Advances in
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VOLUME 24

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Editorial Board

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PARASITOLOGY

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PREFACE

We hope that this volume will provide, as we hope previous volumes have done, an interesting mixture of stimulating and up-to-date reviews in the broad field of parasitology. Now that so much emphasis is being placed on the "molecular" aspects of the subject—with very fruitful results in many areas—we feel it is important not to forget that parasitology is, essentially, an ecological subject concerned fundamentally with inter-specific relationships. The reviews in this volume by R. M. Anderson and R. M. May, L. E. A. Symons, and H. Hoogstraal particularly remind us of this, as indeed does that by J. J. Petersen—while also emphasizing a practical and economically important aspect of the subject. Dr. Petersen's review, covering the Mermithidae, will be complemented by a second instalment by R. Bedding in a subsequent volume, dealing with the Tylenchida and Rhabditida. M.-C. Durette-Desset's review is in the classical tradition of evolutionary morphology and taxonomy—fundamental building blocks in the structure of parasitology, the importance of which should not be forgotten. It also provides fascinating reasoned speculations on the coevolution of parasites and hosts. We intend that any apparent bias against protozoology in this volume will be corrected in the next two, though the protozoa are of course, included within the two general reviews in the current volume and Dr. Hoogstraal's contribution also relates very closely to protozoology.

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Helminth Infections of Humans: Mathematical Models, Population Dynamics, and Control

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I. Introduction

The methods employed in the epidemiological study of helminth infections within human communities have changed surprisingly little over the

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past 60 years. The pioneering work of various American and European epidemiologists in the early 1920s, on hookworm and other intestinal nematodes, compares very favorably in quality with much of the recently published work (e.g., Stoll, 1923; Cort, 1922; Payne, 1924; Augustine, 1923a,b, 1926; Chandler, 1925; Sawyer, 1925; Hill, 1926; Docherty, 1926; Kendrick, 1934). The methods they employed, the large samples of people they examined, and the conclusions they arrived at remain as relevant today as when their work was first published.

In one sense this is a tribute to the early research. In another sense, however, it is perhaps an indication of a lack of progress in this field of epidemiological study. Many factors may help explain this observation, not least of which are the numerous practical difficulties inherent in the field study of endoparasites of man, where ethical considerations prohibit certain forms of experimental work and where indirect methods must be employed to record changes in parasite prevalence and intensity within human communities. The hope that advances in our understanding of immunological responses to helminth invasion would yield reliable diagnostic methods, of a quantitative character, has as yet to be realized. This is to a large extent a consequence of the complexity of the surface antigenic structure of macroparasites and the difficulties encountered in the identification of stage-specific surface or excretory antigens which do not cross-react serologically with those of other parasite species. Modern biochemical methods employing monoclonal antibody techniques may resolve these difficulties. Encouragingly, some progress has already been made in this direction; for example, reliable diagnostic methods should soon be available for detecting the presence or absence of filarial infections in man (Maizels *et al.*, 1983). It could be argued, however, that past concern with the relevance of immunological processes in helminth transmission have to some extent distracted attention from the basics of good epidemiological study such as quantitative measures of levels of infection, good sampling design, innovative experimental approaches in field study, and analysis of the significance of human or vector behavior.

To an ecologist it may appear surprising that the advances made over the past 50 years in our understanding of the population dynamics of animal and plant species have not had a greater impact on epidemiological research. This may be a consequence of the tendency for medical attention to be focused on the course of parasitic infection (and the associated pathology) within an individual person as opposed to the community as a whole. Indeed this trend is equally apparent in research on the control of helminth parasites. There exists a marked discrepancy between our knowledge of how to treat an individual and how to control the infection within a community.

A community approach clearly depends on a thorough and detailed understanding of the population dynamics of human parasites. This important but neglected area of epidemiological study is one in which mathematical methods can play a significant role. The rationale and philosophy behind the application of mathematics to medical or biological research have been expounded by many people in recent years (e.g., Fisher, 1930; Bartlett, 1960; Maynard-Smith, 1968; May, 1974; Bailey, 1975). We therefore do not wish to repeat these arguments but simply point out a few of particular relevance to helminth epidemiology.

There has been a tendency among tropical public health workers to reject the insights produced by mathematical models on the grounds that too many simplifying assumptions are made despite known biological complexity. This is sometimes true and needs to be rectified, but there is an important counterargument. It is often necessary, and indeed helpful, carefully to eliminate simple hypotheses as explanations of observed phenomena before moving onto more complex postulates. The failure to do so will leave the lingering doubt that although the biological phenomena under study is complex by nature, a few simple processes may dominate the generation of observed patterns. Simple mathematical models in which the biological assumptions are clearly and precisely defined can be of great help in removing or confirming these doubts. Indeed, as illustrated in this article, simple sets of assumptions can lead to complicated patterns of dynamic behavior and it is as well to be aware of this when interpreting observed patterns. Helminth life cycles are often complex, involving more than one host species and many distinct parasite development stages. In such circumstances, the most refined intuition, perhaps built up from many years of field experience, may often fail correctly to interpret the factors responsible for dynamic changes in parasite abundance and distribution. In the face of biological complexity the rigour of mathematical description can aid in interpretation and, equally importantly, point to the factors or processes which must be measured or quantified in order to understand observed events. In the sense defined above, mathematical or theoretical work serves as (1) a means of eliminating hypotheses as explanations of observed trends; (2) an aid to the interpretation of multidimensional processes; and (3) a guide to field measurement and experimentation. In these roles mathematical methods are primarily of value in the elucidation of qualitative as opposed to quantitative concepts or principles.

In a quantitative sense, if enough is known about the biology and epidemiology of a particular parasite, models can also be employed as predictive tools. This role is of particular importance in the design of policies and methods for parasite control or eradication within human communi-

ties. The success of this type of approach, however, is critically dependent on a detailed and thorough knowledge of the population biology of the parasite and its host (or hosts).

This article considers the role of mathematical models in investigations of the population or transmission dynamics of human helminths. Throughout, mathematical details are kept to a minimum and we concentrate on the biological assumptions employed in model construction, the insights that emerge from model analysis, the comparison of predictions with observed trends, and the estimation of parameter values from epidemiological data. The article is organized as follows. We first give a brief account of observed epidemiological patterns, concentrating on age–prevalence and age–intensity trends. The next section gives a brief historical review of the development of mathematical models of helminth infections. The following three sections discuss mathematical models for schistosome flukes, for intestinal nematodes, and for the filarial infections. Section VIII attempts to condense the essential features of the models for specific infections in order to provide a general framework for the description of helminth transmission dynamics. The general framework is employed in Section IX to consider the design of control policies for helminth infections in human communities. The final section focuses on future developments.

II. Epidemiological Patterns

Much of the mathematical literature on the dynamics of infectious diseases is open to the criticism that insufficient attention is given to the comparison of predictions with observation and to the estimation of the model's parameters from epidemiological data. Before proceeding to discuss various types of models for the dynamics of helminth infections, we therefore provide a very brief overview of the available kinds of data. Our aim is simply to point out a few general patterns and trends arising from a comparative study of epidemiological surveys of helminth infections in human populations.

The majority of published data records changes in the prevalence and average intensity of infection over a series of age classes within the human community. Invariably such data is collected at one point in time, or over a short time interval, and may therefore be described as horizontal in nature. More rarely, longitudinal studies are performed where changes through time are recorded. Note, however, that if parasite population abundance within the human community has remained relatively stable over long periods of time (as is often the case in rural communities in developing countries) changes with human age are equivalent to changes

through time. We refer to the graphical representation of changes in prevalence and intensity with human age as age–prevalence or age–intensity curves. Their form in a given community clearly reflects the magnitude of parasite transmission. The average intensity of helminth infection is invariably measured by indirect means, such as faecal egg counts. These indirect measures are often a poor reflection of worm load, being subject to much variation due to sampling error and other factors. These problems are discussed more fully in Section VIII. For the time being we assume that indirect measures are simply a crude reflection of worm abundance.

We focus on the major helminths of man: the schistosome flukes, the intestinal nematodes (hookworms, *Ascaris, Trichuris*), and the filarial nematodes. Four general points emerge from a review of epidemiological survey data. (In this review we have concentrated on studies employing sample sizes greater than 500 people.)

1. A most remarkable feature is the comparative stability of helminth populations within human communities in the face of peturbations induced either by climatic factors or by human intervention. This is in part a consequence of the human hosts' inability to acquire strong immunity to reinfection, so that helminth infections are persistent in character with hosts being continually reinfected. A marked contrast exists between human helminths and human viral or bacterial infections: the latter invariably exhibit considerable fluctuations in prevalence through time. Some examples of helminth population stability are displayed in Fig. 1. These represent three different facets of the issue: the rate of return of helminth abundance to the precontrol level following intervention by chemotherapy, changes in age–prevalence curves over a 13-year period in one community, and changes in the overall prevalence of infection over a 7-year period.

This observed stability suggests that regulatory constraints on parasite population growth—induced by density-dependent checks on parasite survival, establishment, and fecundity—play an important role in the transmission dynamics of helminths within human communities. Such mechanisms may arise as a consequence of host responses to infection or as a result of resource limitation within the habitat of the parasite.

2. The major helminth parasites of man do not reproduce within the human host to directly increase adult worm population size but produce transmission stages which either pass to the exterior via the faeces or urine or leave the host via ingestion by a biting arthropod vector. As such, adult parasite population growth within an individual person is simply controlled by immigration and death processes. In the simplest case in which the immigration and death rates are constant and unaffected by factors such as host age or parasite density, the average burden of adult parasites

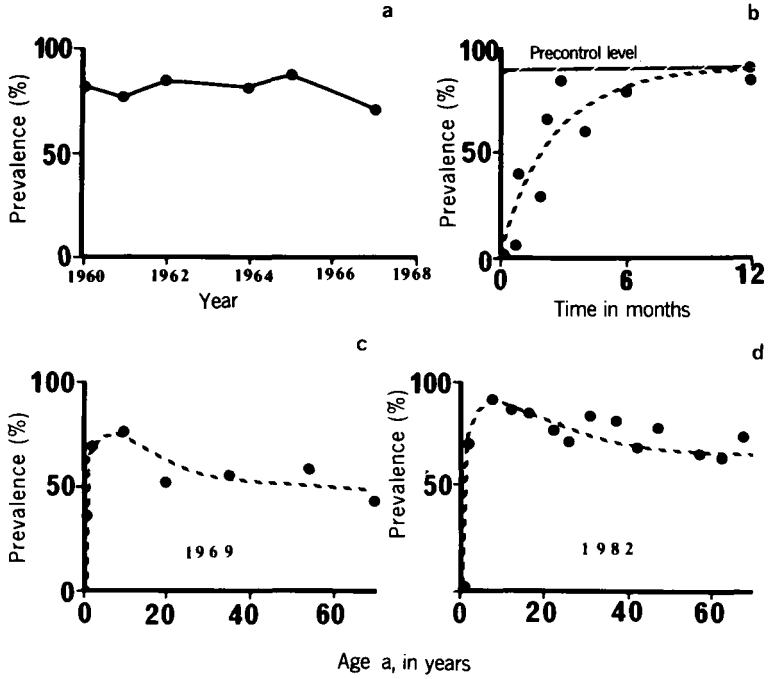

FIG. 1. Examples of long- and short-term changes in helminth abundance. (a) Changes in the overall prevalence of *Schistosoma haematobium* within a community in Iran over a 7-year period (data from Rosenfield *et al.*, 1977). (b) The rate of return of the prevalence of infection of *Ascaris lumbricoides* to its precontrol level following chemotherapy within a rural community in Iran (data from Croll *et al.*, 1982). (c) and (d) Age–prevalence data for *A. lumbricoides* infection in a rural community in Burma obtained from surveys carried out in 1969 (c) and 1982 (d) (data from Hliang *et al.*, 1983).

will grow monotonically as the human host ages to reach a plateau. The level of this plateau is simply determined by the rate of immigration per unit time multiplied by the average life expectancy of the adult worm. Thus, in the absence of any complications induced, for example, by host responses to infection, we might expect age–prevalence and age–intensity curves to reflect the basic qualitative properties of an immigration–death process as outlined above. This is partially the case as illustrated in Figs. 2–6. In general, prevalence increases initially as the human host ages to approach a maximum value. Thereafter a variety of trends are apparent, depending on the species of parasite, the geographical location, and the behaviour and habits of the human community. In certain instances, particularly noticeable among the patterns recorded for the intestinal nematodes (Figs. 2–4), the prevalence increases monotonically with age to a plateau in a manner entirely consistent with a simple immigration–death process. In other instances, as illustrated by the patterns re-

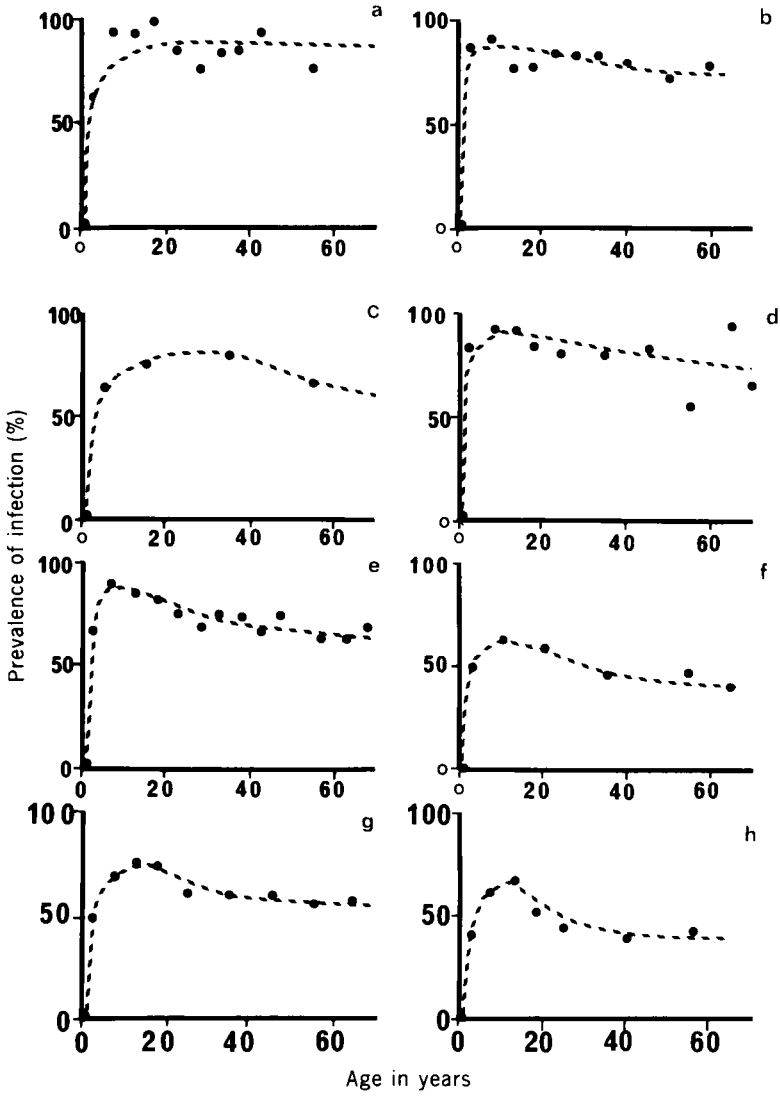

FIG. 2. Age–prevalence curves for *Ascaris lumbricoides*. (a) Iran (data from Croll *et al.*, 1982). (b) Philippines (Palo, inland districts) (Pesigan *et al.*, 1958). (c) Java (Cross *et al.*, 1970). (d) Philippines (Cabera *et al.*, 1975). (e) Burma (Hliang *et al.*, 1983). (f) Latin America (Botero, 1975). (g) Sri Lanka (Fernando and Balasuriya, 1976). (h) Bangladesh (Hossain *et al.*, 1981).

corded for the schistosome flukes and filarial worms (Figs. 5 and 6), prevalence declines after the attainment of a maximum value as people move into the older age classes. These trends may reflect any combination of a variety of processes including age-dependent contact with infec-

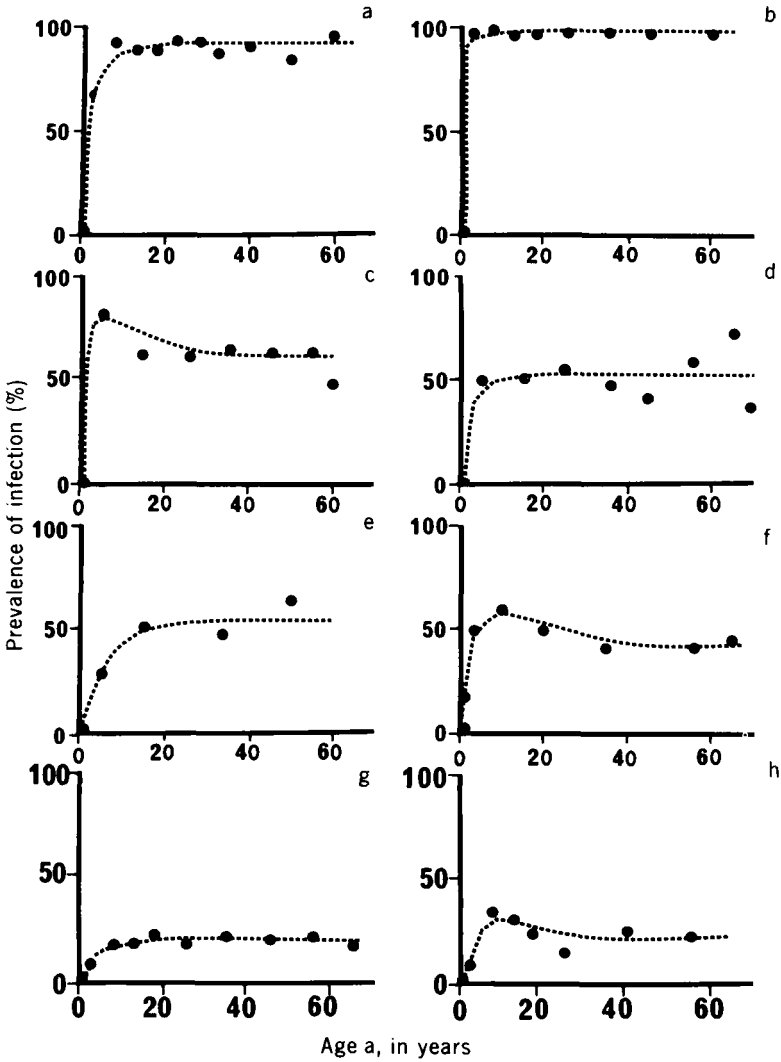

FIG. 3. Age–prevalence curves for *Trichuris trichiura*. (a) Philippines (Palo, coastal regions) (Pesigan *et al.*, 1958). (b) Philippines (Lewert *et al.*, 1979). (c) Singapore (Schacher and Danaraj, 1960). (d) Malaysia (Khan and Anuar, 1977). (e) Philippines (Cross *et al.*, 1970). (f) Latin America (Botero, 1975). (g) Sri Lanka (Fernando and Balasuriya, 1976). (h) Bangladesh (Hossain *et al.*, 1981).

tive stages, host responses whose severities increase with age as a consequence of repeated exposure to infection (acting on either parasite establishment or survival or both), age-dependent human mortality dependent on experience of parasitic infection, and age-related changes in

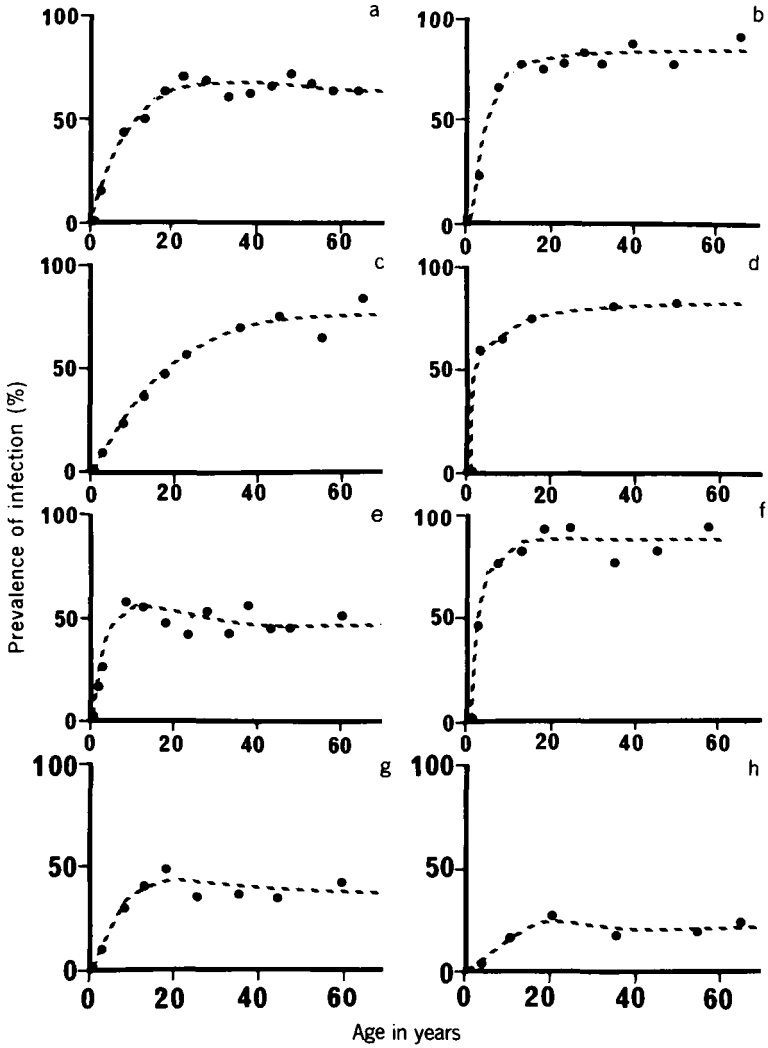

FIG. 4. Age–prevalence curves for hookworm (*Ancylostoma duodenale* and *Necator americanus*). (a) Taiwan (Hsieh, 1970). (b) Philippines (Palo, inland districts) (Pesigan *et al.*, 1958). (c) Sri Lanka (Fernando and Balasuriya, 1976). (d) India (Chandler, 1927). (e) Zambia (Wenlock, 1978). (f) India (Chowdhury and Schiller, 1968). (g) Philippines (Lewart *et al.*, 1978). (h) Thailand (Papasarathorn *et al.*, 1967).

the degree of parasite aggregation within the human community. There has been a tendency among epidemiologists to favour explanations based on partial acquired immunity to infection, but increasingly in recent work there are strong indications that age-related changes in contact with infec-

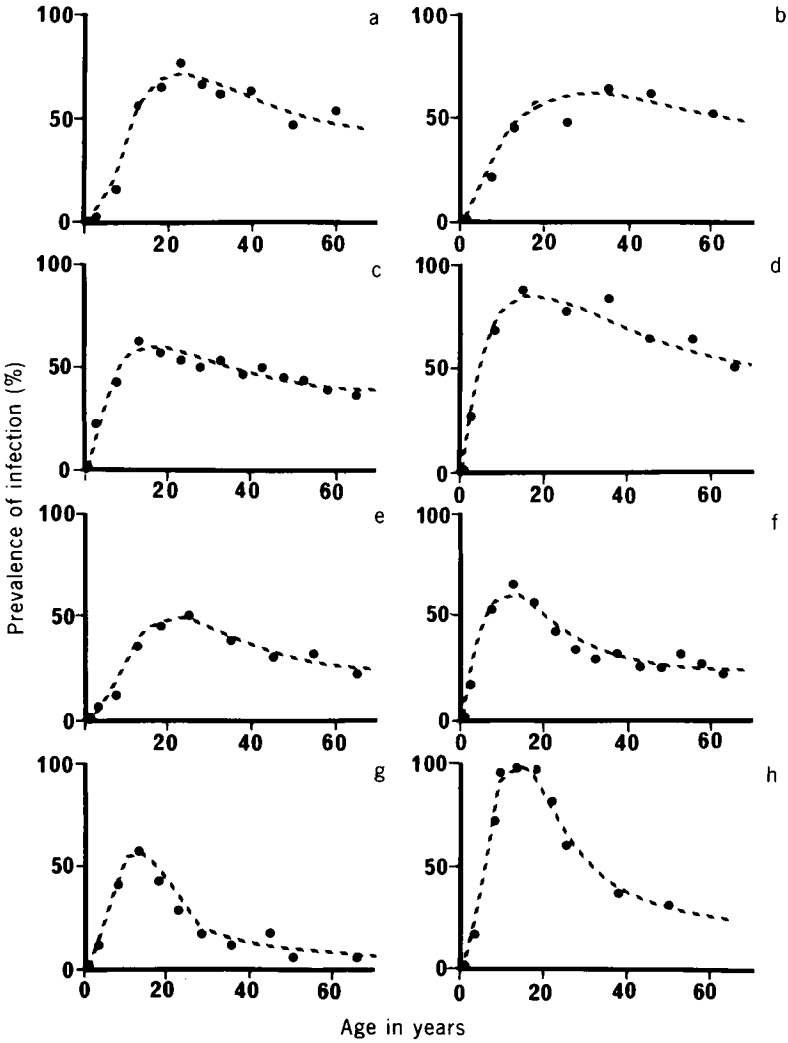

FIG. 5. Age–prevalence curves for schistosome infections (*Schistosoma mansoni, S. haematobium,* and *S. japonicum*). (a) Philippines (Palo, coastal region) (Pesigan *et al.*, 1958). (b) Philippines (Lewert *et al.*, 1979). (c) Philippines (Hairston, 1965). (d) Egypt (Abdel-Salam and Abdel-Fattah, 1977). (e) St. Lucia (Cook *et al.*, 1977). (f) Kenya (Hairston, 1965). (g) Egypt (Mansour *et al.*, 1981). (h) Gambia (Wilkins, 1977).

tive stages play a dominant role (Warren *et al.*, 1978). These issues are discussed more fully in Section VIII. Perhaps the most striking feature of the patterns displayed in Figs. 2–6 is the rapid rise in prevalence during early childhood and the teens.

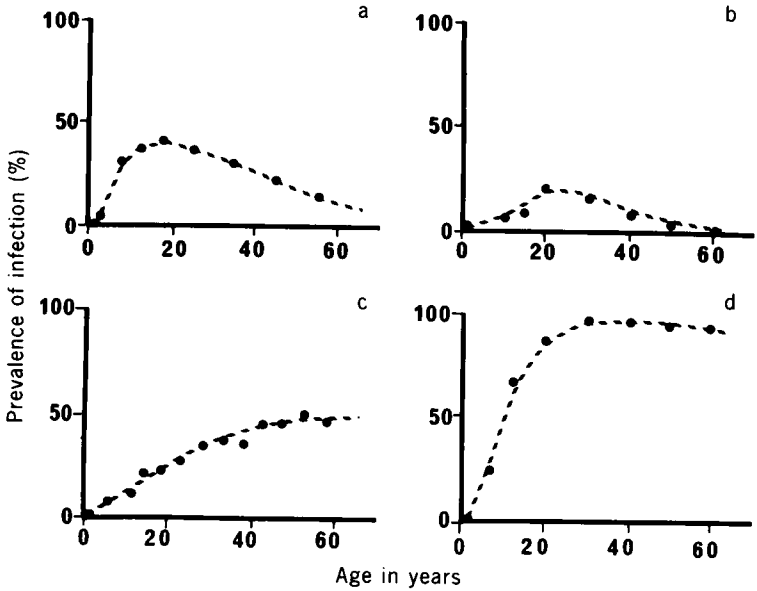

FIG. 6. Age–prevalence curves for filarial infections (*Dracunculus medinensis, Wuchereria bancrofti, Onchocerca volvulus*). (a) Ghana (Lyons, 1972). (b) Nigeria (Nwosu *et al.*, 1982). (c) American Samoa (Hairston and Jackowski, 1968). (d) Mali (Rougemont *et al.*, 1976).

