Parasitology

The Biology of Animal Parasites

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FOURTH EDITION

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Section I

Introduction

Introduction to Parasitology

During the millions of years that animals and plants have competed among themselves for food and space, parasites have invaded practically every kind of living body. These bodies, called **hosts**, also provide protection, and since hosts generally furnish different kinds of space in the form of external surfaces, organs, tissues and fluids, they usually acquire more than one kind of parasite. Today, most animals have on or within their bodies several species of parasites, sometimes totalling hundreds or even millions of individuals. There are, therefore, more kinds and numbers of animal parasites than free-living animals. The major groups of animal parasites are found among the Protista, the helminths (flatworms and roundworms) and the arthropods. The host and its parasites constitute a community of organisms living in close intimacy and exerting a profound effect upon each other.

To illustrate the kinds of parasites that an animal might support and some of the interrelationships and problems that are involved in parasitism, we will select the fish as a typical vertebrate host. Almost any vertebrate would be satisfactory, but fish may easily be secured by students for examination. This book is concerned only with animal parasites, so we shall disregard the numerous bacterial, fungal and viral infections that plague all animal groups. A careful dissection of a single fish usually reveals three or four species of animal parasites, seldom more than five or six, and sometimes only one.

An examination of any host for its parasites should start with the outside. The skin and scales of a fish are commonly the home of copepods and other Crustacea, encysted larval stages of digenetic trematodes (flukes), adult monogenetic trematodes, leeches, and several kinds of Protozoa. Copepods often have sharp claws that enable them to cling to the skin, or anchoring devices that are deeply embedded under scales. Fish lice (Branchiura) are temporary parasites of the skin. Encysted larvae of digenetic trematodes are called metacercariae, and the fish must be eaten by another host (e.g., a bird or another fish) before the larval flukes can develop into adult worms. Monogenetic trematodes may damage the host's skin by means of clawlike hooks on the posterior ends of their bodies. Leeches suck the fish's blood and may thereby transmit blood parasites from one fish to another. Protozoan parasites on the skin occasionally cause so much damage that the fish dies.

The next place to look is inside the mouth and on the gills. Here may be found the same kinds of worms as on the skin, plus additional kinds of parasites. Isopod crustaceans often cling to the gills or mouth lining; sometimes a single parasite is so large that it almost fills the mouth cavity. Hundreds of copepods may be

partly embedded in the gills. Cysts of the protozoan order Myxosporida may appear as white spots or lumps. Thousands of metacercariae may be embedded in the gill filaments, as well as monogenetic trematodes.

If the fish is alive or freshly killed, blood smears should be made, and the fresh blood scrutinized for such parasites as the flagellated trypanosomes (related to those that cause African sleeping sickness in man), and another protozoan form, the haemogregarines, which live within red cells. Fish often have more internal parasites than external ones, and any organ may be infected. Many parasites from the digestive tracts of fish have been described, especially nematodes and flukes. Thorny-headed worms, called acanthocephalans, are common in the intestine. Several kinds of Protozoa may be mixed with the fecal material. Coiled, larval nematodes are easily seen in the mesenteries and walls of the coelom as well as in the muscles. Larval tapeworms of several kinds inhabit a variety of organs. Myxosporida are very common in the gallbladder, urinary bladder, kidneys, muscles and other organs. Another group of protozoan parasite, called Microsporida, may infect the cells of most organs of the fish. Both Myxosporida and Microsporida may cause fatal diseases although, generally, death and disease seldom occur as the result of parasitic infections.

One of the first questions that a student usually asks is, "How is it possible for a fish (or any host) to live in apparent good health with so many parasites crowding its body?" The answer is a complicated one, involving a consideration of the results of gradual adaptations between hosts and parasites during their evolution together. After all, it is not to the advantage of the parasite to kill or even injure its host, because a healthy host means a healthy environment for the parasite.

Another question often asked by students is, "How do these parasites get into the host and what are their life cycles?" The answers are numerous and can be found throughout the pages of this book, where the various kinds of parasite and host relationships are described in detail. Many parasites have a relatively simple, direct life cycle whereby the infective stage (such as a cyst, spore or motile larva) released by one host is directly taken up (often eaten) by another host, in which the parasite grows and develops. Other species of parasites may have a complicated, indirect life cycle, requiring one or more intermediate hosts (such as a mosquito) to complete their development.

More specific questions that may be asked are: What are the important morphologic and physiologic features of parasites? How do parasites live within a host? How does a host respond to parasites? What are the nutritional requirements of infective stages? Upon what factors in a host do parasites depend? Do parasites provide anything of value to a host? How does the life cycle and behavior of a host affect its parasites? How do the parasites of one species affect those of another species in the same host? What factors trigger each developmental change during the life cycle of a parasite? What genetic and developmental factors have particular significance in parasitism? We have enough information to answer some of these questions in part, but all of them and many others need to receive much more attention, especially by experimental parasitologists.

Symbiosis

The term "symbiosis" was proposed in 1879 by de Bary[11] to mean the "living together" of two species of organisms. This term came to be used in a more restricted sense to connote mutual benefit, as exemplified by the termite and its gut protozoans. Indeed, de Bary used a lichen as the clearest example of symbiosis. O. Hertwig defined symbiosis as "the common life, permanent in character, of organisms that are specifically distinct and have complementary needs." However, a cursory examination of symbiotes (= symbionts)—those organisms living together symbiotically—reveals a wide variation in permanency of the association, degree of intimacy, and degree of pathogenicity.

Textbooks on parasitology frequently distinguish the following three general kinds of symbiosis: commensalism, mutualism, and parasitism.

