# PARASITOLOGY

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# *Preface*

Almost every biology department has an undergraduate parasitology course, generally taught by those of us who find parasites an unending source of interest. Each of us teaches the subject from his or her own viewpoint and emphasizes those organisms we feel to be important or to which we have some attachment, for whatever reason. As such, this book is a personal statement of what we feel to be important in parasitology.

Parasites in the context of this book (protozoa, helminths, arthropods) have a direct impact on humans or on domesticated animals that is almost beyond comprehension. Five of the six diseases considered to be most devastating to human health by the World Health Organization (WHO) are caused by parasites. These are global problems that concern us all and that have an effect on the majority of people on earth. As human populations increase, the need for food and fiber increases, and parasitic diseases of livestock reduce the amount of food available to people everywhere. In a complex, changing world, parasites remain with us and are a part of the ecosystem with which we must contend. Our feeling is that parasitology is an aspect of applied biology, and because of the enormous impact of parasites on human activities we consider the subject of controlling parasitic diseases as the principal focus of our courses.

The question then is, "What do students need to know about principles of control?" A part of the answer is simple—they need to know what organism is causing the problem and to know about certain aspects of its biology. But control is not carried out in a vacuum; not only the parasite but all human institutions, culture, politics, economics, food habits, and religious beliefs influence a program's success or failure. Thus, we attempt to overlay structure and biology of an organism with the so-called real world. We will leave the assessment of our success to others, but our nonrandom, biased survey of selected students indicates that it is well received.

Probably all of us hope that students will complete our courses and go away with certain principles tucked tidily in their minds. The question is how to achieve this exalted goal. We conclude that students need a good grasp of what a particular parasite is all about before they can assess its impact and thus determine what kind of control program may be needed. Examples come from parasitic disease of humans, domesticated animals, and wildlife of interest to us. One should approach a control program differently, depending on what is considered (e.g., human health or economic return from a herd of cattle). We have tried to point out the similarities and differences in what is desirable and possible in various circumstances.

As the late Asa C. Chandler pointed out in his address entitled *The Making of a Parasitologist*, the wide range of knowledge required to be effective in parasitology is one of the truly challenging aspects of the field. Those of us who have worked on parasites for many years may approach adequate knowledge in a number of areas, but students do not usually have a grasp of vertebrate

and invertebrate structure and physiology, let alone principles of pathology and pharmacology. We have tried to address these subjects with terminology that is as simple as possible, so that students will not be impeded by arcane words but will be able to see what the phenomenon is without difficulty.

Writing this book has sometimes been interesting, frequently enjoyable, but always educational. We hope that students will find equal dosages of interest, enjoyment, and education in reading and using the book.

## ACKNOWLEDGMENTS

Writing a book of this size becomes such a long and tortuous journey that one sometimes gets lost in the wilds of syntax, organization, and necessary simplifications. We were fortunate that many persons gave freely of their time and experience to guide us back to the main road and the completion of the odyssey. Gregory W. Payne and Eileen Schlesinger of Macmillan were patient and helpful in ensuring that the final product attained high standards. Reviewers of the manuscript in interim stages were Gerald W. Esch, John S. Mackiewicz, Theodore Lund, and William S. Romoser. Norman D. Levine and Donald Heyneman reviewed the completed manuscript and offered crucial insights that improved the final product greatly. We cannot help mentioning that Norman, in his inimitable way, edited the whole manuscript in detail, not only clarifying inept phrasing but pointing out errors of which we were unaware. We are grateful to all of the reviewers for their helpful criticisms and constructive suggestions. Whatever the shortcomings and errors of this book, we remain responsible for them.

Nancy Heisler typed most of the manuscript and eliminated many first-draft glitches; she was encouraging in her own way by admitting that even though the subject matter is repugnant, it is interesting.

W.C.M.
R.S.D.

# Contents

# Introduction

Nearly everyone has had some experience with parasites and knows in general terms what they are. If we have a dog or cat, it will require worming at some time or need to be treated for mange mites. Horse owners know that treatment for intestinal worms is needed periodically. We nearly all have had chiggers or ticks feed on us after a picnic in a rural area. Travelers to tropical areas take their chloroquine faithfully to prevent malaria. We will be concerned in this book primarily with parasitic worms, protozoa, and arthropods that are in some way important to humans. These organisms comprise only a small fraction of the total number that inhabit various parasitic niches throughout the biotic world.

In this introduction, we will answer four questions:

What is parasitism?

How does the parasitic relationship work?

How do the host and parasite respond to each other?

How are parasitic diseases controlled?

The themes developed here will be reiterated and reexamined throughout the book. It is likely that some of what is set forth here will make more sense as the student becomes better acquainted with the various organisms discussed. We encourage students to return to this introduction periodically with the hope that the basis of the definitions and concepts will become clearer as knowledge is accumulated.