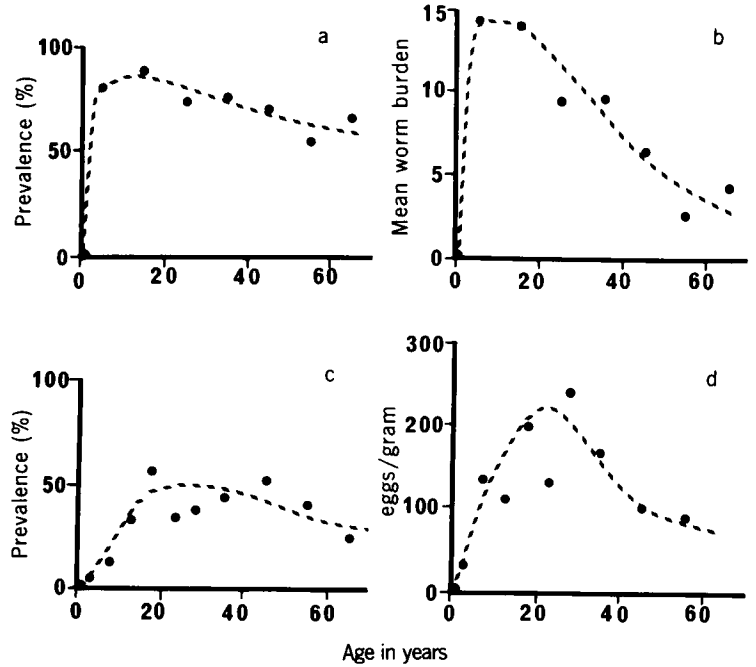

FIG. 7. Examples of differential changes in prevalence and intensity of infection with human age. (a) and (b) *A. lumbricoides* in Burma (data from Hliang *et al.*, 1982). (c) and (d) *S. japonicum* in the Philippines (data from Domingo *et al.*, 1980).

3. Where age–prevalence and age–intensity data are available for a given human community, the decline in intensity following attainment of its maximum level is invariably more rapid in the older age classes than is the associated decline in prevalence (Figs. 7–9). Such patterns have been interpreted as evidence for the existence of acquired responses to parasitic invasion. They are, however, to be expected in the absence of host responses, provided the distribution of parasite numbers within the human community is highly aggregated. In epidemiological work it must always be remembered that measures such as prevalence and average intensity are but two statistics of the probability distribution of worm numbers per person. The relationship between prevalence and intensity is determined by the form of this distribution (Fig. 10). From Fig. 10 it can be seen that quite large decreases in intensity may be associated with

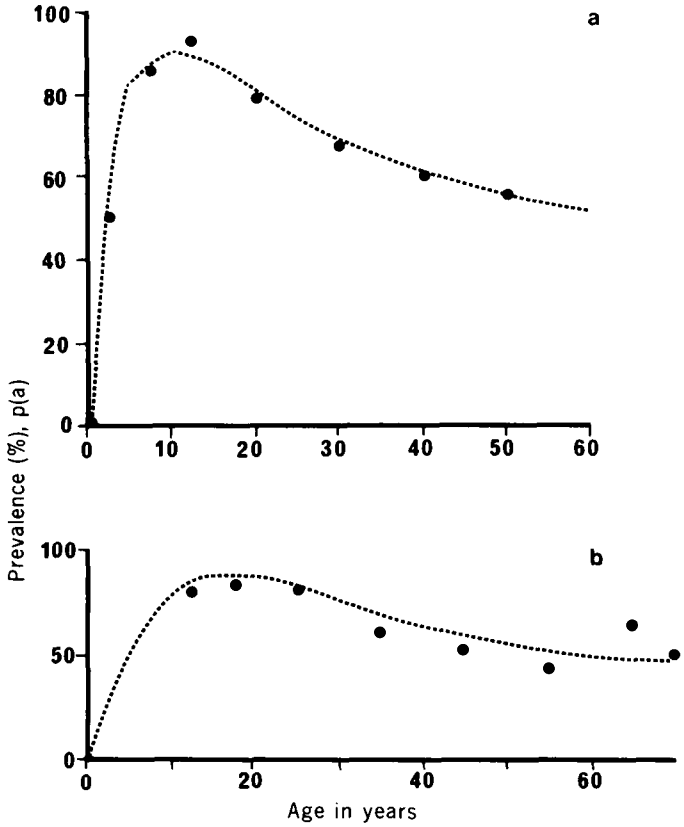

FIG. 8. Changes in prevalence with age of (a) *S. haematobium* in Ghana (data from Scott *et al.*, 1982) and (b) *S. mansoni* in Brazil (data from Cheever *et al.*, 1977).

modest declines in prevalence, if the parasites are highly overdispersed within the host population (small value of k). This theme is also expounded more fully at a latter stage (Section VIII).

4. The distribution of worm numbers per person is usually extremely aggregated in character, in which the majority of worms are harboured by a few individuals (and the majority of people harbour few worms). Two such patterns are recorded in Figs. 11 and 12. These clumped or aggregated distributions are of considerable importance both in understanding the transmission dynamics of the parasite and in the implementation of control policies.

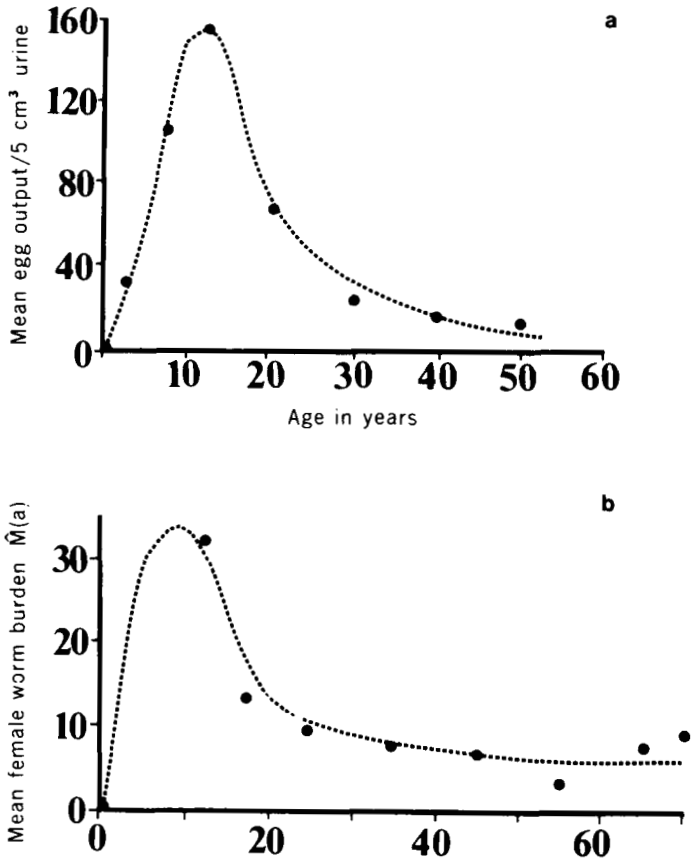

FIG. 9. Changes in intensity with age of (a) *S. haematobium* in Ghana and (b) *S. mansoni* in Brazil. To be compared with the associated changes in prevalence recorded in Fig. 8 (data sources as recorded in the legend to Fig. 8).

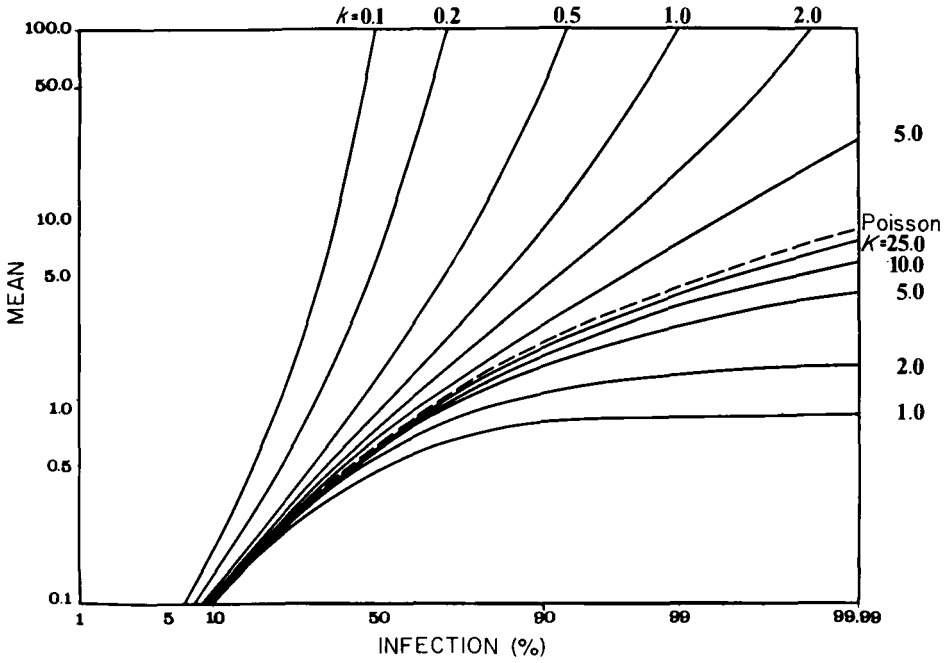

FIG. 10. Relationships between the mean worm burden per host and the prevalence of infection for three probability distributions of worm numbers per host: the positive binomial (K), the Poisson, and the negative binomial (k). Note that for high degrees of worm aggregation (measured inversely by k) large changes in mean worm burden induce only relatively small changes in prevalence.

III. SOME HISTORY

In a seminal paper published in 1934, Kostitzin developed a mathematical model of host–parasite interactions which explicitly described the distribution of parasite numbers within the host population (Kostitzin, 1934). His treatment was essentially deterministic, consisting of an infinite series of differential equations to describe changes in the densities of hosts harbouring any specified number of parasites. He recognized both the importance of the many population processes involved in the interaction between host and parasite in determining the form of this distribution, and also the significance of the distribution to the dynamics of the population association. He also stressed the difficulties inherent in drawing biological conclusions, concerning the dominant population processes influencing the interaction, from observations on the form or pattern of parasite distributions. These themes have since been reechoed many times (e.g., Bartlett, 1960; Crofton, 1971a; Anderson, 1974; May, 1977b; Anderson

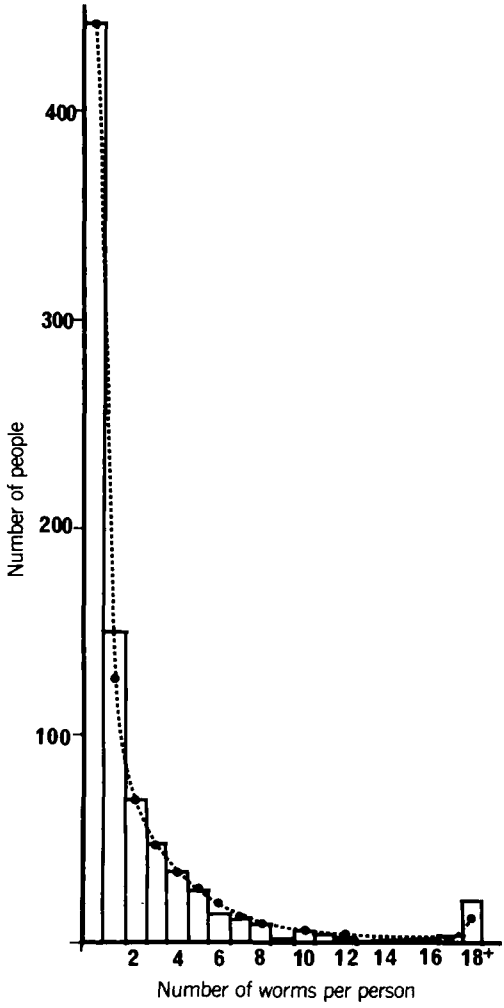

FIG. 11. Frequency distribution of *Ascaris lumbricoides* in a rural community in Korea (data from Seo *et al.*, 1979). The histogram bars are observed values and the dashed line denotes the predictions of the negative binomial model. Parameter values: mean = 2.18 worms, k = 0.32, sample size = 853 people, prevalence = 52%.

and Gordon, 1982). Kostitzin's major contribution to the study of parasitism was simply his recognition that the classical epidemic models (developed by Hamer, 1906; Ross, 1911, 1915; Lotka, 1923; Kermack and McKendrick, 1927; Soper, 1929) were inappropriate descriptions of the dynamics of associations in which the pathology induced by parasitic infection, the fecundity and mortality of the parasites, and the host re-

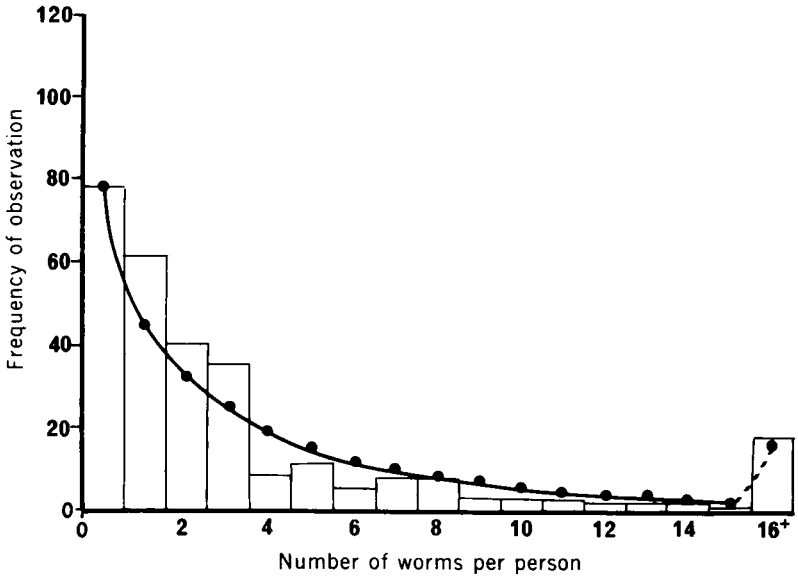

FIG. 12. Frequency distribution of *Wuchereria bancrofti* in Samoa (data from Hairston and Jackowski, 1968). The histogram bars are estimates of female worm burden frequencies (in males 15 years and older) and the dashed line denotes the predictions of the negative binomial model. Parameter values: mean = 4.1, k = 0.67, sample size = 292, prevalence = 73%.

sponses generated by infection all typically depend on the number and burden of parasites harbored by the host.

Subsequent to Kostitzin's work, interest in mathematical models of helminth parasite populations was not rekindled until the early 1960s. The stimulus for further developments was provided by parasites of medical and veterinary significance, in particular the human schistosome parasites with their indirect (two-host) life cycles involving man and an aquatic mollusk.

IV. SCHISTOSOME MODELS

The ecologist Hairston first aroused interest in the population biology of schistosome parasites by his attempts to employ life table or actuarial methods to study their dynamics within human communities (Hairston, 1962, 1965a). He focused attention on the numerous population processes, arising in the two-host life cycle, which contribute to the overall reproductive success of the parasite. He argued that this overall measure of transmission determines the observed patterns of helminth intensity

and prevalence within human communities. He therefore introduced the idea that the numerical magnitudes of the many transmission, mortality, and reproductive rates involved in the parasite's life cycle could be combined in a single composite measure of reproductive success. Today we refer to this measure as the *basic reproductive rate*, R_0, and define it as the average number of female offspring (in the case of a dioecious species) produced by one adult female parasite that attain reproductive maturity in the absence of constraints on population growth (see Anderson, 1982a; Anderson and May, 1982a). Hairston's idea is clearly based on Fisher's concept of net reproductive success (Fisher, 1930). The notion of a basic reproductive rate, however, is of great importance today in the study of helminth epidemiology and disease control.

Hairston also introduced a further technique, the use of Muench's so-called *catalytic models* to estimate rates of parasite transmission within human or intermediate host populations, from observations recording the change in parasite prevalence (the proportion or percentage of the population infected) with host age (Muench, 1959; Hairston, 1965b). Prior to Hairston's work these models had only been employed in the study of viral and bacterial infections.

An epidemiologist, George Macdonald, celebrated for his important work in extending the early mathematical studies by Ross (1915) and Lotka (1923) on the dynamics of human malarial infections to encompass greater biological realism, was also thinking along similar lines to Hairston. In 1965 Macdonald published a seminal paper on the dynamics of schistosome infections within humans and snail populations and proposed a simple model to further understanding of the epidemiology and control of schistosomiasis. The mathematical details of Macdonald's model are vague in the original publication but this does not detract from the originality of his approach. The most important advance made by Macdonald was his formal treatment of the mating success of dioecious helminths and the recognition of its significance to the parasites' transmission dynamics. Macdonald suggested that a breakpoint in transmission occurred when the average worm burden per host fell below a critical level which was necessary to ensure sufficient mating success for parasite transmission and hence maintenance within the host community. He also argued that combinations of population parameters determined transmission success from man to snail and snail to man. The basic reproductive rate of the parasite is the composite measure of the magnitudes of transmission via both pathways. By the nature of its definition the value of the basic reproductive rate R_0 must exceed unity if the parasite is to persist, and hence the point $R_0 = 1$ defines a *transmission threshold.*

Shortly after the publication of Macdonald's paper, Tallis and Leyton (1966) and then Leyton (1968) developed stochastic models to describe

the dynamics of dioecious helminth populations with their definitive hosts. These authors, who were unaware of Macdonald's work, provided a layer of formalism to the treatment of mating probabilities and, more importantly, demonstrated that aggregated distributions of parasite numbers per host could be generated by heterogeneity in exposure to infection within the host population. Contagion arises as a consequence of the compounding of a series of Poisson processes (with different means) generated by the infection and mortality processes controlling parasite population growth within individual hosts.

The papers of Hairston (1962, 1965a), Macdonald (1965), Tallis and Leyton (1966), and Leyton (1968) stimulated much interest in models of schistosome dynamics during the 1970s. In chronological order the principal papers are by Nåsell and Hirsch (1972, 1973), Lewis (1975a), Nåsell (1976a,b, 1977), May (1977a), Cohen (1977), Fine and Lehman (1977), Barbour (1978), Goddard (1978), Bradley and May (1978), and Anderson and May (1979a).

We attempt to summarize the main themes of this work by reference to a general deterministic model whose structure (broadly speaking) underpins most of the published models. Differences exist between published models, both in structure and method of analysis, but these are, in general, of minor significance with respect to the biological conclusions that emerge from investigations of their properties.

The general structure of the model is captured by the flow chart displayed in Fig. 13, which denotes the principal populations (both of parasites and hosts) involved in the parasite's life cycle. We denote the mean number of worms per human host, the number of miracidia, the numbers of susceptible, infected but latent, and shedding snails, and the number of cercaria, respectively, by the following time-dependent variables: $M(t)$, $L_1(t)$, $X(t)$, $Z(t)$, $Y(t)$, and $L_2(t)$. We assume that the human and snail populations are constant in size and let $x(t)$, $z(t)$, and $y(t)$ denote the proportions of snails in the susceptible, latent, and shedding classes. The assumption of constant host population size is not universal in published models of schistosome dynamics. Certain authors assume that the host population (either human or snail or both) are subject to immigration–death processes (see Nåssell, 1976a; Lewis, 1975a) but such refinements make little difference to the qualitative dynamics of parasite transmission.

A system of differential equations can be formulated to describe temporal changes in the population variables. These are as follows:

$$dM/dt = \beta_1 L_2 - \mu_1 M \tag{1}$$

$$dL/dt = \tfrac{1}{2}\lambda_1 M N_1 \Phi - \mu_2 L_1 - \beta_2 N_2 L_1 \tag{2}$$

$$dx/dt = \mu_3(x + z) + \mu_4 y - \beta_2 x L_1 - \mu_3 z \tag{3}$$

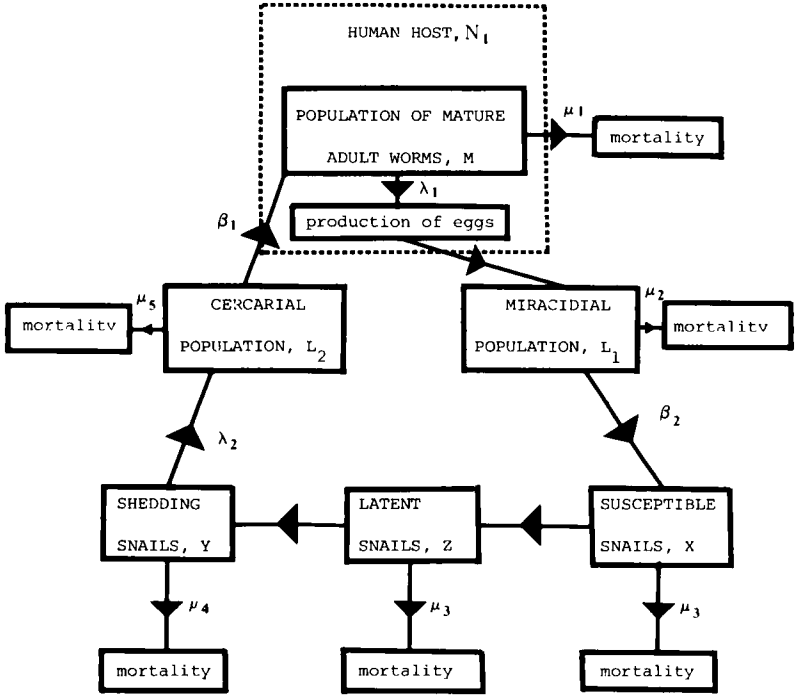

FIG. 13. Diagrammatic flow chart of the principal host and parasite populations involved in the life cycle of human schistosomes. The rate parameters and processes controlling the flow of parasites via the life cycle are also depicted.

$$dz/dt = \beta_1 x L_1 - (\sigma - \mu_3)z \tag{4}$$

$$dy/dt = \sigma z - \mu_4 y \tag{5}$$

$$dL_2/dt = \lambda_2 y N_2 - \mu_5 L_2 - \beta_1 N_1 L_2 \tag{6}$$

It is here assumed that the total human population and the total snail population are of constant sizes, denoted by N_1 and N_2, respectively. It is further assumed that for Eqs. (3), (4), (5), representing changes in the proportions of susceptible (uninfected), latent, and shedding snails, new births into the uninfected class (x) exactly balance deaths from all three classes. A summary of the symbols used to represent various parameters in the model is presented in Table 1. Several assumptions, however, require further clarification.

1. The function Φ represents the probability that a female worm is mated, and is dependent on the sexual habits of the parasite (i.e., whether it is monogamous or polygamous, etc.), the average worm load, and the

TABLE 1
Population variables and parameters of the basic schistosome model

	Interpretation
Population variables	
N_1	Density of the human host
N_2	Density of the snail intermediate host
M	Mean worm burden per human host
L_1	Density of miracidia in the aquatic habitat of the snail intermediate host
L_2	Density of cercariae in the acquatic habitat of the snail host
x	Proportion of uninfected snails in the population
z	Proportion of infected snails not yet shedding cercariae (latent infections)
y	Proportion of shedding snails
Parameters	
β_1	Transmission coefficient denoting the per capita rate of human infection per cercaria per unit of time
β_2	Transmission coefficient denoting the per capita rate of snail infection per miracidia per unit of time
λ_1	Per capita rate of egg production by female worms
λ_2	Per capita rate of cercarial production per shedding snail
μ_1	Per capita death rate of mature worms in man ($1/\mu_1$ = life expectancy)
μ_2	Per capita death rate of miracidia ($1/\mu_2$ = life expectancy)
μ_3	Per capita death rate of uninfected and latent snails ($1/\mu_3$ = life expectancy)
μ_4	Per capita death rate of shedding snails ($1/\mu_4$ = life expectancy)
μ_5	Per capita death rate of cercaria ($1/\mu_5$ = life expectancy)
σ	Per capita rate at which latent snails join the shedding class where $\tau = 1/\sigma$ is the latent period
Φ	The mating probability function denoting the probability that a female worm is fertilized and producing viable ova; a function of the distribution of worm numbers per human host

distribution of parasite numbers per host. In his original paper Macdonald assumed that the worms were randomly distributed (Poisson) within the host population (Macdonald, 1965). This assumption has been adopted in many subsequent models (see Nåssell and Hirsch, 1973). Empirical evidence, however, suggests that the worms are aggregated in their distribution and May (1977a) and Bradley and May (1978) have encorporated this added realism into the framework of schistosome models. Table 2 lists the structures of the mating probability function Φ for various assumptions concerning the distribution of worm numbers per host and the sexual habits of the parasite (May, 1977a). Given that the function Φ is depen-

TABLE 2
The mating function Φ[a]

Sexual behavior	Mating function
Hermaphroditic, self-fertilization possible	$\Phi = 1$
Dioecious, worms monogamous (males and females distributed together)	
Random distribution	$\Phi(M) = 1 - \frac{e^{-M}}{2\pi}\int_0^{2\pi}(1 - \cos\theta)e^{-M\cos\theta}d\theta$
Negative binomial distribution	$\Phi(M, k) = 1 - \frac{(1-\alpha)}{2\pi}\int_0^{2\pi}\frac{(1-\cos\theta)}{1+\cos\theta}d\theta$ where $\alpha = M/(k + M)$
Dioecious, worms polygamous (males and females distributed together)	
Random distribution	$\Phi(M) = 1 - e^{-M/Z}$
Negative binomial distribution	$\Phi(M, k) = 1 - (1 + M/2k)^{-(k+1)}$

[a] See May (1977a).

dent on the probability distribution of worm numbers, the model defined by Eqs. (1)–(6) is essentially hybrid in structure containing stochastic and deterministic elements. The term $\frac{1}{2}$ appears in Eq. (2) as a consequence of the assumption that the ratio of male to female worms in man is 1 : 1 (only female worms produce eggs).

2. The equations for changes in x, z, y take no account of multiple miracidial infection of snails. This component of the model is based on a prevalence framework, since the parasite undergoes rapid asexual multiplication within the snail host. Empirical evidence suggests that multiple miracidial infections do not increase cercarial output over that arising from a single infection (Jordan and Webbe, 1969; Chu *et al.*, 1966). It is important to note that this assumption serves as a severe form of density dependence acting to regulate parasite transmission via the life cycle (i.e., the rate of cercarial production per infected snail, λ_4, is assumed to be independent of the number of miracidia penetrating the host).

3. The latent period during which snails are infected but not yet shedding cercariae is captured in Eqs. (3)–(5) by a constant exponential decay from the latent to the shedding class (the average duration of stay in the latent class is given by $1/\sigma$).

This rather crude approximation can be amended by the inclusion of a

formal time delay of length τ such that Eqs. (4) and (5) become

$$dZ/dt = \beta_1 X(t) N_2 L_1(t) - \mu_3 Z(t) - \beta_1 X(t-\tau) N_2 L_1(t-\tau) \exp(-\mu_3 \tau) \quad (7)$$

$$dY/dt = \beta_1 X(t-\tau) N_2 L_1(t-\tau) \exp(-\mu_3 \tau) - \mu_4 Y(t) \quad (8)$$

As shown by May (1977a), however, this modification is of little consequence to the qualitative properties of the model given the short duration of the time delay τ (roughly 30–35 days for *Schistosoma mansoni*; see Anderson and May (1979a), relative to the life expectancy $1/\mu_1$ of the adult worms (years as opposed to weeks).

4. The transmission terms representing parasite passage between man and snail, and snail and man ($\beta_1 X N_2 L_1$, $\beta_1 N_1 L_2$, respectively) assume that the net rate of transmission in both cases is directly proportional to the density of infective stages (either miracidia or cercaria) times the density of hosts (either snails or man). In general, experimental evidence gained from laboratory studies supports this assumption (see Anderson, 1978, 1982b).

5. Note that the death rates of uninfected and latent snails (μ_3) are assumed to be identical. The available empirical evidence supports this assumption and further suggests that the death rate (μ_4) of shedding snails is much greater than μ_3 (see Anderson and May, 1979a).

As indicated in point 3 above, the relative times spent by the parasite (or infected host) in the different stages of the life cycle are of considerable importance to the analysis of model behavior. A rough guide to these time scales, for *Schistosoma mansoni* in man and *Biomphalaria glabrata*, are detailed in Table 3 by reference to the expected life spans of each developmental stage. The life spans of the two infective stages, the mira-

TABLE 3
Life expectancy characteristics of the population biology of Schistosoma mansoni *in man and* Biomphalaria glabrata[a]

Host and parasite life cycle stages	Life expectancy
Man	40–60 years
Adult parasite in man	3–4 years
Biomphalaria glabrata (infected snails)	3–6 weeks
Cercarial stage	8–20 hours
Miracidial stage	4–16 hours

[a] Data from Anderson and May (1979b, 1982a) and Anderson *et al.* (1982).

cidia and cercaria, are extremely short, being a matter of hours. In such circumstances we may effectively take the densities of the two stages as being instantaneously adjusted to their stationary or equilibrium values ($dL_1/dt = dL_2/dt = 0$). In this manner, Eqs. (1)–(6) may be collapsed to form three equations to represent changes in the epidemiological variables of principal interest, namely the mean worm burden per host, M, the prevalence of latent snails, z, and the prevalence of shedding snails, y. The mean worm load per person is in dynamic balance between forces of infection (transmission) and worm death.

$$dM/dt = \mu_1(T_1 Y - M) \tag{9}$$

The parameter μ_1 is the death rate for mature schistosomes (life expectancy $= 1/\mu$) and T_1 is the quantity, defined by Nåsell and Hirsch (1973) and May (1977a), which characterizes the transmission of parasites from *snail to man*. Specifically, $T_1 = N_2\lambda_2\beta_1/[\mu_1(\mu_5 + \beta_1 N_1)]$ with λ_2 the rate of cercarial shedding per infected snail, $\beta_1/(\mu_5 + \beta_1 N_1)$ the probability for a cercaria to infect a given human, and N_2 the snail density. Note that implicit in Eq. (9) is the assumption that human hosts do not exhibit immune responses or other density-dependent effects which would tend to increase the worm death rate as mean density rises (or decrease the rate of egg production).