Commensalism occurs when one member of the associating pair, usually the smaller, receives all the benefit and the other member is neither benefitted nor harmed. The basis for a commensalistic relationship between two organisms may be space, substrate, defense, shelter, transportation or food (Fig. 1-1). If the association is merely a passive transportation of the commensal by the host, it is called **phoresy.**

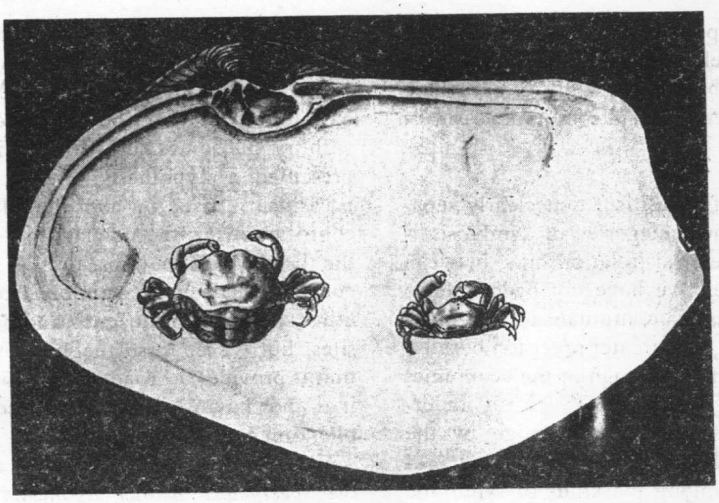

Fig. 1-1. Commensal male (small) and female pea crab, *Pinnixa faba,* in shell of gaper clam, *Schizothaerus nuttalii.*

Mutualism occurs when each member of the association benefits the other. For example, in the association between termites and their flagellates and between ungulates and their ciliates, the parasites digest the food (cellulose) of the host in return for free board and lodging (see pp. 452 to 456 for details). Similar to this kind of symbiosis is the ubiquitous association between animals and such parasites as bacteria, yeasts and other fungi. These symbionts provide essential vitamins for their hosts. They are parasites, as defined below, and rightly belong in a textbook on parasitology.

Parasitism The original meaning of the word "parasite" (from the Greek *parasitos*) was "one who eats at another's table" or "one who lives at another's expense," and had no reference to pathogenicity. In some textbooks the definition of parasite includes the statement that it often inflicts some degree of injury or damage. One difficulty with this definition, however, lies in its emphasis on harm or lack of benefit. How can we be certain that a symbiont does *not* affect its host in a way more subtle than causing obvious physical damage or change in behavior? Numerous parasites apparently act as commensals most of the time, but are pathogenic when their numbers become unusually high. *Entamoeba histolytica,* a well-known parasite of man, can cause dysentery, but most of the time it lives in the small intestine as a nonpathogen, and becomes pathogenic only when certain physiologic changes take place in the host and probably also in the parasite. Textbooks on parasitology are not necessarily restricted to a study of pathogenic parasites, and a parasitologist is frequently not concerned with pathogenic parasites at all.

Parasitism: Concepts and Hypotheses

Trager[43] has described, in a delightful manner, the interplay between parasite and host as it occurs between protozoa living within host cells.

"In intracellular parasitism the host cell is a true and hospitable host. The parasite does not have to break in the door. It has subtle ways of inducing the host to open the door and welcome it in. One of the exciting fields in the future of parasitology is to find out what these ways are and why they are sometimes so highly specific that the cell that invites one parasite in will not open the door to another closely related species. Once inside, the parasite not only exploits nutrients already available in the cell and the cell's energy-yielding system, but it further induces the cell to assist actively in its nutrition. Like a bandit who has cajoled his way in, the parasite now forces his host to prepare a banquet for him. Finally it may destroy its host cell . . . or it may stimulate its host cell to abnormal increase in size or to have an altered metabolism with the formation of new products. Or it may even

contribute some positive benefit to the host cell or to the multicellular organism of which the cell is a part, so that the two kinds of organisms then live together in a state of mutualism or symbiosis."

The concept of parasitism that clearly separates it from other categories of symbiosis is based on biochemical relationships between host and parasites. We have not been able to describe commensalistic, mutualistic, and parasitic relationships with greater precision because we do not understand enough of the economics of these various associations. Such an understanding requires precise knowledge of the biochemistry involved. However, making precise distinctions among the kinds of symbiotic associations is not really important. As our knowledge increases and the details of each partnership are analyzed and understood, the arbitrary boundaries of each category tend to disappear.

If a species of parasite has lived with its host species for millions of years, each partner must have had to adapt itself to the other in many ways. Among the morphologic and functional changes that a free-living organism must undergo to become a parasite are metabolic changes that require the presence of host tissues or fluids. Parasites, therefore, are metabolically dependent upon their hosts.

This concept of parasitism has been developed by several parasitologists during the past 15 to 20 years. Cameron[5] stated that a parasite is "an organism which is dependent for some essential metabolic factor on another organism which is always larger than itself." Smyth[40] also described parasitism as an intimate association between two organisms in which the dependence of the parasite is metabolic. His definition, however, included an important addition when he said that in parasitism "some metabolic by-products of the parasite are of value to the host."