## WHAT IS PARASITISM?

Organisms of the same and different species interact with one another in a myriad of ways. When organisms of different species have an intimate association, it is termed *symbiosis* (Read, 1970; Whitfield, 1979). DeBary coined this term in 1879 to encompass associations involving close physical contact between partners that are not of the same species. Students who have taken a beginning biology course usually know of various symbiotic relationships such as lichens, which are composed of an alga and a fungus, ants that keep aphids as a source of food, crabs that keep a sea anemone on their backs as camouflage, tapeworms that live in the intestines of mammals, and mosquitoes that need a blood meal in order to lay eggs. What these symbiotes have in common is a close association; neither benefit nor harm is implied in the term symbiosis.

The subject of this book is parasites, and parasitism is a particular subset of symbiosis.

**Parasitism:** an association between the populations of two species in which the smaller (parasite) is physiologically dependent on the larger (host), the prevalence of the parasites and the intensity of infection in the host population are nonrandom, and the parasite species has a higher reproductive potential than the host species; the parasite has the potential of harming the host.

Definitions of parasites and parasitism have changed

over time, and through the influence of Read (1970) and Crofton (1971a & b), some of the inconsistencies have been weeded out and the ideas reworked by a number of authors; among them is Whitfield (1979), who wrote a small, readable book about parasitism in general. The definition of parasitism we have given takes ideas from these authors and simplifies some of the concepts for use by incipient parasitologists. Before beginning a discussion of parasitism, we need two more definitions:

**Commensalism:** symbiosis in which there is no discernible damage to the host.
**Mutualism:** symbiosis which benefits both partners.

Consider the major thrust of these three definitions. Note that parasitism implies harm, or at least potential harm, commensalism implies no harm, and mutualism involves a relationship in which both partners benefit. Categorizing a symbiote, and having it remain in that category, is among the more difficult tasks. An example or two will point up the problem. *Entamoeba histolytica* is the cause of amebic dysentery in humans; it can become invasive and cause severe disease, but it often remains as a mild-mannered commensal in the gut. *E. histolytica* is therefore a commensal that can become a parasite. *Trypanosoma musculi* is a flagellated protozoan that lives in the blood of mice and does not usually cause damage to the host. Careful studies have shown that mice actually benefit from nutrients produced by the protozoa (Lincicome, 1971). By definition, then, *T. musculi* moves from a commensal to a mutualistic relationship with its host. Thus, organisms may move into parasitism under some conditions, or their status may change as we gain more knowledge.

In another vein, we know that many parasites damage the host, but we have no way of measuring the damage. Take, for example, the intracellular protozoa called the *coccidia*; the coccidia rupture the host cell at the end of a phase of development and then enter uninfected cells for further development. We know that cells have been destroyed, but in most coccidial infections there is no way to measure the damage. Another example comes from large ruminants in whom extraordinary volumes of tapeworm may be found without any measurable production losses. Nutrient that would have gone into meat, milk, or fiber is now in tapeworm tissue, but we have no way of measuring the economic loss because the host seems to compensate somehow for the presence of the worms.

We hope that the student will recognize that definitions are an essential part of precise communication in shorthand, but no definition fits all the situations for which it was designed. In addition, we are sometimes inconsistent in our use of particular terms. Organisms that traditionally have been called parasites are now covered by the term *symbiote*, but those of us who work in the field still call ourselves parasitologists, not symbiotologists, nor do we often distinguish between parasites and commensals in our research or teaching. Be that as it may, there are important implications in the preceding definition and in those given a little later.

Although this textbook concerns only certain eukaryotic parasites, there are a myriad of parasites in other taxonomic groups of protists, plants, and animals. Consider the range of some parasites:

| | |
|---|---|
| Viroids | 50,000 molecular weight |
| Viruses | $5 \times 10^6$ molecular weight |
| Rickettsia | 0.5 – 2 μm |
| Bacteria | 1 – 10 μm |
| Yeasts | 5 – 10 μm |
| Protozoa | 1 – 150 μm |
| Nematodes | 300 μm to 30 cm (or more) |
| Platyhelminths | 1 mm to 10 m |
| Mollusks | 0.5 – 10 mm |
| Ticks and mites | 0.1 – 15 mm |
| Insects | 0.1 mm to 2 cm |
| Horsehair worms | up to 15 cm |
| Mesozoa | up to 100 μm |
| Leeches | 1 – 5 cm |

This list is only a superficial approach to showing the widespread nature and diversity in parasitism.

Parasites pervade our world and our lives, and the organisms that have established themselves as parasites have arisen in nearly all groups of livings things. Parasitism is a subculture that goes almost unrecognized by most people, and few appreciate the impact of parasites in the biotic world. If we consider only a few human parasitic diseases, the World Health Organization (WHO) has stated:

Furthermore, blood flukes infect 200 million people in 73 countries, and in some areas where dams have been built, the prevalence of infection has risen from 10% to nearly 100%. Filarial nematodes cause gross deformities or blindness in several hundred million people and there are still no satisfactory drugs to treat them. Chagas' disease, which is caused by a flagellated protozoan, affects 24 million people in Latin America, but there is still neither satisfactory treatment nor a vaccine to prevent infection. (*Tropical Disease Research*, No. 18, May 1982)

Parasitic diseases also limit livestock production. There are 160 million cattle and 286 million sheep and goats in Africa, for example, mostly raised by subsistence farmers and pastoralists. It is estimated that twice this number could be supported if two parasitic diseases, trypanosomiasis and East Coast fever, could be eliminated (Lewin, 1982).