Similarly, z is in balance between forces of infection and snail death:

$$dz/dt = \frac{\mu_4(\mu_3 + \sigma)}{\sigma}\left[T_2 M\Phi x - \frac{\sigma}{\mu_4} z\right] \tag{10}$$

The equation for y remains

$$dy/dt = \sigma z - \mu_4 y \tag{11}$$

In Eq. (10) the term T_2 represents the transmission of parasites from *man to snail* where

$$T_2 = \lambda_1 N_1 \beta_2 \sigma/[(\mu_3 + \sigma)(\mu_2 + \beta_2 N_2)\mu_4]$$

Here λ_1 is the rate of egg laying per mated female, N_1 is human density, $\beta_2/(\mu_2 + \beta_2 N_2)$ is the probability for an egg to produce a miracidium which infects a susceptible snail, $\sigma/(\mu_3 + \sigma)$ is the proportion of latent snails that survive to shed cercariae, and μ_4 is the death rate of the shedding snails.

Given that $x + y + z = 1$, we can express Eqs. (10) and (11) in terms of the three dynamic variables $M(t)$, $y(t)$, and $z(t)$. This in conjunction with Eq. (9) gives a set of three coupled, first-order differential equations. These three equations [Eqs. (9)–(11)] reflect the essential details of most of the published models of schistosome dynamics (see May, 1977a). Various refinements to this framework have been made and before outlining

the general dynamic properties of the basic hybrid model, we briefly summarize the most important of these.

Latency in snail infections has received considerable attention (Lee and Lewis, 1976; Lewis, 1975a,b; Nåsell, 1976a; May, 1977a) and the inclusion of a formal time delay τ between infection and snails shedding cercariae generates the following equations for z and y.

$$dz/dt = hz(t) - hx(t - \tau)f - \mu_3 z(t) \tag{12}$$

$$dy/dt = hx(t - \tau)f - \mu_4 y(t) \tag{13}$$

where $h = \frac{1}{2}\beta_2\lambda_1 M N_1 \Phi/(\mu_2 + \beta_2 N_2)$ and $f = \exp(-\mu_3\tau)$.

A formal discussion of this refinement is given by May (1977a), with the general conclusion that it adds little to the dynamic properties of the basic model [Eqs. (9)–(11)] due to the short duration of the time delay τ, relative to the life expectancy of the adult worm in man ($1/\mu_1$).

Various attempts have been made to construct fully stochastic models of the transmission dynamics of the parasite (e.g., Nåsell and Hirsch, 1973; Lewis, 1975a). Such studies, however, invariably suggest that the stationary distribution of worms per human host is approximately Poisson in form as a consequence of the immigration–death processes controlling adult worm abundance, combined with the assumption that each host is equally susceptible to infection. Empirical evidence does not support this view and, as shown by May (1977a), the more realistic assumption of an aggregated distribution of worm numbers substantially alters the quantitative conclusions arising from the study of such models. Hybrid models, in which the probability distributions of the population variables are replaced by expected values, are more amenable to analytical treatment but most studies have falsely assumed that the worms are randomly distributed within the human community.

Heterogeneity in exposure to infection within the human population has been considered within a deterministic framework by Barbour (1978, 1982). Some interesting results emerge from his model which considers a human community with varying degrees of contact with, and access to, a series of infected water bodies. If contact with infection is heterogeneous the total parasite population is more stable to changes in the underlying population parameters which control transmission, when compared with a homogeneous situation: a further confirmation of the ecological principle that heterogeneity is stabilizing.

The topic of acquired immunity to reinfection within the human host has received little attention (Barbour, 1978). This is understandable, given the current biological controversy concerning the relative importance of acquired immunity, versus age-related changes in contact with infection, as determinants of convex age–prevalence curves in human communities (Warren, 1973; Anderson and May, 1982a).

A. DYNAMIC PROPERTIES OF THE BASIC SCHISTOSOME MODEL

The general properties of the basic model [Eqs. (9)–(11)] have been extensively discussed by May (1977a) and others. We here present a brief summary of these properties, concentrating on the major biological conclusions that emerge from model analysis. The variable of major interest is M, the mean worm burden per human host. It is clear from Eqs. (9) and (10) that the characteristic dynamical response times of $M(t)$ and $y(t)$ are $1/\mu_1$ and $1/\mu_4$, respectively. As indicated in Table 3 $\mu_1 << \mu_4$ and hence it follows that $y(t)$ has a much faster response time than $M(t)$. We may therefore take the fraction of shedding snails as being instantaneously adjusted to the stationary value, y^*, and reduce the basic model to a single dynamic equation for the variable $M(t)$.

$$dM/dt = \mu_1 M \left(\frac{\frac{1}{2} T_1 T_2 \Phi}{\frac{1}{2} T_2 M \Phi (\sigma + \mu_4)/\sigma + 1} - 1 \right) \tag{14}$$

The approximation $\mu_4 >> \mu_1$ is implicit in the work of Macdonald (1965), Lee and Lewis (1976), and Barbour (1978).

An analytical solution of Eq. (14) for arbitrary Φ is not feasible, given the complexity of the mating function (see Table 2). The qualitative dynamic properties can, however, be explored. First, consider the case $\Phi = 1$. This corresponds to a high endemic average worm load per person such that the likelihood of any female worm being mated is essentially unity. In such circumstances a number of points emerge from Eq. (14). First note that $M^* = 0$ is one solution. Of more interest is the case:

$$M^* = (\tfrac{1}{2} T_1 T_2 \Phi - 1)/[\tfrac{1}{2} T_2 \Phi (\sigma + \mu_4)/\sigma] \tag{15}$$

For this state to be positive the following inequality must be satisfied:

$$\tfrac{1}{2} T_1 T_2 \Phi > 1 \tag{16}$$

The left-hand side of this inequality represents the basic reproductive rate, R_0, of the parasite (the average number of female offspring produced by one mature female worm that survive to attain reproductive maturity in the absence of density dependent constraints within populations of man and snails of densities N_1 and N_2, respectively). The quantity R_0 is simply formed from the product of the net rate of transmission from snail to man, T_1, times the rate of transmission from man to snail, T_2, modified by the factor $\frac{1}{2}\Phi$ which denotes the assumed 1 : 1 sex ratio of the adult worms (the quantity $\frac{1}{2}$) and the likelihood that a female worm is mated (Φ). For parasite persistence R_0 must be equal to, or exceed, unity in value. For this condition to be satisfied the product of snail density times human density, $N_1 N_2$, must be greater than a threshold value determined by a complex of parameter values. (This can be derived by setting $R_0 = 1$ and substituting for T_1 and T_2 by the combinations of parameter values they

represent.) The host density threshold, which plays such an important role in determining the dynamics of viral, bacterial, and protozoan disease, is therefore implicit in models of helminth dynamics. Its practical relevance is limited, however, since empirical evidence suggests that the majority of human helminth parasites can persist within a very low density host population (May and Anderson, 1979). This is in marked contrast to viral infections which tend to induce lasting immunity in those hosts that survive parasitic onslaught (Anderson and May, 1979b). These aspects will be discussed more fully in Section IX, which deals with disease control.

For $\Phi \neq 1$ (i.e., $0 < \Phi < 1$), the analysis is more complex although the general properties can be illustrated by phase plane analysis. First, it should be noted that schistosome parasites are thought to be monogamous (mating for life) and the appropriate functional form of Φ (dioecious, monogamous species distributed in a negative binomial manner) is listed in Table 2. We consider the isoclines of M on y for $dM/dt = dy/dt = dz/dt = 0$. Two general cases emerge.

In the first, when $R_0 < 1$, the two isoclines intersect only at the origin and all trajectories are attracted to $M = 0$, $y = 0$. In other words the infection cannot maintain itself and the point $R_0 = 1$ defines a transmission threshold for disease persistence (Fig. 14a). In the second (Fig. 14b), when $R_0 \geq 1$, there are three points of intersection of the isoclines corresponding to two stable points (at $M = 0$, and at $M = M_\mu$). Points (initial values of M and y) originating to the left of the dashed line which passes through M_μ are attracted to the origin. Points originating to the right of the dashed line are attracted to the point M^* at which the infection is maintained in a stable manner (a stable endemic infection). The dashed line in Fig. 14b divides the $y - M$ plane into the two points' respective domains of attraction. The point M_μ, the unstable state, is therefore often referred to as the "breakpoint," for if the average worm burden is lowered (say by chemotherapeutic treatment) below this point the infection will die out ($M^* = 0$). Macdonald (1965), on the basis of his assumption that the adult worms were randomly distributed within the host population, thought the breakpoint concept was of major importance to the design of control policies. More recent work by May (1977a) and Bradley and May (1978) suggests however, that, given the realistic assumption of worm aggregation, this is not necessarily true. As illustrated in Fig. 15, increasing degrees of worm aggregation result in the unstable boundary shifting toward the stable state of parasite extinction ($M^* = 0$). In the limit when all the worms are harboured by one host, all others being uninfected, the unstable state M_μ disappears.

A further conclusion drawn by Macdonald concerned the relative merits of changing the transmission parameters T_1 and T_2 in attempting to

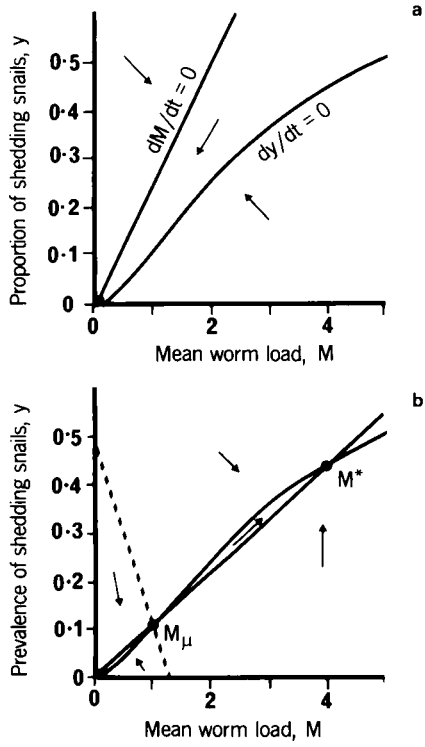

FIG. 14. Phase plane analysis of the basic schistosome model defined by Eqs. (9)–(11) (after May, 1977a). The arrows indicate how the dynamic trajectories of snail prevalence of infections $y(t)$ and mean worm load in man $M(t)$ behave in the various regions into which the $y - M$ plane is dissected by the isoclines $dy/dt = 0$ and $dM/dt = 0$. (a) corresponds to the situation in which $R_0 < 1$, when the infection cannot maintain itself and all trajectories are attracted to the origin (sexes distributed separately in a negative binomial manner with $k = 1$, $T_1 = 4$, and $T_2 = 1$). (b) corresponds to the situation in which $R_1 > 1$. There are two alternative stable states, one at M^* and one at the origin ($M^* = 0$), each with its own domain of attraction. The boundary between the two regions depends in part on the ratio μ_1/μ_4 (here taken to be 3); points to the left of the dashed line are attracted to the origin and points to the right to the state of stable endemic infection, M^*. Where $\mu_4 >> \mu_1$ (as is usually the case) this boundary becomes a vertical line through the unstable state M_μ, and we can speak of a "breakpoint" at a worm burden of M_μ.

reduce the net force of transmission below the threshold $R_0 = 1$. He concluded that the threshold condition is more sensitive to changes in T_1 (snails to man) than to changes in T_2 (man to snails). Hence his statement that "safe water supplies are more important than latrines." As discussed much more fully elsewhere (May, 1977a), Macdonald's conclusion tends to be true if T_1 is small; in this event the probability for a given host to harbour both a male and a female worm, and these to be able to continue

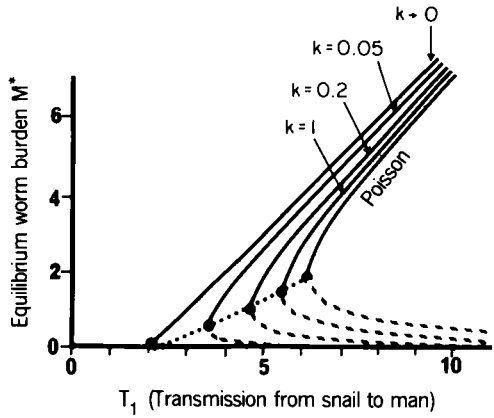

FIG. 15. The influence of worm aggregation as the value on the breakpoint burden M_μ. The equilibrium worm loads M^* are shown as a function of the transmission coefficient T_1 (snail to man) for T_2 (man to snail) fixed at a value of unity (after May, 1977a). The solid curved line to the far right is for a Poisson distribution of worms ($k \to \infty$). The dashed line denotes the breakpoint and the solid lines the states of stable endemic infection (M^*). To the left of the Poisson line are curves for various degrees of parasite aggregation as noted inversely by the value of the negative binomial parameter k. Note that as aggregation increases ($k \to 0$) the breakpoint phenomenon becomes less conspicuous, finally disappearing in the limit $k \to 0$ (essentially all worms harboured by one individual).

the cycle, is proportional to T_1^2, and thence R_0 varies roughly as $T_1^2 T_2$. But if T_1 is relatively large, as it is in most places where schistosomiasis is endemic, hosts possessing a worm of one sex tend to harbour one of the other sex (especially if worm aggregation is allowed for), and R_0 varies simply as $T_1 T_2$; in this circumstance, changes in T_1 are not more effective than changes in T_2. In short, although Macdonald's conclusions were valid for the limited range of transmission parameters he chose to explore in his numerical studies, these conclusions are not representative. As emphasized below, moreover, any evaluation of the relative efficacy of various control measures needs to account for economic and social factors as well as purely biological ones.

A final point of general interest concerns the significance of density-dependent constraints, perhaps induced by immunological responses, on model behavior. At present, the only regulatory constraint within the basic model is linked to the assumption that multiple miracidial infections do not increase cercarial output when compared with single infections. Worm death or reproduction rates dependent on worm burden will act to reduce the equilibrium worm load M^* and increase the stability of the system. This topic is discussed further in Section VIII, which considers a general age-structured model for the dynamics of human helminths.

Detailed comparisons between the predictions of schistosome models and observed patterns of disease prevalence and intensity in endemic regions of the world have unfortunately been of a very limited nature.

Rosenfield (1975) has employed statistical methods to fit empirical formula to data on prevalence and intensity within human and snail communities but the equations employed are not derived theoretically from a set of biological assumptions (for a detailed evaluation of the relation between Rosenfield's empirical model and those discussed above, see May, 1977a). The greatest attention has been given to observed changes in the prevalence of snail infection with age (Sturrock and Webbe, 1971; Cohen, 1973; Anderson and May, 1979b). This body of work is examined in the following section.

There is a clear need for more data-orientated mathematical studies in which the comparison of prediction with observation is a major priority. It is clear, for instance, from field studies of age-related changes in the prevalence and intensity (measured indirectly by faecal egg counts) within human communities that acquired immunity to reinfection, and age-dependent human contact with infection, are important determinants of overall transmission (Figs. 5, 8, and 9). The majority of epidemiological surveys show an initial increase in both prevalence and intensity with age, followed by a decline in the older age classes within the community (the decline in egg output is invariably more marked than that in prevalence) (Figs. 8 and 9). Simple deterministic models which do not include age structure fail to mirror these important general trends. A discussion of the modifications required to mirror such observations is given in Section VIII.

B. CATALYTIC MODELS OF AGE-RELATED CHANGES IN PREVALENCE

Simple deterministic models can be useful in mimicking trends in age–prevalence of infection and in providing a framework for parameter estimation. Such models are commonly called *catalytic models*, a title which derives from their development by Muench (1959) as an adaptation of equations employed to describe chemical reactions. They have been used to analyze age–prevalence curves of human schistosome infection (Hairston, 1965a), but inappropriately so given the underlying assumption of randomness in the distribution of worms within human communities. More commonly their application has been to the interpretation of age-related changes in snail prevalence (Sturrock and Webbe, 1971; Cohen, 1973; Sturrock *et al.*, 1975; Barbour, 1978; May, 1977a; Anderson and May, 1979b; Coutinho *et al.*, 1981). In this section we summarize the main themes of this work by reference to an age–prevalence model which incorporates details of differential mortality between infected and unin-

fected snails, latency in snail infection, and recovery from infection (May, 1977a; Anderson and May, 1979).

Consider a cohort of newly born snails, numbering N at time $t = 0$, all of which are assumed to be uninfected. The members of this cohort will progress through a sequence of categories at rates dependent on a force of infection λ, the duration of snail latency τ (period from infection to start of cercarial shedding), and the rate of loss of infection b. These categories are uninfected snails, infected snails not releasing cercariae, shedding snails, and recovered snails denoted respectively as $X(t)$, $Z(t)$, $Y(t)$, $W(t)$ at time t. The force of infection λ, in terms of the basic schistosome model detailed in the preceding section [Eqs. (9)–(11)], is simply

$$\lambda = \tfrac{1}{2}\beta_2\lambda_1 M N_1 \Phi/(\mu_2 + \beta_2 N_2) \tag{17}$$

The notation is as presented in Table 1. The parameter λ is taken to be constant and independent of snail age and time, which implies that the system is at a stable equilibrium state with M^* worms per human host. As before, μ_3 is the death rate of infected snails, while b is defined as the instantaneous rate of recovery from infection. This notation can be employed to describe changes in $X(t)$, $Z(t)$, $Y(t)$, $W(t)$ with respect to time (which here means age) by means of four coupled, first-order differential equations.

$$dX/dt = -(\lambda + \mu_3)X \tag{18}$$

$$dZ/dt = \lambda X - \mu_3 Z - X(t - \tau)\exp(-\mu_3\tau)\Theta(t - \tau) \tag{19}$$

$$dY/dt = \lambda X(t - \tau)\exp(-\mu_3\tau)\Theta(t - \tau) - \mu_4 Y - bY \tag{20}$$

$$dW/dt = bY - \mu_3 W \tag{21}$$

Here $\Theta(u)$ is a step function such that $\Theta(u) = 1$ if $u > 0$ and $\Theta(u) = 0$ if $u < 0$. The variables X, Z, W, and Y have the initial values $X(0) = N$, $Z(0) = W(0) = Y(0) = 0$. At age t, the prevalence of infection, $y(t)$, defined as the proportion of that age class releasing cercariae, is given by

$$y(t) = Y(t)/[X(t) + Y(t) + Z(t) + W(t)] \tag{22}$$

In some field studies, the proportion of infected snails within an age or size class is estimated by examining squashed snails for the presence of larval parasites. In such circumstances the prevalence of infected snails $y(t)$ is

$$y(t) = [Y(t) + Z(t)]/[Y(t) + Z(t) + Y(t) + W(t)] \tag{23}$$

Prevalence data based on cercarial release techniques underestimate the proportion of infected snails (latent plus shedding hosts) by a factor d where

$$d = 1 + [\exp(\mu_3\tau) - 1](\mu_4/\mu_3) \quad (24)$$

(Anderson and May, 1979b; Barbour, 1978).

The age–prevalence model defined by Eqs. (18)–(21) possesses an exact analytical solution where

$$X(t) = Ne^{-(\lambda + \mu_3)t} \quad (25)$$

$$Z(t < \tau) = Ne^{-\mu_3 t}(1 - e^{-\lambda t}) \quad (26)$$

$$Z(t > \tau) = Ne^{-(\lambda + \mu_3)t}(e^{\lambda\tau} - 1) \quad (27)$$

$$Y(t < \tau) = 0 \quad (28)$$

$$Y(t > \tau) = N(\lambda/\alpha)e^{\lambda\tau - (\lambda + \mu_3)t}(e^{\alpha(t-\tau)} - 1) \quad (29)$$

$$W(t < \tau) = 0 \quad (30)$$

$$W(t > \tau) = N(b\lambda/\alpha)e^{-\mu_3 t}[(e^{\beta(t-\tau)} - 1)/\beta - (1 - e^{-\lambda(t-\tau)})/\lambda] \quad (31)$$

given $\alpha = \lambda + \mu_3 - \mu_4 - b$ and $\beta = \mu_3 - \mu_4 - b$.

The dynamic predictions of the model are illustrated in Fig. 16 for a particular set of parameter values. A comparison of predictions with experimental results, where the experiments were designed to test model assumptions, is presented in Fig. 17 (Anderson and Crombie, 1984). These experiments, in which a cohort of snails were exposed to a constant force of infection over a period of 40 weeks, were also designed to assess the dependency of the force of infection on the net rate at which miracidia are introduced into the aquatic habitat of the snail. Encouragingly, the relationship between λ and the rate of input of miracidia is approximately linear (as assumed in all published models of schistosome dynamics); see Fig. 18 (Anderson, 1978; Anderson & Crombie, 1984).

A selection of observed age–prevalence curves for infections in various species of snails is displayed in Fig. 19. A variety of patterns is represented, with some curves rising to a plateau while others either fail to reach a plateau or exhibit a declining proportion of infected snails in older age classes.

The reason for an apparent decline in old age classes is not clear at present. It may be due either to the ability of certain snails to recover from infection or to age-related changes in the force of infection. Laboratory studies clearly indicate that some strains of *B. glabrata* are able to recover (Teesdale, 1962; Sturrock *et al.*, 1975; Minchella and Loverde, 1983), but the relevance of these observations to field situations is not at all clear. In natural habitats, for example, snails have fairly short life spans (Table 4). Recent experimental work suggests that observed convexity in age–prevalence curves may be generated by a dependence of the force of infection on snail age and size (Anderson *et al.*, 1982; Anderson

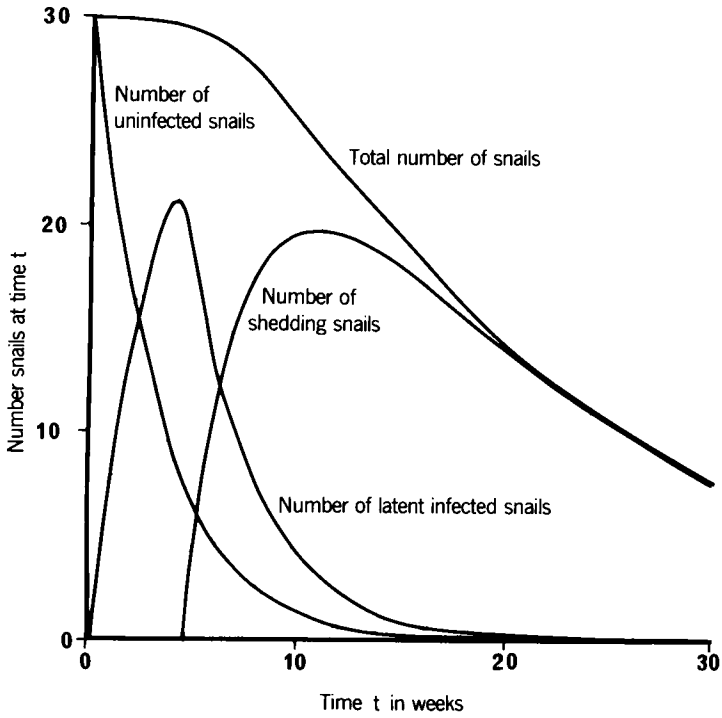

FIG. 16. Age–prevalence curves of schistosome infections in snail populations. Predictions of the model defined by Eqs. (25)–(31) recording changes in the total numbers of snails $N(t)$, the number of uninfected $X(t)$, the number of latent $Z(t)$, and the number of shedding snails $Y(t)$ with respect to snail age at time t under the impact of a constant force of infection λ on a single cohort of snails, of initial density $N(0) = 30$ (after Anderson and May, 1979a). Parameter values are $\tau = 4.5$ weeks, $\mu_3 = 0.062$ week^{-1}, $\mu_4 = 0.00285$ week^{-1}, $\lambda = 0.308$ week^{-1}.

and Crombie, 1984). These studies also demonstrated that the death rate of shedding snails (μ_4) depends on the length of time during which individual snails shed cercariae (Anderson and Crombie, 1984). Age-structured models have been developed which incorporate these refinements plus a term to reflect the continual addition of uninfected snails to the population. Comparisons between model predictions and experimental studies support the view that age-dependent infection rates are important determinants of observed patterns of infection in endemic areas (Anderson and Crombie, 1984).

The prevalence of snail infections (shedding snails) is characteristically low in areas where schistosomiasis is endemic. High figures have been recorded in a few areas, but where large samples of snails have been examined the average prevalence, throughout the year or over a large

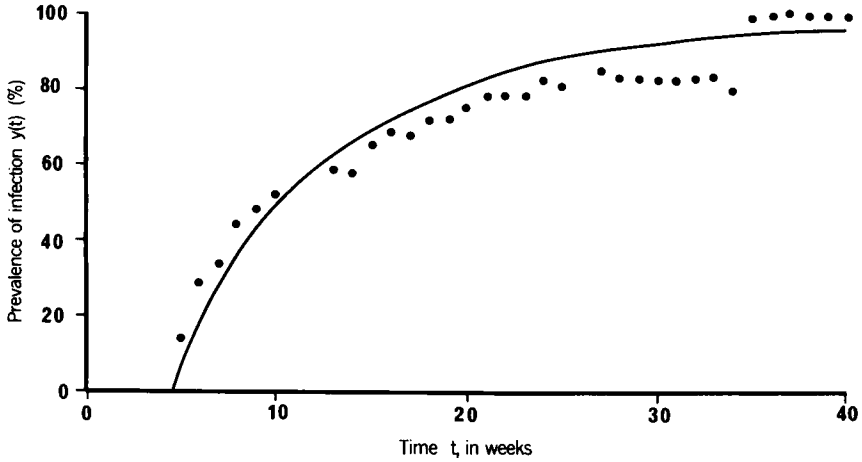

FIG. 17. Age–prevalence curves of schistosome infections in snail populations. Predictions of the model defined by Eqs. (25)–(31) compared with observed values obtained from a laboratory study of the exposure of a cohort of *Biomphalaria glabrata* to a constant density of *S. mansoni* miracidia over a period of 40 weeks. The graph records changes in prevalence $y(t)$ with time; the solid line denotes model prediction and the solid circles are experimental results. Parameter values are $\tau = 4.5$ weeks, $\mu_3 = 0.062$ week^{-1}, $\mu_4 = 0.00285$ week^{-1}, $\lambda = 0.308$ week^{-1}, $N(0) = 30$ snails of size 4–6 mm (after Anderson and Crombie, 1984).

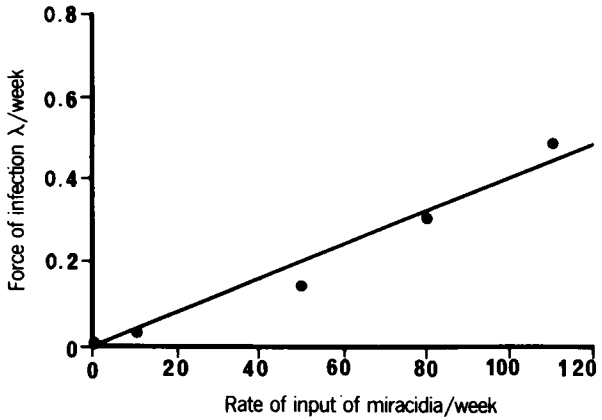

FIG. 18. Age–prevalence curves of schistosome infections in snail populations. Relationship between the force of infection λ and the rate at which miracidia (*S. mansoni*) were introduced into an experimental system containing a cohort of *B. glabrata*. This rate is directly proportional to the density of miracidia in the aquatic habitat of the experimental snail population (after Anderson and Crombie, 1984). The solid circles are observed values and the solid line is the best fit linear model constrained to pass through the origin.

