal cell divisions. The cells division are by meiosis (sexual cell divisions), and the proliferating haploid cells are referred to as *sporoblasts*. Sporoblasts undergo numerous cell divisions themselves, producing thousands of sporozoites. Finally, within 10 to 24 days after the mosquito's blood meal, the sporozoite-filled oocysts rupture, releasing the sporozoites, which make their way to the ducts of the insects' salivary gland. The parasite is now ready to be injected into a new host.

A noteworthy postscript to the story of malaria infection is the resistance to the disease brought about by the *sickle-cell trait*. The gene responsible for it contains the substitution of a valine amino acid in place of glutamic acid in the β chain of the hemoglobin molecule. Sickle-cell is invariably fatal to those homozygous for the trait, but in the heterozygous state it confers substantial protection against falciparum malaria. Red blood cells infected with the parasite are subject to low oxygen tensions and potassium leakage during the cell's passage through the capillaries. This kills the parasite.

11.3 Host–Parasite Interactions

In order for an endoparasite to succeed, it must overcome two major obstacles: getting into the host's body and defeating the host's immune system. The host, of course, reacts to the invasion. There ensues a struggle between the host's immune system and the parasite's defenses. Over the ages, the parasite has won. It continues to exist and conduct its life cycle within an internal universe of one or more hosts. Further, it has evolved so as to keep its host alive, albeit debilitated, and thereby ensure itself a long reproductive life.

Gaining entrance to the host.

Unihost parasites gain entrance to their host principally by utilizing an existing orifice. This admits the organism to the gut, the lungs, or the sex organs. This is also usually the site where they carry on their life cycle. From Table 11.1.1, we see that the normal mode of transmission of a parasite inhabiting the gut is by way of a cyst.

While multihost parasites can do the same, they can also exploit an alternative mechanism that admits them directly to the bloodstream. This is by hitching a ride on an organism, the vector, having the capability and practice of penetrating the host's body directly. The most convenient way to be at the right place at the right time is by living within or on such a vector, hence the evolution of multihost parasitism.

Of course, now the multihost parasite must also breech the vector's body. However, this is a solved problem: The simplest and most convenient mechanism is just to

go back the way they came in, at the moment the vector is again feeding on the host. And so we have a tidy, closed cycle waiting to be exploited. As we have seen, multihost parasites have many morphological and physiological adaptations to accomplish their life cycle in multiple hosts.

Immunological response and counterresponse.

From the moment a parasite breeches its host's body, it comes under immunological attack. The parasite must counter or be eliminated; as a result, a kind of arms race ensues in which each side attempts to overcome the defense of the other. Much is known about this struggle, especially with respect to malaria and several of the diseases we have examined above.

The body's defenses include antibodies, cytotoxic cells, lysosomal enzymes, toxic metabolites, and predatory phagocytes. Some of the principal players in mediating these defenses are immunoglobins (IgA, IgD, IgE, IgG, and IgM), lymphocytes, CD4+ helper T-cells, CD8+ cytotoxic T-cells, cytokines, macrophages, and granulocytes (see Section 10.2).

The role of antibodies is mainly confined to stages circulating in the bloodstream. Antibodies attack the merozoite stage of the malaria parasite. In addition, part of the resistance of adult humans against malaria in endemic regions is their antibody attack on the sporozoite stage. In another example, although *Giardia lamblia* is confined to portions of the small intestine, the antibodies IgA and IgM help control giardia infection in the submucosal epithelium.

For their part, plasma-based parasites respond by forging complicated life cycles alternating between the bloodstream and an intracellular subsistence. The time spent in the bloodstream is limited and they do so in various forms, thereby presenting differing surface antigens. Some species are even able to present a surface mimicking that of their host and thus be mistaken as "self" to the host's immunological system. This is called *molecular mimicry*. The parasite produces hostlike molecules on its body surface or its surface becomes covered with host molecules themselves. As a result, the host is duped into accepting the parasite as self.

However, a most remarkable feat is the ability of some species to present variable surface antigens. This has been observed in trypanosomes. If single parasite cells are cloned from different infected animals or patients, the surface coat is biochemically different—not just a bit different, but so different that the coat protein must come from the expression of different genes by trypanosomes in each animal. Moreover, if cells are taken from a defined wave of parasitemia in the same patient, it is found that all of the trypanosomes in that wave of organisms are expressing the same single-surface antigen, whereas in other waves, all of the parasites are expressing a single but completely different antigen. The organism is presenting variable surface antigens or variable surface glycoproteins (VSGs) in each wave.

In the laboratory, it has been observed that no antigen has been repeated even after hundreds of these waves. It follows that there must also be an equal number of VSG genes. In fact, there are probably 1000–2000 such genes. Thus 10% of the

cell's genome is devoted to genes that express these surface molecules allowing the organism to be one step ahead of the host's immune response.

As the host mounts an attack to each new wave of trypanosome parasitemia, eventually the host's lymphoid organs become depleted of lymphocytes, and immunodepression sets in. As we have seen, this is a technique also exploited by the HIV virus.

Another tactic used by parasites to avoid destruction is the adaptation to leave the bloodstream and take up residence inside a cell of the host. As a bonus, the cell's cytoplasm can be used for nutrition as well! Although an intracellular habitat shields the invader from antibodies, it does invoke a new form of immunological attack.

An infected cell of the host will react to the presence of an intruder. First, an attempt is made to lyse, or break up, the intruder by the action of the cell's lysosomes. Lysosomes are the cells' garbage disposal system. A section of rough endoplasmic reticulum wraps itself around the intruder and forms a vacuole. Then vesicles containing lysosomal enzymes fuse with it. The pH becomes more acidic and this activates the enzymes that break up the contents. Lysosomes also degrade worn-out organelles such as mitochondria.

As expected, parasites have evolved to counter this threat. One means is by encapsulation within the cell. Failing to rid itself of the parasite in this way, the cell consigns itself to suicide. With the help of the endoplasmic reticulum, the cell presents antigens of the intruder on its own surface. T-cells respond to such antigens and mature into cytotoxic killers, combining with and lysing any cell expressing these antigens (cf. Section 10.2).

With respect to malaria, cytotoxic defense is mounted against parasites invading liver cells, the exoerythrocytic schizonts, but obviously not against those in red blood cells (erythrocytic schizonts), since the latter are not living cells.

Despite its attempts to do so, the body is not able to totally eliminate intracellular parasites; the most it can hope for is to keep them in check.