In the political arena, the worst pejorative that can be used against individuals or groups is to call them "parasites." It is as if only seed eaters, herbivores, and predators are admirable organisms, and those that live inside them are behavioral degenerates worthy only of disdain. But, like most of us, parasites seek only to find a place in the world where they can live and propagate. If certain structures or sense organs are lost in parasites, it might be better to look upon this evolutionary change as specialization rather than degeneracy. A tapeworm is a marvel of specialization; it maintains intimate contact with the host in order to obtain nutrients through its surface, and it has retained only those structures necessary to live in the intestine of a vertebrate. Surely it is commendable to be economical with one's resources and not to produce eyes where there is no light, ears where there is no sound, or other structures that have no use.

Most of the organisms we deal with are *obligate parasites*, those that require a host for the completion of the life cycle. There are a few *facultative parasites* that can remain as free-living organisms but can invade a host if the proper conditions are presented. Parasites may live on the surface of a host (*ectoparasites*), or they may live in the internal organs (*endoparasites*). Those that come to a host occasionally to feed are sometimes called *temporary parasites*, and those that remain in a host are called *permanent parasites*, but this terminology is not often used.

Some parasites have life cycles in which there is both sexual and asexual development. In this case, it is necessary to distinguish between the kinds of hosts. The host in which the parasite is sexually mature is the *definitive host*, and the one in which the organism is sexually immature or reproduces asexually is the *intermediate host*. Sometimes a parasite is passed from one host to the next, with no development occurring; such a host is called a *paratenic* or *transport host*.

Nearly all parasites that are infectious for humans develop in other hosts as well. Those organisms are called *zoonotic agents* and they cause *zoonoses* (singular: zoonosis). Some authors subdivide this term into *zoonosis*, a disease humans acquire from other animals, and an *anthroponosis*, a disease other animals acquire from humans, but this is an unnecessary complication in terminology. As a general rule, the host from which humans acquire infection, or in which the agent normally cycles, is termed the *reservoir host*. This term is also used in livestock in cases where a domestic animal acquires a disease from a host in which infection is inapparent or the disease is of no importance. In fact, the connotation of the term *reservoir* is that the infection occurs in a host that we do not care much about.

Surveys are often done to determine whether and at what level disease agents occur in a population. The *prevalence of infection* is determined by taking a sample from a population and determining the proportion of the population infected. Note that this term is used when we dip into a population and pull out a sample at a particular time. In contrast, when we determine how many individuals become infected each year, or some other unit of time, we speak of the *incidence of infection*. The terms are also used for the occurrence of disease as well as infection. Figures are often expressed as percentages, but in human public health figures are given as the number of infections per hundred thousand population.

Over the years some looseness of terminology has developed in referring to infections and states of disease. The terms *infection* and *infestation*, for example, have often been used for quite similar conditions. We will use the term *infection* for nearly all parasitic associations, regardless of whether it is outside or inside or whether the organism reproduces in the host or not. Also, it is not easy to distinguish between the suffixes *iasis* and *osis*. We can speak of *helminthiasis*, which means infection with helminths. *Helminthosis*, on the other hand, means to be clinically affected by helminths. Unfortunately, terms such as *trypanosomiasis* refer to a disease state. We have generally adhered to commonly accepted

terminology except where it may be necessary to distinguish between mere infection and clinical disease.

Additional kinds of hosts that we must consider are vectors and intermediate hosts. A *vector* is an arthropod, mollusk, or other invertebrate that transmits a parasitic agent to a vertebrate host. Vectors come in two models: *mechanical*, in which no development takes place, and *biological*, in which development or replication occurs. We have already discussed intermediate hosts in a general context, but we wish to point out similarities and differences between intermediate hosts and vectors. Note that a vector is an invertebrate of some sort. Thus, we rule out cattle as a vector of the beef tapeworm of humans, but cattle are intermediate hosts because the worm is immature in them. Mosquitoes are vectors of various viruses, but mosquitoes are definitive hosts as well as vectors of malaria, because the parasite is sexually mature in them. Snails are intermediate hosts and vectors of the blood flukes of humans; the worms are sexually immature in the snails. Tsetse are vectors of African sleeping sickness, but they are neither intermediate nor definitive hosts because the parasite does not reproduce sexually.

Diseases occur both in an explosive form, running through a population in a short period of time, and at a level involving only a small proportion of the population at any one time. When the course through the population is rapid, we speak of its being *epidemic* in humans or *epizootic* in other animals. When there are occasional but continuous cases, the terms are *endemic* and *enzootic* in humans and other animals, respectively. The terms used to cover both humans and animals can also be *epidemic* and *endemic*.