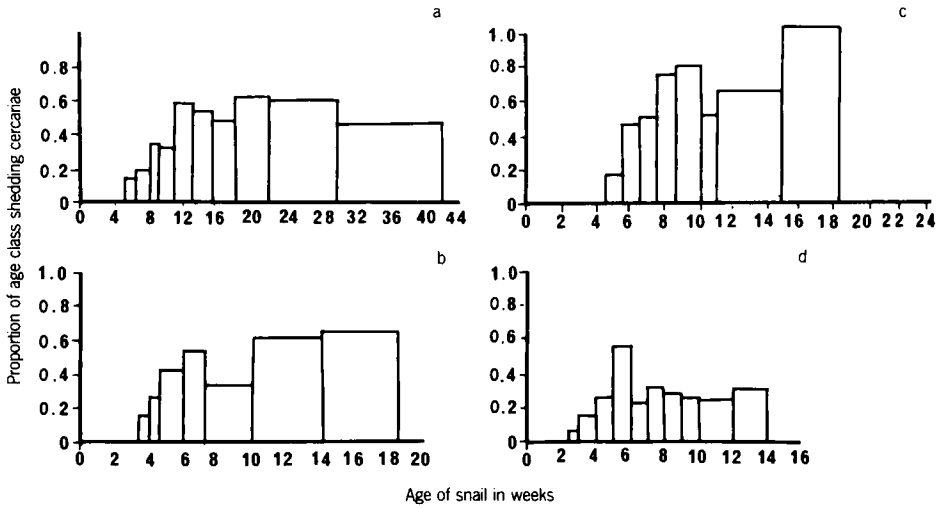

FIG. 19. Age–prevalence (shedding snails) curves of schistosome infections in snail populations. Some examples recorded from field studies. (a) *S. haematobium* in a *Bulinus nasutus productus* population (data from Sturrock and Webbe, 1971). (b) *S. mansoni* in *B. glabrata* (data from Sturrock and Webbe, 1971). (c) *S. mansoni* in *B. glabrata* (data from Sturrock and Webbe, 1971). (d) *S. mansoni* in *B. pfeifferi* (data from Sturrock and Webbe, 1971).

sampling area, tends to lie in the range 1–5%, irrespective of the species of snail or schistosome or the geographical location (Anderson and May, 1979b). This pattern is to be expected, whatever the force of infection in a given area, provided the death rate of shedding snails is much higher than that of uninfected or latent individuals. The catalytic model defined by Eqs. (25)–(31) can be employed to demonstrate this point. Empirical evidence, derived from both laboratory and field, suggests that this is indeed one of the principal determinants of observed patterns (Table 4; Anderson and May, 1979b).

The major use of catalytic models has been to estimate parameter values (e.g., for λ, μ_3, and μ_4) from field data (Sturrock *et al.*, 1975). Their significance as epidemiological research tools for the study of schistosomiasis is to some extent limited, however, by the relative time scales on which changes occur within the parasite population in man and the infected snail population (see Table 3). The epidemiological variable of major interest is parasite intensity within the human community (M) since this reflects the frequency of occurrence of disease symptoms. Under such circumstances it seems sensible to focus mathematical models (and data collection) on the dynamics of change in the worm burden and distribution with the human population. Transmission via the snail segment of the life cycle can be reasonably subsumed into a single gain term for the

TABLE 4
Population parameter values for schistosome infections in snails[a]

Parasite	Latent period τ (average value)	Expected life span of uninfected snails ($1/\mu_3$) (field data)	Expected life span of infected snails ($1/\mu_4$) (field data)
S. mansoni	32 days at 20°C	3–8 weeks	1–6 weeks
S. haematobium	70 days at 20°C	3–6 weeks	2–4 weeks
S. japonicum	70 days at 20°C	10–16 weeks	4–6 weeks

[a] Data from Anderson and May (1979b).

equation determining average worm burden [see Eq. (14)]. Observed patterns of change in parasite prevalence and intensity in man provide a basis for estimating parameters—particularly the basic reproductive rate R_0. Recently this approach has been attempted but much remains to be done (Barbour, 1982; Anderson and May, 1982b).

V. Direct Life Cycle Intestinal Helminth Models

Until recently, very few attempts have been made to use mathematical models to study the dynamics of helminths with direct life cycles. This is somewhat surprising given the amount of attention devoted to schistosomes (which have more complicated life cycles and hence are more difficult to study by mathematical methods) and the wide prevalence (and medical significance) of intestinal nematode infections throughout the world (Hoagland and Schad, 1978; Anderson, 1982a).

The intestinal helminths of greatest interest (in terms of global medical significance) have relatively simple life cycles which may be summarized as depicted by the flow chart of Fig. 20. The major species are hookworms (*Ancylostoma duodenale, Necator americanus*), the roundworm (*Ascaris lumbricoides*), and the whipworm (*Trichuris trichiura*).

The life cycles of all directly transmitted nematodes are basically of similar structure, involving two principal populations: the sexually mature parasites and the free-living infective stages. The infective stage may be a mobile larva as in the hookworm life cycle or a resistant egg as in the case of *Ascaris lumbricoides*. The two principal populations play a central role in determining the overall transmission success of the parasite; the sexually mature worms are responsible for reproduction (which occurs only within this phase of the life cycle, for all species excepting *Strongyloides stercoralis*), while the infective stages determine the rate at which

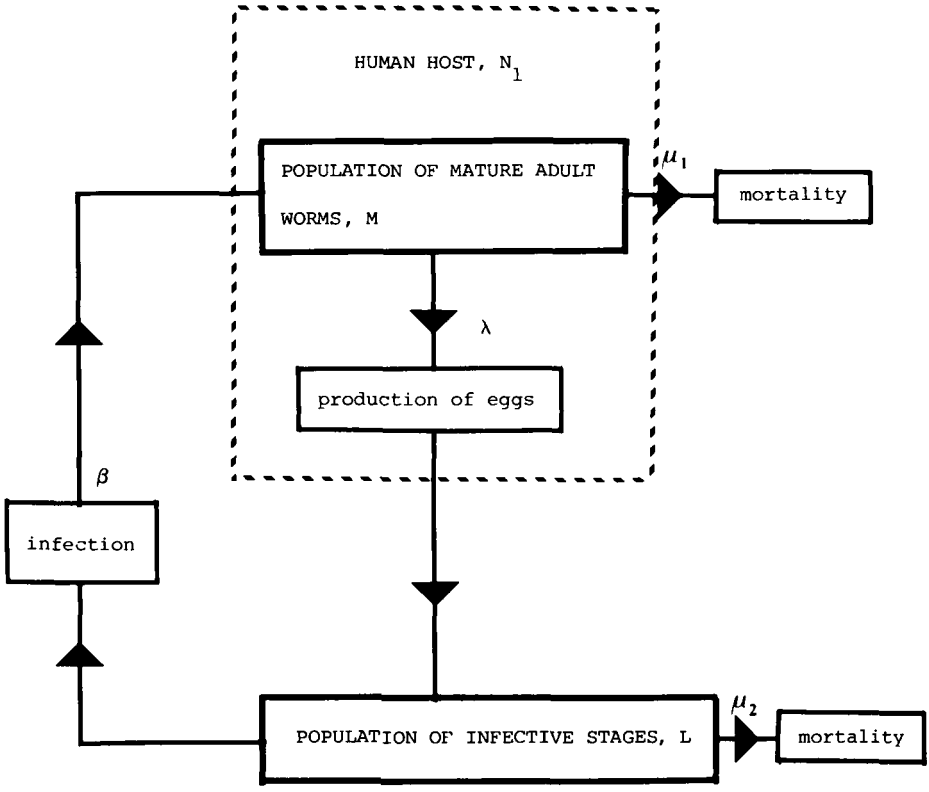

FIG. 20. Diagrammatic flow chart of the principal populations involved in the life cycles of directly transmitted intestinal helminths of man. The rate parameters and processes controlling the flow of parasites via the life cycle are also depicted.

uninfected hosts are "colonized" and the rate of recruitment to established parasite populations.

In the design of a mathematical framework for the study of human infections it is clearly important to base the structure on the variables of major epidemiological interest. For nematode infections these are the prevalence of infection (the proportion or percentage of the human community infected) and the average intensity of infection (the average worm burden per person) in various age classes of the community. Such data may be collected by sampling at one point in time (horizontal survey) or over successive periods in time (longitudinal survey). Intensity is often measured by indirect methods such as faecal egg counts.

Published models of the population dynamics of intestinal nematodes consist of two equations to describe changes in the densities of adult worms and infective stages (Anderson, 1980, 1982a; Croll *et al.*, 1982a;

Anderson and May, 1982a). The equation for the mean number of sexually mature worms, $M(t)$ at time t, consists of one gain and two loss terms. The gain term, which represents parasite recruitment to the sexually mature population, may be expressed as $\beta L_1(t - \tau_1)d_1$ (here β is the transmission coefficient representing contact between human hosts and infective stages); and $L(t - \tau_1)$ is the density of infective stages at time $t - \tau_1$ in the habitat of the human community. After the infective stages gain entry to the human host, a period of time, τ_1, will elapse before the parasite develops and attains sexual maturity. We use the parameter d_1 to denote the proportion of infective stages that gain entry to the host and survive to reach sexual maturity. The two loss terms represent parasite mortalities due to natural causes and/or host-induced effects (immunological attack) and human mortality. If the human host's per capita death rate is $\hat{\mu}$, where $1/\hat{\mu}$ denotes life expectancy, and if $p(i)$ is the probability that a host contains i worms, then the net loss of parasites due to host deaths is $\hat{\mu}$ $\Sigma_{i=0}^{\infty} ip(i)$. Similarly, the net loss due to natural parasite mortality may be expressed as $\Sigma_{i=0}^{\infty} \mu_1(i)\ ip(i)$ where the term $\mu_1(i)$ denotes the per capita rate of parasite mortality as a function of worm density within the host. Laboratory studies of nematode infections within rats, mice, and dogs indicate that worm mortality is often density dependent, but the relevance of these observations to human infection is as yet unclear due to the practical difficulties inherent in measurement (Krupp, 1962; Keymer, 1982; Anderson, 1982a).

The equation for $L(t)$, the density of infective stages at time t, also consists of one gain and two loss terms. The net output of transmission stages by the total parasite population may be expressed as $s\Phi N \Sigma_{i=0}^{\infty} \lambda(i)$ $ip(i)$ where s represents the proportion of female worms in the population, Φ is the mating function (see discussion of schistosome models and Table 2), N is human density (assumed constant), i and $p(i)$ are as defined above, and $\lambda(i)$ is the per capita rate of egg production by female worms formulated as a density dependent function. Egg production by intestinal helminths of man is known to be density dependent; some examples are presented in Fig. 21. Of the total output of transmission stages only a proportion d_2 will survive the average time period τ_2 required to develop to the infective state. The net recruitment of parasites to the population of infective stages at time t is thus

$$sd_2\Phi N \sum_{i=0}^{\infty} \lambda(i)\ ip(i, t - \tau)$$

A rough guide to the lengths of the maturation delays τ_1 and τ_2 and to the life expectancies of the infective stages and mature worms, for the major intestinal nematodes of man, is given in Table 5. The two loss terms

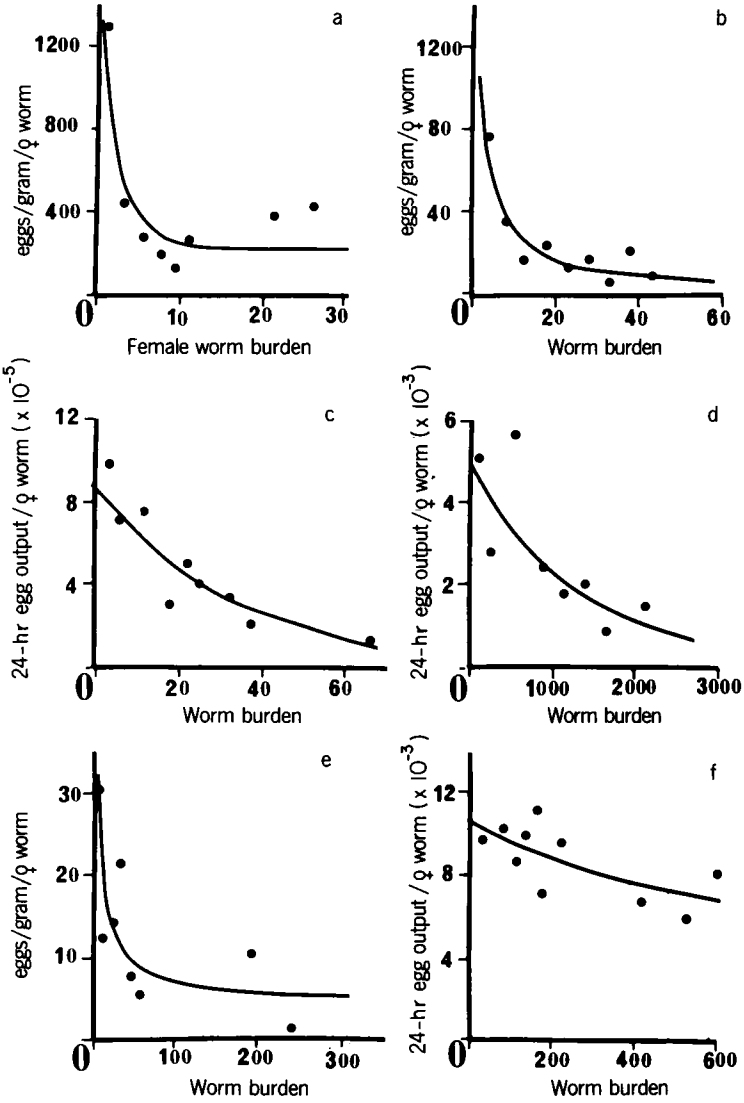

FIG. 21. Examples of density-dependent worm fecundity within the human host. (a) *A. lumbricoides* (data from Martin *et al.*, 1983). (b) *A. lumbricoides* (data from Croll *et al.*, 1982). (c) *A. lumbricoides* (data from Hliang *et al.*, 1983). (d) *N. americanus* (data from Hill, 1926). (e) *S. mansoni* (data from Cheever, 1968). (f) Hookworm (*N. americanus* and *A. duodenale*) (data from Stoll, 1923). Note that in (a), (b), and (e) the vertical axes record eggs per gram faeces per female worm, while in (c), (d), and (f) the equivalent axes are 24-hour egg output per female worm. The solid circles are observed values and the solid lines are the best fit power, (a), (b), and (e), or exponential, (c), (d), and (f), functions.

TABLE 5

Maturation delays and life expectancies of intestinal nematodes of man[a]

Parasite	Delay from infection of man to production of eggs (τ_1) (in days)	Delay from release of eggs to development of stage infective to man (τ_2) (in days)[b]	Life expectancy of mature parasite ($1/\mu_1$) (in years)[c]	Life expectancy of infective stage ($1/\mu_2$) (in days)[d]
Ascaris lumbricoides	50–80	10–30	1–2	28–84
Necator americanus	40–50	3–6	2–4	3–10
Ancylostoma duodenale	28–50	3–6	2–4	3–10
Trichuris trichiura	50–84	11–80	1–3	10–30
Enterobius vermicularis	15–43	0.2–0.4	0.1–0.2	14–56

[a] Data from Anderson and May (1982a) and Muller (1975).

[b] The maturation delay τ_2 is very dependent on the prevailing climatic conditions.

[c] Only rough approximations due to the practical difficulties inherent in estimation.

[d] Life expectancy highly dependent on prevailing climatic conditions.

represent deaths due to natural mortalities, at a per capita rate μ_2, and losses due to infection at a net rate βNL.

The above assumptions result in two coupled nonlinear differential equations for $M(t)$ and $L(t)$.

$$dM/dt = \beta L(t - \tau_1)d_1 - \hat{\mu} \sum_{i=0}^{\infty} ip(i) - \sum_{i=0}^{\infty} \mu(i)\, ip(i) \tag{32}$$

$$dL/dt = sd_2\Phi N \sum_{i=0}^{\infty} \lambda(i)\, ip(i, t - \tau_2) - \mu_2 L - \beta NL \tag{33}$$

The model has a deterministic framework but is essentially hybrid in structure, containing the probability elements $p(i)$ (probability of observing i parasites within a single host) which influences the mating function Φ and the density-dependent parasite mortality and fecundity terms $\mu(i)$ and $\lambda(i)$. Some simplification in model structure can be achieved by making a phenomenological assumption concerning the distribution of the probability terms [the $p(i)$ values] (Anderson and May, 1978; May and Anderson, 1978). This procedure is only a crude approximation to the more exact treatment arising from the development of a fully stochastic model (see Nåsell and Hirsch, 1973; Barbour, 1978). It should be noted, however, that stochastic models of nonlinear processes [e.g., the assumption embodied in Eqs. (32) and (33)] are somewhat intractable to analytical investigation. A phenomenological assumption about the way worms are distributed among hosts therefore generates greater flexibility and facilitates the biological interpretation of model properties.

Quantitative knowledge of the nature of nematode parasite distributions within human communities is limited, although it has increased substantially in recent years. This is a consequence of the growing use of chemotherapeutic agents in epidemiological studies to expel intestinal helminths in the faecal output of infected persons. An example of the data collected by the use of this technique is presented in Fig. 11. Without exception, the distributions are aggregated in form: a few people harbour heavy worm burdens and the majority harbor few or none. The patterns are well described empirically by the negative binomial distribution; this probability distribution is defined by two parameters, the mean M and a parameter k which varies inversely with the degree of parasite contagion (Bliss and Fisher, 1953). Table 6 documents some of the available quantitative data on the magnitude of k for various human helminths in different regions of the world. The vast majority of estimates find k less than unity, indicating severe aggregation. It is not uncommon for more than 70% of the total worm population to be harboured by fewer than 10% of the human community; this property of the negative binomial distribution is portrayed graphically in Fig. 22.

TABLE 6
Degree of parasite aggregation in the human or vector host population as measured inversely by the negative binomial parameter k

Parasite	Geographical location	Host	k	Reference
Ascaris lumbricoides	Iran	Man	0.2–0.9	Croll *et al.* (1982)
	Burma		0.3–0.9	Hliang *et al.* (1983)
	Korea		0.3–0.55	Seo *et al.* (1979)
	Bangladesh		0.2–0.5	Martin *et al.* (1983)
	Japan		0.2–0.5	Fushimi (1959)
Necator americanus	India		0.03–0.6	Anderson (1980)
Ancylostoma duodenale and *N. americanus*	Taiwan		0.05–0.4	Anderson (1980)
Enterobius vermicularis	Korea		0.3–0.4	Chai *et al.* (1976)
Trichuris trichiura	Jamaica		0.2–0.3	Bundy *et al.* (1982)
Schistosoma mansoni	Brazil		0.03–0.5	Anderson and May (1982a)
Wuchereria bancrofti	Surinam and Samoa		0.6–0.7	This article
Wuchereria bancrofti (infective larvae)	Tahiti	*Culex pipiens quinque fasciatus*	0.24	Pichon *et al.* (1980)
	Tanzania		1.68	Pichon *et al.* (1980)
	Volta	*Anopheles gambiae*	0.54	Pichon *et al.* (1980)
Onchocerca sp.	Toga	*Simulium damnosum*	0.04–0.07	Cheke *et al.* (1982)

Further simplifications in the structure of the model can be achieved by noting the considerable differences in time scales (life expectancies) associated with the mature adult worms versus the infective stages (excepting *E. vermicularis*), as displayed in Table 5. In addition, the maturation delays τ_1 and τ_2 are in general short when compared with the life expectancies of the mature worms in man. It is therefore reasonable to assume that the dynamic properties of Eqs. (32) and (33) may be effectively captured by a single equation for M in which the time delays are assumed to be of negligible significance, such that

$$\frac{dM}{dt} = \frac{\beta d_1 d_2 s \Phi N \sum \lambda(i)\, ip(i)}{(\mu_2 + \beta N)} - \hat{\mu} M - \sum \mu(i)\, ip(i) \qquad (34)$$

To proceed further with the analysis of the model it is necessary to define the density-dependent functions $\lambda(i)$ and $\mu(i)$. It has been assumed in

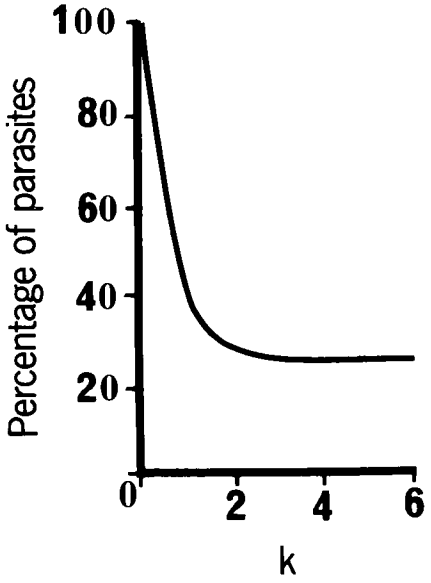

FIG. 22. The relationship between the percentage of the total parasite population harboured by the most heavily infected 10% of the human community and the degree of worm contagion (measured inversely by the negative binomial parameter k). The worms are assumed to be distributed in a negative binomial manner with a mean worm burden M of 10 parasites per person.

previous work that the dominant density-dependent term is that of fecundity, $\lambda(i)$, and that the death rate of adult worms is essentially constant and independent of worm burden (Anderson, 1982a; Croll *et al.*, 1982). This approach is based on the wealth of empirical evidence which demonstrates the density-dependent nature of worm fecundity (see Fig. 21) and the lack of evidence, due primarily to difficulties in measurement, of similar dependencies in worm mortality. The measurement of rates of adult worm mortality, and any dependence these rates may have on worm burden, is beset with many practical problems. The estimates of adult worm life expectancies listed in Table 5 are only crude approximations and hence must be treated with caution. In addition, the absence of data does not necessarily imply that density-dependent worm mortality or establishment is not of great significance to the dynamics and stability of intestinal helminths.

With the limitations in mind, the model defined by Eq. (34) can be further simplified by noting that the observed dependence of egg production on worm burden is well described empirically by an exponential decay function of the form $\lambda(i) = \lambda \exp(-\gamma i)$ (see Fig. 21 and Anderson and May, 1982a). With the assumption that the worms are distributed in a

negative binomial manner within the human community, Eq. (34) may be simplified to give

$$\frac{dM}{dt} = \frac{M}{C}\left\{R_0\left[1 + \frac{M}{k}(1 - z)\right]^{-(k+1)} - 1\right\} \tag{35}$$

Here C is the life expectancy of the adult parasite, $C = 1/(\hat{\mu} + \mu_1)$; k is the aggregation parameter of the negative binomial, $z = \exp(-\gamma)$; and R_0 is the basic reproductive rate of the parasite. Specifically, R_0 is defined as

$$R_0 = zs\Phi\beta d_1 d_2 N\hat{\lambda}/[(\hat{\mu} + \mu_1)(\mu_2 + \beta N)] \tag{36}$$

Note that the mating term Φ is a function of the probability distribution of parasite numbers per host and hence of M and k. Intestinal nematodes are dioecious species, and are thought to be polygamous in their mating habits. In other words, if a host contains four female and one male parasites, all four females are likely to be inseminated (in contrast to the supposed monogamous habits of schistosome parasites). The appropriate functional form of Φ for a dioecious polygamous parasite, distributed in a negative binomial manner, is defined in Table 2 (see also Fig. 24).

The analysis of Eq. (35) follows lines identical to those described for the basic schistosome model [Eqs. (9)–(11)]. Further, the general properties are virtually identical: there is a transmission threshold at $R_0 = 1$ and a breakpoint worm burden M_μ generated by the mating probability term (see Anderson, 1982a). The density-dependent constraint which regulates parasite abundance is generated by the fecundity term in Eq. (35), while in the schistosome model it arises from the assumption that multiple miracidial infections of the snail host do not increase cercarial production over that arising from single infections. The net effects of the two processes, however, are identical, acting to constrain parasite population growth at high densities. For intestinal helminths the severity of density-dependent constraints is partially determined by the degree of worm aggregation within the human community. Highly clumped distributions result in a greater proportion of the parasite population being influenced by density-dependent processes, when compared with random distribution with the same average worm burden.

The mating probability terms act as a form of inverse density dependence, since the likelihood of a female worm being able to produce viable offspring increases as average density rises.

The comparative simplicity of the direct life cycles of intestinal nematodes, when compared with the indirect cycles of schistosome parasites, has enabled crude estimates to be obtained for the majority of the parameters embodied in Eq. (35). As a consequence, it has been possible to obtain approximate estimates of the basic reproductive rate R_0 in certain

communities with endemic infections and hence roughly to calculate the value of the breakpoint state M_μ. An illustration of one such attempt is given in Fig. 23 which pertains to *Ascaris lumbricoides* within rural communities in Iran (Croll *et al.*, 1982). With an overall average worm burden (over all age classes) of 22 and an R_0 value of 4.3, the breakpoint is approximately 0.2 worms per host. The low level of this value is a consequence of the high degree of parasite contagion ($k = 0.34$). Similar estimates have been obtained for hookworm infections in India (Anderson, 1980) and whipworm infections in Jamaica (Bundy *et al.*, 1982).

The probability distribution of worm numbers per host determines the relationship between the prevalence of infection $P(t)$ and the average intensity $M(t)$ at time t. For a negative binomial distribution this relation-

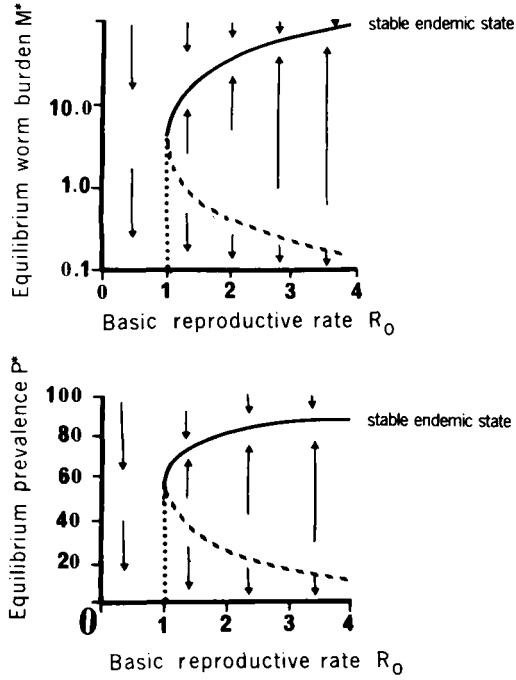

FIG. 23. The relationships between the equilibrium mean worm burden M^* (a) or the equilibrium prevalence of infection P^* (b) and the basic reproductive rate R_0 for a polygamous intestinal nematode (i.e., *A. lumbricoides*) which is distributed in a negative binomial manner within the human population ($k = 0.34$). The dashed line denotes the unstable breakpoint M_μ, and the arrows show how the dynamic trajectory of M behaves following a perturbation from one of the two equilibrium states M^* (endemic infection) and $M^* = 0$ (parasite extinction). The vertical dotted line denotes the transmission threshold $R_0 = 1$, below which the infection cannot be maintained. See text for further details.

ship is simply

$$P(t) = 1 - (1 + M(t)/k)^{-k} \tag{37}$$

A consequence of high degrees of parasite aggregation (k small) is that for moderate to high levels of the average worm burden M, the value of Φ is essentially unity (Fig. 24). This is particularly so for polygamous parasites. Under such circumstances the equilibrium worm burden M^*, denoting stable endemic infection, can be derived from Eq. (35) by setting $dM/dt = 0$:

$$M^* = k[R_0^{1/(k+1)} - 1]/(1 - z) \tag{38}$$

The equilibrium prevalence P^* is obtained by substituting M^* for $M(t)$ in Eq. (37).

The value of M^* rises approximately linearly as R_0 increases, provided the degree of parasite contagion is high ($k << 1$). The prevalence P^*, however, approaches an asymptote whose value is set by the magnitude of k. For random distributions the asymptote is 100%, while for contagious distributions the value is inversely related to the magnitude of k. If k is very small, as often appears to be the case (see Table 6), the asymptotic

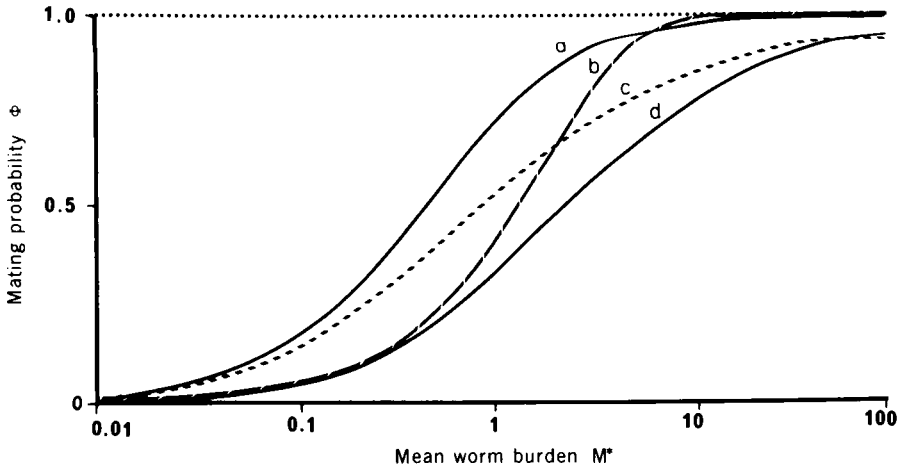

FIG. 24. The relationship between the mating probability Φ and the average worm burden M^* for various assumptions concerning parasite distribution within the human community and parasite sexual habits (see Table 2 for explicit functions). The horizontal dotted line ($\Phi = 1$) is for a hermaphroditic species which is able to self-fertilize. Curve a, polygamous parasites distributed in a negative binomial manner; curve b, polygamous parasites distributed randomly; curve c, monogamous parasites distributed in a negative binomial manner; curve d, monogamous parasites distributed randomly. In all cases female and male worms are assumed to be distributed together as opposed to separately (see Anderson 1980).