In a discussion of the chemical basis of parasitism, Lincicome[28] viewed parasitism as a fundamental expression of a chemical (or molecular) relationship between two living organisms where there is a "giving and a taking. This is the emphasis that has been lacking in all attempts to view parasitism philosophically to the present time. Parasitism is a great pattern of life on this planet." In 1971 Lincicome[29] developed the concept of "goodness" accompanying the parasite-host relationship that is "the structural foundation of this phenomenon." On the basis of many years of experimental research with trypanosomes and with trichina worms, he presented a hypothesis of "the goodness of parasitism" based on considerable evidence of contributions of the parasite to its host, and of the host's contributions to the parasite. The concept needs more support from studies of other species of protozoans and helminth parasites, but we endorse the hypothesis and feel that it provides a broader basis for understanding and having a so-called feeling for the phenomenon of parasitism.

We define parasitism as *an association between two specifically distinct organisms in which the dependence of the parasite on its host is a metabolic one involving mutual exchange of substances. This dependence is the result of a loss by the parasite of genetic information.*

Comparison Between Predatory and Parasitic Modes of Life

The tabulation on page 7 was prepared by Dr. Ralph Audy for classroom use (1966, unpublished) and is printed here with his permission. Each mode of life has its own kind of feeding relation "between one partner that is dependent on the other for its food supply, and the other partner (the victim) that provides its living substance or at least parts of itself to the other. Most of the statements should be qualified by 'customarily' or 'characteristically'."

Physiology

The basic physiology and biochemistry of parasites is similar to these basic functions in free-living organisms. There are, however, significant differences due to the unique requirements of parasitism.

"Because the two components of this system (host and parasite) are living organisms, and are themselves attempting to maintain equilibrium, there must exist continual interchange between the two in order to allow the basic relationships to continue. All physiological and biochemical attempts to visualize and understand this interchange must, sooner or later, involve some consideration of the host-parasite interface. The

	DEPENDENT PARTNER	
	Predator	Parasite
Victim is known as	Prey	Host
Manner of feeding on individual victim	Destructive consumption	Cropping or sampling
Food provided by victim	Whole of body or fragment	Selected tissues, body fluids, excretions, etc.
Lethal to victim?	Yes, usually	Exceptional
Habitat	Co-exists with prey	Usually lives in or on host ("host as habitat") in its parasitic stage(s)
Size, compared with victim	Larger (or stronger)	Smaller or much smaller
Numbers, compared with victim	Less numerous	More or much more numerous
Encounter with prey or host	Momentary	Prolonged and/or repeated
Effect of grouping or crowding of victims	May protect prey	Encourages parasitism
Disease caused?	Rare and indirect through stress	Common, direct; may be great variety
Rate of multiplication compared with victim	Slower	Much faster

interface may be regarded as that surface through which interchange of material of physiological and immunological importance takes place. This involves the passage of substances, possibly antigenic, out from the parasite and into the host in the form of excretions, secretions and egestions. The movement inward consists of the absorption of nutrients, osmotic and ionic interchange and the eventual entry of antibodies from the host."[13]

Since many parasite habitats contain little oxygen, there has been much discussion of aerobiosis and anaerobiosis. Details are given later. One must remember that oxygen may be required for processes other than respiration (e.g., oxidation of amino acids). As one observer stated, parasites are metabolic opportunists. If a molecule is present it may be utilized. Thus, if oxygen is available (usually there is at least a trace of it) it may be used for respiration or for some other metabolic function. (See Bryant[3] for CO_2 fixation and involvement of carbon in intermediary metabolism.)

Parasitism results in, or is accompanied by, loss of various structures (e.g., appendages in copepods). There may also be a loss of biochemical functions as an adaptation to living within another organism. Sometimes, however, the lack of a function may be due to the absence of the function in the ancestral free-living animal. For example, parasitic worms cannot synthesize cholesterol so they must depend on dietary intake. But some free-living nematodes also do not synthesize cholesterol so are also dependent on an adequate exogenous source of sterols.[2]

A relatively new area of study is revealed by the following quotation from Davey.[10] It concerns nematodes but may be adapted to other parasites.

"If there is a link between the environment and developmental and physiological events in nematodes, what is its nature? How are the environmental stimuli mediated? Given the relative lack of sophistication of the integrative aspects of the nematode central nervous system, and the apparent scarcity of peripheral connections, it is unlikely that there is much in the way of direct nervous control of developmental events. Another means of linking the environment to various developmental events is by endocrines, and since the study of endocrinology becomes increasingly the study of neurosecretion as one proceeds down the evolutionary scale, it is hardly surprising that nematodes have proved to contain nerve cells which exhibit the staining properties of neurosecretory cells . . . stimulation of the sense cells may lead directly

to release of hormones without further integration, providing the possibility of a direct link between the environment and as yet undetermined target organs."

A tremendous amount of work has been done and is being done on parasitic respiration, excretion, and carbohydrate, protein and lipid metabolism. Within the sections where these are discussed, there are references to specific studies and reviews.

Immunity

Immune Reactions in Vertebrates

The ability to ward off organisms invading body tissues has always been an essential component of internal defense mechanisms, collectively termed the "immune response." This response is equally important for the parasite because in order to become successfully established within its host, the defenses must be overcome. It is this dilemma that has served to bind firmly together the disciplines of parasitology and immunology, and it represents one of the most rapidly expanding fields of research in parasitology today.

Mammals, and most other vertebrates, respond to invading parasites either by producing **antibodies** (protein molecules) and thereby promoting **humoral immunity** or by activation of lymphocytes (special blood cells) that bring about **cellular immunity.** These two types of immunity, however, are not mutually exclusive, but may interact in a complex manner. **Active immunity** occurs when foreign material gains access to tissues and fluids; **passive immunity** results from the artificial introduction (e.g., vaccination) of serum or living cells from an immune animal.