## HOW DOES THE PARASITIC RELATIONSHIP WORK?

With the exception of some kinds of interactions between the parasite and host, parasitism is not a unique relationship compared with free-living organisms. The same general ecological principles apply to both free-living and parasitic organisms, because both need a physical place in the ecosystem, adequate food, and the ability to reproduce.

The life cycles of some parasites seem rather bizarre at first, but many parasites follow a course of development similar to that of their free-living counterparts. A parasite may have a *direct life cycle*, one in which there is only a single species of host and transmission takes place directly from one host to the next by close contact or through development to the infective stage in the free-living environment. Most protozoa that live in the intestines of their hosts are transmitted through a cyst stage from one host to the next; *Entamoeba coli* is a commensal found in the large intestine of humans and it is transmitted by means of a resistant cyst; many free-living amebas also form cysts and use them to bide their time until they find proper conditions again for growth and multiplication. All roundworms or nematodes develop through five larval stages separated by four molts; the same stages are seen in both the free-living and the parasitic nematodes. Many parasitic nematodes develop to the third-stage larva as free-living forms and then wait until they reach a proper host before continuing their development. The parasitic cycle is simply a modification of the free-living one with the addition of a host in which the worm becomes sexually mature.

In other instances, a parasite may have a *complex* or *indirect life cycle*; the completion of the life cycle requires more than one host, most often of different species. A well-known example of an indirect life cycle is that of the organism that causes malaria in humans: transmission takes place through mosquitoes, and without the mosquito the organism would disappear. In some organisms such as the nematodes, the indirect cycle can be readily derived from the cycle of free-living forms; the cycle stops and starts on two or more occasions, but the same stages are always seen. In some instances, such as the tapeworms and digenetic flukes, the free-living precursors are so shrouded in evolutionary mystery that deriving the cycles of the present-day forms requires considerable conjecture.

The large reproductive potential of parasites is sometimes pointed to as a characteristic of parasites, and the numbers are truly impressive. For example, the large ascarid of humans and hogs produces half a million eggs per day, and apparently can do so for many months; the common liver fluke of sheep and cattle, *Fasciola hepatica*, lays about 5,000 eggs a day and can live in a sheep for ten years; one mosquito can infect 50 or more persons and bring about a small malaria epidemic all by itself. The question is whether this reproduction is different from that of free-living organisms. It has been calculated that one pair of house flies could produce $1.9 \times 10^{20}$ offspring from April to August and cover the earth 47 ft deep (Herms & James,

1961). A single oyster produces tens of thousands of eggs in a breeding season, and bacteria often have generation times of 20 min. Each organism develops its own strategy for ensuring the survival of its offspring, and some parasites are highly reproductive. Parasites are opportunistic, and given the chance, they will increase their numbers dramatically in a short period of time.

Most parasites are not randomly distributed through the population of available hosts. Crofton (1971a, b) has referred to this type of distribution as being overdispersed, but we have used the term *nonrandom* in our definition of parasitism. The concept of overdispersion or nonrandomness, together with other mathematical models of population ecology, is being used to better describe host–parasite population dynamics as well as to predict the occurrence of epidemics and the likelihood of controlling them.

Two useful concepts are the *r*- and *K*-strategies (Esch et al., 1977) and the equations expressing the dynamics of parasite populations (Anderson, 1976). In the former, the term *strategy* refers to an inherited characteristic that is shaped by the pressures of natural selection. Parasites that are *r*-selected put their energy into producing large numbers of offspring, usually within a short period. In this type of strategy, there are essentially no density-dependent effects and little or no competition. At the opposite end of the population are *K*-selected species, which produce only a few extremely fit offspring because density effects are maximal and the environment is nearly saturated with organisms (Pianka, 1970).

The equation for the *K*-strategy is

$$\frac{dN}{dt} = rN\left(\frac{K-N}{K}\right)$$

where $dN/dt$ = rate of population increase
$r$ = maximal growth rate
$N$ = number of individuals in the population
$K - N/K$ = realization of the maximal growth rate

The equation for *r*-strategy is

$$\frac{dn}{dt} = rN$$

Most parasites fall into the *r*-selected category because parasites usually are opportunists. Examples of *r*-selected parasites are mosquitoes, which reproduce rapidly when conditions are suitable (Chap. 55), and the dysentery ameba (Chap. 9), which has a short generation time in the host. At the far end of the spectrum we have some *K*-selected parasites such as tsetse, which serve as vectors of African trypanosomes; tsetse females produce one larva at a time and average only about nine offspring during a lifetime. Further complicating the situation are those parasites that have different strategies at different phases of the life cycle; examples are most taeniid tapeworms (Chap. 29) and Monogenea (Chap. 20). Last, reproduction in parasites is influenced by substances produced by the host such as antibody, hormones, and specific nutrients.