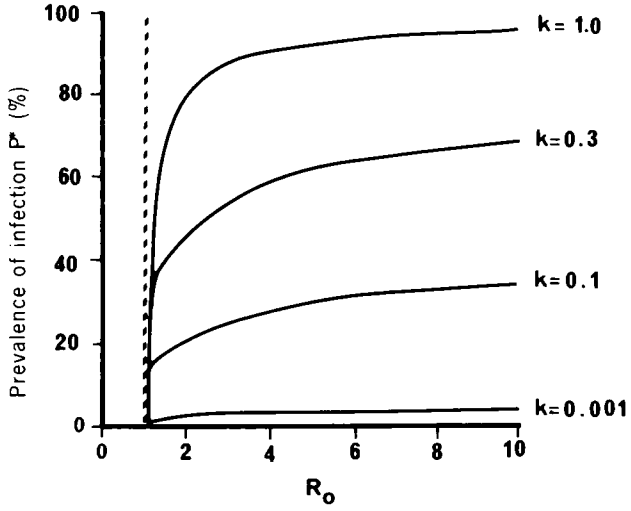

FIG. 25. The influence of the degree of parasite aggregation, as measured inversely by the negative binomial parameter k, on the relationship between the prevalence of infection and the value of the basic reproductive rate R_0 (assuming $z = 0.9$). Dashed line depicts transmission threshold, when $R_0 = 1$.

prevalence will never attain 100% irrespective of the degree of transmission success (the value of R_0); see Fig. 25.

The relationship between P^* and M^* for high degrees of parasite contagion has important implications for the interpretation of changes in prevalence and intensity, both with respect to host age and as a consequence of man's intervention. As illustrated in Fig. 25, significant changes in average intensity of infection (recorded in this figure as R_0 because M is approximately linearly related to this parameter for small k values) may have relatively little impact on the prevalence. For example, with a k value of 0.2, halving the average worm burden from 20 to 10 will only reduce the prevalence by 6% (from 60 to 54%). Note, however, that such calculations are based upon the assumption that a change in average worm burden does not alter the degree of parasite aggregation within the community. Despite this caution, these observations are of considerable epidemiological interest; they help explain why substantial changes in parasite intensity with age do not necessarily result in concomitant changes in prevalence (see Fig. 10).

A final point of interest to emerge from Eq. (35) concerns the use of indirect measure of average worm burden, such as faecal egg counts, in epidemiological surveys. Given the empirical evidence for density-dependent worm fecundity (see Fig. 21), it follows that people with the heaviest worm burdens may not necessarily produce the largest number of eggs.

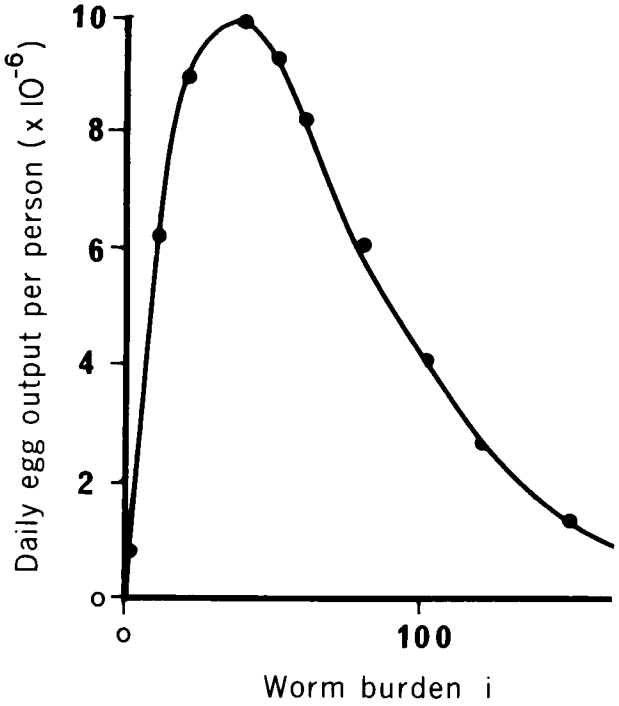

FIG. 26. The relationship between the total daily egg output and worm burden i, given an exponential relationship between the per capita female worm egg production rate and worm burden, $\lambda(i) = \lambda \exp(-\gamma i)$, where the constants λ and γ have the values 8.285×10^5 and -0.03, respectively (see Fig. 21c). The specific relationship shown is for *A. lumbricoides* in a rural community in Burma (see Hliang *et al.*, 1983).

For a person with i worms, the net production of eggs is simply $i\lambda(i)$ per unit of time. The relationship between $i\lambda(i)$ and i, for parameter values thought to be appropriate to the biology of *Ascaris lumbricoides*, is portrayed in Fig. 26. This pattern is revealing and suggests that considerable caution must be exercised in the interpretation of intensity data based on egg output measures. In certain instances the pathology of infection is closely correlated with egg production (e.g., schistosomes) but more commonly (e.g., the intestinal nematodes) it is directly related to worm burden.

VI. FILARIAL WORM MODELS

To our knowledge the only formal mathematical work on the transmission dynamics of the nematode filarial infections is that of Dietz (1980,

1982a). In this section we briefly summarize the main themes of this work and attempt to draw parallels with the analyses of the models for schistosome and intestinal helminth parasites.

Dietz considers in detail one of the major filarial diseases, onchocerciasis or river blindness. The causal agent is the nematode *Onchocerca volvulus* which is transmitted indirectly by blackflies belonging to the genus *Simulium*. The transmission cycle is shown schematically in Fig. 27. The main difference between this form of life cycle and that of the directly transmitted intestinal helminths that were considered above is the presence of a biting arthropod vector, which facilitates transmission success from man to man; the situation is broadly similar to that for schistosomiasis (with its molluscan intermediate vector), but the details are different. In areas where onchocerciasis is endemic, the prevalence of infection often approaches 100%, although great variation exists between villages in the average worm burden and hence the prevalence of disease symptoms. For this reason it is again necessary to consider a model whose framework takes account of changes in worm density per person, as well as changes in the overall prevalence. An added complication arises, however, from the observation that the impact of the larval parasites on the fly vector is also determined in part by parasite density (Fig. 29). It is therefore necessary to consider two epidemiological variables: M, the mean number of mature adult parasites per person, and L, the mean number of infective larvae per fly. These variables are precisely the ones most commonly studied in epidemiological surveys (although the mean adult worm burden is measured indirectly by estimates of microfilarial density in man; microfilariae are the larval stages released by the mature female parasites into the blood or skin of man and which are picked up by the biting vector).

The model of Dietz considers changes in $M(a,t)$ and $L(a,t)$ both with respect to time t and host age a (whether man or fly). The coupled nonlinear partial differential equations are of the general form:

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial a} = \{T_1\bar{L}/[1 + f_1(T_1,\bar{L})]\} - \mu_1 M[1 + g_1(M)] \tag{39}$$

$$\frac{\partial L}{\partial t} + \frac{\partial L}{\partial a} = \{T_2\bar{M}/[1 + f_2(T_2,\bar{M})]\} - \mu_2 L[1 + g_2(L)] \tag{40}$$

The variables $\bar{M}$ and $\bar{L}$ represent average values of the parasite densities where the averages are taken with respect to the age distribution of the human and intermediate host populations. If the human and vector populations have stable, exponential age distributions with constant per capita mortality rates b_1 and b_2, respectively, the average values $\bar{M}(t)$ and $\bar{L}(t)$

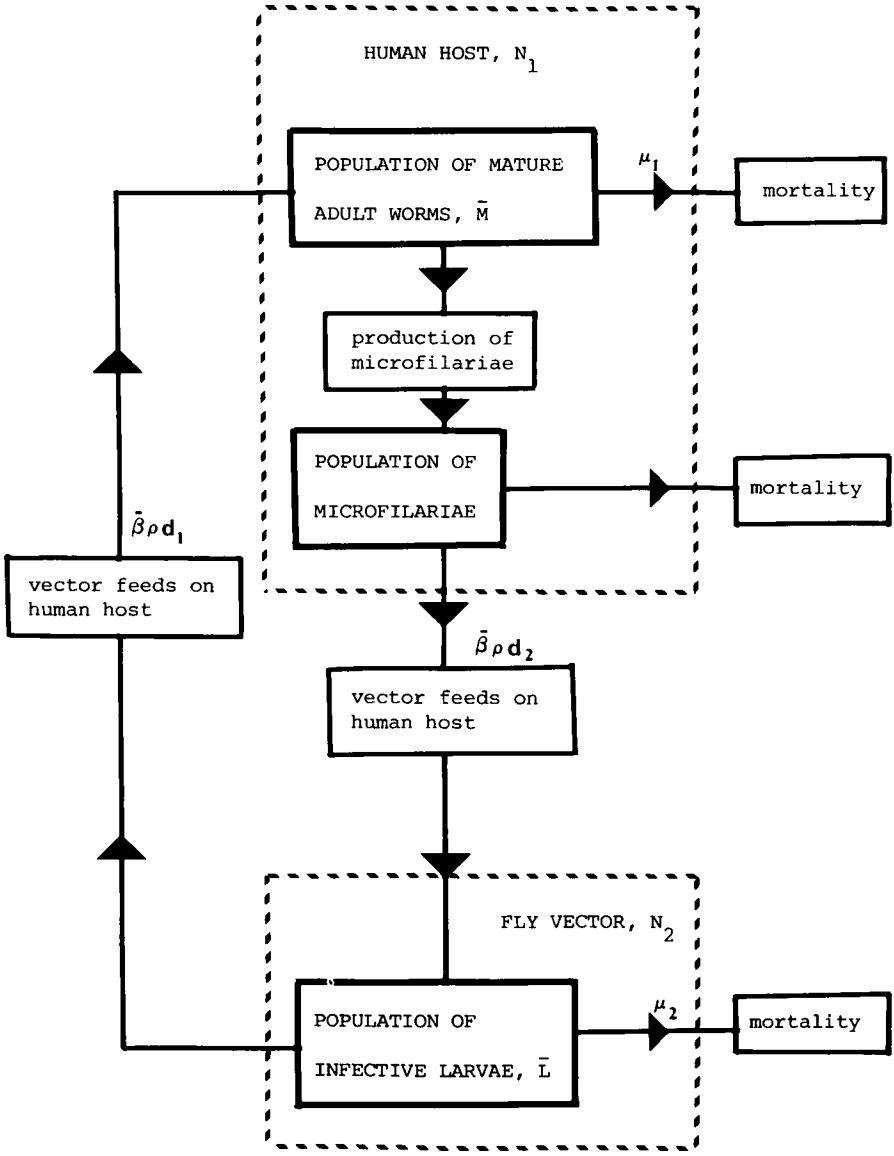

FIG. 27. Diagrammatic flow chart of the principal host and parasite populations involved in the life cycles of the human filarial nematodes. The rate parameters and processes controlling the flow of parasites via the life cycles are also depicted.

are

$$\bar{M}(t) = \int_0^\infty M(t,a)\, e^{-b_1 a}\, da \tag{41}$$

$$\bar{L}(t) = \int_0^\infty L(t,a)\, e^{-b_2 a}\, da \tag{42}$$

The parameters T_1 and T_2 denote the effective rates of transmission from vector to man and man to vector, respectively (as in the schistosome model). The parameters μ_1 and μ_2 represent the density-independent death rates of the adult and larval parasites, respectively, while the functions g_1 and g_2 denote the additional mortality imposed by density-dependent effects. The functions f_1 and f_2 represent density-dependent constraints on the recruitment of parasites to the adult worm population and the production of infective larvae, respectively. The parameters T_1 and T_2 can be dissected to reveal a finer parameter structure. For example, $T_1 = N_2 d_1 \bar{\beta} p / N_1$ where N_1 is human density, N_2 is vector density, d_1 is the number of worms which attain maturity (resulting from the number of infective larvae ingested during one blood meal on man), p is the proportion of blood meals taken from man (as opposed to other vertebrate species), and $\bar{\beta}$ is the number of blood meals taken per unit of time. Similarly, $T_2 = \bar{\beta} p d_2$ where d_2 is the number of larvae ingested during one blood meal taken from man.

An expression for R_0, the basic reproductive rate, may be obtained from the equilibrium equations ($\partial M/\partial t = \partial M/\partial a = 0$) of the model defined by Eqs. (39) and (40):

$$R_0 = T_1 T_2 / (\mu_1 + b_1)(\mu_2 + b_2) \tag{43}$$

Note that a term N_2/N_1 is embodied in the above expression for R_0 denoting the ratio of vectors to humans. This is to be compared with the product $N_1 N_2$ arising in the expression for R_0 derived from models of schistosome parasite dynamics. The difference is a consequence of the differing modes of transmission: one via a biting arthropod (filarial worms), the other by free-living infective stages (schistosome parasites). For filarial worms and other infections borne by biting arthropods, the intermediate vector tends to make a fixed number of bites per week, independent of the number of human hosts available to feed on. Transmission is therefore dependent on the ratio of vectors to man (see May and Anderson, 1979). (If, however, the biting vector takes its fixed number of blood meals from several different species, the proportion p taken from man may be proportional to N_1; in this event, R_0 is again proportional to $N_1 N_2$ rather than to the ratio N_2/N_1.)

The dynamic properties of the partial differential equation model [Eqs. (39) and (40)] are dependent on the density-dependent functions $f_1, f_2, g_1,$

and g_2. Unfortunately, however, empirical data concerning these relationships are virtually nonexistent at present. Dietz considers three possible cases: (1) a single density-dependent constraint represented by an association between the death rate of the human host and the parasite burden ($g_1 \neq 0, f_1 = f_2 = g_2 = 0$); (2) a single constraint represented by an association between the death rate of the vector and its parasite burden ($g_2 \neq 0$, $g_1 = f_1 = f_2 = 0$); and (3) density-dependent constraints on the establishment of parasites within both the human and intermediate host ($g_1 = g_2 = 0, f_1 \neq 0, f_2 \neq 0$). For case (3), Dietz assumes linear functions for f_1 and f_2 such that $f_1(\bar{M}) = \alpha_1 \bar{M}$ and $f_2(\bar{M}) = \alpha_2 \bar{M}$, where α_1 and α_2 are constants of proportionality.

Each of the three cases gives rise to a different relationship between the equilibrium average worm load per human, $\bar{M}^*$, and the equilibrium average infective larval burden per vector, $\bar{L}^*$. Respectively, for cases (1), (2), and (3), these relationships are

$$\bar{M}^* = \bar{L}^*(b_2 + \mu_2)/T_2 \tag{44}$$

$$\bar{M}^* = \bar{L}^* R_0(b_2 + \mu_2)/T_2 \tag{45}$$

$$\bar{M}^* = \bar{L}^*(b_2 + \mu_2)/[(N_2/N_1)T_2(1 + \alpha_2 \bar{L}^*)] \tag{46}$$

Aside from the trivial equilibrium state $\bar{M} = \bar{L} = 0$ (for $R_0 < 1$), all three models have a single positive stable equilibrium. The breakpoint concept, arising for the schistosome and intestinal helminth models, is not relevant because Dietz assumes that adult worms are highly aggregated in their distribution within the human community such that the mating probability Φ is essentially unity in value for all positive values of $\bar{M}$.

It is clear from Eqs. (44) and (45) that for cases (1) and (2) $\bar{M}^*$ and $\bar{L}^*$ are simply proportional to each other. Case (3), illustrated by Eq. (46), is of more interest since the value of $\bar{M}^*$ will approach an asymptote as $\bar{L}^*$ increases. In other words, very substantial changes in the average density of infective larvae per vector ($\bar{L}^*$) may not necessarily result in significant changes in the average worm load within the human population. To assess the validity of these rather crude assumptions concerning the density-dependent checks on parasite population growth, it is necessary to examine empirical observations on the relationship between $\bar{M}$ and $\bar{L}$. Unfortunately, quantitative data are limited and indirect measures of $\bar{M}$ must be employed. Specifically, worm intensity in man is usually assumed to be proportional to the density of microfilariae in a unit weight of skin (1 mg skin snip). This assumption may be false given the broad association, for other nematode species of man, between parasite density and worm fecundity (see Fig. 28). In the absence of any data for filarial parasites, however, the assumption of direct proportionality at least has the merit of simplicity.

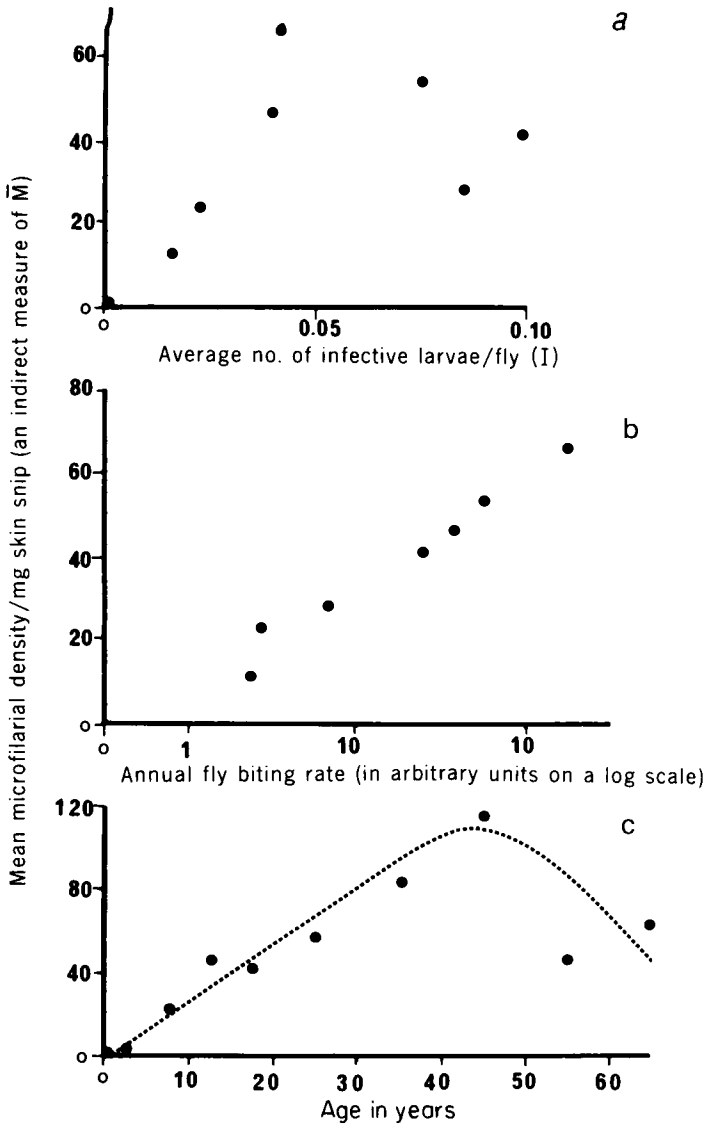

FIG. 28. The relationships between the mean density of *Onchocerca volvulus* microfilariae per milligram skin snip (an indirect measure of $\overline{M}$) and (a) the average number of infective larvae per fly vector (*Simulium damnosum*), $\bar{L}$, (b) the annual fly biting rate; and (c) human age in years. See text for further details. (From Dietz, 1982b.)

The data examined by Dietz (1982a) were taken from studies in Cameroon, Upper Volta, and the Ivory Coast. Figure 28 shows observed relationships (1) between $\bar{M}$ (measured indirectly by microfilarial density in skin snips) and $\bar{L}$; (2) between $\bar{M}$ and the annual fly biting rate (proportional to T_1, the transmission rate from vector to man, and measured by recording over a full year the average number of flies attempting to feed per unit of time on human baits stationed in villages with endemic disease); and (3) between intensity of human infection and human age. The relationship between $\bar{M}$ and $\bar{L}$ is somewhat inconclusive, although it does hint at the presence of an asymptote in $\bar{M}$ as $\bar{L}$ increases (Fig. 28). The association between $\bar{M}$ and the annual fly biting rate is of much greater interest and provides evidence for the existence of a transmission threshold (in terms of the fly biting rate) for parasite persistence. Dietz employed this information to calculate values for the basic reproductive rate R_0 in a series of villages. These estimates, as recorded in Table 7, are highly variable among villages. This variability is also reflected in age-related changes in the intensity of infection in man.

The age-associated changes in parasite intensity, recorded in Fig. 28c, may be due to a variety of factors. Age-related changes in contact with the vector, along with differential survival rates between lightly and heavily infected people, are thought to be the dominant effects (Dietz, 1982a). Using empirical relationships between human age, contact with vectors, and the death rate of infected people, Dietz (1982a) employed numerical methods to examine both the temporal dynamics of the model defined by Eqs. (39) and (40) and the impact of various forms of control on disease prevalence and intensity. In these calculations it is assumed that the adult worms in man have a life expectancy of roughly 8 years. The fly vector is thought to have a life span of a few weeks (as opposed to months or

TABLE 7
Estimates of the basic reproductive rate R_0 *for* Onchocerca volvulus *in various villages*[a]

Village name	Country	R_0
Rey Manga	Cameroon	3.1
Douffing	Cameroon	3.5
Nasso	Upper Volta	9.0
Péndié	Upper Volta	33.7
Mayo Galké	Cameroon	50.3
Dangonadougou	Upper Volta	74.0
Fétékro	Ivory Coast	166.7

[a] Data from Dietz (1982a).

years). Given this enormous discrepancy in the life spans of the adult parasite in man and the infective larvae in the fly vector, it is hardly surprising that Dietz (1982a) was drawn to the conclusion that even perfect vector control over long periods of time (10–20 years) will still leave sufficient adult worms alive within the human community to reestablish parasite transmission once vector control ceases.

Quantitative studies, employing mathematical methods, of the dynamics of filarial infections are in their infancy at present, and much remains to be done. A major problem in this area, however, is the lack of quantitative population data although recent work is helping to rectify this situation (Kirkwood *et al.*, 1983a,b). At present it is only possible to speculate upon the types and severities of density-dependent processes acting on the parasites' dynamics. This situation can easily be improved with respect to the parasites' association with the fly vector. Indeed, experimental studies of filarial infections in laboratory animals clearly demonstrated an association between vector mortality and parasite burden (Christensen, 1978). At present, however, it is difficult to envisage how such information may be acquired with respect to the associations between filarial parasites and man.

VII. Hybrid Models Incorporating Heterogeneity in Exposure to Infection

The models discussed so far are essentially deterministic, even though they do incorporate probability elements to describe both the distribution of parasite numbers per host and the likelihood that a female worm is successfully inseminated. The form of the distribution of worm numbers has been treated as a fixed entity, unaffected by changes in the average worm burden and associated population rate parameters. The observed aggregation patterns in such distributions are in part induced by heterogeneity in exposure to infection, resulting from the action of genetic, spatial, or behavioural mechanisms. Recent work by Dietz (1982b) attempted to include heterogeneous exposure within mathematical models of helminth dynamics. The model considers changes in the number of hosts, $n(a,i,h)$, of age a with i parasites and exposure index (exposure to infection) h. The index h is assumed to be constant throughout the lifetime of an individual host and to have a gamma distribution within the population of hosts. The probability density function of this distribution $g(h)$ is

$$g(h) = s^s h^s e^{-sh}/M(s) \tag{47}$$

with a mean of unity and a variance s^{-1}. The rate of exposure to infection is defined as β, such that the rate of acquisition of parasites of an individ-

ual with exposure index h is βh. The parameter β is also assumed to be constant and independent of the size of the total parasite population (a constant force of infection). Parasites have a constant per capita natural mortality rate of μ, while hosts have an age-dependent (but parasite-independent) death rate $b(a)$ and a parasite-induced death rate αi (where α is a constant of proportionality). Changes in $n(a,i,h)$ with respect to host age can be expressed as infinite series of differential equations:

$$\frac{dn(a,i,h)}{da} = -[\beta h + b(a) + \mu i + \alpha i]n(a,i,h) + \beta h n(a,i-1,h) + \mu(i+1)\, n(a,i+1,h) \tag{48}$$

By the introduction of the probability-generating function

$$\pi(a,z,h) = \sum_{i=0}^{\infty} n(a,i,h)\, z^i \tag{49}$$

the infinite system of equations can be reduced to one partial differential equation with the solution

$$\pi(a,z,h) = Ng(h) \exp\left[-\int_0^a b(\tau)\, d\tau - \alpha \int_0^a m(\tau,h)\, d\tau + m(a,h)\,(z-1)\right] \tag{50}$$

Here the mean number of parasites, $m(a,h)$, in hosts of age a and exposure index h is given by

$$m(a,h) = [\beta h/(\alpha + \mu)][1 - e^{-(\alpha+\mu)a}] \tag{51}$$

The initial conditions required for the solution [Eq. (50)] are $n(0,0,h) = Ng(h)$, where N is total host population size and $n(0,i,h) = 0$ for $i > 0$ (hosts uninfected at birth).

The distribution of parasite numbers in hosts of age a with exposure index h is Poisson in form, with mean $m(a,h)$ [see Eq. (51)]. Hence, the distribution of parasite numbers in all hosts of age a (with different exposure indices) is negative binomial in form with generating function $G(a,z)$ (arising from the compounding of a series of Poisson distributions with the means distributed in a gamma form) and mean $M(a)$

$$M(a) = m(a,1) \Big/ \left[1 + (\alpha/s) \int_0^{\infty} m(\tau,1)\, d\tau\right] \tag{52}$$

Interestingly, whereas the average number of parasites in one individual increases monotonically and approaches an asymptote $\beta h/(\mu + \alpha)$, the average number of parasites in the total population rises to a maximum level but then declines to approach zero. This is a consequence of the relatively early death of highly exposed individuals such that the

average exposure index—and therefore the average parasite load—declines above a certain age (Dietz, 1982b).

The probability-generating function of the number of parasites in the total host population, $H(z)$, is a mixture of negative binomial distributions (one for each age class):

$$H(z) = \int_0^\infty L(a)\, G(a,z)\, da \Big/ \int_0^\infty L(a)\, da \tag{53}$$

Here $L(a)$ is defined as

$$L(a) = \exp\left[-\int_0^a b(\tau)\, d\tau\right]\left(1 + \frac{\beta\alpha}{s(\alpha+\mu)}\left\{a - \frac{[1 - e^{-(\mu+\alpha)a}]}{(\mu+\alpha)}\right\}\right)^{-s} \tag{54}$$

The general biological conclusion to emerge from this sort of approach is that heterogeneity in exposure to infection generates heterogeneity in the distribution of parasite numbers per host. These aggregated distributions (negative binomial in form for the specific example considered by Dietz, 1982b) differ from one age group to the next, and the overall distribution of parasite numbers within the total host population is formed from a mixture of aggregated distributions. Provided the life expectancy of the parasite ($1/\mu$) is short in relation to that of its human host, the mixture is itself approximately negative binomial in form. In practical terms, therefore, it would be difficult (unless a very large number of observations are available) to distinguish between the mixture distribution and a single negative binomial distribution for the overall pattern within the human community. Aside from its virtue of simplicity, the phenomenological assumption of a single negative binomial distribution, employed in the schistosome and intestinal helminth models, thus appears to be a good approximation to the more complicated, and presumably more realistic, assumptions made in the model of Dietz (1982b).

Further studies along the lines outlined above have recently been published by Hadeler and Dietz (1983). They again adopted Kostitzin's approach (Kostitzin, 1934) of taking accounts of changes in the number of hosts with i parasites, but they examine temporal as well as age-related changes. In contrast to the work of Dietz (1982b), they assumed that exposure to infection is constant and not a random variable within the human community. However, despite the model's considerable mathematical complexity, they arrived at the predictable conclusion that the parasites (in the absence of heterogeneity in exposure) are randomly distributed within any given age class of the host population. Since each age class has a different average worm burden, the distribution of parasite numbers in the total host population is formed from a mixture of Poisson distributions and is therefore aggregated or overdispersed in form. It should also be noted that these conclusions are based on a model whose structure excludes density-dependent parasite mortality or fecundity.

VIII. General Age-Structured Models of Human Helminth Infections

A number of general concepts emerge from the mathematical studies outlined in the previous sections. Five principal factors appear to control the observed dynamics of the major helminth infections of man (Anderson and May, 1982a).

