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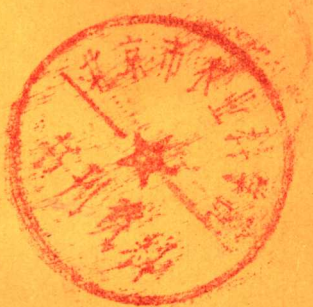
Edited by
E. J. L. SOULSBY

PATHOPHYSIOLOGY OF PARASITIC INFECTION



PATHOPHYSIOLOGY OF PARASITIC INFECTION

Edited by
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PREFACE

Advanced changes in cells, tissues, and organs are the characteristic responses we expect following parasitic infections, and observations of such have contributed greatly to our knowledge of the parasitic process. These end results are the summation of a multitude of processes, often quantitative in nature, which lead to qualitative changes. It is only in the last decade or so that parasitic disease has been related to abnormal or altered biological processes which are finally expressed as the qualitative manifestations that represent the classical pathology of parasitic infections.

This symposium identifies some of the areas that have received intensive study. In almost all cases, it is obvious that the full implication of the disease process may be missed without the application of modern, sophisticated techniques of measurement. When these are applied, a dynamic process is revealed, the outcome of which may or may not be expressed as overt disease. Furthermore, the overt expression may be contrary to expectations, as for example in the case of gastrointestinal parasitism of ruminants. Here, despite morphological and physiological changes in the parasitized intestine, compensatory mechanisms operate to an extent such that malabsorption is not a major factor even in the most heavily parasitized animal. In sheep, for example, the effects of parasitism are expressed by the reduced incorporation of protein precursors into muscle and the like, rather than by malabsorption.

Studies of plasma protein metabolism have shown a dynamic state of synthesis and catabolism, resulting in an apparent normal balance, but which on investigation proves to be of great liability to a parasitized host should it have greater than usual demands placed on it. A similar situation exists with the anemias of parasitism. The etiology of parasite induced anemias is by no means simplistic, as we shall see in these proceedings, and undoubtedly we need much more study of the mechanisms that lead to and control this manifestation of parasitism, which is possibly the oldest and most widely recognized clinical sign of parasitic infection.

Immunological responses play a dual role in defense and injury mechanisms. The responses that we have so long regarded as beneficial to a host—immediate and

delayed hypersensitivity, antigen-antibody reactions, and activation of complement—now take on new meaning in terms of immunopathology. The delayed response in granuloma formation, antigen-antibody interactions with activation of complement and the rôle of this in immune glomerular and other vascular membrane associated disorders, and the contribution of immune events to the activation of pharmacologically active amines now constitute an important area of research and provide an impressive emphasis of the need to adopt a multidisciplinary approach to the study of parasitic infection.

The culmination of these various processes can be expressed as the "pathophysiology of parasitic infections." However, the parasites we study choose to inhabit the most unlikely locales of the vertebrate body. Those which parasitize the lymphatic and vascular systems are also endowed with a remarkable longevity and thereby are highly specialized, inducing specialized and often dramatic manifestations of their presence. It is possible that the epitome of parasitism is manifested by the filarial worms: our conference should provide a better understanding of these forms as well as others, which are the major pathogens of the world today.

As with other International Conferences of the World Association for the Advancement of Veterinary Parasitology, a theme, this time "Pathophysiology of Parasitic Infections," was the focus for invited papers by distinguished experts who have reviewed the present knowledge in their respective fields of interest. Supporting these are contributions selected from numerous short communications that are representative of the work in progress in the area of the pathophysiology of parasitic infections.

The art and science of medicine owe much to Greece, so that Thessaloniki provided the historical background, the scholarly perspective, and the organizational success that with the Macedonian hospitality made this, the Seventh International Conference of the WAAVP, a memorable occasion. To Professor Himonas and his colleagues we owe our grateful thanks.

As editor of the volume, I wish to thank the contributors for their cooperation in providing manuscripts—some required a little extra prodding—and to the staff of Academic Press, I extend my special thanks for their patience during the preparation of the manuscripts. The production of such a volume requires understanding, diligence, and energy on the part of the office staff, and I thank Ms. Margo Bradford and Ms. Cleola Taylor for their assistance.

As is usual, my wife, Annette, has provided the moral support and incentive to undertake this task: I thank her.