Antigens are foreign substances that trigger the immune mechanism by stimulating the production of antibodies specific to the antigen. Specificity of the antibody is an important consideration in determining the antigenicity of a substance. Only a small portion of the foreign protein, called an "antigenic determinant," may elicit the production of antibodies which will react only with that determinant. Large protein molecules, however, may possess more than one antigenic determinant.

A wide range of substances has been found in parasite tissues that have the ability to stimulate antibody formation. The majority are proteins, occasionally with conjugated lipid, carbohydrate or nucleic acid moieties associated with the molecule. Cell-bound or secreted polysaccharides may also serve as antigens with broad specificities. In parasites, there may be a number of sources for antigenic complexes. They may be components on the surfaces of protozoa, eggs or larvae, substances found in metabolic secretions (called "ES antigens"), or even shed cuticles of worms or pieces of tissue or cells from injured parasites (called "somatic antigens"). Somatic antigens may be identified experimentally in ground-up whole worms or in specific tissue extracts of, for example, cuticle or muscles from whole worms.

Compared with the immune responses caused by bacteria and viruses, the antigen-antibody manifestations involved with metazoan parasites are exceedingly complex. This complexity stems from the multiplicity of the antigen systems of each metazoan parasite. Because of the great variety of cells and tissues in the parasite body, many kinds of antigens are produced. During the development of a helminth parasite, especially one that goes through two or more stages of development and requires one or more intermediate hosts, biochemical and physiologic changes constantly occur that add to the complexity of the antigenic mosaic. Heyneman[19] has stated,

"This is the essential difference between microbial and helminth immunity—the worm's size and its antigenic complexity. . . . An individual nematode larva, passing through various growth stages as it migrates through its host, presumably undergoing metabolic phases as well, sheds antigens not only as successive larval cuticles, but more importantly as a spewing out of metabolic waste products and a variety of other secreted and excreted antigenic substances."

Hosts and parasites may have antigens in common. At least four were found to occur in both *Schistosoma mansoni* and the laboratory mouse.[9] Kagan[25] reported that only 9 of 19 components in hydatid fluid (from a larval tapeworm) were of parasite origin. The concept of "eclipsed antigens" has been proposed by Damian.[8] When an antigen of a parasite resem-

bles an antigen of its host, the host does not recognize the parasite antigen as being foreign. Thus the parasite antigen is "eclipsed" and the host does not produce antibodies against it. Such a relationship would obviously be disadvantageous to the host.

A somewhat similar method of protecting the parasite occurs when a worm incorporates its host antigens into its body surface. These antigens might help to disguise the worm as part of the host and thus prevent its rejection as foreign tissue.

In general, host immune responses to metazoan parasites are "manifested by changes in their [the parasite] numbers, rate or extent of growth, morphogenesis, extent of migration and reproduction rate."[46] Antigen-antibody complexes initiate a rapid inflammatory response in immune hosts. Proteolytic and other enzymes are activated, and the increased glycolytic processes result in greater acidity at the site of inflammation. A variety of tissue lesions may be produced. The complexity of responses is a logical corollary to the heterogeneity of antibodies.

The phenomenon of **cross reaction** occurs when antibodies formed from the action of antigens from one species of parasite react with the antigens of another species of parasite, for example, when immunization in albino mice by larvae of the nematode, *Nippostrongylus brasiliensis*, was followed by a challenge infection with *Schistosoma mansoni* cercariae. Recovery of schistosomes was significantly lower as compared with controls.

If the parasite or parasitic substance used to reinfect (i.e., challenge) a host is of the same species as that which started the original infection (or is a vaccine made from the original species), the experiment is a **homologous** one; if the parasite or substance is of a different species, the experiment is a **heterologous** one and is used to demonstrate cross reaction.

Concurrent infections (see p. 451) with two or more species of parasites in one host body are common. Therefore, the similarities and dissimilarities of antigens of the different parasites must be considered, as well as the immune responses of the host. Schad[37] has proposed a hypothesis stating that "when co-occurring parasites are likely competitors, cross immunity may be a device evolved to limit the abundance of a competing species." In this theory, parasite species A produces an antigen that elicits an immunologic response against parasite species B, but not against A.

Premunition is a special kind of immunity to some parasites that do not provoke a lasting immunity by a single attack upon the host. Continued reinfection, however, maintains a state of relative immunity that protects the host from disease, with few if any symptoms. Premunition may be considered a compromise situation between parasite and host wherein both are able to remain alive.

Dineen[12] has proposed that the immune response creates an environment for the selection of genetic variants during the evolution of the parasite-host relationship. He described the factors that might determine the mean threshold level of parasitic infection as: (1) the degree of antigenic disparity between host and parasite, and (2) the rate of flow of antigenic information. If an antigen does not stimulate a response influencing the survival (or "fitness") of the parasite, it is immunologically impotent. There is no immunologic selective pressure to modify the parasite that produced the antigen, and such a parasite may remain highly antigenic. This situation might explain the presence of antibody with little or no resistance to infection. Dineen concluded that "the role of the immunological response in the 'adapted' host/parasite relationship is to control the parasite burden rather than to cause complete elimination of the infection."