So why is the immune response not more effective at combating parasites? Some of the explanations that have been proposed are the following:

- Parasites show considerable antigenic diversity and variation—between species, between strains, between stages, and during the course of an infection.
- Parasites avoid immunity by hiding inside cells.
- Infection stimulates T-cell mediated immunity, but there is little T-cell memory.
- Parasites misdirect or suppress the immune response.

Incidence and control of parasitic diseases.

Epidemiology is the study of the factors responsible for the transmission and distribution of disease. Contagious diseases are those that are transmitted from person to person directly. The life cycle of the organisms responsible for such diseases can be quite simple. Indeed, contagious diseases are often caused by viruses or bacteria. These perpetrators are frequently highly virulent, resulting in acute diseases that are deadly. Of course, pathogens themselves die with the patient, but by then the disease has already been passed on, ensuring the survival of their genes.

Common-source diseases are those that are not transmitted directly but instead by some third party, or common source. The common source need not be another organism—for example, it can be the soil—but nevertheless it often is an organism. Utilizing a third party already requires a more complicated life cycle because the agent must survive in at least two different environments. As we have seen, parasitic diseases are usually common source, since they are acquired via a vector or some contaminated inanimate material. (PCP is an exception in that it can be caught from an infected person directly. Even in this case the organism must survive for a time outside the host.) Thus it is not surprising that there is a large overlap between higher organisms, protozoans and helminths, and parasitism. These organisms, with their more extensive genome, can accommodate complicated life cycles.

Parasitic diseases are usually chronic. If death comes, it is usually after a lengthy period of debilitation. Of course, this works to the favor of the parasite; it is not advantageous to kill its host. This suggests that parasitic disease have been around for some time and have evolved to prolong the life of their host as long as possible.

Especially as a result of the differing mechanisms for gaining entrance to the host, certain environments are conducive to the differing parasitic life cycles. The tropics and subtropics favor multihost parasitism among humans. Factors for this are the warm weather, allowing an insect vector to be active all year around; abundant bodies of stagnant water; more diverse ecosystems supporting greater numbers of species; and the fact that human hosts generally present more bare skin and sleep exposed.

The host's behavior can also be a factor in the incidence of parasitic diseases. Unsanitary conditions and inadequate cooking are major contributors to disease. The same can be said for certain social and ethnic customs such as communal bathing and the ritual consumption of undercooked meat.

It might seem that the multitude of forms and attendant multitude of proteins for bringing them about constitutes many opportunities for the control and even eradication of a given parasite species. And indeed, this is the hope and design of modern research efforts. For example, in the case of multihost parasites, their vector can be attacked and thereby the chain of infection broken. Many efforts have been directed at the *Anopheles* mosquito for the control of malaria. These efforts have been only partially successful. Between the 1940s and 1960s, malaria eradication was achieved in the USA, the USSR, Southern Europe, and most Caribbean Islands mainly by vector control. Much progress was also made in the Indian subcontinent and parts of South America.

It even appeared for a time that eradication would also be successful in major problem areas such as Nigeria. But ultimately vector eradication failed and malaria vengefully resurged; see Section 11.4. The reason is that in endemic regions, where transmission is high, people are continuously infected, so that they gradually develop a degree of immunity to the disease. Until they have acquired such immunity, children remain highly vulnerable. Initially, the eradication program greatly reduced the mosquito population and incidence of malaria was low for several years. People lost immunity, and a cohort of children grew up with no immunity. When the control measures failed and were discontinued, widespread incidence ensued.

The problem with mosquito control is that it is very hard to do. There are, in effect, an infinite number of breeding sites for them. In rural areas in the wet tropics, *Anopheles* may breed in every water-filled foot- and hoofprint, and larval control is an almost hopeless undertaking. Equally important, insect vectors can eventually gain resistance to chemical treatments.

Chemical eradication programs can have a very damaging effect on the environment, generally because of their broad-based activity. The insecticide most widely used for house spraying aimed at the adult *Anopheles* mosquito has been DDT. DDT has continued to be recommended for this purpose long after it was banned for agricultural use in the USA and many other countries. It is recommended because of its cheapness per unit weight and its durability, which allows programs to be based on spraying twice a year, or only once in areas with a short annual malaria mosquito season. However, unfortunately in low-income countries, it is almost impossible to prevent illicit diversion of insecticides intended for antimalaria use to farmers. The consequent insecticidal residues in crops at levels unacceptable for the export trade have been an important factor in recent bans of DDT for malaria control in several tropical countries.

One can also attempt to control the parasite directly either by a preinfection drug poised to kill the parasite immediately upon its entrance or by a postinfection one designed to work after infection. With respect to malaria, some preinfection drugs are Proguanil, chloroquine, mefloquine, doxycycline, and malarone. Chloroquine is also a postinfection remedy. Arteminisin is a postinfection drug effective against drug resistant *P. falciparum* infections.

The problem with attacking the parasite itself is that protozoa tend to develop resistance to drugs even faster than insects develop resistance to sprays. Chloroquine was hugely successful in combating malaria when launched in the 1950s, but the malaria parasite gradually became resistant. *Plasmodium falciparum* has proved extraordinarily adept at evolving to combat many of the drugs currently on the market.

Still, the multiplicity of forms of the organism does provide targets. Understanding the details of each form, including for example metabolic pathways, offers the possibility of drugs specific to the parasite. We will encounter a success of this very kind in the section on genomic medicine, Section 14.4.

11.4 Mathematical Models for Parasitic Diseases

In Section 11.2, *we studied the life cycle of the parasites causing malaria. Now we will take that information into account and formulate a mathematical model for the incidence of malaria. The model divides the population into three groups, or compartments: those susceptible to the disease, those infected with it, and those in some form of recovery.*

We analyze the basic model and two refinements, time-dependent immunity and drug-resistant parasites. These models are due in part to Professor Sylvanus Aneke.

SIRS is a compartmental differential equations system.

The most widely used model for studying malaria is a modified SIRS system of differential equations. This means that the population is assumed to consist of three groups: Susceptibles (S) are those at risk of contracting the disease; infectives (I) are those who have the disease and are spreading it; and the removed (R) are those recovered with immunity. The population moves from S to I to R and back to S. The first main modification for malaria is that the susceptibles do not catch the disease from the infectives directly, and the removed are only partially removed, as we will explain. In the SIRS model for contagious diseases, there is a term of the form $-\alpha SI$ in the equation for $\frac{dS}{dt}$. This is a mass action term such as we have seen in our study of the Lotka–Volterra equation in Section 4.4, which provides for susceptibles getting sick from infectives. But there is no such term in a common source disease.