Population dynamics for parasites have been reviewed by Anderson (1976) for those that do not mature in the host and for those that multiply in the host. For the former, the expression is

$$\frac{dNt}{dt} = \lambda - \mu Nt$$

If the parasites multiply in the host, the expression is

$$\frac{dNt}{dt} = \lambda - (a + \mu)Nt$$

where $Nt$ = the number of parasites in the system
$t$ = time
$\lambda$ = the immigration rate
$\mu$ = the death rate
$a$ = constant birth rate per parasite per unit time

A more extended discussion is in Anderson (1976) and Hirsch (1977).

One common aspect of reproduction in parasites is alternation of generation. An asexual cycle is alternated with a sexual cycle. Although such a mode of development is not unknown in free-living organisms (ferns and aphids are examples), it is a theme seen in a number of taxa of parasites. The Apicomplexa in the protozoa alternate sexual and asexual development; some nematodes such as *Strongyloides* alternate parthenogenesis with sexual development; the digenetic trematodes have asexual development in the snail intermediate host and sexual reproduction in the vertebrate; some tapeworms have evolved means of asexual reproduction, the most striking one being the replication of the sexual organs in each segment, but a few reproduce also as larvae.

We discussed the supposed degeneracy of parasites

earlier, and the life-cycle patterns of parasites present an opportunity to consider the subject further. An organism such as a digenetic fluke may have three hosts in the life cycle and five or even more stages. Each of these stages requires control of development and has its own niche in the ecosystem. Some stages pass through the external environment for development or exist as free-swimming forms; others have an intimate association with at least two hosts and sometimes three. Fairbairn (1970) has considered the issue of whether parasites so exquisitely dependent on a host that they cannot survive elsewhere have lost genetic capacity. He concludes, in general, that parasites have the genome to survive and develop in other niches but do not use it. He takes his examples principally from helminths with complex life cycles and shows that they have the capacity for development and survival in a wide spectrum of niches as they pass through the life cycle. Further evidence can be drawn from *Plasmodium*, the cause of malaria. We generally consider this organism to be an obligate intracellular parasite, but the oocyst stage in the mosquito is extracellular. The organism has maintained the ability to develop extracellularly, but uses this capacity only in the vector. Thus, we see that parasites are not degenerate genetically; rather, they maintain a genome only a portion of which is used at any specific stage of the life cycle, and they are similar to other eukaryotes.

Nearly all parasites need to contend with the external environment at some stage of their life cycles. Many nematodes with direct life cycles feed, grow, and develop as free-living organisms before entering a host to become sexually mature. The type of environment that the free-living stages require limits the distribution of the parasites. A parasite's ability in its external stages to survive harsh conditions such as freezing and drying usually means that it will have a broader distribution than those susceptible to such conditions. Studies of the limits and optima for development and survival of a particular parasite represent the kind of basic biological study required for developing rational control programs. The parameters that are applied in defining the ecological and physiological requirements of free-living organisms pertain likewise to parasites during this phase of their lives.

It is when a parasite comes into contact with a host that it reaches the stage of physiological dependence that defines the unique nature of parasitism. The pattern of development for a eukaryotic (and some prokaryotic) parasite is to proceed with development in a particular environment (host or external) to the infective stage and then to stop and wait. When the potential host is contacted, development then proceeds. We speak of the organism being "triggered" by the environment in the host, and usually specific signals of temperature, pH, redox potential, and organic chemicals are sensed by the parasite and it is stimulated to proceed to its next stage of the life cycle. In many cases we know what the stimuli are, but we do not know the exact mechanism except in a few instances.

## HOW DO HOSTS RESPOND TO PARASITES?

When two organisms live in close, usually intimate association, each responds to the presence and activities of the other. This is especially true of the host–parasite association. First, we will discuss how the vertebrate hosts respond to the presence of parasites and then how parasites respond to the hosts.

Vertebrate hosts respond to the presence of nonself material, that is, parasites, in two ways. The first is called *nonspecific responses*. The host is able to differentiate "nonself" from "self," but these responses are not dependent upon *specific* recognition of a nonself molecule. The second is called *specific responses*, which depend upon exposure to, and specific recognition of, foreign or nonself molecules.

### *Nonspecific Responses*

One of the first lines of defense against small foreign invaders, be they bacteria or parasitic protozoa, is *endocytosis*, the process of ingestion of material. Endocytosis is often referred to as *phagocytosis*, literally cell eating, or *pinocytosis*, literally cell drinking; it is often impossible to separate the processes of ingestion of fluids and solids; thus, the term *endocytosis* is preferred to describe the overall process. Endocytosis is accomplished by several cell types, including monocytes and polymorphonuclear white blood cells, histiocytes in tissues, and the sinus-lining reticuloendothelial (RE) cells, especially those in the liver and spleen. The function of endocytosis is to engulf foreign material and digest it in lysosomes. Endocytosis can occur independently of specific responses but is greatly facilitated by certain specific responses such as *opsonizing antibodies* and

serum proteins called *complement*. Detailed discussion of these topics is beyond the scope of this text (Barriga, 1981).