Antibodies belong to the blood proteins known as **immunoglobulins** (Ig), and each antibody molecule consists of two pairs of amino acid (polypeptide) chains. Five types of heavy chains are called IgM, IgG, IgA, IgD, and IgE. They differ considerably in their function and occurrence in different infections and will be referred to in several chapters in this book. Development of the antibody-producing cells depends on a lymphoid organ termed the "bursa of Fabricius" (a pouch attached to the gut near the cloaca) in birds or the equivalent cells in mammals. These lymphoid cells are called **B** cells. Cell-mediated immunity (CMI) results from activities of lymphocytes, called T cells, developing in the thymus gland. Both T cells and B cells have a common origin in the hemopoietic (blood-forming) stem cells in bone marrow. B cells become plasma cells that actively synthesize and secrete millions of anti-

bodies until they die within a few days. For details of the development of the immune system, see Cooper and Lawton.[7]

Sensitized T cells in CMI are responsible for delayed hypersensitivity (e.g., as occurs in allergic reactions after contact with poison ivy), success or failure in skin grafts, phagocytosis by macrophages, **autoimmunization** (occurring when host cells are so altered by parasitic infection that they are rendered antigenic toward the host; and autoantibodies against these host cells are formed), and the like.

Suppression of the immune response has been described in several infections (e.g., malaria, toxoplasmosis, trichinellosis). The cause of this phenomenon called "immunosuppression" is obscure, but possibilities include disturbance of the macrophage function, impairment of the processing of antigens, depletion of sensitized lymph cells, antigenic competition; or perhaps immunosuppression occurs only during relatively acute parasitemia.[22]

Recent advances in CMI have introduced the concept of soluble, nonspecific, nonantibody mediators ("lymphokines") of cellular events. There is also increasing conviction that the once clear distinction between the functions of T cells and those of B cells (e.g., CMI is achieved primarily by lymphoid cells rather than by humoral antibody, and CMI is transferred by lymphoid cells but not by serum) is no longer so clear. "In these complex immune systems that attend many, if not all, parasitic infections it is especially difficult to separate component parts."[41] There is increasing evidence that in many parasitic infections both humoral and cellular immunity take place. For the great majority of infections by parasitic animals it is not yet possible to achieve resistance by a safe and effective vaccine.[38]

For detailed discussions of immunity to parasites, see reviews by Jackson et al., Vol. 2,[24] and by Soulsby.[41] Also see Feldmann and Nossal[14] on the cellular basis of antibody production, Porter[34] on structure of antibodies, Kagan[26] on advances in immunodiagnosis, and Larsh and Weatherly[27] on cell-mediated immunity.

Immune Reactions in Invertebrates

Like the vertebrates discussed above, coelomate invertebrates (e.g., arthropods, molluscs, annelids) possess the ability to distinguish self from nonself materials and to react against these foreign materials, eventually leading to their elimination or isolation. Also, as in vertebrates, there are basic mechanisms by which immunity is mediated, namely "cellular" and "humoral" immune reactions. Cellular reactions involve small, motile amoeboid cells referred to as hemolymph cells, leucocytes, amoebocytes or hemocytes, which occur in large numbers in the hemolymph or blood circulation. Humoral reactions involve soluble substances in the hemolymph which have bacteriolytic, agglutinating or similar activity that limits the growth or viability of foreign organisms. Although these kinds of reactions superficially parallel those in vertebrates, the absence of antibodies (immunoglobulins) and the immunocyte system responsible for antibody synthesis in the invertebrates has led to the general conclusion that the mechanisms responsible for the recognition of foreignness in the latter group are *not* comparable to those operative in the vertebrates.[4]

Because many parasites of medical, veterinary or commercial importance utilize invertebrates as intermediate or definitive hosts, the study of internal defense mechanisms in these hosts is at present an area of considerable research interest to parasitologists and comparative immunologists. In a discussion on protozoan parasites in arthropod hosts, Garnham[16] has stated that the invertebrate host provides the most interesting features of infection, "tantalizing because most of the phenomena are inexplicable . . . the essence of the problem is the physical and chemical basis of susceptibility, or its converse, resistance. We have scarcely reached the stage of being able to define this problem." Cellular reactions are currently recognized as of primary importance in the isolation and/or elimination of foreign material in coelomate invertebrates.[6] Small foreign particles, such as bacteria, viruses, or some protozoans, or foreign soluble substances such as parasitic secretions or excretions, are removed from the host by the process of endocytosis (including both phagocytosis and pinocytosis, see p. 20). If particles are too large for endocytosis, as is usually the case in larval helminth infections, blood cells respond by accumulating in layers around the parasite, forming an encapsulating nodule. Extracellular fibrils may also take part in capsule formation, as occurs in capsules formed by the American oyster, *Crassostrea virginica*, on larval cestodes.

Encapsulation may involve different hemolymph cell-types. For example, molluscan hyalinocytes are responsible for the encapsulation of renicolid sporocysts in the marine prosobranch, *Cerithidea californica*,[47] whereas capsule formation in the pulmonate, *Biomphalaria glabrata*, around the larval nematode, *Angiostrongylus cantonensis*, involves only granulocytes.[17] Encapsulation of larval helminths, nematodes in particular, in insect hosts is often accompanied by melanin pigment deposition in the granuloma (melanotic encapsulation).[33] The precise role of melanin in the internal defense system of insects, however, is still poorly understood. For further reading on invertebrate immunity, see review edited by Jackson et al. Vol. 1.[23]

A benign immunologic relationship between host and parasite has been termed "immunological tolerance." This state of "compatibility" hangs in a precarious balance. Pan[31,32] has found that in its natural snail host, *Biomphalaria glabrata*, healthy larval stages of the blood fluke, *Schistosoma mansoni*, stimulate little or no cellular reaction. Dead or dying parasites, host age, or even differences in parasite or host strains can affect the degree of immune compatibility or incompatibility in an association.