Instead, it is assumed that the susceptibles become infected at a rate in proportion to their numbers, $-hS$, for an infection rate parameter h. This choice is influenced by the fact that the feedback dynamics from mosquito to man and back to mosquito involve considerable delay, mostly due to the incubation periods of the several forms of the parasite. Also, in certain cases, it has been observed that the incidence of infected mosquitoes remains very close to 3 per cent under widely varying circumstances, thus constituting an approximately steady threat [2, 3].

Secondly, by the nature of malaria, a large fraction of those who recover from the disease are, in fact, only partially recovered. What we are calling infectives are those with severe symptoms. Most who overcome this state are still infected, having milder symptoms and being capable of passing gametocytes to mosquitoes. So the "removed" group here refers to this group, those partially recovered.

The movement between groups is shown in Figure 11.4.1 along with the rates, and the system model looks like this:

$$\begin{aligned} \frac{dx}{dt} &= -hx + \rho y + \beta(h)z, \\ \frac{dy}{dt} &= hx - \rho y - ry, \\ \frac{dz}{dt} &= ry - \beta(h)z. \end{aligned} \tag{11.4.1}$$

This is a compartmental model; those leaving one group do so by entering another. The behavior of such systems is well known; solutions tend to a unique globally asymptotically stable stationary point.

The model tracks the experience of a birth cohort, i.e., a group of people of about the same age, moving through time with t representing their age. The variables x, y, and z, all functions of t, denote, respectively, the relative size of the susceptible, the infective, and the partially recovered groups. Since these are relative sizes, their sum is 1 or 100%:

$$x(t) + y(t) + z(t) = 1, \quad t \geq 0. \tag{11.4.2}$$

Implicit in this statement is that mortality acts approximately equally on all groups. Initially, $x = 1$ and $y = z = 0$.

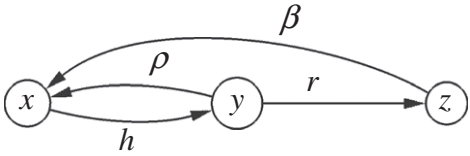

Fig. 11.4.1. Basic Aron–May malaria model.

As above, h is the infection or "happening" rate. The parameter r is the rate of (partial) recovery, that is, the transition rate from group y to group z. Hence $\frac{1}{h}$ is the mean time until infection, and $\frac{1}{r}$ the mean time until recovery. The model postulates that the mildly symptomatic can arise only from the severely symptomatic. The terms ρy and $\beta(h)z$ are due to Aron and May [1, 2]. The *recovery rate* ρ corresponds to how quickly parasites are cleared from the body. High recovery rates are associated with drug treatments.

Note. Greek symbols are not part of MAPLE or MATLAB, and so the parameters ρ and β will be coded as `rho` and `beta`, respectively, in the computer codes.

The term $\beta(h)y$ allows for a return path from the partially recovered back to the susceptibles. Furthermore, β is taken as a function of h in deference to the observation by many that the greater the endemicity of the disease, the greater the extent of immunity among the population. Thus β should decrease with increasing h. The exact relationship is in terms of a parameter τ and takes the form

$$\beta(h) = \frac{he^{-h\tau}}{1 - e^{-h\tau}}, \tag{11.4.3}$$

where τ is mean duration of partial recovery; see Figure 11.4.2. If a person is reexposed before this time has elapsed, then another interval of duration τ without exposure is required before return to the susceptible group (probabilistically).

As a test of their models, and as a source of parameter estimation, mathematical epidemiologists often use real-life data. The Garki Project data and the Wilson data are well known and useful for these purposes.

In 1980, the World Health Organization (WHO) attempted to determine whether intensive spraying could eradicate malaria in and around Garki, Nigeria. As part of the project, WHO coordinated mass drug administration in 164 villages in addition to the spraying. The Garki Project had an enormous impact on the mosquito population in that area, reducing the biting rate of mosquitoes by 90%. But despite this dramatic decline, the prevalence of the malaria parasite among villagers did not significantly change. The vectorial capacity of the surviving mosquitoes was simply too high to be overcome by these extensive measures.

Figure 11.4.3 is a result of the Garki Project, showing that prevalence of the disease decreased at first but then rose to higher levels than controls upon cessation of treatment. That is, the prevalence curves crossed each other. This phenomenon is the motivation for the aforementioned infection-dependent recovery rate $\beta(h)$.

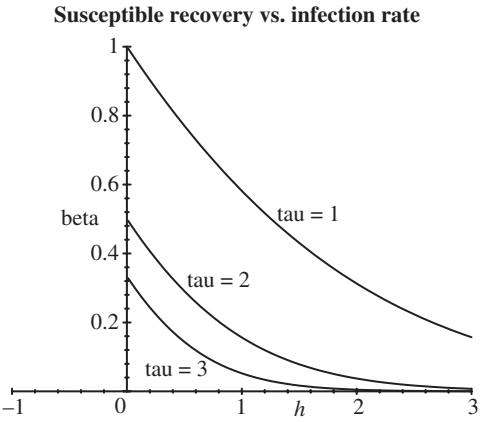

Fig. 11.4.2. Recovery rate β vs. infection rate h for various τ.

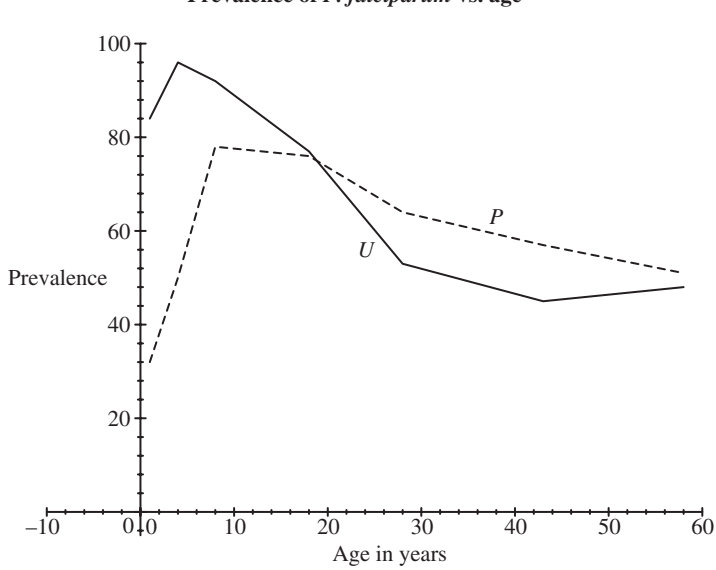

Fig. 11.4.3. Garki Project data. U refers to the controls, P to the treated.