A. TIME SCALES

The relative time scales on which the dynamics of host and parasite populations operate are largely determined by the expected life spans of the human host and the various developmental stages of the parasite. The human host typically has a life span an order of magnitude or more in excess of any of the parasitic stages (certain filarial species may be an exception to this trend), while the free-living stages of the larval parasites within insect or molluscan intermediate hosts have life spans much shorter than those of the sexually mature parasites in man. These empirical observations enable significant simplifications to be made in the construction of mathematical models and in the analysis of their properties, without any serious loss of biological detail or accuracy. The dynamics of the population of adult parasites in man (which is the population of greatest epidemiological significance since it is directly or indirectly the cause of disease symptoms) can be examined under the assumption that the human population is approximately constant in size on a time scale appropriate to changes in adult parasite population size. Furthermore, it is reasonable to assume that the population of infective stages are essentially at equilibrium, due to the rapidity with which changes in these populations occur compared with those in the adult worm populations. This observation is of relevance not only to the schistosome parasites and the intestinal helminths but also to the filarial worms. It is therefore often appropriate to base mathematical models on a single equation to describe changes in the average worm burden within the human community.

B. DENSITY-DEPENDENT PROCESSES

As noted by Bradley (1972) and Anderson (1980), the observed stability of helminth populations in human communities is largely a consequence of density-dependent constraints on adult worm establishment, survival, and fecundity. Although man is unable to develop an effective protective response to helminths, in the sense that reinfection is the rule rather than the exception, he can mount nonspecific and immunological responses to the invasion of helminths; these responses act in a manner dependent on the degree of antigenic stimulation (parasite numbers) (Wakelin, 1978a,

1984). The net severity of these constraints is critically dependent on the statistical distribution of worm numbers per host. As we have seen for schistosomes, filarial nematodes, and intestinal worms, our current knowledge of those processes is rather limited. However, mathematical models show clearly their significance to overall dynamic behavior.

C. PARASITE DISTRIBUTIONS

The statistical distributions of worm numbers per host are invariably highly aggregated, with the majority of worms often being harboured by a minority of the host population. This appears to be the case irrespective of whether the host population is man (Fig. 11) or an intermediate invertebrate species (Fig. 29). The generative mechanisms of such patterns are

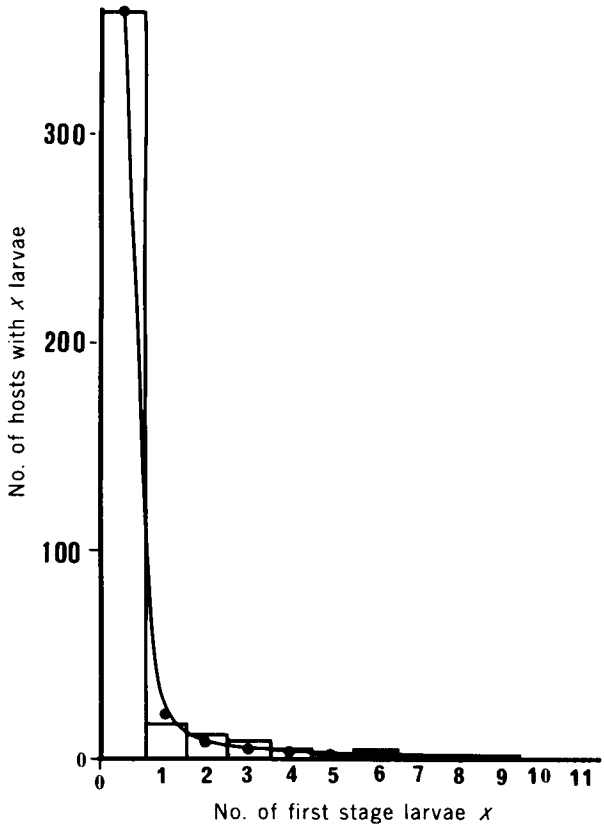

FIG. 29. Frequency distribution of the number of first-stage larvae of *Onchocera* spp. per fly vector (*Simulium damnosum*) (data from Cheke *et al.*, 1982). The histogram bars are observed values and the solid line denotes the best fit negative binomial model. Parameter values: $k = 0.073$, mean = 0.29.

many and varied, but include genetic, spatial, and behavioral factors. The negative binomial probability distribution has proved to be a good empirical model for observed patterns of aggregation; the degrees of aggregation (as measured inversely by the parameter k) are usually severe, with k typically being below unity (see Table 6). Such patterns clearly enhance the severity of density-dependent checks on the growth of adult parasite populations.

In certain instances the degree of worm contagion changes with host age. The general trend in such cases is for aggregation to decrease with age. More commonly, however, there is a remarkable degree of uniformity in aggregation throughout the various age classes of human communities (Fig. 30). This observation is somewhat surprising, since if repeated exposure to reinfection acts to enhance the immunological competence of man to resist invasion it might be expected that parasite aggregation would decline markedly in the older age classes. Density-dependent mechanisms induced by immune responses are known to decrease the variance of worm numbers per host (Anderson and Gordon, 1982; Crompton *et al.*, 1983). Observed uniformity, as seen in Fig. 30, may simply be a consequence of the few available data sets which permit aggregation estimates to be obtained for a variety of age classes within human communities. More data are required in this area.

D. MATING SUCCESS

The mating function is of obvious importance to the dynamic properties of mathematical models of human helminth transmission. Its nonlinearity creates multiple stable states and thus gives rise to the concept of an unstable breakpoint. It is important to note, however, that in practical terms its relevance is far less than was originally thought (Macdonald, 1965). For monogamous and polygamous species, the high degrees of parasite aggregation observed in human communities imply that the chance of a female worm being inseminated is essentially unity in value for all but very low average worm burdens per host. For example, recent studies of *Ascaris* and hookworm infections suggest that the breakpoint is of the order of 0.3–0.5 worms per host (Anderson, 1980; Croll *et al.*, 1982). For most practical purposes, therefore, the mathematical complexities induced by the formal inclusion of mating success in transmission models can safely be ignored.

E. THE BASIC REPRODUCTIVE RATE R_0

The concept of a basic reproductive rate, which combines measures of the various individual population rates involved in transmission into a

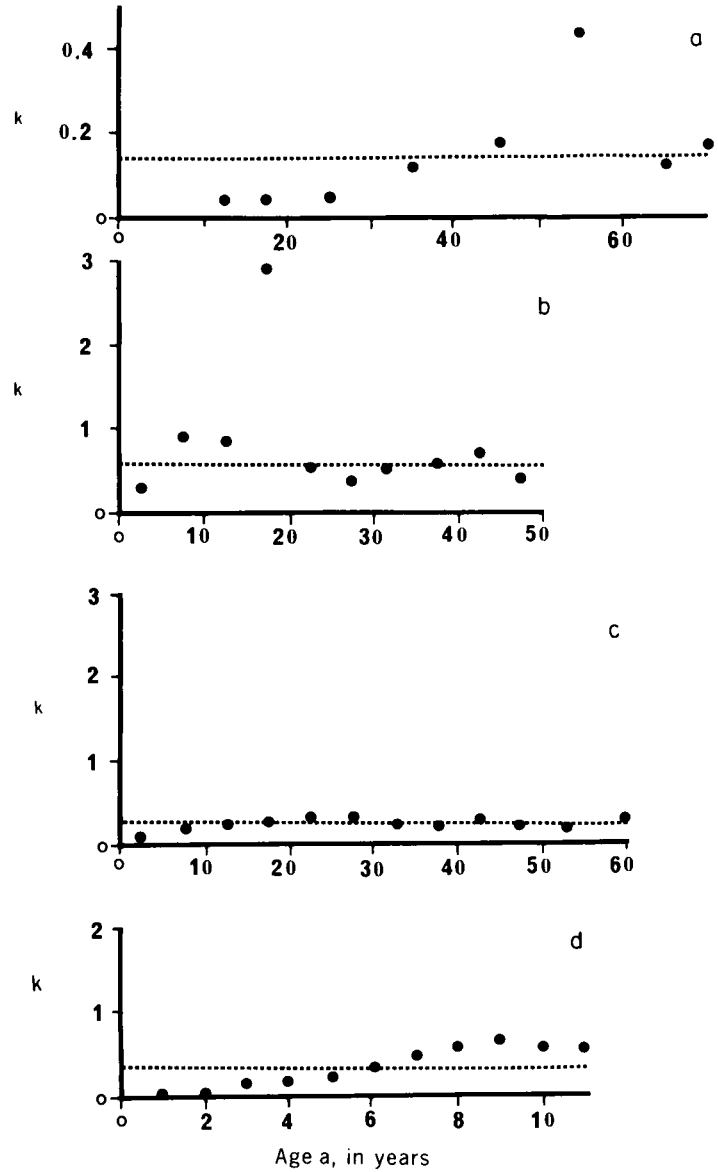

FIG. 30. Examples of age-dependent trends in the value of the negative binomial parameter k, which varies inversely with the degree of worm aggregation within the human population. (a) *S. mansoni* in Brazil (data from Cheever *et al.*, 1977). (b) *A. lumbricoides* in Iran (data from Croll *et al.*, 1982). (c) Hookworm in Taiwan (data from Hsieh, 1970). (d) *N. americanus* in India (data from Anderson, 1980).

single composite parameter, is of great theoretical and practical significance to epidemiological study. Most importantly, the condition $R_0 = 1$ defines a transmission threshold below which the parasite is unable to maintain itself in the human population. This condition therefore provides a focus for measures designed to control parasite abundance. If the helminth population attains a steady (equilibrium) state within the human community, the effective reproductive rate, R, is unity in value. In other words, each female parasite exactly replaces herself in the next generation. The magnitude of R_0 plays a dominant role, in conjunction with density-dependent factors and parasite distributions, in determining the shapes of observed age–prevalence or age–intensity curves. We will return to this issue later when dealing with the problems of estimating the value of R_0 from epidemiological data.

The principles summarized above (this section; A–E) can be embodied in a general mathematical framework to describe the transmission of helminth parasites within human communities. The framework must incorporate the age structure of the human population, because epidemiological data are most commonly collected in the form of age-related changes in parasite prevalence and intensity. Consider changes in the average burden of adult worms per person, $M(a,t)$, with respect to age a (horizontal changes) and time t (longitudinal changes). We can write down a general partial differential equation for $M(a,t)$:

$$\partial M(a,t)/\partial a + \partial M(a,t)/\partial t = \Lambda(a,t) - M(a,t)\, f_2(M,k) \qquad (55)$$

Here the function $\Lambda(a,t)$ is defined for notational convenience as

$$\Lambda(a,t) = T(a,M,k) \int_0^\infty L(a)\, M(t,a)\, f_1(M,k)\, da \Big/ \int_0^\infty L(a)\, da \qquad (56)$$

The functions f_1 and f_2 represent density-dependent constraints on parasite fecundity and mortality, respectively. They are formulated as functions of the mean worm burden M and the degree of parasite contagion within the host population k (assuming a negative binomial distribution of numbers per person). The net output of parasite transmission stages into the environment is represented by the integral

$$\int_0^\infty L(a)\, M(t,a)\, f_1(M_1k)\, da \Big/ \int_0^\infty L(a)\, da$$

which represents the contribution from each age class of the human community weighted by the proportion of the total population of people who are in that age class. The quantity $L(a)$ is the probability that a host survives to age a; human life expectancy L is simply $L = \int_0^\infty L(a)\, da$ (the human community is assumed to be of constant size with a stable age distribution). The term $T(a,M,k)$ denotes the collapsed details of parasite

survival, reproduction, and transmission via the segments of the life cycle not involving man. It is expressed as a function of worm density, worm distribution, and host age to encompass density-dependent establishment of the parasites in man and age-specific rates of human contact with the transmission stages.

Although the model is a fairly general statement of the potential dynamics of a human helminth infection, it is of limited application as it stands due to the unspecified nature of the functions T_1, f_1, and f_2. To illustrate the model in action, we consider the intestinal worm *Ascaris lumbricoides*. For this species it is believed that the major density-dependent constraint on parasite population growth falls on the fecundity term (in the absence of empirical evidence concerning establishment and survival). A good example is illustrated in Fig. 26, where the total egg output per female worm is shown to decay exponentially as total worm burden rises. Given a negative binomial distribution of parasites, the function f_2 is of the form

$$f_2(M|k) = [1 + (1 - z)(M/k)]^{-(k+1)} \tag{57}$$

where $z = \exp(-\gamma)$ [see Eq. (35)]. If the establishment and survival are assumed to be density independent, and contact with infective stages assumed to be independent of host age, Eq. (56) simplifies to

$$\Lambda(t) = (R_0/AL) \int_0^\infty L(a)\, M(a,t)\, f_1(M,k)\, da \tag{58}$$

where L is human life expectancy, $A = (1/\mu_1)$ is the life expectancy of adult worms, and R_0 is the basic reproductive rate as defined in Eq. (36). Given estimates of the various parameters, Eq. (47) can be solved by standard numerical procedures. Difficulties arise, however, in obtaining estimates of the basic reproductive rate R_0.

One approach, recently adopted by Anderson and May (1982a), is as follows. For certain endemic infections such as *Ascaris*, hookworm, and *Trichuris* (see Figs. 2, 3, and 4) the average worm burden rises rapidly as host age increases, reaching a plateau such that the mean worm burden $M(a,t)$ in the majority of age classes is essentially equal to the mean worm burden of the total population $\bar{M}(t)$. If the parasite is at a stable equilibrium within the community, with overall mean burden $\bar{M}^*$, a good estimate of Λ is given from Eqs. (57) and (58) by

$$\Lambda = (R_0\bar{M}^*/A)[1 + (1 - z)(\bar{M}^*/k)]^{-(k+1)} \tag{59}$$

At the stable state ($\partial M(t,a)/\partial t = 0$), changes in worm burden with age are therefore given by

$$dM(a)/da = \Lambda - [M(a)/A] \tag{60}$$

This equation has the solution

$$M(a) = \Lambda A(1 - e)^{-a/A} \tag{61}$$

The corresponding expression for the prevalence $P(a)$ is

$$P(a) = 1 - [1 + M(a)/k]^{-k} \tag{62}$$

It is here assumed that the distribution of parasites in the entire community remains approximately negative binomial in form with mean M^* and clumping parameter k. The precise overall distribution will be formed from a mixture of negative binomial distributions (one for each age class) as a consequence of the age-dependent human mortality terms, $L(a),si$ (Dietz, 1982b). The use of a common aggregation parameter, however, remains a good approximation provided parasite life expectancy is short in relation to that of man (see the discussion in previous sections). Empirical evidence suggests that the negative binomial model remains a good approximation for helminth numbers per host, even when samples consist of a mixture of individuals from different age classes of hosts (see Fig. 11).

Given independent estimates of worm and human life expectancy (A and L), of the degree of parasite aggregation (k), and of the severity of density-dependent constraints on worm fecundity (z), Eqs. (61) and (62) can be used to obtain estimates of R_0 from age–intensity and age–prevalence data. Two examples of the application of this method are displayed in Fig. 31: one concerns age–intensity data, and the other concerns the rate at which people reacquire worms after the application of chemotherapy within a community. Table 8 records estimates of the basic reproductive rate for a variety of helminths in different geographical locations.

In the estimation of R_0 by the method outlined above, it is assumed that independent estimates of worm life expectancy in man (A) are available. The estimation of this parameter is beset by obvious practical difficulties and hence widely quoted values (a summary of these is presented in Table 5) are often no more than guesses, based on qualitative as opposed to quantitative observations. For example, there is much confusion in the epidemiological literature between maximum and expected worm life spans. For the purpose of model construction and analysis, expected life span is the relevant parameter to describe the survival characteristic of the parasites in man. Unfortunately, maximum life span is more easily established on the basis of observations on the release of infective stages (eggs in faeces) by individuals who are no longer exposed to reinfection.

One way to estimate the life expectancy of worms is to monitor a sample of infected people, who are no longer exposed to reinfection (and do not receive treatment which increases the death rate of the worms), over a long period of time to record the rate at which individuals cease to show symptoms of infection (i.e., cease to have positive faecal egg counts

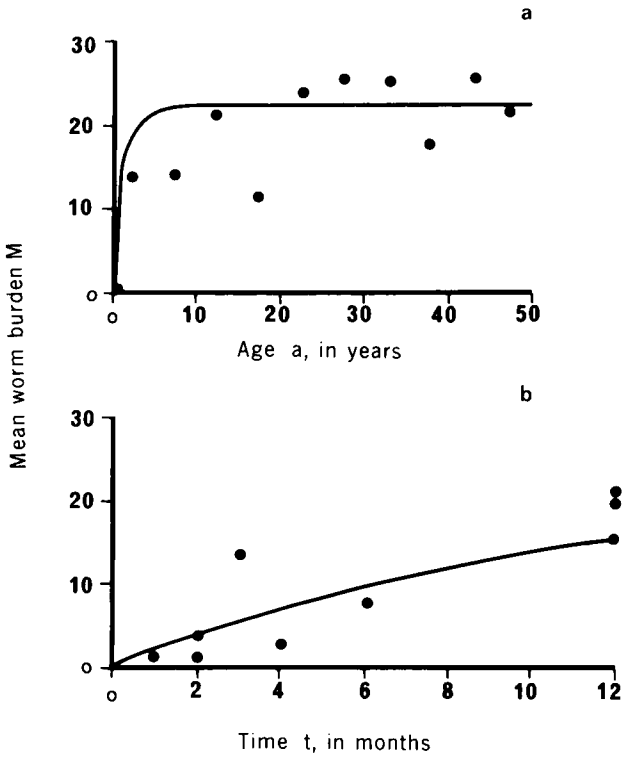

FIG. 31. Age–intensity data for *A. lumbricoides* within a rural community in Iran (data from Croll *et al.*, 1982) from which estimates of the basic reproductive rate R_0 can be obtained. (a) Changes in intensity with host age; the solid points are observed values and the solid line is the prediction of Eq. (61). Estimates of the parameters of the model are as follows: $R_0 = 4.3$, $M^* = 22$, $A = 1y$, $z = 0.96$, $k = 0.34$. (b) The increase in the average worm burden over a period of 12 months following chemotherapy (at time $t = 0$) (data from Croll *et al.*, 1982). The solid points are observed values and the solid line is the prediction of Eq. (61). Parameter values as defined for (a).

or positive microfilarial counts in skin snips). Cessation of symptoms is taken to imply that the individual is no longer infected. With data of this kind it is possible to use the simple models detailed in Eqs. (60) and (62) to gain rough estimates of worm death rates. For example, in the absence of reinfection, the average worm burden in a sample of people, $M(t)$, at time t from the cessation to infection is simply

$$M(t) = M(0) \exp(-t/A) \tag{63}$$

Here $M(0)$ is the initial average worm burden at $t = 0$ and A is worm life expectancy. The prevalence of infection at time t, $P(t)$, within the sample

TABLE 8
Estimates of the basic reproductive rate R_0 *for different species of helminths in different geographical locations*

Parasite	R_0	Country	Reference
Ascaris lumbricoides	4–5	Iran	Croll *et al.* (1982)
	1–3	Burma	Hliang *et al.* (1983)
	1–2	Bangladesh	Martin *et al.* (1983)
Necator americanus	2–3	India	Anderson (1980)
Trichuris trichiura	4–6	Jamaica	Bundy *et al.* (1982)
Schistosoma haematobium	2–3	Egypt	Hairston (1965a)
Schistosoma mansoni	1–2	Brazil	Anderson and May (1982a)
	1-2	Egypt	Hairston (1965a)
Schistosoma japonicum	1–4	Philippines	Barbour (1982)
Onchocerca volvulus	50	Cameroon	Dietz (1982a)
	9–74	Ivory Coast	Dietz (1982a)

is then given by

$$P(t) = 1 - \{1 + [M(0) \exp(-t/A)]/k\}^{-k} \tag{64}$$

where k is the dispersion parameter of the negative binomial. Note that for a high degree of parasite aggregation (low k) the average worm burden $M(t)$ decays much more rapidly than the prevalence $P(t)$ (Fig. 32). Equation (64) has three unknowns, namely $M(0)$, A, and k. Nonlinear statistical procedures can be used to estimate these parameters given the availability of extensive data which record the value of $P(t)$ over many time intervals. An example of the application of this approach to data concerning infections of the filarial nematode *Wuchereria bancrofti* is presented in Fig. 33a.

In these circumstances, the initial decline in prevalence is relatively slow, and depends in a complicated way on the average worm burden and on the pattern of distribution of worms among the host population. Once the time elapsed since cessation from exposure is long compared with the average life span of a worm, $t >> A$, most hosts harbour either one or no worms, and Eq. (64) simplifies to the approximate relation

$$P(t >> A) \simeq M(0)e^{-t/A} \tag{65}$$

Equivalently, this relation has the form

$$\ln P \simeq (\text{constant}) - t/A \tag{66}$$

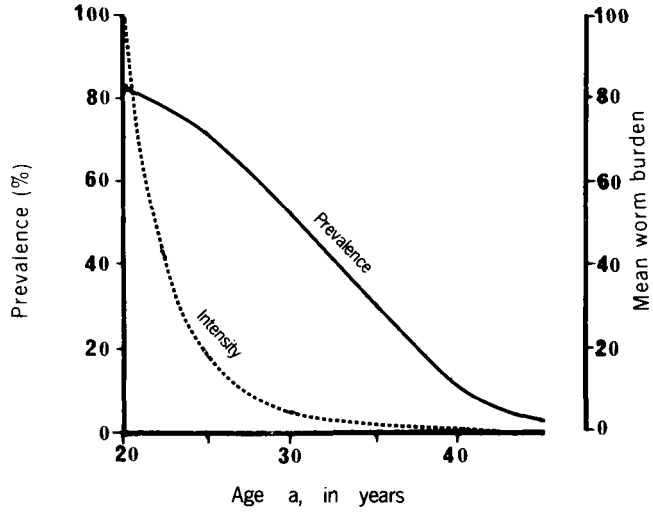

FIG. 32. The decay in prevalence and intensity of infection in man following a cessation in transmission or exposure to infection. Based on predictions of Eqs. (63) and (64) with parameter values of $M_0 = 100$, $k = 0.3$, $\mu = 0.333$ year^{-1}.

Thus a plot of ln P against t tends toward a straight-line relationship for large values of t; the slope of this line gives a direct estimate of A. Figure 33b (differing from Fig. 33a in that prevalence is plotted logarithmically rather than linearly) illustrates these "two phases" of decline in prevalence: an initial slow and complicated decline and a later straight line decay. Webber (1975) noted this pattern in his data, but the explanation he offers is unnecessarily involved.

The agreement shown in Fig. 33a and b between the data and the simple model is encouraging, because this model (and associated method of estimating A) is crude. Among other approximations, it assumes that the death rate of adult parasites is age and density independent and that the degree of parasite clumping (k) is independent of the average worm burden.

A simplification of the model defined by Eq. (55) can also be used to approximate changes in the overall mean worm burden $\bar{M}(t)$ with respect to time, where $\bar{M}(t)$ is given by

$$\bar{M}(t) = \int_0^\infty M(a,t)\, L(a)\, da \Big/ \int_0^\infty L(a)\, da \tag{67}$$

A crude approximation to temporal changes may therefore be expressed as

$$d\bar{M}(t)/dt = [\bar{M}(t)/A][R_0 f_1(\bar{M}(t),k) - 1] \tag{68}$$

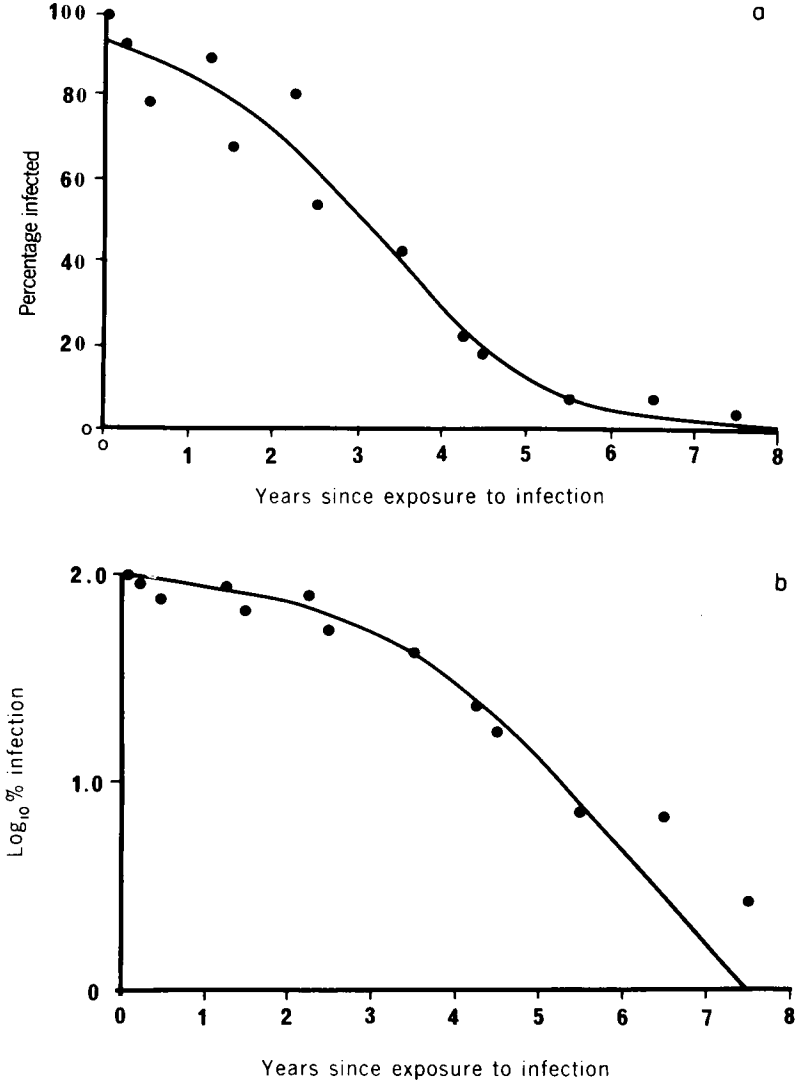

FIG. 33. (a) The decay in the prevalence of infection with *Wuchereria bancrofti* within a sample of people who were no longer exposed to infection. The solid circles are observed values (data from Webber, 1975) and the solid line is the prediction of the model defined by Eq. (64). Parameter values, estimated by a nonlinear least-squares technique, are $k = 0.61$, $\mu = 1.1$ year^{-1}, $M_0 = 39.2$. (b) Identical to (a) except the vertical axis is plotted on a logarithmic scale.

where f_1 is as defined in Eq. (57) with M replaced by $\bar{M}$. The equilibrium average worm burden $\bar{M}^*$ and prevalence $\bar{P}^*$ within the total population are obtained by setting $d\bar{M}(t)/dt = 0$. This gives

$$\bar{M}^* = [R_0^{1/(k+1)} - 1][k/(1 - z)] \tag{69}$$

and

$$\bar{P}^* = 1 - [1 + \bar{M}^*/k]^{-k} \tag{70}$$

Equation (69) makes clear how the parameters R_0, k, and z influence the overall average worm burden.

For a fixed value of the basic reproductive rate R_0, the mean burden declines rapidly as the degree of parasite aggregation (measured by the smallness of the value of k) and the degree of density-dependent constraints on fecundity (measured by the smallness of the value of z) increase (Fig. 34a). Also note that provided the value of k is constant and independent of changes in $\bar{M}^*$, the prevalence of infection declines much more slowly than the average worm burden (Fig. 34b). It is also clear from Eq. (69) that R_0 must be equal to or exceed unity in value if the parasite is to maintain itself within the community ($\bar{M}^* > 0$).

In both simplifications discussed above, the net rate of infection is assumed to be independent of host age and to depend only on the average number of transmission stages in the environment of the human community. Age-related changes in parasite intensity and prevalence are a feature of many sets of epidemiological data (see Fig. 35 and Fig. 36). The force of infection (Λ) may be related to host age due to a wide variety of factors including rates of contact with infective stages (or infected vectors), the severity of density-dependent factors (mediated by age-related changes in host nutrition and/or host resistance to infection), or the degree of worm contagion in different age classes of the population. Acquired partial immunity was thought to be of particular significance for schistosome and filarial infections (Warren, 1973). Indeed, for schistosomes the term *concomitant immunity* arose, on the basis of laboratory studies, to denote protection to reinfection despite the presence of "disguised" adult worms within the host (Smithers and Terry, 1969). Today, the significance of acquired protection to helminth infection in man is a matter of some controversy. Specifically, for schistosome parasites studies of rates of human contacts with water suggest that age-related changes in this variable may explain a substantial proportion of age-related variation in parasite intensity and prevalence (Warren, 1973, 1981; Dalton and Pole, 1978).

Although both immunity and contact probably play a role, it is beginning to appear as though age-related changes in the force of infection are of major significance as determinants of observed epidemiological patterns.