E.J.L. Soulsby,
Philadelphia, 1976

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Introduction to the Seventh International Conference of the World Association for the Advancement of Veterinary Parasitology on Pathophysiology of Parasitic Infections

Dr. Georg Lämmler, President
Institute for Parasitology and Parasitic Diseases of Animals
Justus Liebig University, Giessen
Federal Republic of Germany

Minister, Mister Dean, distinguished guests, ladies and gentlemen:

It is my special duty and high honor to open the Seventh International Conference of the World Association for the Advancement of Veterinary Parasitology. The scientific program of the conference again follows the endeavor and intent of the Association to focus on topics of importance and contemporary interest in the field of parasitology.

Since the first conference twelve years ago in Hanover (1963) on the "Evaluation of Anthelmintics," which was the first formal meeting of the Association, various subjects have been selected and discussed: "Biology of Parasites" (Philadelphia, 1965), "Reaction of the Host to Parasitism" (Lyon, 1967), "Pathology of Parasitic Infections" (Glasgow, 1969), "Immunology of Parasitic Diseases" (Mexico City, 1971), and "Parasitic Zoonoses" (Vienna, 1973). These have been topics of major contemporary interest and with a major impact on modern parasitology.

The previous conferences have demonstrated in a very positive manner the broad spectrum of interest and the scientific plurality in parasitology, and the highly beneficial influence of ideas and techniques from other scientific areas. Thus, veterinary parasitology, which is the basic interest of our association, has received immeasurable benefit from the fruitful interaction with the various disciplines in the natural sciences.

The topic of this Seventh International Conference, "Pathophysiology of Parasitic Infections," has been designed to serve the same objective. The invited papers and short communications will give authoritative accounts on our present knowledge and experience in the field of pathophysiology of parasitism. We hope they will stimulate fruitful discussions and lead to new ideas for research.

Pathophysiology, or pathologic physiology, as the term implies, is concerned with disturbances in normal physiology, the mechanisms producing these functional abnormalities, and the way in which they are expressed as symptoms and clinical signs. The basis of the discipline is the knowledge and understanding of the normal physiological, biochemical, physical, and morphological processes, and therefore the topic represents the scientific basis of preventive and curative medicine.

Pathophysiological abnormalities may accompany or result from anatomical defects, but more frequently they occur in the absence of any pathological anatomical change. Often only "biochemical lesions" are present, which express cellular disfunction before the process is severe enough, or has been present long enough, to cause detectable damage at the macroscopic or microscopic level. Pathophysiologic disturbances represent the mechanisms whereby etiologic agents effect their damage, and include the many phases of pathogenesis of diseases.

Pathophysiology elucidates the reaction pattern between the causative agent and the host and is, therefore, a connecting link permitting a synthesis between theoretical and practical medicine. In the field of parasitology, pathophysiology represents a relatively new discipline, although a variety of parameters of different body systems and organs have already been investigated in various parasitic diseases.

Some of the problems of the evaluation of the pathophysiologic responses of the host to parasitic agents result from the multiplicity of parasitic species and of their infective stages that enter the body in very different ways. The differences in the subsequent development, migration, or multiplication in a variety of cells, tissues, and organs are also important considerations in the pathogenic mechanisms produced by the various causative agents.

Because of the major importance of parasitic infections in most parts of the world, and the widespread occurrence of diseases in domestic animals caused by helminths, protozoa, and arthropods, it is probable that further important advances will be made in the field of pathophysiology in the future. These should provide a better understanding of the impact of parasitic diseases on the host, both at the cellular level and at the whole body level. In addition, they should give more information on the differential mechanisms that disturb normal physiology.

It is important also to know more about the functional interaction between host and parasite and to understand better and more precisely how the host is able to eliminate the parasite or to limit its establishment and development in the host. The inclusion of the topic "pathophysiology" in the program of this conference will, we hope, stimulate further developments in this special field of parasitology and give rise to further close cooperation between parasitologists and scientists of other natural and medical science disciplines.

I would like to thank especially the President of the Local Organizing Committee and Director of the Institute of Applied Helminthology and Entomology, Professor Himonas, the other members of the Organizing Committee from Athens and Thessaloniki and all their helpful co-workers for the hard work they have undertaken to make this conference a success. In addition, we thank the Hellenic Ministry of Culture and Science for the sponsorship of the conference and the industrial

companies for their very helpful financial assistance.