The program for the Garki figure follows. This will be useful for comparing predicted incidence with actual prevalence:

```
  MAPLE
> with(plots):
> controls:=[[1,84], [4,96], [8,92], [18,77], [28,53], [43,45], [58,48]];
> cPlot:=plot(controls,-10..60,-5..100,labels=['Age in years','Prevalence'],
            title='Prevalence of P. falciparum vs. age',titlefont=[COURIER,BOLD,16]):
> treated:=[[1,32], [4,50], [8,78], [18,76],[28,64], [43,57], [58,51]];
> tPlot:=plot(treated,linestyle=3):
```

```
> text:=textplot({[24,56,'U'],[38,63,'P']}):
> display({cPlot,tPlot,text});
```

MATLAB

```
> cx=[1,4,8,18,28,43,58];
> cy=[84,96,92,77,53,45,48];
> tx=[1,4,8,18,28,43,58];
> ty=[32,50,78,76,64,57,51];
> plot(cx,cy,tx,ty,[0,60],[0,0])
> axis([0,60,0,100])
> title('Prevalence of P. falciparum vs. age');
> xlabel('Age in years');ylabel('Prevalence');
```

Another relevant data set, reported by Wilson [8], compares prevalence in urban areas with that in rural communities. Rural victims have much less access to drugs as compared to their urban counterparts. This accounts for the higher prevalence of infection in rural areas, as shown in Figure 11.4.4.

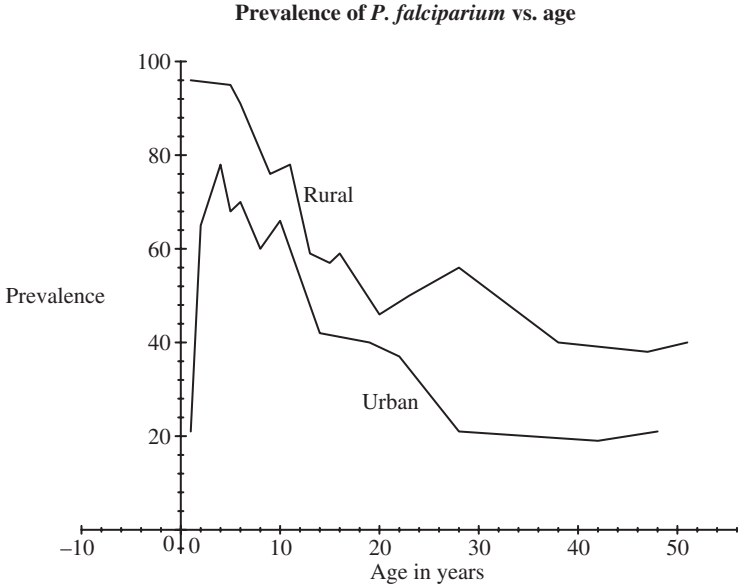

Fig. 11.4.4. Wilson data showing urban vs. rural prevalence.

Note the strong similarity between the untreated group in the Garki Project data and the rural group of the Wilson data.

We begin the mathematical analysis by finding the stationary point of the system. Setting the derivatives to zero gives

$$\begin{aligned} 0 &= -hx + \rho y + \beta(h)z, \\ 0 &= hx - \rho y - ry, \\ 0 &= ry - \beta(h)z. \end{aligned}$$

Also take normalization, (11.4.2), into account. In MAPLE, we have the following:

```
MAPLE (symbolic, so no MATLAB equivalent)
> eSys:={-h*x+rho*y+beta*z=0, h*x-rho*y-r*y=0, r*y-beta*z=0, x+y+z=1};
> solve(eSys,{x,y,z});
```

So

$$y = \frac{1}{\left(\frac{\rho+r}{h} + 1 + \frac{r}{\beta}\right)}$$

and

$$x = \frac{\frac{\rho+r}{h}}{\left(\frac{\rho+r}{h} + 1 + \frac{r}{\beta}\right)}, \qquad z = \frac{\frac{r}{\beta}}{\left(\frac{\rho+r}{h} + 1 + \frac{r}{\beta}\right)}. \tag{11.4.4}$$

Next, we explore the predicted incidence itself by solving the Aron–May system (11.4.1). The following computer programs do this for three sets of parameter values.

Code 11.4.1.

```
MAPLE
> restart:
> sys:=diff(x(t),t)=-h*x(t)+rho*y(t)+b*z(t),
        diff(y(t),t)=h*x(t) - rho*y(t) - r*y(t),
        diff(z(t),t)=r*y(t) - b*z(t);
> sol:=dsolve({sys,x(0)=1,y(0)=0,z(0)=0},{x(t),y(t),z(t)}):
> ysol1:=unapply(subs(sol,y(t)),(h,rho,r,b,t)):
> tau:=2; rho:=1/6; r:=1/8;
> beta:=h–>h*exp(-h*tau)/(1-exp(-h*tau));
> plot([subs(h=5,ysol1(h,rho,r,beta(h),t)),subs(h=5/10,ysol1(h,rho,r,beta(h),t)),
        subs(h=5/1000,ysol1(h,rho,r,beta(h),t))], t=0..50,0..1, color=[red,green,blue]);

MATLAB
% make up an m-file, beta.m, with
%   function b=beta(h,tau);
%   b=h*exp(-h*tau)/(1-exp(-h*tau));
% make up an m-file, parasConst.m, with
%   function parasParms = parasConst(t);
%   h=5; tau=2; b=beta(h,tau);
%   rho=.167; r=0.125; v=0; u=0; % v not used yet
%   parasParms=[h,rho,b,r,v,u];
% make up an m-file, aronmay.m, with
%   function SIRSprime=aronmay(t,X);
%   %X(1)=x, X(2)=y, X(3)=z
%   params=parasConst(t);
%   h=params(1); rho=params(2);b=params(3);
%   r=params(4);v=params(5);u=params(6);
%   SIRSprime=[-h*X(1)+rho*X(2)+b*X(3); h*X(1) - rho*X(2) - r*X(2); r*X(2) - b*X(3)];
> [t,X]=ode23('aronmay',[0 50],[1;0;0]);
> plot(t,X(:,2))
> hold on;
  % change h=5 to h=0.5 in parasConst.m
> [t,X]=ode23('aronmay',[0 50],[1;0;0]);
> plot(t,X(:,2))
  % change h=0.5 to h=0.005 in parasConst.m
> [t,X]=ode23('aronmay',[0 50],[1;0;0]);
> plot(t,X(:,2))
```

The results are plotted in Figure 11.4.5. Note that this model shows the crossover effect. In the exercises, we explore the possibilities further.