A case of acquired immunity or resistance in invertebrates to parasites has yet to be clearly demonstrated. This situation probably can be attributed to a lack of antibody-mediated immunologic memory in these animals, though anamnesis has been indicated in studies on graft rejection in earthworms, *Lumbricus terrestris* (reviewed by Hostetter and Cooper[20]). A few investigators have presented evidence which is suggestive of acquired resistance in molluscs to infection by larval trematodes. For example, Michelson[30] found that if the snail, *Australorbis glabratus*, is inoculated with *Schistosoma mansoni* eggs and an extract is made from the infected snails, the extract possesses a substance that immobilizes miracidia of *S. mansoni*. Much more experimental work must be done, particularly with regard to the specificity of the reactions and the use of tissue culture techniques.[11]

Interferon is a protein that can be extracted from cells and was originally found to inhibit the multiplication of viruses. There are several theories to account for the antiviral effect of this substance but the explanation is still obscure. Recently it has been learned that the reproduction of some parasitic protozoa can also be inhibited by interferon and by interferon inducers. Interferon-containing serum from mice conferred protection against the malarial parasite *Plasmodium berghei*. Mouse interferon, but not chick, gave protection against the widespread protozoan parasite, *Toxoplasma gondii*. When chick kidney cells infected with the coccidian, *Eimeria*, were treated with interferon in culture, the developmental stages of the parasite were decreased. Infections of mice with the protozoan, *Leishmania donovani*, however, were enhanced when the animals were injected with potent inducers of interferon.

There is thus impressive evidence that malarial parasites are inhibited by interferon. Its effect on other intracellular parasites seems to vary. Probably there is little, if any, effect on the flagellates belonging to the Trypanosomatidae.[18]

Zoonoses

Zoonoses are diseases or infections that are naturally transferable between animals and man. In a broad sense, all animals are included in the definition, but most studies of zoonoses involve only diseases of vertebrates. The term **anthroponoses** means human diseases that are transmissible to animals.

The overall concept of zoonoses is complex. It involves man, another vertebrate, often an arthropod, the agent that causes the disease, and the environment—all forming a biologic whole. The interaction of these parts involves more than just a sum of the parts. A serious study of zoonoses should thus include the ecology of all organisms involved—parasite, animal, vector and man.

Many zoonoses, such as balantidiasis (caused by an intestinal ciliate), fascioliasis hepatica (liver fluke disease) and tongue-worm infection, are found almost exclusively in animals and only rarely in man. Others, such as leishmaniasis (Oriental sore), flea infestation, African sleeping sickness and opisthorchiasis (Chinese fluke infection), are common in both animals and man. Well over 100 zoonoses are known, and they may be grouped on the basis of the causative organisms: viruses, rickettsiae, bacteria, fungi, protozoa, nematodes, trematodes, cestodes and arthropods.

Hydatidosis is an example of a parasitic zo-

onosis with worldwide distribution. Hydatid disease is caused by a larval stage of the minute tapeworm, *Echinococcus granulosus* (see pages 240 to 244 for a description of the life cycle). Figure 1-2 illustrates the major factors involved in the study of this disease. Animal infection involves various farm and wild animals, but centers around dogs. The fight against the spread of this infection is a public health problem and is based on the treatment of all dogs in infected areas, prevention of reinfection and elimination of stray dogs. For a thorough review of the zoonoses, see Beaver,[1] Van Der Hoeden,[45] Fiennes,[15] Soulsby[42] and Hubbert et al.[21]

An Ecologic Approach to the Study of Parasitism

The whole assemblage of parasites associated with a host population, or a single host, may be called the **parasite-mix.** Such an assemblage is a small biocoenose, and it includes all the viruses, bacteria, protozoa, molds, rickettsiae, worms and arthropods that live on or in another organism. The small biocoenose is a biologic entity that is constantly changing as it reacts with the environment. Parasitology is thus a study in ecology. Such an approach has been emphasized only in recent years.

When we label morphologic or physiologic features as specific adaptations to parasitism we must bear in mind the universal need to adapt to the **environment.** Many characteristics that are described as hallmarks of the parasitic habit are also to be found among free-living species. The hallmark is sometimes present in only one or two species, or it may even disappear during a phase in the life cycle of an individual parasite. For example, cyst formation, so characteristic of parasitic protozoa, is common among free-living protozoa and metazoa. The complicated and significant alternation of sexual with asexual generations during life cycles of sporozoa, trematodes and other parasites is duplicated in foraminifera, hydroids and many other free-living species. The saprozoic form of nutri-