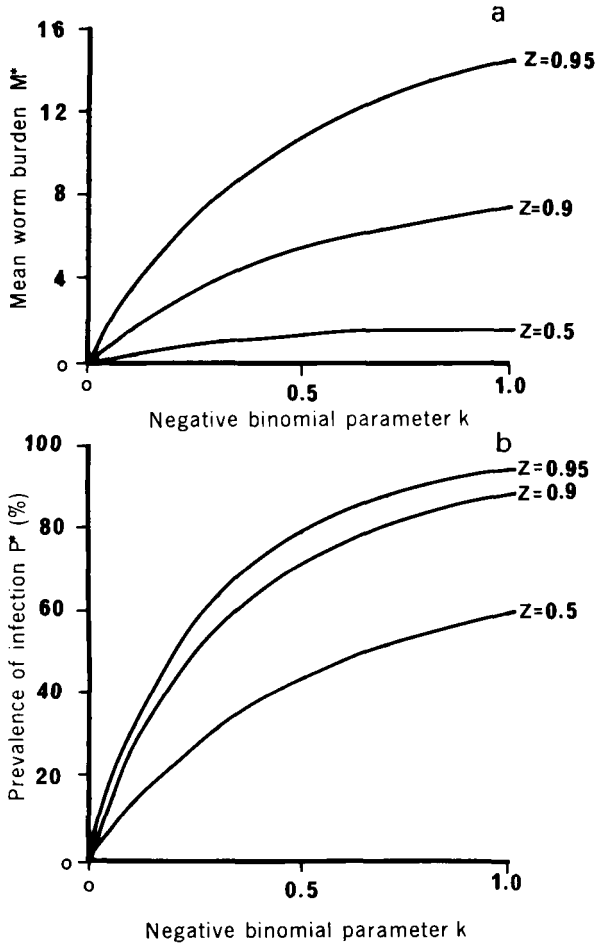

FIG. 34. The relationship between the mean equilibrium worm burden M^* (a) and the equilibrium prevalence of infection (b) and the degree of parasite contagion (measured inversely by the negative binomial parameter k) and the severity of density-dependent constraints on worm fecundity (measured inversely by the parameter z) based on the predictions of Eq. (61) in the main text. Parameter values: $R_0 = 3$, $A = 1$.

A rough guide to the impact of an age-dependent force of infection $\Lambda(a)$ (on age–intensity and –prevalence trends) may be obtained by modification of Eq. (60), to give

$$dM(a)/da = \Lambda(a) - M(a)/A \tag{71}$$

This has the solution

$$M(a) = e^{-a/A} \int_0^a \Lambda(u)\, e^{u/A}\, du \tag{72}$$

Figure 35 illustrates the changes in $M(a)$ and $P(a)$ [see Eq. (62)] with age, for an arbitrary chosen function $\Lambda(a)$ which initially increases in value during early childhood but then declines in the older age classes. The differential rates of decline in intensity and prevalence in the older age classes are reminiscent of patterns recorded for age-related changes in schistosome intensity and prevalence (see Fig. 5). This example further illustrates the dangers inherent in using measures of helminth prevalence

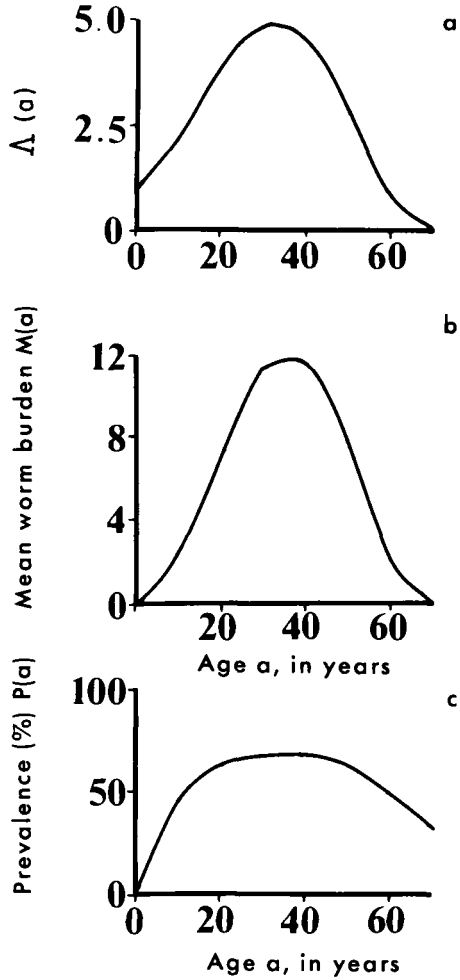

FIG. 35. The impact of an age-dependent force of infection $\Lambda(a)$ (in graph a) on changes in the average worm burden (b) and the prevalence of infection (c) with respect to host age. An arbitrary function for $\Lambda(a)$ is chosen of polynomial form where $\Lambda(a) = d_1 + d_2a + d_3a^2 + d_4a^3 + d_5a^4$ (with parameter values: $d_1 = 1.08$, $d_2 = 0.011$, $d_3 = 0.014$, $d_4 = -4.252 \times 10^{-4}$, $d_5 = 3.72 \times 10^{-6}$). The predictions displayed in (b) and (c) are obtained by the numerical solution of Eq. (72) (with parameter values: $\Lambda(a)$ as defined in this legend, $k = 0.3$, $A = 3$).

as an indication of the magnitude of parasite abundance (and hence the frequency of disease symptoms) within the human community. A specific example of age-related changes in $\Lambda(a)$ for hookworm infections in a rural community in Taiwan (data from Hsieh, 1970) is displayed in Fig. 36.

Analytical insights into the dynamic properties of the age-structured

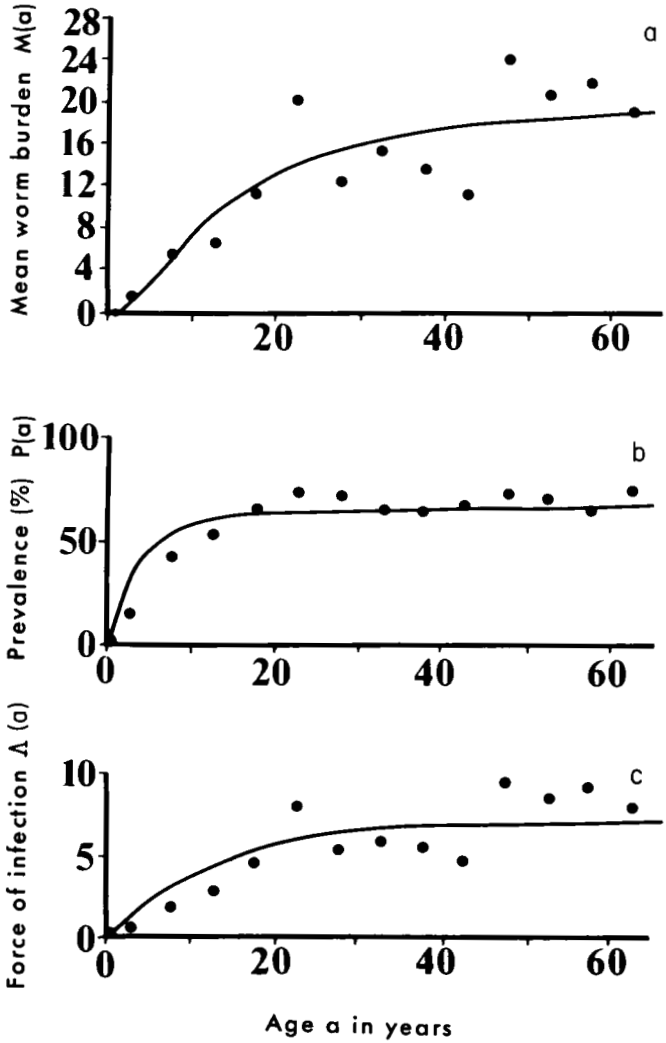

FIG. 36. Age–intensity (a) and age–prevalence (b) curves for hookworm infections in a rural community in Taiwan (data from Hsieh, 1970). The solid points are observed values and the solid lines are the predictions of the model defined by Eqs. (71) and (72) in the main text (parameter values: $M^* = 17.5$, $A = 2.5y$, $z = 0.99$, $k = 0.08$). The force of infection $\Lambda(a)$ is as defined in (c) and the observed values (solid points) are well described empirically by the function (solid line) $\Lambda(a) = d_1(1 - e^{-d_2 a})$ where $d_1 = 7$ and $d_2 = 0.08$.

model defined at the start of this section [Eqs. (55) and (56)] have been made possible by the consideration of special cases. Analytical treatment is made difficult if a variety of density-dependent processes operate within the life cycle of the parasite, and if age-related changes influence the force of infection. In such circumstances numerical methods can be employed to generate temporal predictions of age-related changes in parasite abundance and prevalence; this approach is, however, dependent on the availability of parameter estimates of the numerous population rates involved in helminth life cycles. Most importantly, the manner in which the basic reproductive rate R_0 is estimated from age–intensity and age–prevalence data depends on the assumptions incorporated into the framework of the model. Future work in this area must focus both on the question of how sensitive such estimates are to model structure, and on the design of data collection programmes aimed at improving our biological knowledge of density-dependent factors and worm life expectancies.

IX. Control of Helminth Infections

A wide range of methods are currently used in attempts to control helminth infections in human communities. These include chemotherapy, improved sanitation and hygiene, education, and—in the case of indirectly transmitted parasites such as schistosomes and filarial worms—vector and intermediate host control. New techniques based on the use of monoclonal antibodies raise the exciting possibility that vaccination against human helminths may be feasible in the future.

Chemotherapy is one of the most widely employed techniques and today safe, effective, and cheap chemotherapeutic agents are available for the majority of the major helminth infections of man, excluding the filarial infections (Miller *et al.*, 1974; van den Bossche, 1978; Katz *et al.*, 1979; Wagner, 1980). However, there remains a need, often unperceived, for a better understanding of the most cost-effective ways of delivering these drugs, not at the individual level, but in the community as a whole. Effective community control of helminths is greatly aided by a sound and detailed understanding of the factors that regulate parasite transmission and abundance, and contribute to the frequently observed stability of their populations (Schad and Rozeboom, 1976; Anderson and May, 1982a).

Mathematical models not only help to improve our understanding of population dynamics, but also provide a powerful tool for the assessment and evaluation of different approaches to control. If used sensibly, they can generate both qualitative and quantitative guidelines for the application of specific chemotherapeutic agents. Central to their use is the notion

of the parasites' basic reproductive rate R_0, and the concept of a transmission threshold at the point $R_0 = 1$ (below which the parasite is unable to maintain itself within the human community). In this section we summarize the major principles to emerge from mathematical studies of control; we concentrate on chemotherapy and vaccination, but also briefly comment on hygiene, sanitation, and vector control.

A. CHEMOTHERAPY

Many of the drugs currently in use to control helminth infections are extremely effective. Often a single dose, or short course of treatment, removes more than 95% of an individual's worm burden (van den Bossche, 1978; Miller *et al.*, 1974). The central questions in community control, however, concern the long-term suppression (or eradication) of infection within a population. How best can this be achieved, given the all important constraint of limited resources for drug purchase and the remarkable ability of helminth populations to return rapidly to their precontrol levels once chemotherapy ceases? Is the selective treatment of the more heavily infected individuals of greater benefit to the community (both in terms of cost and reducing the prevalence of disease symptoms) than random or blanket chemotherapy?

Some insight into these problems can be obtained by adapting the models outlined in the previous section to include an extra parasite mortality term to mimic the effects of drug application. We first consider mass chemotherapy and focus on the long-term effects of different levels of application. Initially, for simplicity, we adopt the model defined by Eq. (68); this model ignores age structure and describes temporal changes in the mean worm burden within the total population, $\bar{M}(t)$.

If a drug is administered randomly within a population by treating a proportion g of the community per unit of time and if the drug has an efficacy h (the average proportion of the worm burden killed by a single, or short course of treatment), the resulting increase in the per capita death rate of adult worms, c, is given by (Anderson, 1980):

$$c = -\ln(1 - gh) \tag{73}$$

By subtracting the additional death rate due to treatment, cM, from the right-hand side of Eq. (68), the average worm burden $\hat{M}$ at the new equilibrium established by the control program is

$$\hat{M} = k(\{R_0/[1 - A \ln(1 - gh)]\}^{1/(k+1)} - 1)/(1 - z) \tag{74}$$

To eradicate the infection, the effective reproductive rate R (the basic reproductive rate R_0, modified by the action of chemotherapy) must be

reduced below unity. To achieve this, the proportion of the population treated at random per unit of time must exceed a critical value $\hat{g}$ where

$$\hat{g} = \{1 - \exp[(1 - R_0)/A]\}/h \tag{75}$$

To take a specific example, this equation suggests that given a parasite with R_0 and A values of 3 and 1 year^{-1}, respectively, a drug of 95% (h) efficacy would have to be administered to greater than 91% of the population each year. If the value of the basic reproductive rate was as high as 5 (with the same A and h values) then treatment at yearly intervals would not suffice to achieve eradication. On a monthly treatment schedule, an R_0 value of 5 would require the treatment of 28% of the population every month. The relationship between the actual value of $\hat{g}$ and various values of R_0 and A is displayed in Fig. 37.

The effective application of chemotherapy within a community must take into account not only the value of the basic reproductive rate R_0 but also the stability properties of the parasite population. If chemotherapy ceases before the mean worm burden falls below the breakpoint level M_μ (see Fig. 37), the parasite population will return to its precontrol equilibrium level. The rapidity of return will depend on the the magnitudes of the

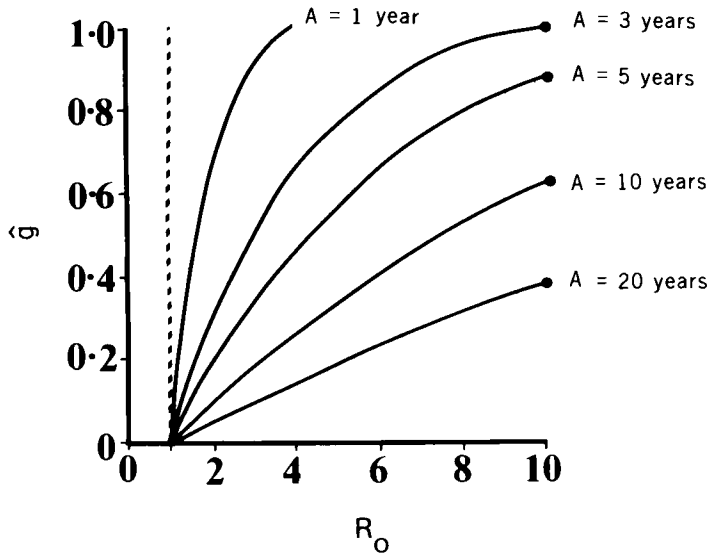

FIG. 37. The influence of changes in adult worm life expectancy A and the basic reproductive rate R_0 on the value of the critical proportion, $\hat{g}$, of the population that must be treated with anthelmintics per unit of time for parasite eradication. The curves are based upon the prediction of Eq. (75) (parameter value: $h = 0.05$). Dotted line depicts transmission threshold, $R_0 = 1$.

parameters R_0 and worm life expectancy A, as illustrated in Fig. 38. As discussed earlier, the breakpoint M_μ appears to be very low for many helminths (probably an average worm burden of less than one per host, given the high degrees of parasite contagion that are observed; see Table 6).

Treatment, therefore, must be continued at a rate above the critical value $\hat{g}$ for a period in excess of the maximum life span of the longest lived stage in the parasites' life cycle (invariably the adult worm). This result is

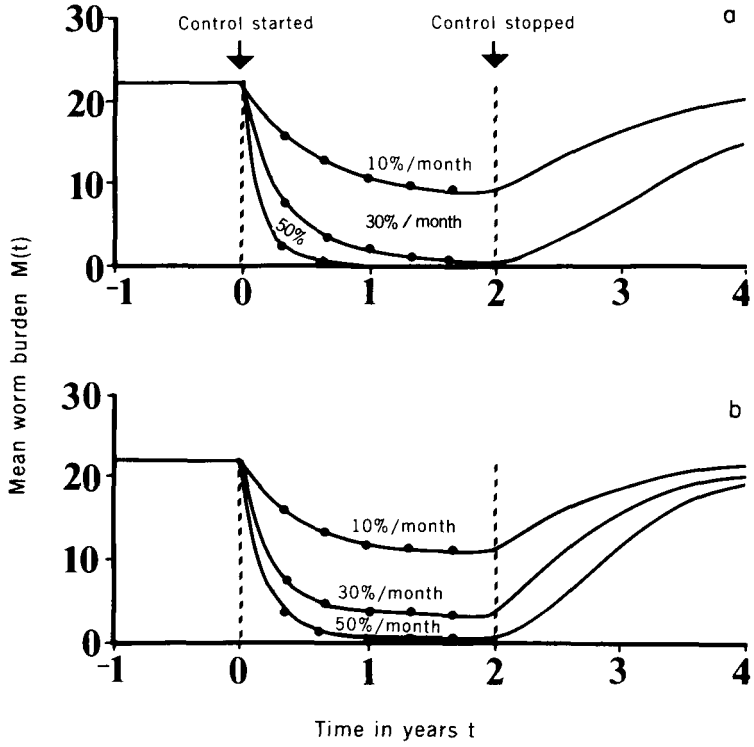

FIG. 38. The impact of cessation in community chemotherapy on the rate at which the average worm burden returns to its precontrol level (M^*). Two examples are given based on the numerical solution of Eq. (68) with the addition of an extra mortality rate c to mimic the action of anthelmintic treatment [see Eq. (73)]. Time-dependent solutions are recorded for various levels of drug treatment recorded as the percentage of the population treated per month. The mean burden M^* prior to treatment was set at 22 worms and at time $t = 0$ chemotherapy is administered on a continual basis to varying proportions of the population for a period of 2 years. After 2 years control ceases. Parameter values: in (a) $R_0 = 4.3$, $h = 0.9$, $k = 0.57$, $z = 0.96$, $A = 1y$; (b) $R_0 = 8.6$, $h = 0.9$, $z = 0.96$, $k = 0.57$, $A = 1y$. The simulations are designed to mimic the impact of chemotherapy on the dynamics of *A. lumbricoides*.

not encouraging and argues that eradication by mass random chemotherapy is not always a practical objective, given the complications induced by immigration of infected people from communities outside the control area. Eradication will only be achieved if chemotherapy is applied intensively over long periods of time and this of course will be a costly course of action. Practical experience substantially supports these conclusions. Many examples exist in the literature showing that worm burdens rapidly return to their precontrol levels once chemotherapy ceases (Fig. 31b) and that treatment must be applied frequently for substantial suppression of parasite prevalence and abundance (Fig. 39).

On a more practical note, our simple model for the way chemotherapy acts on the dynamics of parasite populations illustrates a theme that has emerged in earlier sections: the differential impact of changes in parameter values on the prevalence and intensity of infection. As displayed in Fig. 40, the equilibrium worm burden, under the impact of control, decays approximately exponentially as the intensity of treatment increases. The prevalence, however, remains relatively high until the proportion treated g approaches the critical value $\hat{g}$.

In view of the difficulties of parasite eradication by mass chemotherapy, a slightly different approach is to aim at disease, as opposed to parasite eradication. Infection with helminth parasites is not synonymous with disease symptoms, since the latter invariably tend to depend on the

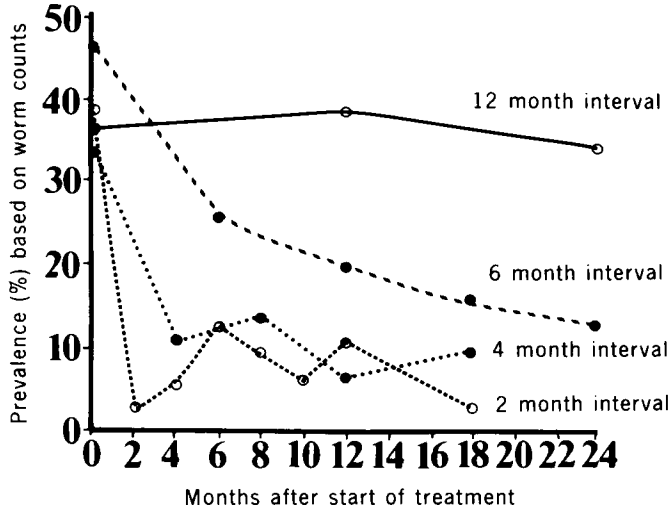

FIG. 39. The impact of various chemotherapy treatment intervals on the prevalence of *A. lumbricoides* in rural communities in Korea (data from Seo *et al.*, 1980) over a total period of 2 years. All individuals within the populations examined were treated at either 2, 4, 6, or 12 monthly intervals.

burden of worms harboured by an individual (Walsh and Warren, 1979; Warren, 1979, 1981; Davis *et al.*, 1979). If clinical symptoms of disease within a given community are known to be absent at a specific average worm burden, say m, then the aim of control may be viewed as the reduction of M^* (the mean burden prior to control) below the critical level m. If the proportion m/M^* is denoted by q, then the proportion $\hat{g}$ of the population that must be treated per unit of time to reduce M^* below m is given by

$$\hat{g} > \{1 - \exp[(1 - R_0)(1 - q)/A]\}/h \tag{76}$$

The successful application of this approach is of course dependent on a knowledge of the value of m. In practice, due to the highly clumped

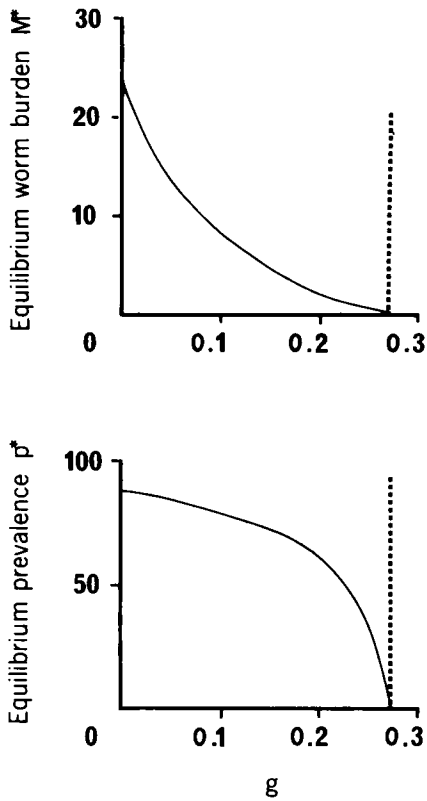

FIG. 40. The impact of chemotherapy (as expressed by g, the proportion of the population treated per month) on the equilibrium mean worm burden and equilibrium prevalence of infection. Parameter values: $R_0 = 4.3$, $A = 1y$, $k = 0.57$, $h = 0.9$. Based on the predictions of Eqs. (67) and (68) with the addition of an extra mortality term to mimic drug action on parasite survival [Eq. (73)].

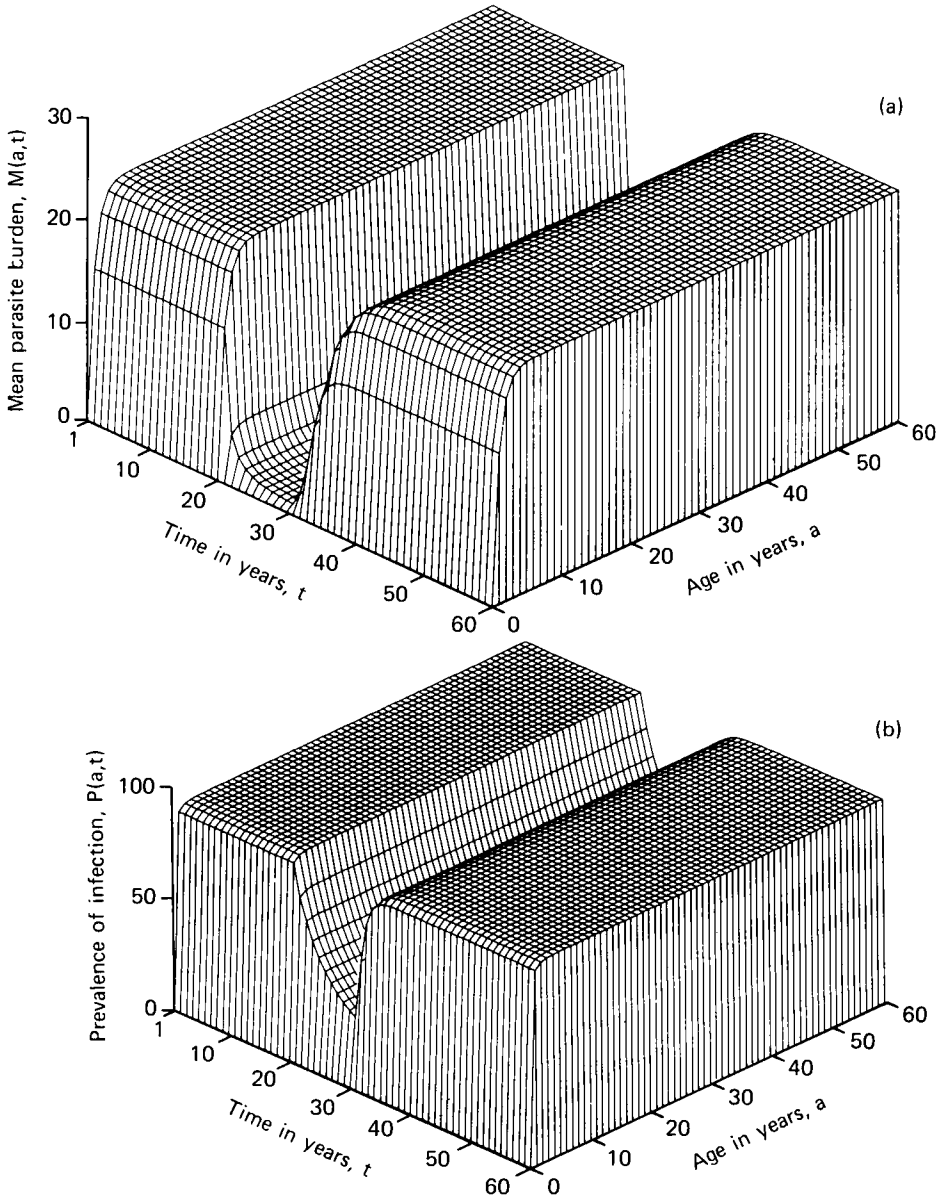

FIG. 41. Three-dimensional graphs obtained by the numerical solution of Eq. (55) (after Anderson and May, 1982a). The simulations are designed to mimic the dynamics of endemic ascariasis in a human community both with respect to time and host age. The two graphs portray changes in average worm load (a) and prevalence (b). For the first 20 years the helminth infection is its endemic equilibrium (with $\overline{M}^*$ set at 22 worms per host). In year 20 chemotherapy is initiated and applied randomly in the community on a continual basis where 20% of the population is treated each month ($g = 0.20$/month) with a drug of 95% efficiacy ($h = 0.95$). After 10 years the treatment is stopped and the parasite population

nature of helminth distributions, m may be a rather low average burden. A better approach might be selectively to treat the most heavily infected individuals to suppress symptoms of disease, as opposed to mass random treatment.

Before considering selective treatment, it is worth noting that the approach outlined above for random treatment can be generalized to encompass representation of the age structure of the human community. Essentially we return to the partial differential equation mode [Eq. (55)] which described changes in the average worm burden in age class a at time t, $M(a,t)$, with respect to time and age, and add an extra death rate to represent the action of chemotherapy. Numerical methods can be employed to generate time- and age-dependent changes in parasite burden under the influence of various mass treatment programmes (see Anderson and May, 1982a; Dietz, 1982a). An example of such projections is displayed in Fig. 41. The frequency of drug application can be made to depend on host age. Often, for example, both symptoms of disease and worm burdens are most intense within the child segment of the community. Aiming the bulk of chemotherapeutic treatment at this segment of the population is a crude form of selective application (age group targeting) (Fig. 42) and may be very beneficial for the suppression of disease prevalence. The benefits to be gained from this approach, however, depend critically on the distribution of worm numbers among the age classes within a community. For the example displayed in Fig. 43, representing the distribution of *Ascaris* in different age classes of a rural community in Burma, selective treatment of the 0- to 15-year-old age group would clearly be of great value (Hlaing *et al.*, 1983).

Anthelmintic drugs are often used intensively over short periods of time to reduce the prevalence of disease symptoms in a community. Frequently, such applications are given at irregular intervals with relatively long time periods between successive treatments. The objectives are to maximize the short-term benefits and minimize the number of treatments and hence cost. In 1924 Smilie argued that the optimum way to apply mass chemotherapy was selectively to treat the most heavily infected individuals. More recently, Warren has refocused attention on this approach to helminth control (Warren, 1981; Mahmoud and Warren, 1980; Warren *et al.*, 1978; Warren and Mahmoud, 1976). There are obvious advantages attached to selective or targetted treatment in terms of cost and additional benefits accrue if the drug has side effects, or if there are

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returns to its precontrol equilibrium level. The human survivorship function $L(a)$ was chosen to mimic typical patterns in the developing world with a life expectancy L set at 50 years. Density dependence was assumed to act solely on worm fecundity (an exponential decay function) and the parameter values were set at $R_0 = 4.3$, $k = 0.57$, $z = 0.96$, $A = 1y$.