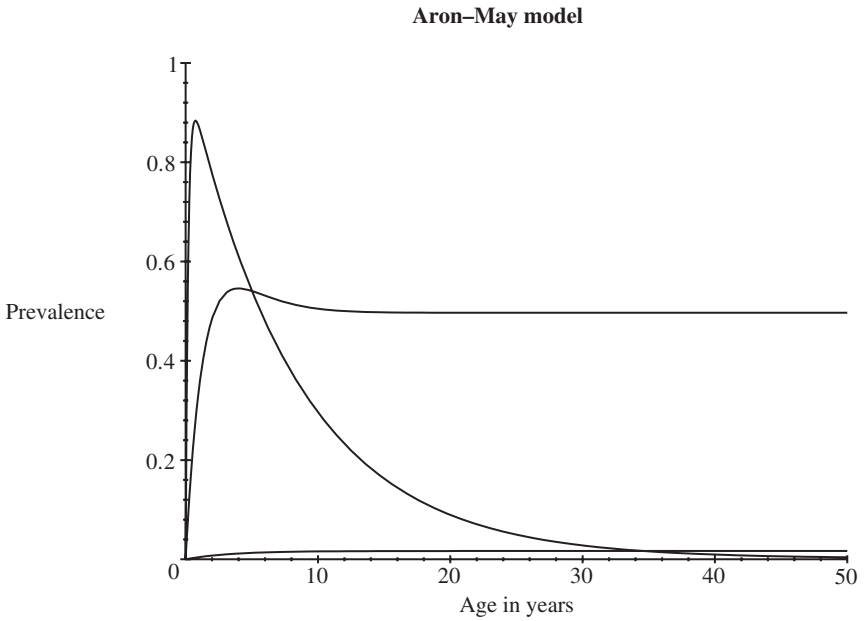

Fig. 11.4.5. Predicted prevalence of a cohort as a function of age for three sets of parameter values.

Time-dependent immunity (TDI) model.

Understanding that immunity is acquired and develops over time with exposure can be taken into account using a time-dependent immunity acquisition rate, $r = r(t)$. The assumptions are that immunity is initially nil, $r(0) = 0$; that upon exposure, there is a startup delay in acquiring immunity, $\dot{r}(0) = 0$; and that immunity tends asymptotically to a limiting value, say, R. These principles are captured in the simple differential equation

$$\frac{dr}{dt} = (\text{rate}) \cdot t \cdot (R - r), \quad r(0) = 0,$$

for some rate parameter. Let v, called *exposure*, denote twice the rate parameter. Then solving the differential equation gives

$$r = R(1 - e^{-vt^2}). \tag{11.4.5}$$

A plot of r vs. t for various v is shown in Figure 11.4.6 using the following code:

MAPLE
```
> restart: with(plots):
> rsol:=dsolve({diff(r(t),t)=2*v*t*(R-r(t)),r(0)=0},r(t));
> r:=unapply(subs(rsol,r(t)),(v,t));
> R:=1;
> plot([r(1/1000,t),r(2/1000,t),r(3/1000,t)],t=0..50,view=[-10..50,-0.2..1],color=[blue,green,red]);
```

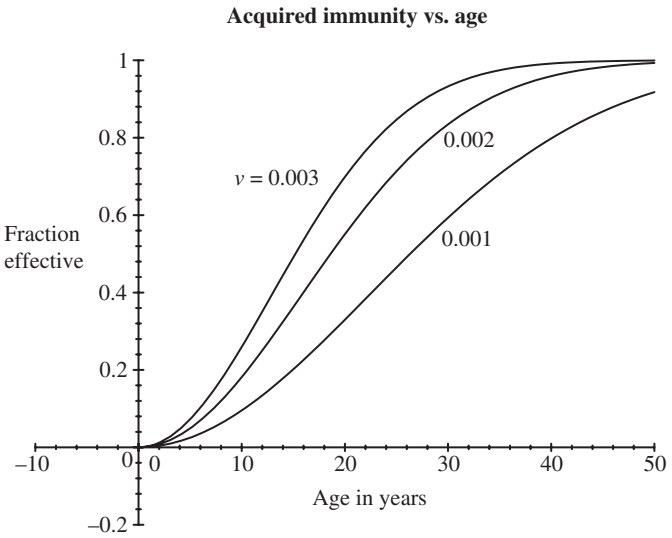

Fig. 11.4.6. Acquired immunity profile.

```
MATLAB
% make up an m-file, tdifcn.m, as
%   function r=tdifcn(R,v,t);
%   r=R*(1-exp(-v*t.^2));
> R=1;t=0:.1:50;
> v=.001; y1=tdifcn(R,v,t);
> v=.002; y2=tdifcn(R,v,t);
> v=.003; y3=tdifcn(R,v,t);
> plot(t,y1,t,y2,t,y3)
```

With this modification to system (11.4.1), we have the time-dependent immunity (TDI) model:

$$\begin{aligned}\frac{dx}{dt} &= -hx + \rho y + \beta(h)z,\\ \frac{dy}{dt} &= hx - \rho y - R(1 - e^{-vt^2})y,\\ \frac{dz}{dt} &= R(1 - e^{-vt^2})y - \beta(h)z.\end{aligned} \tag{11.4.6}$$

The modification has no effect on stationary values, since $r \to R$ as $t \to \infty$. So the stationary point is the same, only with R replacing r in (11.4.4).

Some runs with various parameter values are shown in Figure 11.4.7. The only change to the program listing code, Code 11.4.1, is to replace r by the right-hand side of (11.4.5):

```
MAPLE
> R:=0.08; v:=0.01;
> sys:=diff(x(t),t)=-h*x(t)+rho*y(t)+b*z(t),
>       diff(y(t),t)=h*x(t)-rho*y(t)-R*(1-exp(-v*t^2))*y(t),
>       diff(z(t),t)=R*(1-exp(-v*t^2))*y(t)-b*z(t);
```

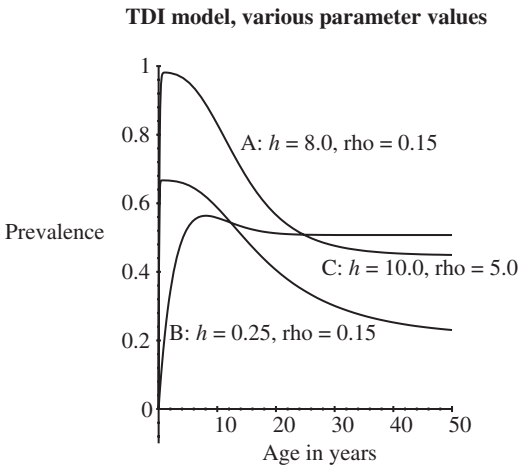

Fig. 11.4.7. $\tau = 0.6$, $R = 0.08$, h, and ρ as shown.

```
> sol1:=dsolve({sys,x(0)=1,y(0)=0,z(0)=0},{x(t),y(t),z(t)},type=numeric,output=listprocedure);
> ysol1:=subs(sol1,y(t));
```