If the foreign invader is small, it may be surrounded by endocytotic cells and immobilized by a deposition of collagen around it. If the invader is large, a second type of nonspecific response occurs—the *inflammatory response*. This response is often divided into three stages. The first, *acute inflammation*, lasts from days 1 through 3. It is characterized by capillary dilation leading to fluid accumulation or *edema*, and an accumulation of polymorphonuclear white blood cells in the tissues, probably attracted by chemotaxis. The second phase, *subacute inflammation*, lasts from 3 days to over a week. This phase is characterized by the presence of mononuclear cells (monocytes and lymphocytes) in the perivascular space and fibroblasts that secrete collagen. Collagen secretion leads to the production of a fibrous capsule commonly referred to as a *scar*. The third phase, *chronic inflammation*, involves the same cells as subacute inflammation plus *plasma cells*. Often in chronic inflammation, such as that caused by a trapped schistosome egg, a *granuloma* will form. This is an ovoid arrangement of mononuclear cells surrounded by the fibrous connective tissue and cells that secrete it.

The third nonspecific response to parasites is sometimes called *abnormal growth responses*. These include *hyperplasia*, in which the activities of the parasite stimulate the host to produce an increased number of cells. A good example of this is the liver fluke, *Fasciola hepatica*, which induces the host to enlarge greatly the bile ducts, which the parasite then eats. Another abnormal growth response induced by parasites is *neoplasia* or cancer formation. A number of parasites are suspected of inducing neoplasia. The tapeworm larva of *Taenia taeniaformis* in the liver of rats, and the adults of the nematode *Spirocerca lupi*, in the esophagus of dogs, are associated with the formation of sarcomas, connective tissue cancers (Schwabe, 1955). The exact mechanism of parasite-induced sarcomas is unknown.

## *Specific Responses*

Parasite surfaces have characteristic macromolecules such as proteins and polysaccharides, which the host can recognize as nonself. The surface material, or a substance secreted by the parasite, is called an *antigen*. These antigens trigger the specific *immune response* when immunoglobulins (Ig), serum proteins secreted by plasma cells, attach to antigens using *specific molecular recognition*. This attachment usually triggers further host responses. There are five classes of immunoglobulins in humans—IgA, IgD, IgE, IgG, and IgM—which are distinguished by polypeptide differences. The basic Ig molecule is a Y-shaped structure (Fig. 1.1), with the antigen-binding site at the ends of the arms of the Y. Production and secretion of immunoglobulins into the serum is called the *humoral response* and is manifested in a number of different ways.

Each of the Ig molecules has particular functions. IgE responses are often elevated in helminth infections. IgE antibodies bind to mast cells and basophils; this binding of antigen to cell-bound IgE induces these cells to release vasoactive substances such as histamines, which increase capillary permeability.

In addition, IgM and IgG are very important in protozoan infections because they can activate the *complement system*. This system consists of nine protein complexes that can combine with many different antigen–IgM or antigen–IgG complexes. The first component of the complement system binds to antigen-bound IgM or IgG, initiating a sequential series of reactions involving up to nine components of the

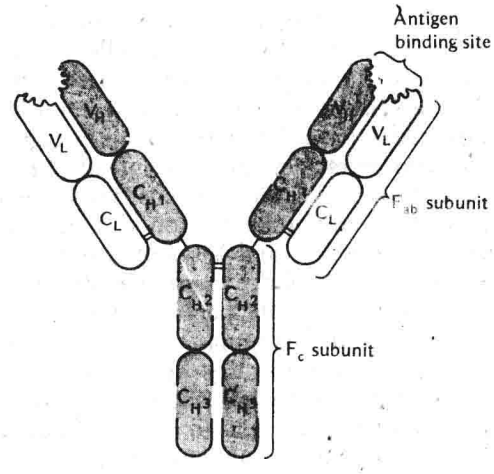


**FIG. 1.1**
Structure of immunologulin G (IgG). [Redrawn from Whitfield, 1979. *The Biology of Parasitism: An Introduction to the Study of Associating Organisms*. University Park Press, Baltimore.]

complement system. This series of reactions triggers a number of biological activities; one of the most important in parasitic infections is the damaging of cell membranes, which often leads to cell lysis and death. A serological test for the presence of activated complement, with its ability to lyse cells, is the *complement fixation test.*

The other half of the immune response involves not secreted immunoglobulins, but another kind of lymphocyte, the T-lymphocyte, which releases proteinaceous substances when bound to antigens. These substances, called *lymphokines*, cause nonspecific reactions on other cells, often leading to inflammation. This part of the immune response is referred to as *cell-mediated immunity (CMI).* Lymphokines most relevant to parasitic infections include (1) *migration-inhibitory factors*, which prevent the migration of white blood cells; (2) *macrophage-stimulating factors*, which enhance macrophage activity against cells with the target antigen; (3) *chemotactic factors*, which attract inflammatory cells to the site of release; (4) *mitogenic factors*, which stimulate the division of lymphocytes; and (5) *cytostatic factors*, which delay or stop cell proliferation. The exact functions of most of these substances in parasitic infections are poorly understood and are the subject of many studies.