There is much to discuss in the conference and I wish you a successful conference, scientifically and socially, and I hope you have a memorable stay in beautiful Thessaloniki.

CONTENTS

**Invited Paper*

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DETERMINANTS OF PARASITISM: FACTORS IN PATHOGENESIS

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INTRODUCTION

The factors that determine the pathogenesis of an infectious disease are often unclear: this is particularly so with parasitic infections. The present topic is an attempt to dissect the mechanism(s) of pathogenicity from the structural and physiological processes which may be expressed as the pathophysiology of parasitic infections. We know a great deal more about the mechanisms of the pathophysiological changes than the mechanisms of pathogenesis and it is probable that a fuller comprehension of the latter will come only when we understand more of the factors which permit a parasite to maintain itself in the host niche to which it has become adapted.

The functional and morphological changes which follow parasitic infections are frequently non specific, the parasitized host responding in a limited number of ways to a variety of aetiologic agents. Examples of this are the response of the bowel mucosa to a variety of noxious stimuli, the catabolism of protein in various parasitisms, the various anaemias in several parasitic infections and the immunopathologic events to a similar array of infections.

Nevertheless, it is obvious also that a thorough knowledge of what makes an individual parasite pathogenic for its host is lacking and until we understand the determinants of this we will continue to lack the knowledge essential for the control of these infections.

FACTORS DETERMINING HOST-PARASITE COMPATABILITY

One of the unanswered questions of modern biology is that of the molecular basis of host-parasite specificity. Under natural conditions each parasitic species has a relatively well defined host range. It is certain that there is a molecular basis for this and it is probable that the evolution of this basis occurred as host and parasite co-evolved. The degree of integration between host and parasite possibly

explains the breadth or the narrowness of the host range. It is generally considered that the evolution of host parasite associations occurred over an enormous span of time and number of generations of hosts and parasites (Cameron, 1964). However, the role of short term influence has received little study and it is possible these are also determinants of host parasite compatibility. An example of this might be the recent marked increase in equine hydatid infections in Great Britain (Thompson and Smyth, 1974). Epidemiological and experimental studies indicate that the major definitive hosts for this strain of *Echinococcus granulosus* are dogs belonging to hunting packs (Thompson and Smyth, 1975). Protoscolices of this strain differ in their *in vitro* requirements from the sheep strain (Smyth and Davies, 1974) and human infection with the horse strain appears rare. It is interesting to speculate whether the determinants of host specificity co-evolved with the association of horse and dogs of hunting packs (hounds), which, on an evolutionary scale, must be a negligible period of time or whether changes in the determinants of host specificity are related to dietary practices of hunt kennels, which, because of very recent economic pressures, lead to an increase in the feeding of raw horse flesh and offal to hounds (Thompson and Smyth, 1975).

Studies of the molecular basis for host-parasite compatibility have progressed further with the protozoa than with the helminths. For example, the basis of red cell susceptibility to *vivax* malaria (*Plasmodium vivax*) may be associated with Duffy blood group determinants (Fy^a or Fy^b) which may function as erythrocyte receptors for the parasite (Miller, Mason, Dvorak, McGinniss and Rothman, 1975). Evidence that Duffy blood group negative human erythrocytes are resistant to infection with *Plasmodium knowlesi* has been correlated with the resistance of West Africans and American blacks to *Plasmodium vivax* which corresponds to the distribution of Duffy negative erythrocytes in the world. If this factor, alone or in association with another determinant, serves as a receptor for this merozoite of *P. vivax*, then the uniqueness of host-parasite compatibility becomes evident since other human malarias are not dependent on this factor, in that persons resistant to *P. vivax* are susceptible to other species of the genus.

A further example of the molecular basis for host-parasite compatibility is the induction of enzyme activity in host cells for the biochemical needs of the parasite. Thus Oelshlagel, Sander and Brewer (1975) have produced evidence for the introduction of a pyruvate kinase isozyme into host red cells, by malaria parasites, in amounts sufficient to alter

red cell glycolysis. They consider this direction favourable to the parasite because it will increase red cell adenosine triphosphate (ATP) which is needed by the parasite. These authors also speculate that "pyruvate kinase perturbations" may be a general phenomenon in host-parasite relationships and if so, then the role of the parasite in the determination of its destiny becomes more obvious than hitherto.