MATLAB

```
% make up an m-file, tdi.m, with
%   function SIRSprime=tdi(t,X);
%   %X(1)=x, X(2)=y, X(3)=z
%   params=parasConst(t);
%   h=params(1); rho=params(2);b=params(3);
%   R=params(4);v=params(5);u=params(6);
%   SIRSprime=[-h*X(1)+rho*X(2)+b*X(3); h*X(1)-rho*X(2)-R*(1-exp(-v*t^2))*X(2);
%              R*(1-exp(-v*t^2))*X(2)-b*X(3)];
% don't forget to set correct param values in parasConst.m.
% Also r in that file now plays the role of R.
```

Note that this time-dependent immunity model preserves the crossover phenomenon and the urban vs. rural phenomenon. Thus for $\rho = 0.15$, the curve for high h crosses that for low h, curves A and B of the figure. In addition, a high value of ρ, $\rho = 5.0$, gives a profile matching the urban group of the Wilson data, curve C.

A weighted nonlinear least squares fit to the Garki Project data produces the parameters given in Table 11.4.1. The corresponding predicted prevalence curve is shown in Figure 11.4.8 superimposed on the U Garki data.

Table 11.4.1. Time-dependent immunity.

Parameter specification	Error	Stationary values
$h = 1.99$, $\rho = 0.074$, $R = 0.113$, $\tau = 1.5$, $v = 0.0024$	0.003	$\bar{x} = 0.04$, $\bar{y} = 0.46$, $\bar{z} = 0.50$

One would like to know how sensitive the predictions are to the various parameters. This is done by differentiating the variables with respect to the parameters

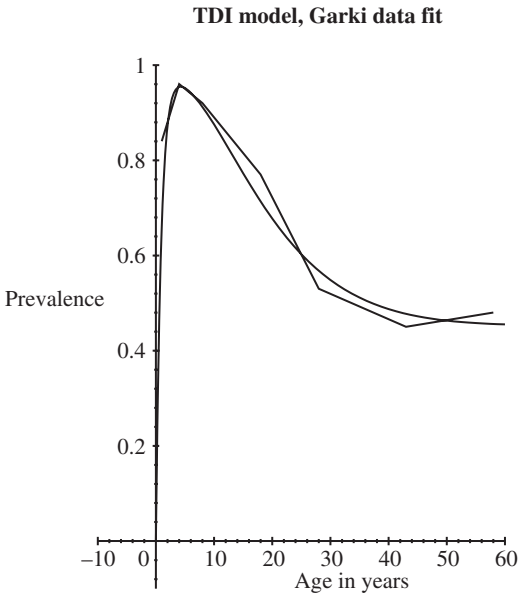

Fig. 11.4.8. Predicting the Garki urban data, parameters from Table 11.4.1.

themselves. Thus we compute the partial derivative of x with respect to h, then with respect to ρ, then to R, and finally to τ. Do the same for y and z. The results can be presented in matrix form, called the *Jacobian*. For the parameter set in Table 11.4.1, the sensitivity at stationarity to parameter fluctuation is this:

$$J = \begin{bmatrix} -0.22 & 0.26 & 0.18 & -0.22 \\ 0.13 & -0.19 & -0.28 & -0.27 \\ 0.09 & -0.08 & 0.10 & 0.48 \end{bmatrix}.$$

The rows are ordered x, y, and z and the columns h, ρ, R, and τ. Thus x is most sensitive to change in ρ, y is most sensitive to change in R, and z is most sensitive to change in τ.

Drug-resistant model.

While the models above deal largely with the natural course of the disease, in this section we assume that the entire cohort at risk is treated with drugs to clear internal parasites. Treatment and control have become more difficult in recent years with the spread of drug-resistant strains of *P. falciparum* [3, 4, 9]. Drugs such as chloroquine, nivaquine, quinine, and fansidar are used for treatment. More recent and more powerful drugs include mefloquine and halofantrine.

To proceed, we distinguish resistant infectives from sensitive infectives; the former are those infected with parasites that are resistant to drugs. While this model cannot track the dynamics between sensitive and resistant strains of parasites—in

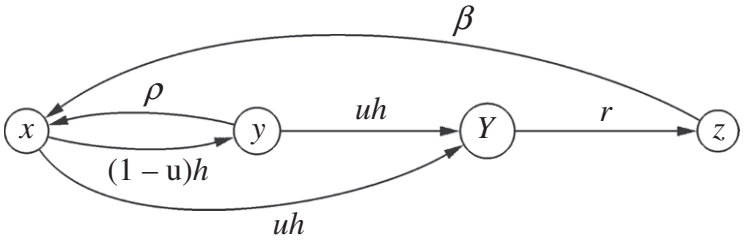

Fig. 11.4.9. Resistant model compartment flow chart.

areas where drug use is extensive, resistant strains are selected for and increase in number—it can show the effect on the prevalence graph and on the stationary point.

We assume that all infected individuals receive treatment. Treatment consists in the administration of chloroquine or other 4-aminoquinoline derivatives. It is well known that these popular drugs do not have any significant activity against the exoerythrocite or gametocite stage of malaria parasites (see Section 11.2). It is assumed that sensitive infectives respond quickly to treatment and return to the susceptible class. On the other hand, individuals infected with resistant strains do not respond to this treatment and must acquire immunity and pass through the partially recovered group before returning to the susceptibles.

Let y represent the infectives stricken with sensitive parasites only and Y those stricken with resistant parasites and, possibly, sensitive strains as well. Let u be the probability that when an individual is infected, it is with a resistant strain of the parasite, with or without sensitive strains, and let $1 - u$ be the complementary probability, that is, the probability that an individual is infected with sensitive strains only. With the rest of the notation as before, we have the following sensitive–resistant strain model; Figure 11.4.9 illustrates the possibilities:

$$\begin{aligned}
\frac{dx}{dt} &= -hx + \rho y + \beta z,\\
\frac{dy}{dt} &= (1-u)hx - \rho y - uhy,\\
\frac{dY}{dt} &= uhx + uhy - R(1 - e^{-vt^2})Y,\\
\frac{dz}{dt} &= R(1 - e^{-vt^2})Y - \beta z.
\end{aligned} \tag{11.4.7}$$

As before, β is a fuction of h given by (11.4.3). By normalization,

$$x(t) + y(t) + Y(t) + z(t) = 1 \tag{11.4.8}$$

with initial condition $x(0) = 1$.