Both Ig-producing lymphocytes (B-lymphocytes, or plasma cells) and lymphokine-producing lymphocytes (T-lymphocytes) originate as stem cells in the bone marrow. The processing of these cells in the thymus (T-cells) or in an organ equivalent, the bursa in birds (B-cells), determines which response will be elicited. An outline of both processes is presented in Figure 1.2.

In general terms, macrophages (endocytotic cells) ingest and process parasite antigens. These "processed" antigens are then distributed on the surface of the macrophage. Both T- and B-lymphocytes contact the surface of the macrophage or parasite directly and are primed against the specific parasite antigen. Both types of lymphocytes are stimulated to divide and then produce either humoral antibodies (Ig) or lymphokines. Antigen combines with IgE bound to mast cells and basophils, causing these cells to release histamines. The subsequent increase in capillary permeability allows white cells to reach the parasite. T-cells combine with parasite surface materials (antigens) and release lymphokines, which attract more endocytotic cells and keep them there, releasing their cytotoxic products. The final result is tissue injury by the cytotoxic products and nonspecific inflammation which changes the parasite's immediate environment, usually to its disadvantage.

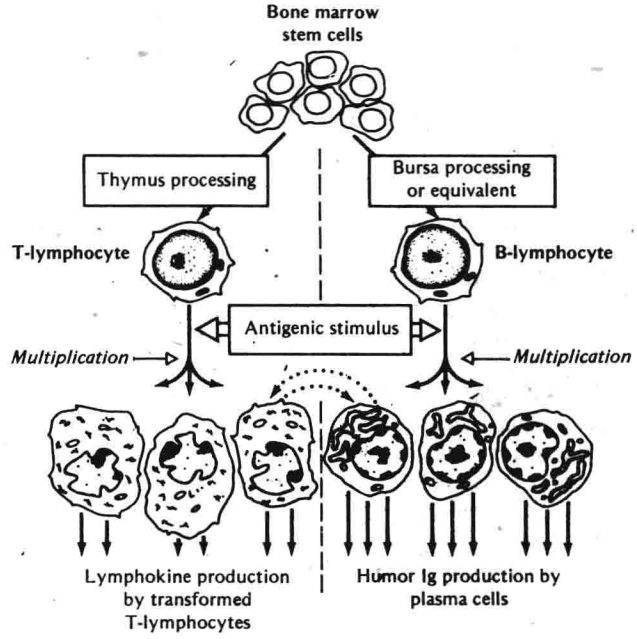


**FIG. 1.2**
The origin, processing, and activities of T- and B-lymphocytes. [Redrawn from Whitfield, 1979. *The Biology of Parasitism: An Introduction to the Study of Associating Organisms.* University Park Press, Baltimore.]

## *Parasite Countermeasures to Host Responses*

Hosts respond to the presence of parasites and take certain measures to eliminate them. Parasites can often react to these responses, and in some cases have evolved ingenious methods of escaping the host's responses. Many of these methods will be discussed with each particular parasite in the text, so only a couple of examples will be mentioned here. For additional information, see Bloom (1979), Whitfield (1979), and Barriga (1981).

One unique way to escape the host response is used by the blood-dwelling protozoan, *Trypanosoma brucei*, which causes African sleeping sickness (Chap. 3). These

protozoa undergo *antigenic variation*. As the host recognizes their surface material and attacks it, the remaining parasites change the composition of their surfaces, and the original immune response is not effective against these new organisms. This change in surface can happen many times, leading to parasite population explosions followed by population crashes as the host's immune system responds to the new surfaces, resulting in another explosion, and so on.

Another countermeasure used by some tissue-dwelling parasites is to live inside host cells. Once the foreigner is inside the host cell, the host cannot recognize and attack it. Many protozoa such as *Toxoplasma gondii* and *Trypanosoma cruzi* exploit this method. Some carry this countermeasure one step further by living in macrophages. Macrophages ingest the parasites but are unable to destroy them with internal digestive enzymes. *Leishmania* lives in functionally active macrophages, but the manner in which it escapes the digestive enzymes is incompletely known (Bloom, 1979).

The human blood flukes of the genus *Schistosoma* have evolved *antigenic mimicry*. Adult worms in host blood vessels coat themselves with host-produced molecules and thus appear to the host as self (Damian, 1964).

## HOW ARE PARASITIC DISEASES CONTROLLED?

Parasites cause diseases in humans, in domesticated and companion animals, and in wild animals. Each of these four kinds of hosts poses different problems that require different approaches to alleviating their effects. Although we will approach each agent or group of agents individually in the rest of the book, we can set forth some general principles here that apply to most of them.

As indicated earlier, parasites are constant companions of all groups of animals, and they have the potential of harming the host. We are still rather ignorant of the reasons parasites cause disease in some instances but remain innocuous in others; however, we can list some of the factors that contribute to disease:

1. Overpopulation
2. Manipulation of the environment
3. Monoculture and inbreeding
4. Migration and movement of humans and livestock
5. Individual susceptibility

Parasites are among the many factors that modulate populations of organisms. Cycles in which numbers of animals rise and fall, sometimes with regularity, are familiar. Food, space, social interactions, and predation all contribute to the number that can be supported at any one time, but infectious diseases (in the broad sense) are also a factor. A part of the definition of parasitism is the parasite's higher reproductive potential than that of the host, and this is one of the keys to the inception of disease and modulation of populations. We need merely to tip the scales slightly for the number of parasites in the ecosystem, and therefore exposure to them, to increase.