Alterations of function of host cells which determine the outcome of the infection are seen in the interactions between *Toxoplasma gondii* and cells (Hirsch, Jones and Len, 1974). These organisms have the ability to induce phagocytosis in cells which are not ordinarily phagocytic and subsequently they are able to block the delivery of lysosomal constituents into the phagocytic vacuole in which they live. Consequently they create for themselves a microenvironment which permits their replication and in which they are sheltered from the effects of antibody. The situation with *T. gondii*, where the parasite inhibits fusion of lysosome with the phagosome is evident also with *Mycobacterium tuberculosis* and other organisms (Hirsch *et al.*, 1974). However, with other protozoa different mechanisms are employed to deal with the digestive enzymes produced by the lysosome. Thus with *Leishmania* species fusion of lysosomes with the phagocytic vacuole occurs, but the organism resists the enzymes and the low pH which results. On the other hand the membrane of the vacuole in which the invasive stage of *T. cruzi* is found after invasion of a cell, is quickly lost and the parasite then lives in the cytoplasm of the cell where it is free from the effect of lysosomal enzymes (Trager, 1974).

The need for a recognition factor, or receptor, has been referred to above, with respect to malaria. With the developmental stages of *Leishmania donovani* Dwyer, Langreth and Dwyer (1974) have demonstrated polysaccharides in the surface membranes. Various carbohydrates (e.g. α -1,4 and α -1,6 glycan bonded polysaccharides) are distributed randomly on the pellicular and flagellar membranes and it has been suggested that the negative charge of the promastigote membrane may induce phagocytosis and internalization of the organism and, in addition, the surface saccharides may impact a resistance in lysosomal enzymes. The loss of certain saccharides during *in vitro* culture is associated with a loss of infectivity, in the case of *Leishmania braziliensis* (Davidowicz, Hermandez, Infante and Convit, 1975).

The relationship of these surface saccharides to the antigens which are modulated on the surface of promastigotes and amastigotes by immune serum, resulting in a "capping" phenomenon, (Doyle, Behin, Mauel and Rowe, 1974) is not known.

However, in part they might serve as a mechanism to evade the host response by antigenic modulation or they may assist in recognition and invation of the host cell, possibly aided by the various receptors for subunits of immunoglobulin or complement present on macrophages.

The factors which determine host-parasite compatability for helminths are largely unknown. The majority of the infective stages of helminths have a low resting metabolism and are in a state of semi-dormancy (Lackie, 1975) requiring some specific stimulus for activation. The majority are ingested and hatching, excystment or ecdysis are now generally considered to be active processes on the part of the parasite induced by physical and chemical factors present in the portion of the bowel where these forms commence their parasitic existence. The various mechanisms of this have been reviewed by Lackie (1975), and it is clear that the receptors for these environmental factors which initiate the parasitic process are just as finely tuned as those for some of the protozoa. The factors which initiate exsheathment of infective larvae of *Haemonchus contortus* and *Trichostrongylus axei* are examples of such fine tuning and furthermore the result of these exsheathment stimuli is the production of leucine amino peptidases which are highly specific and which will attack the substrates in the sheaths of their own infective larvae only (Rogers, 1966).

Conceptionally, the major determinant(s) of host parasite compatibility must be expressed at the interface of the initial contact between host and parasite. The evidence to date indicates that they are.

FACTORS DETERMINING PATHOGENICITY

Again we need to turn to the protozoa for molecular explanations of pathogenicity. Extensive studies have been undertaken by Honigberg and his colleagues of the pathogenesis of *Trichomonas* species (Honigberg, 1973). Thus avirulent strains of trichomonads are richer in antigens and are capable of stimulating a stronger immune response than the virulent strains, such as the Jones' Barn strain. This property of avirulence, with its increased number of antigens is maintained in culture.

Comparison of several strains indicates that the virulent Jones' Barn (JB) strain had a more limited capacity to stimulate antibody production than others of lesser virulence. The increase in the number of antigens occurs in non-virulent organisms irrespective of whether they are fresh isolates or whether they have been rendered avirulent by *in vitro* cultivation (Stephvanski and Honigberg, 1972).