The modification to the computer code is again straightforward—the following, for example:

MAPLE
```
> beta:=h–>h*exp(-h*tau)/(1-exp(-h*tau));
```

```
> tau:=.6; u:=0.8; R:=0.08; v:=0.0024; h:=.25; rho:=.15; b:=beta(h);
> sys:=diff(x(t),t)=-h*x(t)+rho*y(t)+b*z(t),
>       diff(y(t),t)=(1-u)*h*x(t)-rho*y(t)-u*h*y(t),
>       diff(Y(t),t)=u*h*(x(t)+y(t))-R*(1-exp(-v*t^2))*Y(t),
>       diff(z(t),t)=R*(1-exp(-v*t^2))*Y(t)-b*z(t);
> sol1:=dsolve({sys,x(0)=1,y(0)=0,Y(0)=0,z(0)=0},{x(t),y(t),Y(t),z(t)},type=numeric,output=listprocedure);
> ysol1:=subs(sol1,y(t));
> Ysol1:=subs(sol1,Y(t));
> ysum:=ysol1+Ysol1:
> plot([ysum,t,0..50]);
```

MATLAB

```
% make up an m-file, resis.m, with
%   function SIRSprime=resis(t,X);
%   %X(1)=x, X(2)=y, X(3)=Y, X(4)=z
%   params=parasConst(t);
%   h=params(1); rho=params(2); b=params(3); R=params(4);v=params(5); u=params(6);
%   SIRSprime=[-h*X(1)+rho*X(2)+b*X(4); (1-u)*h*X(1)-rho*X(2)-u*h*X(2);
%                 u*h*(X(1)+X(2))-R*(1-exp(-v*t^2))*X(3); R*(1-exp(-v*t^2))*X(3)-b*X(4)];
% don't forget to set correct param values in parasConst.m
% Also r in that file now plays the role of R.
> [t,X]=ode23('resis',[0 50],[1;0;0;0]);
> plot(t,X(:,2))
```

For stationarity, use the fourth equation of (11.4.7) to eliminate Y and the second to eliminate x. The resulting equation (two times over) is

$$\frac{u(\rho+h)}{1-u}y-\beta z=0.$$

Solve this for y; the stationary point is given in terms of z by

$$x=\frac{\beta(\rho+uh)}{uh(\rho+h)}z,\qquad y=\frac{\beta(1-u)}{u(\rho+h)}z,\qquad Y=\frac{\beta}{R}z.$$

As before, since solutions must sum to one, (11.4.8), we have a unique asymptotic stationary point.

MAPLE(symbolic, no MATLAB equivalent)

```
> restart;
> equi:=solve([-h*x+rho*y+beta*z=0, (1-u)*h*x-rho*y-u*h*y=0, u*h*x+u*h*y-R*Y=0, x+y+Y+z=1],{x,y,Y,z});
> ze:=simplify(subs(equi,z));
> xe:=simplify(subs(equi,x)/ze)*z;
> ye:=simplify(subs(equi,y)/ze)*z;
> Ye:=simplify(subs(equi,Y)/ze)*z;
> RHSmatrix:=matrix([[-h,rho,0,beta], [(1-u)*h,-rho-u*h,0,0], [u*h,u*h,-R,0], [0,0,R,-beta]]);
```

The effect of u is illustrated in Figure 11.4.10 by plotting some prevalence profiles for the resistant infectives (the number of sensitive infectives is very small) for various values of u. In this figure, it is assumed that all parameters are as in the baseline TDI model, Table 11.4.1, except the recovery rate ρ, which is taken to be much higher. We see from the figure that the profiles are relatively insensitive to u (provided it is not zero).

Next, we examine graphically some predictions of this model in relation to the previous ones. In order for our model to be of practical significance and describe certain hyperendemic situations, we use parameter values that are reported to be the situation in the Nsukka region of Nigeria: $\tau=0.6$, $u=0.8$, $h=0.5$, $\rho=0.8$, and $R=0.2$ (by personal communication from Professor Sylvanus Aneke).

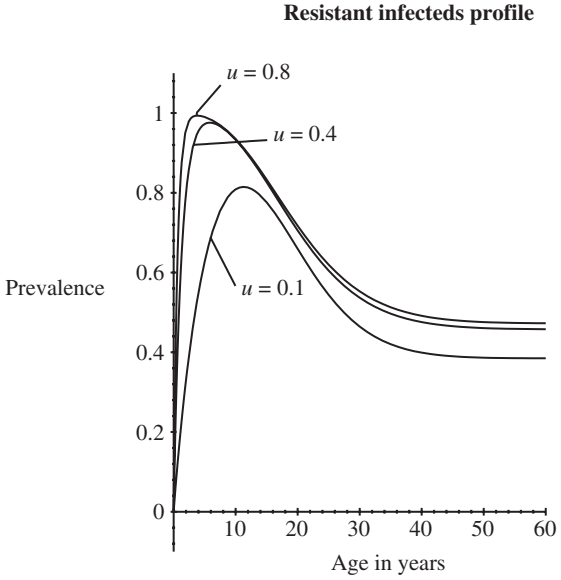

Fig. 11.4.10. Parameter values as in Table 11.4.1 except $\rho = 5$.

With these values the stationary point becomes

$$x = 0.250, \qquad y = 0.021, \qquad Y = 0.541, \qquad z = 0.188.$$

The population of the region is about 2 million.

Solution curves for both y and Y are shown in Figure 11.4.11 for three sets of parameter values as given in the figure. In the figure, y_1 goes with Y_1, y_2 with Y_2, and so on. The corresponding stationary points are given in Table 11.4.2.

It is seen from Figure 11.4.11 that in all cases, the principal infection is from resistant parasites. For low ρ, the resistant curves Y_1 and Y_2 resemble the corresponding curves in Figure 11.4.7. Thus in this setting, the first two sets of parameters could be seen as describing a situation in which infectives are treated initially with a drug that has very little impact on infectives. The third curve, Y_3, still shows that if u is high, sensitive infectives diminish.

An observation that follows from the equilibrium equations is that for large ρ, meaning that treatment is widely administered and effective, most of the population will be in the partially recovered class. This is seen in Table 11.4.2. This occurs even if h is high.