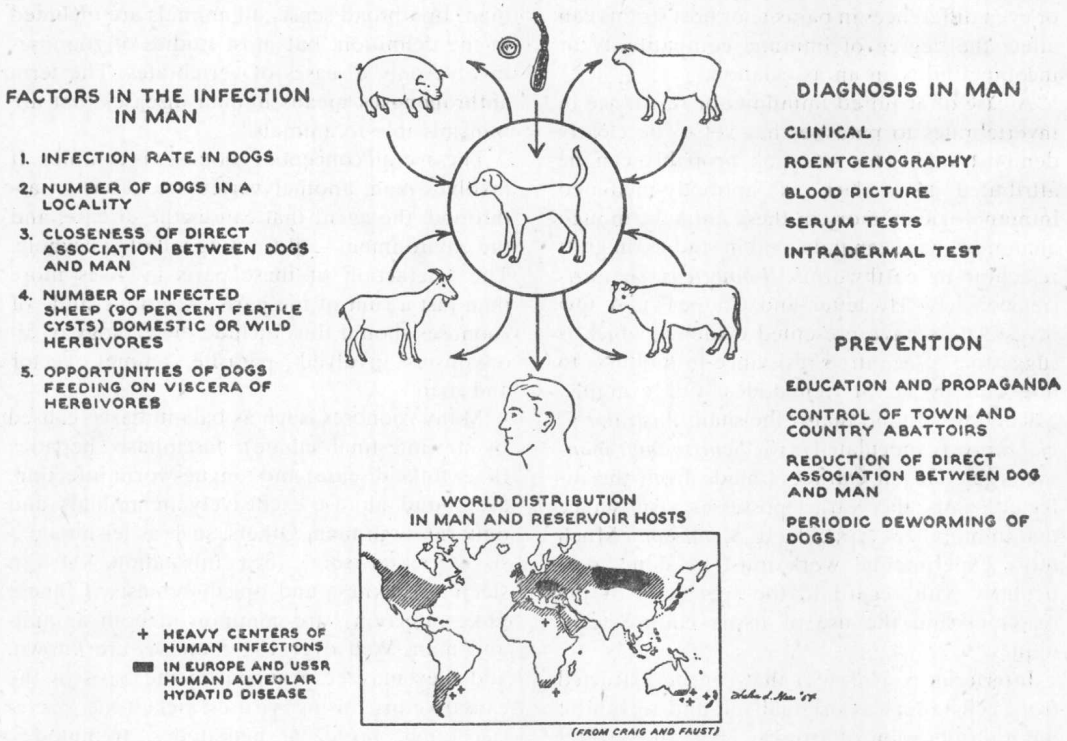

FIG. 1-2. Epidemiology of hydatidosis, a zoonotic disease caused by the minute tapeworm, *Echinococcus granulosus.* (Meyer, courtesy of Univ. California Press.)

tion can be illustrated abundantly among soil-dwelling organisms as well as among parasites.

In order to understand more completely the ecology of parasitism; we must thoroughly review environmental variables. We must avoid the promulgation of too many broad generalizations inadequately supported by specific data. Although generalizations must be synthesized and elaborated, they must emerge from detailed long-term studies, preferably with experimental work.

Ractliffe et al.[35] have given an excellent example of how the conceptual approach known as **systems analysis** can help to overcome the difficulty of formulating a biologic model. Their study involved the nematode, *Haemonchus contortus,* and its sheep host. This approach is new to parasitology, and is a "method of model-building and analysis by which the selection of critical hypotheses can be made in a logical and systematic way."

General Principles

A principle is a fundamental doctrine, theory or belief. Understanding the basic principles of ecology, evolution, genetics, morphogenesis, physiology and immunology is tantamount to understanding the basic principles of parasitology. These principles, however, must be adapted to the needs of parasitologists because parasitism is a great deal more than a combination of parasites and hosts. Associations of these organisms create a system that is unique. The components of the system can effectively be examined separately, but if principles of symbiosis are to be developed, the interrelations among all components of the system must be understood. The generalizations and hypotheses stated below could constitute the beginnings of a statement of "principles" of parasitism. Other principles may be found throughout the book, especially at the ends of the last three chapters.

Parasites have lost the capacity for free-living and have become dependent for their existence upon one or more other living species. They have, in general, lost sense organs, locomotor abilities, and certain metabolic functions such as the elaboration of some digestive enzymes. These losses are compensated by various gains: a habitat that provides abundant food, shelter and some protection, a long individual life, specialized modes of reproduction and life cycles, and specialized organs of attachment.

The host has also lost some freedom. It must share its body with the parasites. The loss of food and the functions of resistance result in the diversion of energy. However, the host gains from the exchange of chemical substances with the parasite. In addition, the presence of one species of parasite often prevents the establishment of another, perhaps injurious, species.

Parasites and their hosts must struggle to keep these gains. They must cooperate so that the host remains in a healthy state and the parasite is not rejected. They must tolerate each other and resist each other, thereby becoming mutually adaptive and mutually beneficial. In this situation, the environment (the host) adjusts to the parasites. Since the host is the environment, the parasite must find a means of transport from environment to environment because a single host body provides limited space and it eventually dies. To satisfy this need, parasites depend upon the food and habits of the host. Appropriate triggering mechanisms initiate the change from infective stages to parasitic stages. Once the parasite has begun its existence in a new host body, other triggering mechanisms initiate each change of the parasite during its development.

In a discussion of principles of parasitism, Read[36] emphasized the dependence of the parasite on the host for chemical compounds that are essential for initiating certain parasite functions or behavior (e.g., hatching of eggs, moulting of larvae). From these considerations he formulated the *Principle of Interrupted Coding* which he defined as: "The host must have genetic information and thus the capacity to furnish the necessary compounds and/or physical conditions to overcome a genetic block in the development of a given symbiote." He felt that Smyth's[39] concepts relating to different nutritional requirements at different stages of a parasite's development could be considered as related to Read's principle of interrupted coding. For example, the yolk sac of a chick egg is rich in nutrients and is often used as a cultivation medium for parasites. Certain tapeworm larvae, however, will not grow in the yolk sac. This failure may be attributed to a lack of chemical "signals." These considerations are highly speculative but they deal with aspects of parasite-host relationships that should be included in any formulation of principles.