One way to increase exposure to the parasite is to provide a large number of potential hosts in close association with one another. We have all had the experience of head colds sweeping through a school until every other person seems to have a cold or is trying to get over one. Infectious agents normally in the population are more likely to reach domesticated animals that are crowded together on pasture or in buildings. We do not subscribe to the notion that diseases were nonexistent in primeval conditions, but it is clear that the probability of transmission increases with crowding, and an epidemic may ensue.

Humankind has had an enormous impact on the biosphere, and through manipulation of the environment for our own ends we have brought about disease problems in ourselves, domesticated animals, and wild animal populations. Some of the problems are a result of overpopulation, as discussed in the previous paragraph, but many are a direct result of other environmental changes. An example that readily comes to mind is irrigation, which may increase habitat for vectors of disease agents such as mosquitoes and blackflies. Roads also may interrupt normal migration patterns of wild-life so that animals tend to frequent certain areas on a year-round basis instead of moving to habitats where they have not been for perhaps a year. The ability to move domesticated animals by rail or truck has made markets accessible to those who raise animals in remote areas, but the shipping may precipitate various kinds of microbial and parasitic diseases, because the animals are upset by the noise, crowding, and lack of proper food and water. When animals were trailed to market

on foot, the time required was long, and adequate food and water were needed to keep the stock in condition; the more leisurely pace prior to high-speed transport reduced the probability of an epizootic.

As we have gained more control over our environment, we have tended to stick to those things that have worked well and provided a measure of security. Animals and plants are selected for high production in a particular environment, and genetic diversity or heterosis is bred out of a population. The result is that the mutation or importation of a parasitic agent may cause a wholesale die-off of the desirable plant or animal. The related aspect, monoculture, produces the same end result: an area where there is a single crop or species of domestic animal is particularly susceptible to an epizootic.

Related to monoculture and lack of heterosis is the migration of humans and livestock. If a parasitic agent is brought into an area that has had no previous exposure to it, the population is likely to be completely susceptible to it. A few examples will suffice. Smallpox was introduced into one of the Northern Plains Indian tribes, the Mandan, and within a few years, the tribe was completely gone. Tropical Africa was known as the "white man's grave" largely because of complete susceptibility to various diseases such as malaria. Syphilis was probably introduced into central Europe by soldiers who had returned from campaigns in the Middle East and Africa late in the fifteenth century; the disease was so virulent that persons usually died within six months of the first signs of infection. European cattle introduced into sub-Saharan Africa die from the protozoan disease nagana or trypanosomosis, while the local breeds are relatively resistant to the infection.

Although all of these factors leading to disease are interrelated to an extent, individual susceptibility and the current physiological state of a potential host are always factors. The definition of parasitism includes the statement that prevalence is nonrandom. A number of factors, including behavior, age, sex, reproductive state, and so-called stress factors, influence whether a potential host may become infected or diseased as a result of infection. At any rate, for all of these reasons, only a portion of the population harbors a sufficient number of parasites to show the effect. A corollary is that infection is not synonymous with disease, a theme which we reiterate frequently. The question of what precipitates a disease has an answer of extraordinary complexity and, more important, obscurity.

The question then becomes, "What means do we have at hand for reducing the impact of various disease agents?" If we were to make a list of the general techniques, it would include the following:

1. Administer drugs or chemicals to prevent or cure the infection.
2. Reduce the population of reservoir hosts.
3. Reduce the population of vectors.
4. Improve the immunity of the potential hosts either naturally or artificially by vaccination.
5. Alter the physical environment to reduce the probability of transmission; sewage disposal might be included here.
6. Avoid areas of high risk.
7. Protect the individual from infection by some sort of barrier, either physical or spatial.
8. Control the parasites biologically through predators or infectious agents that will reduce their number.
9. Separate by age class.
10. Test and slaughter.

All of these general methods except the last two may be applied equally to parasitic infections of humans and other animals. We will be considering all of these methods in detail throughout the rest of the book, so we will not give examples at this point.

Portions of control programs require dissemination of information about a particular disease complex; we put this in the general category of "education." Education is part of an overall control program, but should not be considered as a control method in itself. Education is unimportant until it brings about a change; the change may be an altered conception of how the world works, or it may be a change in behavior. It is the latter that is the control method. Education can bring about a change in behavior, and thereby prevent disease, in a number of ways: cooking shellfish to prevent paragoniamisis, avoiding cats during pregnancy to prevent congenital toxoplasmosis, not going into water that may have cercariae of blood flukes.

In many instances, students feel that eradication of a particular pathogenic agent is the desired objective. This is true in some instances, but it is seldom feasible, and may not be desirable in the long run. Eradication of a