Exercises/Experiments

1. Take as the baseline system the TDI model with these parameter values: $h = 2$, $\rho = 0.07$, $R = 0.1$, $\tau = 1.5$, and $v = 0.002$. Perform five experiments to test the effect of each parameter. Hold all parameters fixed except the one being tested and vary that parameter for a few values above and below the baseline value, say,

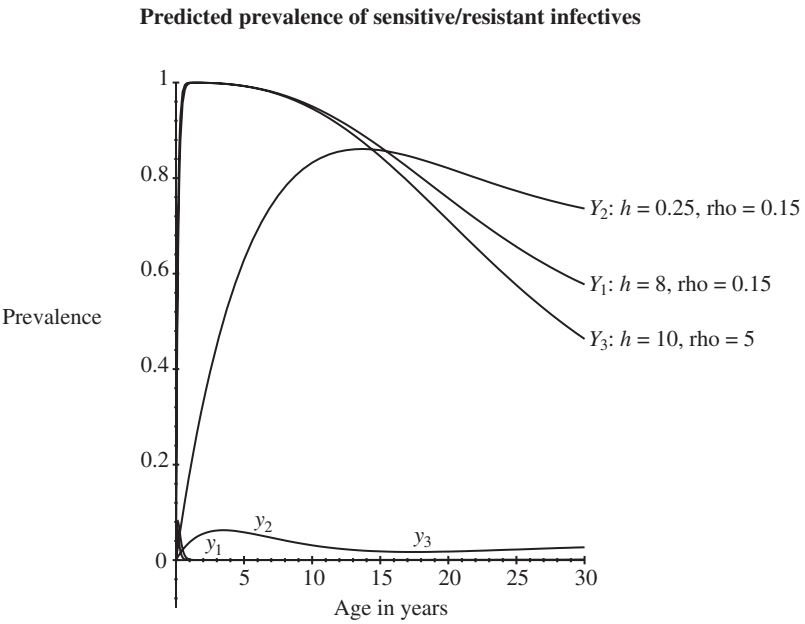

Fig. 11.4.11. $R = 0.08$, $\tau = 0.6$, $v = 0.0024$, $u = 0.8$, h and ρ as shown.

Table 11.4.2. Sensitive–resistant model.

Parameter specification	Asymptotic stationary values
$h = 8,\quad \rho = 0.15$	$x = 0.01,\ y = 0,\quad Y = 0.45,\quad z = 0.54$
$h = 0.25,\ \rho = 0.15$	$x = 0.24,\ y = 0.03,\ Y = 0.69,\quad z = 0.04$
$h = 10,\quad \rho = 5$	$x = 0,\quad y = 0,\quad Y = 0.024,\ z = 0.76$

up to 50%. Plot the result of each test on a single plot along with the baseline. Altogether you will have five plots. Which parameter has the greatest effect on the disease according to your experiments?

2. According to the last two digits of your college registration number, pick graph A in Figure 11.4.12 if these digits are from 00 to 24, pick graph B if from 25 to 49, and so on. Experiment with the parameter values of the TDI model to match the selected graph as closely as you can. What are those values?

3. From the baseline case (see Exercise 1 above), suppose a cohort of individuals are born having very little propensity for acquiring immunity, $R = 0.01$, but for whom the tendency to surmount the disease is high, $\rho = 0.3$. What effect does this have on the prevalence profile and the equilibriums?

4. From the baseline case (see Exercise 1 above), suppose a cohort is born having the tendency to quickly pass into the acquired immunity stage, $R = 0.2$ and

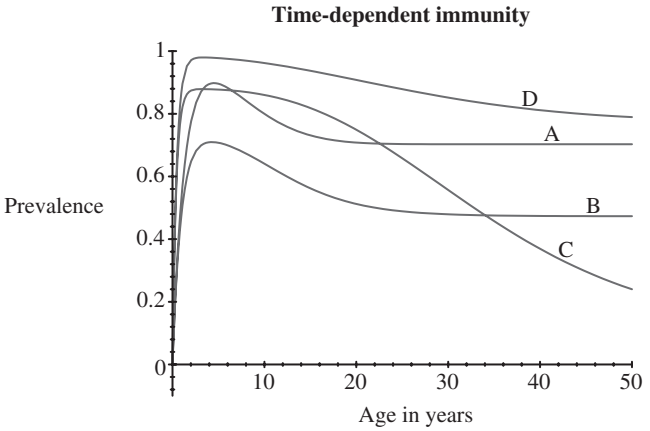

Fig. 11.4.12. Prevalence for four different sets of parameter values, τ, R, ρ, v, h.

$v = 0.01$, and then to stay there, $\tau = 3$. What effect does this have on the prevalence profile in the TDI model and the equilibriums?

5. In this experiment with the Aron–May model, we want to suppose that mosquito control measures are quite effective at first, so $h = 0.2$ while a cohort is young, up to age 20, say, but then reverts to its baseline value $h = 2$. At the same time, put $v = 0.001$ to reflect that infecteds will be delaying acquired immunity. The modifications to the basic program are detailed below. What effect does this have on the prevalence?

```
  MAPLE
> restart:
> h:=t->.2+1.8*Heaviside(t-20);
> beta:=h->h*exp(-h*tau)/(1-exp(-h*tau));
> tau:=1.5; R:=.1; rho:=.07; v:=.001;
> sys:=diff(x(t),t)=-h(t)*x(t)+rho*y(t)+beta*h(t)*z(t),
>       diff(y(t),t)=h(t)*x(t)-rho*y(t)-R*(1-exp(-v*t^2))*y(t),
>       diff(z(t),t)=R*(1-exp(-v*t^2))*y(t)-beta*h(t)*z(t);
> sol:=dsolve({sys,x(0)=1,y(0)=0,z(0)=0},{x(t),y(t),z(t)},type=numeric,output=listprocedure);
> ysol:=subs(sol,y(t));
> plot([ysol],0..50,-0.1..1.0);

  MATLAB
  % modify the m-file, parasConst.m, according to
  %  function parasParms = parasConst(t);
  %  tau= as desired;
  %  if t<20
  %    h=.2;
  %  else
  %    h=2.0;
  %  end
  %  b=beta(h,tau);
  %    rho, r, v, u as desired
  %  parasParms=[h,rho,b,r,v,u];
> [t,X]=ode23('tdi',[0 50],[1;0;0]);
> plot(t,X(:,2))
```

6. In contrast to the previous problem, assume here that the baseline conditions prevail for a cohort until age 20, at which point the infection rate h falls to 0.2. Leave the acquired immunity parameter v at its baseline value.

Questions for Thought and Discussion

1. What would the world be like if malaria were conquered?

2. Discuss a possible evolutionary pathway leading to internal parasitism.

3. How can knowing the genomic sequence of *P. falciparum* help in controlling malaria?

References and Suggested Further Reading

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