References

1. Beaver, P. C.: Zoonoses, with particular reference to parasites of veterinary importance. *In* Soulsby, E. (ed.): Biology of Parasites. pp. 215–227. New York, Academic Press, 1966.
2. von Brand, Th.: The biochemistry of helminths. Zeit. Parasitenkd., *45*:109–124, 1974.
3. Bryant, C.: Carbon dioxide utilization and the regulation of respiratory metabolic pathways in parasitic helminths. Adv. Parasitol., *13*: 35–69, 1975.
4. Burnet, F. M.: Invertebrate precursors to immune responses. *In* Cooper, E. L. (ed.): Contemporary Topics in Immunobiology—Invertebrate Immunology, Vol. 4. pp. 13–24. New York, Plenum Press, 1974.
5. Cameron, T. W. M.: Parasites and Parasitism. New York, Wiley, 1956.
6. Cheng, T. C., and Rifkin, E.: Cellular reactions in marine mollusks in response to helminth parasitism. *In* Snieszko, S. F. (ed.): A Symposium on Diseases of Fishes and Shellfishes, pp. 443–496. Washington, D.C., Am. Fish. Soc., Special Publ. *5*, 1970.
7. Cooper, M. D., and Lawton, A. R., III: The development of the immune system. Sci. Am., *231*:59–72, Nov. 1974.
8. Damian, R. T.: Molecular mimicry: Antigen sharing by parasite and host and its consequences. Am. Naturalist, *98*:129–149, 1964.
9. Damian, R. T.: Common antigens between adult *Schistosoma mansoni* and the laboratory mouse. J. Parasitol., *53*:60–64, 1967.
10. Davey, K. G.: Hormones, the environment, and development in nematodes. *In* Van den Bossche, H. (ed.): Comparative Biochemistry of Parasites. pp. 81–94. New York, Academic Press, 1972.
11. de Bary, H. A.: Die Erscheinung der Symbiose. Strassburg, Karl J. Tübner, 1879.
12. Dineen, J. K.: Immunological aspects of parasitism. Nature (Lond.), *197*:268–269, 1963.
13. Erasmus, D. A.: The Biology of Trematodes. New York, Crane, Russak & Co., 1972.
14. Feldmann, M., and Nossal, G. J. V.: Cellular basis of antibody production. Q. Rev. Biol., *47*:269–302, 1972.
15. Fiennes, R.: Zoonoses of Primates. The Epidemiology and Ecology of Simian Diseases in Relation to Man. Ithaca, N.Y., Cornell University Press, 1967.
16. Garnham, P. C. C.: Factors influencing the development of protozoa in their arthropodan hosts. *In* Taylor, A. E. R. (ed.): Host-Parasite Relationships in Invertebrate Hosts. Oxford, England, Blackwell Sci. Pub., 1964.
17. Harris, K. R.: The fine structure of encapsulation in *Biomphalaria glabrata*. Ann. N.Y. Acad. Sci., *226*:446–464, 1975.
18. Herman, R.: The effects of interferon and its inducers on experimental protozoan parasitic infections. Trans. N.Y. Acad. Sci. Ser. II, *34* (2):176–183, 1972.
19. Heyneman, D.: Host-parasite resistance patterns—some implications from experimental studies with helminths. Ann. N.Y. Acad. Sci., *113*:114–129, 1963.
20. Hostetter, R. K., and Cooper, E. L.: Earthworm coelomocyte immunity. *In* Cooper, E. L. (ed.): Contemporary Topics in Immunobiology—Invertebrate Immunology, Vol. 4. pp. 91–107. New York, Plenum Press, 1974.
21. Hubbert, W. T., McCulloch, W. F., and Schnurrenberger, P. R. (eds.): Diseases Transmitted from Animals to Man. 6th ed. Springfield, Ill., Charles C Thomas, 1975.
22. Hunter, G. W., III., Velleca, W. M., and Crandall, R. B.: Studies on schistosomiasis. XXII. Cross resistance in *Schistosoma mansoni* and *Nippostrongylus brasiliensis* infections in mice. Exp. Parasitol., *21*:15, 1967.
23. Jackson, G. J., Herman, R., and Singer, I. (eds.): Immunity to Parasitic Animals. Vol. 1. New York, Appleton-Century-Crofts, 1969.
24. Jackson, G. J., Herman, R., and Singer, I. (eds.): Immunity to Parasitic Animals. Vol. 2. New York, Appleton-Century-Crofts, 1970.
25. Kagan, I. G.: Seminar on immunity to parasitic helminths. VI. Hydatid disease. Exp. Parasitol., *13*, 57–71, 1963.
26. Kagan, I. G.: Advances in the immunodiagnosis of parasitic infections. Z. Parasitenkd., *45*:163–195, 1974.
27. Larsh, J. E., and Weatherly, N. F.: Cell-mediated immunity against certain parasitic worms. Adv. Parasitol., *13*:183–222, 1975.
28. Lincicome, D. R.: Chemical basis of parasitism. Ann. N.Y. Acad. Sci., *113*:360–380, 1963.
29. Lincicome, D. R.: The goodness of parasitism: A new hypothesis. *In* Cheng, T. C. (ed.): Aspects of the Biology of Symbiosis. pp. 139–227. Baltimore, Univ. Park Press, 1971.
30. Michelson, E. H.: Development and specificity of miracidial immobilizing substances in extracts of the snail *Australorbis glabratus* exposed to various agents. Ann. N.Y. Acad. Sci., *113*:486–491, 1963.
31. Pan, C-T.: Generalized and focal tissue responses in the snail, *Australorbis glabratus,* infected with *Schistosoma mansoni.* Ann. N.Y. Acad. Sci., *113*:475–485, 1963.
32. Pan, C-T.: Studies on the host-parasite relations between *Schistosoma mansoni* and the snail *Australorbis glabrata.* Am. J. Trop. Med. Hyg., *14*:931–976, 1968.