In some protozoans, the need for concomittant bacterial infection to induce virulence is well known (e.g. *Entamoeba histolytica, Histomonas meleagridis*). They are, however, anomalies in this situation since whereas the presence of bacteria is necessary for the pathogenic effects of these organisms, the composition of the bacterial flora is not critical and pathogenic as well as non pathogenic bacteria are associated with this effect. It has been thought that bacteria produce a "suitable environment" (Neal, 1971) to support amoeba. However, the findings of Wittner *et al.* (1970) have suggested that direct contact between amoeba and bacteria is necessary and Honigberg (1973) has suggested that an "episomal factor" capable of phagocytosis to produce a protozoan-bacterial relationship is essential for successful parasitism. Such factors may also pertain to *Histomonas meleagridis* of turkeys where enterohepatitis is not produced in germ free chickens or turkeys, but is regularly produced in "conventional" hosts.

In the majority of cases, *in vitro* cultivation of organisms results in loss of virulence, but in many cases pathogenicity can be restored by serial passage through susceptible hosts. The virulence factors which are rescued by this passage procedure are unknown, as are the mechanisms of their rescue, nevertheless this is evidence for a degree of instability of the factors responsible for pathogenicity (Neal, 1971). Perhaps, however, this is interpretable on the basis that environmental influences play a special part in determining pathogenicity and this is expressed as a spectrum of responses when the host range of the parasite is increased. With the protozoa, variations of pathogenicity are well known and according to the host, members of the genus *Trypanosoma*, express very different capabilities of pathogenesis (Losos and Ikede, 1972).

Parasite factors which determine pathogenicity of helminths, as those which determine host-parasite compatibility, are poorly understood. With the forms which remove blood or essential body nutrients the obvious mechanism is a well adapted oral structure and a powerful oesophagus. Apart from such general information acquired decades ago, we are no nearer to a rational explanation of a mechanism of pathogenesis on the part of the majority of helminth parasites.

SURVIVAL OF PARASITES IN HOSTS

The survival of parasites in their hosts is a topic of increasing interest. The majority of parasites can survive for weeks or months and some may survive for years in hosts which have become sensitized to them. Various mechanisms

are used to accomplish this, some being based on the inability or an altered ability of the host to respond effectively to reject the parasite and some being concerned with the adaptation of the host environment. This general topic is reviewed by Ogilvie and Wilson (1976) under the concept of evasion of the immune response by parasites and a further review of the subject at this time is unnecessary. Notwithstanding, mechanisms such as unresponsiveness in the young, unresponsiveness induced by lactation, immuno-depression induced by antibody or by suppressor cells on the part of the host and antigenic variation (as seen in trypanosomes) and the occurrence of host antigens on, for example, the tegument of schistosomes are entities which variously determine the success or otherwise of an infection.

The "host like antigens" on the tegument of schistosomes are associated with the protection of schistosomula and adult schistosomes against damage by antibodies. These have been shown to be red cell antigens determinants, but it is yet unclear whether such antigens are acquired directly from the host or are synthesized by the parasite. The role of host derived, or host like, antigens in the survival of other parasitic helminths and parasitic protozoa is still unclear. Vickerman (1974) has reported that *Trypanosoma vivax* may bind host serum protein to its surface and this may then disguise the organism from the host response, though in the trypanosomes the ability of the trypanosome population to change its antigenic surface appears to be this principal mechanism whereby the parasite evades the host response.

With the nematodes a hypothesis for prolonged survival, for example, of *Ascaris* has been suggested based on the occurrence of blood group and heterophile antigens on the surface of the larvae (Soulsby, 1971). It has been suggested that the union of specific immunoglobulin with such receptors provides the host protein coat by which these organisms effect their disguise.

A further feature of the survival of parasites in their hosts is the reduced reactivity of parasites upon their entry into a host. Leventhal and Soulsby, (1976) have shown that the early larval stages of *A. suum* have reduced reactivity in terms of binding of immunoglobulins, activation of complement and the attachment of phagocytic cells such as polymorphonuclear leukocytes. This could be interpreted as a mechanism whereby a parasite achieves an initial advantage on invasion of the host, temporary though this may be.

Another aspect of modulation of recognition of a parasite by a host is that reported by Ogilvie (1974) where adaptation of *Nippostrongylus brasiliensis* worms in immune rats is

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