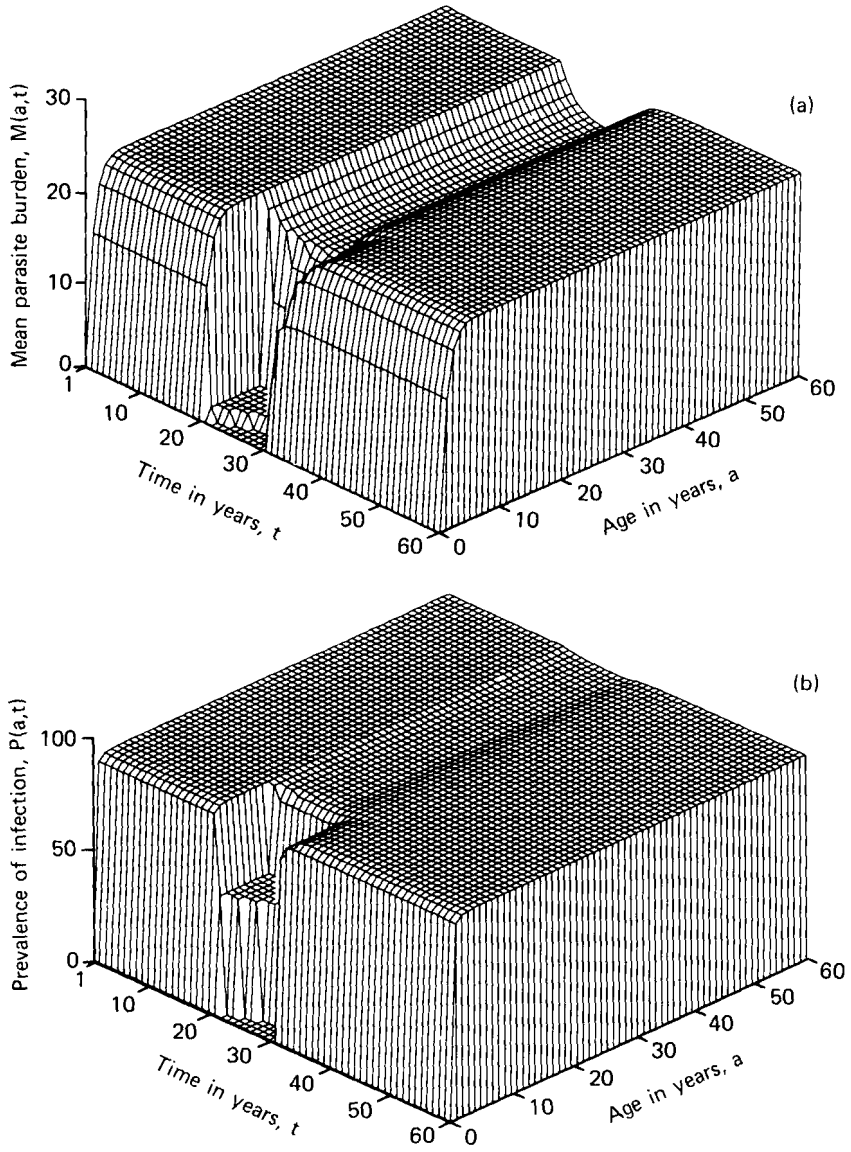

FIG. 42. Identical to Fig. (41) but with chemotherapy applied randomly only within the 0- to 15-year-old age classes. Parameter values as defined in the legend to Fig. 41, excepting g = 0.99 month^{-1}.

any worries about the evolution of drug-resistant strains of the parasite. There are many opponents to this approach, however, who argue that the extra costs involved in identifying the most heavily infected individuals far outweigh the benefits. In practical terms "wormy people" can be

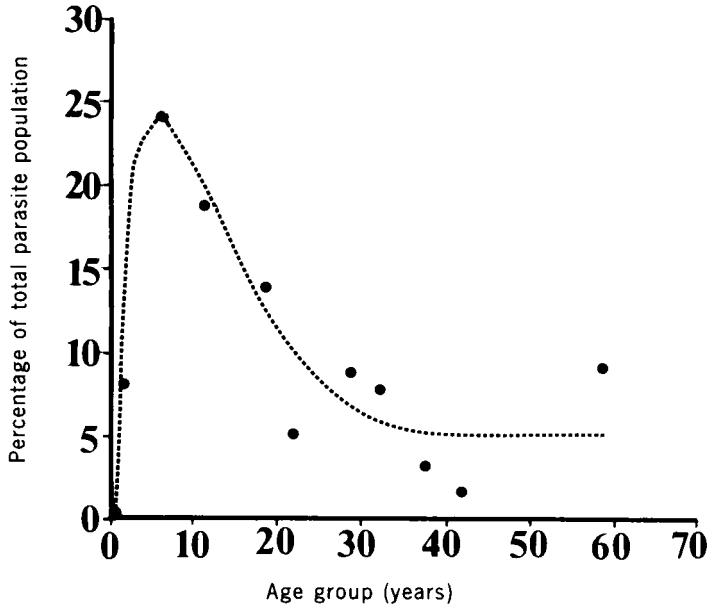

FIG. 43. The distribution of the percentage of the total population of *A. lumbricoides* within different age classes of a rural community in Burma (data from Hliang *et al.*, 1983).

identified by faecal egg counts, urine egg counts, skin snip larval counts, and blood larval counts, or by noting the occurrence of clinical symptoms of disease (Mahmoud and Warren, 1980). Egg counts may have a tendency to be unreliable indicators of worm burden, given the observed density-dependent associations between egg production and worm burdens (see Fig. 21).

Anderson and May (1982a) have recently employed mathematical models to examine the advantages to be gained from selective treatment in terms of short-term reductions in worm burden and disease prevalence. Consider, for example, the proportional reductions in average worm burden from a precontrol level M^* where the probability that an individual harbours i parasites is defined as $p(i)$, and the probability that he receives treatment is defined as $g(i)$. Given a drug with efficiency h, the average number of worms killed per person after selective treatment within a community is

$$\Delta M = h \sum_{0}^{\infty} i\, p(i)\, g(i) \tag{77}$$

Anderson and May (1982a) choose an arbitrary function to define $g(i)$

$$g(i) = f[1 - (1 - \alpha)e^{-i/I}] \tag{78}$$

with the properties that the constant f and α (both <1) define the upper and lower bounds on $g(i)$, respectively. The parameter I is a measure of the selectivity of the treatment. For example, if $I = 40$, approximately 60% of the individuals with 40 worms receive drug treatment. A continuous function for $g(i)$ is more realistic than a step function, because in practice there is always considerable uncertainty about the worm burden harboured by any given individual. The total proportion of the population treated, $\bar{g}$, is given by

$$\bar{g} = \sum_{i=0}^{\infty} g(i)\, p(i) \tag{79}$$

and hence [given the definition of $g(i)$ in Eq. (78)] the average number of worms killed ΔM becomes

$$\Delta M = hf\left[\sum_{i=0}^{\infty} i\, p(i) - (1 - \alpha) \sum_{i=0}^{\infty} i\, p(i)\, z^i\right] \tag{80}$$

where $z = \exp(-1/I)$.

Suppose the parasites are distributed in a negative binomial manner with clumping parameter k and probability-generating function $\Pi(z)$, where

$$\Pi(z) = [1 + M^*(1 - z)/k]^{-k} = \sum_{i=0}^{\infty} p(i)\, z^i \tag{81}$$

Then Eq. (80) becomes

$$\Delta M = hfM^*\{1 - z(1 - \alpha)[1 + M^*(1 - z)/k]^{-(k+1)}\} \tag{82}$$

In the limits $I \to \infty$ and $I \to 0$, denoting extreme selectivity and no selectivity, respectively, we have

$$\underset{I\to\infty}{\Delta M} = hf\alpha M^* \tag{83}$$

$$\underset{I\to 0}{\Delta M} = hfM^* \tag{84}$$

The average proportion treated, $\bar{g}$, under the negative binomial assumption is

$$\bar{g} = f\{1 - (1 - \alpha)[1 + (1 - z)M^*/k]^{-k}\} \tag{85}$$

The statistic of greatest practical relevance is the average proportion of the mean worm burden M^* removed (killed) by selective drug application, $\Delta M/M^*$. Now

$$\Delta M/M^* = \bar{g}h[G(I,M^*,k)/H(I,M^*,k)] \tag{86}$$

where

$$G(I,M^*,k) = 1 - z(1 - \alpha)[1 + (1 - z)M^*/k]^{-(k+1)} \tag{87}$$

and

$$H(I,M^*,k) = 1 - (1 - \alpha)[1 + (1 - z)M^*/k]^{-k} \qquad (88)$$

Similar manipulations can be performed to calculate the proportional reduction in the prevalence of infection, $\Delta P/P^*$, and average egg output by individuals in the population, $\Delta E/E^*$ (where P^* and E^* are the pre-control equilibrium prevalence and average egg output; see Anderson and May, 1982a).

An illustration of the impact of selective treatment with respect to the quantities $\Delta M/M^*$ and $\Delta P/P^*$ is presented in Fig. 44 for various assumptions concerning the distribution of parasite numbers per host, the total proportion treated ($\bar{g}$), and the degree of selectivity (I). The conclusion to emerge from this sort of analysis is that selective treatment is highly

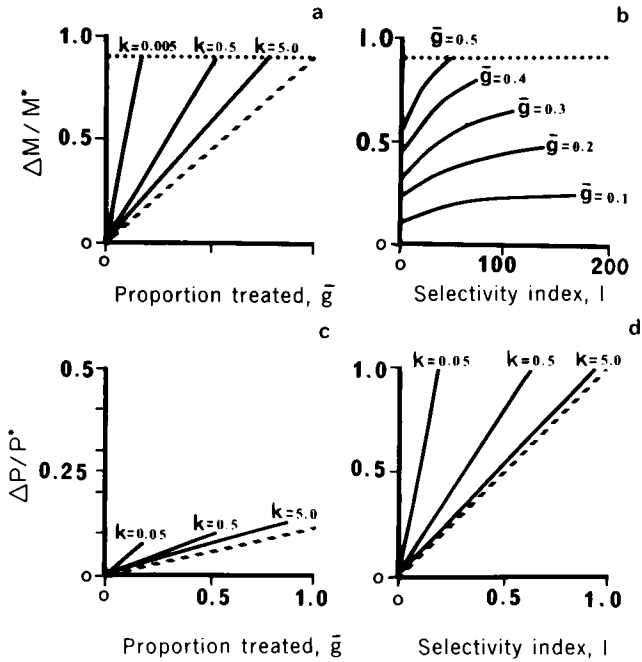

FIG. 44. The impact of selective chemotherapy on the proportional reduction in mean worm burden, $\Delta M/M^*$, and the prevalence of infection, $\Delta P/P^*$. (a) and (b) depict relationships between the proportional reduction in average worm burden immediately after a single mass treatment in a community in relation to (a) the proportion of the population treated, $\bar{g}$, and (b) the degree of selectivity in treatment, I, where the selectivity function is as defined by Eq. (78) for various assumptions about the distributions of worms in the human population (that is, various values of the negative binomial parameter, k). Parameter values: $I = 40$, $\alpha = 0$, $a = 1$, $h = 0.95$, $M^* = 40$; $k = 0.5$ in (b). Graphs (c) and (d) are similar but denote the relationships for the proportional reduction in prevalence. Dashed line depicts Poisson distribution of worms.

beneficial in terms of the number of treatments administered, provided the worms are highly clumped in their distribution within the host population. In practice, such clumping is indeed the case as reflected by the low k values recorded in Table 6. For the case illustrated in Fig. 44, where the selectivity index is set at 40 worms per host, a 50% reduction in average worm burden is achieved by treating 8% of the population when the parasites are highly clumped ($k = 0.05$). If the worms are randomly distributed (Poisson distribution), a 50% reduction can only be achieved by treating 50% of the population. There is little benefit to be gained from being too selective (I large); this is fortunate, given the practical difficulties involved in distinguishing between individuals who carried, say, 50 or 75 worms. Also note that selective treatment acts differently on average intensity than it does on prevalence. For a fixed level of selectivity, a greater reduction is achieved in average intensity than in prevalence. This is in part a consequence of the efficacy of the drug being less than 100%, but it is also a further example of the tendency of aggregated parasite distributions to generate small changes in prevalence for large variations in average worm load.

On theoretical grounds, selective treatment appears highly beneficial. In practical terms, however, the issue of costs is of major significance. On the one hand, costs are reduced by the smaller number of drug doses required to treat selectively. On the other hand, they are increased as a consequence of the necessity to identify "wormy" people. The relative importance of these opposing factors can only be assessed by carefully designed field trials in which the costs of selective treatment are compared in precise terms with the costs of mass or blanket chemotherapy. Work of this kind remains to be done.

An issue which may tip the balance of the arguments for and against selective treatment concerns the processes which generate clumped parasite distributions. A central question is whether or not those individuals with heavy worm burdens are predisposed to this state, not by chance, but by genetic, behavioural, or social factors. Indeed, it will be surprising if such factors are not crucial determinants of parasite distributions. To take but one example, there is an increasing volume of evidence to suggest that the establishment, fecundity, and mortality of helminth parasites are all markedly influenced by the genetic strain of the mouse or rat host employed in laboratory studies (Wakelin, 1978b, 1984).

For helminth infections in man, the answer to this issue is not clear at present although very recent studies provide some clues. In practical terms, field research must aim to monitor rates of reinfection following chemotherapeutic treatment, over a period of a few years, in order to ascertain whether or not those *individuals* with heavy worm burdens prior to treatment on average reacquire more worms than those with light worm

loads prior to treatment. Ideally, such studies should be based on records of worm burdens (expulsion chemotherapy), as opposed to indirect measures (such as fecal egg counts), to eliminate the sampling inaccuracies known to be inherent in these indirect scores and the problems arising from their nonlinear associations with worm burden. Epidemiological research on intestinal nematodes, employing expulsion chemotherapy techniques, would appear to have the greatest potential for improving our understanding of parasite distributions. Work of this nature is currently in progress, but firm results are as yet unavailable. Additional insights will emerge when such expulsion and reinfection studies are linked with research in communities with endemic infection on human behavior, immunology, and population genetics.

A recent study (Schad and Anderson, 1985) provides a strong hint that heavily infected individuals ("wormy persons") are predisposed to this state. The study (on mixed hookworm infections in India) is based on indirect measures of worm burden (faecal egg counts) before, and at various periods after, treatment with antihelminthic agents. It yields a statistically significant positive association (based on nonparametric statistical rank correlation tests) between pretreatment egg counts in individual patients and egg counts following a 1- to 2-year period of reinfection (Schad and Anderson, 1985). Predisposition may result from ecological, genetic, nutritional, social, or behavioural factors, acting either in isolation or in combination. For example, dense populations of infective hookworm larvae abound where human faeces are habitually deposited on loamy soils in warm, moist, and well-shaded sites. Alternatively, social status or occupation may determine the degree of contact with faecally polluted soils or water bodies with high concentrations of cercariae. Similarly, behavioural factors, particularly those associated with personal hygiene and defaecation habits, are likely to play a role in determining exposure to infection. Aggregated distributions of worm numbers per person and predisposition may therefore be explained solely on the basis of transmission-linked factors alone. Such explanations have gained wide acceptance in the absence of direct evidence for genetically controlled resistance mechanisms to helminth infection of man. Recent work on animal models, however, clearly points to the significance of genetic factors as determinants of susceptibility and resistance mechanisms (Cohen and Warren, 1982; Mitchell and Anderson, 1982; Wakelin, 1984). It seems likely that predisposition to heavy infection may arise as a result of a person's inability to mount effective responses (specific and nonspecific) to helminth invasion. Similarly, lightly infected people may have very effective resistant mechanisms. Ineffectiveness and effectiveness (and all degrees of responsiveness) are likely to be under genetic control. We suggest that clumped worm distributions and predisposition arise primar-

ily as a result of the combined forces of heterogeneity in exposure to infection and genetically determined host resistance mechanisms.

Analyses of individual patterns of reinfection in patients, however, do not necessarily provide evidence on the causal mechanisms of predisposition. Much more research is required to elucidate the underlying mechanisms. Irrespective of this, significant positive associations between pre- and posttreatment levels of infections have important practical implications for the planning of drug-based control programmes. Selective or targetted chemotherapy has many practical advantages if predisposition turns out to be a widespread phenomenon for helminth infections. Once identified, treatment could be continually focused on the "wormy persons," thereby eliminating the necessity of repeated identification at each round of drug administration.

The recent work of Anderson and May (1982a) is simply concerned with the short-term benefits (measured as reductions in average worm load or prevalence) following a single or short course of selective treatment. It is clearly necessary to extend this work to examine the long-term impact of repeated selective treatment. This is not easy with the hybrid model employed by Anderson and May (1982a), since the mathematical framework does not take account of the impact of treatment on the distribution of worm numbers per host. By definition, selective treatment will act to alter this distribution, tending to reduce the degree of clumping, and hence a fully stochastic model is probably needed. This type of approach would enable the probability distribution of worm numbers to be determined both by the population processes controlling parasite transmission and by selective treatment.

B. SANITATION, HYGIENE, AND EDUCATION

Excepting the filarial nematodes, the infective stages of most helminth parasites of humans leave the definitive host via the faeces or urine. The effective disposal of sewage together with good standards of personal hygiene are therefore extremely effective forms of parasite control. Education clearly plays an important role in the long-term success of such measures

With respect to the transmission dynamics of the parasite, improved sanitation acts to reduce the net flow of infective stages into the habitat with which man has contact. As such, it serves to reduce the value of the basic reproductive rate R_0 of the parasite. A quantitative assessment of the impact of such measures can therefore be based on observed changes in the age–prevalence and age–intensity curves of infection. Given the availability of a suitable model framework (see Section V), the relative change in the value of the reproductive rate can be determined. Thence an

assessment can be made of the intensity of control required to reduce R_0 below the transmission threshold. This sounds straightforward in theory but it is as yet to be attempted in practice.

Common sense dictates that effective sewage disposal provides the basis for a long-term solution to the control of many helminth infections of man. Many practical difficulties arise, however, in the implementation of such measures, primarily as a consequence of inadequate resources and lack of technical backup for the maintenance of disposal facilities within developing countries. Chemotherapy, therefore, remains a widely used and important method for the control of helminth disease.

C. VECTOR AND INTERMEDIATE HOST CONTROL

The notion of a transmission threshold at the point $R_0 = 1$ is of central importance to control measures based on the reduction of vector or intermediate host abundance. Implicit in the definition of this threshold is the concept of a critical density of hosts necessary to maintain parasite transmission. For schistosome parasites that are transmitted indirectly between hosts by free-living infective stages, the idea of a critical density may be expressed as a product of human density (N_1) times snail density (N_2). For example, on the basis of the model defined by Eqs. (9), (10), and (16), for parasite maintenance within the human community this product must satisfy the following condition:

$$N_1 N_2 > \frac{\mu_1 \mu_2 \mu_4 \mu_5 (\mu_3 + \sigma)}{\lambda_1 \lambda_2 \beta_1 \beta_2 \sigma \, \frac{1}{2} \Phi} \tag{89}$$

(Note that the above is an approximate condition based on the assumption that $\mu_2 \gg \beta_2 N_2$ and that $\mu_5 \gg \beta_1 N_1$.) For parasite eradication ($R_0 < 1$) the density of snails, N_2, must satisfy

$$N_2 < \frac{\mu_1 \mu_2 \mu_4 \mu_5 (\mu_3 + \sigma)}{\lambda_1 \lambda_2 \beta_1 \beta_2 \sigma \, \frac{1}{2} \Phi N_1} \tag{90}$$

It immediately becomes clear from Eq. (90) that this condition is more easily met if human density is low (N_1 small). Practical experience has shown that sustained snail control programmes can substantially reduce parasite transmission if aimed selectively at the water bodies (in a defined area) with which human contact is greatest. Eradication, however, is more difficult to achieve by this approach, due to dynamic complications associated with the major difference in the life expectancies of the parasitic stages in man and in snails. For example, if perfect snail control is achieved [such that the criteria of Eq. (88) is met], and assuming an adult worm life expectancy of approximately 3 years, after 5 years of control

roughly 19% of the parasite population present at the start of the programme will still be alive (assuming an exponential decay survival function). If snail control ceases at this point in time, the high reproductive potential of the intermediate host will result in the rapid recolonization of snail habitats, and the critical density necessary for parasite transmission will again be exceeded. Once this occurs (which may only be a matter of a few months), the remaining population of adult parasites will be sufficient (since the unstable breakpoint means worm burden is extremely low, due to parasite clumping) to restart parasite transmission, and the system will rapidly return to its precontrol equilibrium level (perhaps a matter of a few years, depending on the degree of suppression in parasite abundance initially achieved by snail control). In practice, therefore, effective snail control ($R < 1$) must be maintained for a period of time greater than the maximum life span of the longest lived stage in the life cycle (the adult parasite in man). On these grounds, snail control will only be effective in the long term if combined in an integrated programme with chemotherapy aimed at the adult worms in man. Practical experience substantially supports this conclusion (Jordan, 1977; Jordan and Webbe, 1982).

Similar principles apply to the control of insect vector abundance in the case of the filarial infections. There is, however, one major difference, which arises from the concept of a critical host density for parasite maintenance. As noted previously, for filarial infections and many other infections borne by biting arthropods, the vector tends to make a fixed number of bites on human host. The transmission rate from infected arthropods to people, and from infected people to arthropods, is proportional to the biting rate [$\bar{\beta}$ of Eq. (43)] times the ratio of vector density to human density (May and Anderson, 1979). The threshold condition for the filarial model [Eqs. (39) and (40)] is accordingly

$$\frac{N_2}{N_1} > \frac{(\mu_1 + b_1)(\mu_2 + b_2)}{d_1 d_2 p^2 \bar{\beta}^2} \tag{91}$$

Relative to the product term arising in models of schistosome transmission, infections transmitted by "fixed number of bites" vectors are easier to maintain at low population densities of the human host, provided the ratio N_2/N_1 is sufficiently large. This fact, compounded with the substantial difference in the life spans of infected vectors (a matter of weeks) and of the adult parasite in man (a matter of years), again suggests that vector control by itself will not be a practical solution in the long term. Recent experiences with vector control programmes in areas of endemic onchocerciasis in East Africa add weight to this conclusion (see Dietz, 1982b). Furthermore, the very high values of the basic reproductive rate of *Onchocerca volvulus* recorded in endemic areas in Cameroon, Upper Volta, and the Ivory Coast (see Table 7) suggest that very substantial

reductions in vector density are required to induce any marked reduction in parasite prevalence.

In considering the control of vectors or intermediate hosts, it is important to note that host abundances tend to fluctuate markedly on a seasonal basis, due to climatic factors. The value of R_0 will therefore also fluctuate in response to these changes. It follows that some advantages are to be gained by the application of control measures around the period when R_0 is at its seasonal minimum.

D. VACCINATION

Vaccines against helminth infections of humans are not currently available. Their development, however, is the subject of much current research. We therefore briefly consider the potential benefits to be gained at the community level from their use. It is worth noting that an effective vaccine has already been produced to protect dogs from infection by the hookworm *Ancylostoma caninum* (Miller, 1978; Clegg and Smith, 1978); this work, in conjunction with recent advances in the application of modern biochemical techniques to parasitological problems, argues that vaccines against human helminths may emerge in the not too distant future (Smith *et al.*, 1982; Lloyd, 1981).

The impact of vaccination on the transmission dynamics of helminth parasites can be mirrored by the addition of an extra equation to models of population change, to represent an immune class within the human community. A simple but general conclusion emerges from such modifications. To eradicate a helminth infection by mass vaccination, the effective reproductive rate R of the parasite must be less than unity in value. To achieve this, the proportion p of the population that must be effectively immunized (assuming immune individuals are uninfected, and are therefore not able to produce transmission stages of the parasite) at any one time must satisfy the following condition:

$$p > 1 - (1/R_0) \tag{92}$$

(see Anderson, 1980, 1982a; Anderson and May, 1982a). If, as seems likely at present, the vaccine only provides protection to infection for a period of v years (instead of life-long protection), then the proportion $\hat{p}$ that must be immunized per unit of time must satisfy

$$\hat{p} > [1 - (1/R_0)]v^{-1} \tag{93}$$

For example, if the vaccine provides life-long protection against infection by a helminth with an R_0 value of 3 (appropriate for hookworm and *Ascaris* in endemic areas; see Table 8), it would be necessary to protect 67% of the community by a single programme of mass vaccination (or short

course of immunization) in infancy. However, if the vaccine only gives protection for a few years, then a large proportion of the population must be repeatedly immunized to sustain the necessary level of immunity for community protection. This point is illustrated graphically in Fig. 45. The reason for suggesting that any vaccine is unlikely to achieve life-long protection is associated with the observation that in natural helminth infections man appears, in general, to be unable to mount a fully protective immune response to reinvasion (Wakelin, 1978a, 1984; Mitchell, 1979).

A further complication arises from the observation that, in many areas with endemic helminth infections, the average age at which children acquire infection (have positive faecal egg counts) is typically between the ages of 1 and 5 years. In line with recent work on mass vaccination against viral and bacterial disease, it seems that if eradication is the aim of community immunization, the average age at vaccination must be less than that at which the infection is typically first acquired (Anderson and May, 1982b, 1983).

The relative merits of mass immunization when vaccines become available, compared with chemotherapy, will therefore depend critically on cost factors, since both forms of control will have to be administered repeatedly. Finally, it is of interest to note that the general conclusions outlined above apply equally to the use of devices for the slow release of drugs which provide protection against infection for a defined period of

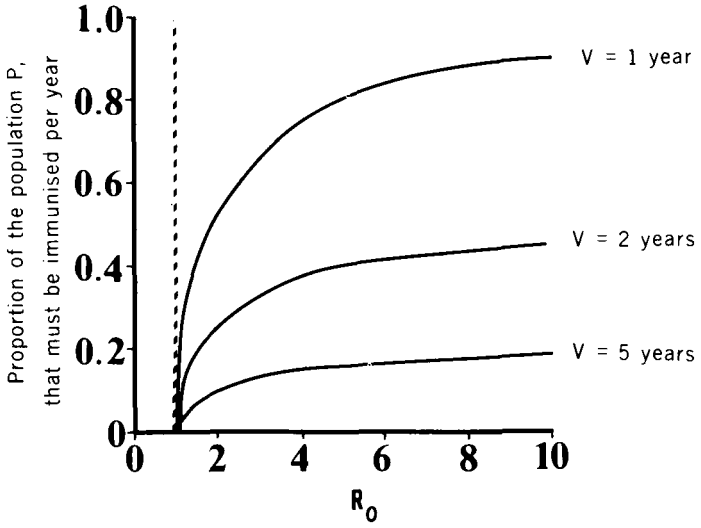

FIG. 45. The relationship between the proportion of the human community, $\hat{p}$, that must be effectively immunized to eradicate a helminth infection, and the basic reproductive rate R_0. The relationship is based on Eq. (93) and is shown for various values of the duration of vaccine protection v against infection. Dashed line depicts transmission threshold, $R_0 = 1$.

time. Technology of this kind is not available for the treatment of helminths of man at present but it has recently been developed for the treatment of intestinal nematode infections in cattle (Jones, 1981).

X. Conclusions

In the introductory section of this article, we suggested that one of the major roles for mathematical models in epidemiological research was to identify areas of inadequacy in the data available for population study. The models discussed in the preceding sections suggest that there are six main areas of weakness.

1. Measures of worm aggregation within human communities are of obvious significance, given their relationship to the prevalence of disease symptoms and the design of control policies. The number of human helminth frequency distributions documented in the literature is extremely limited at present, often for understandable reasons (for example, the habitats of the filarial nematodes and schistosome flukes in the tissues of their human hosts). In the case of intestinal helminths, however, much more information could be acquired. One reason for doing so is the remarkable degree of similarity among the values of those measures of aggregation that have been made, irrespective of the species of intestinal nematode or the geographical location of the human community studied (Table 6). This seems surprising in view of the assumed relevance of human behaviour and habits as determinants of parasite distributions; one might expect these factors to vary widely between different communities and hence to induce variable estimates of parasite aggregation (Dunn, 1976, 1979). Perhaps social conditions and human behaviour are of less relevance to patterns of aggregation than are genetic factors which control host responses to infection (Bodmer, 1980).

2. Following on from the theme of parasite aggregation, there is a concomitant need to initiate research aimed at improving our understanding of the factors which generate such patterns. The examination of predisposition to heavy infection is one such approach, but research should also focus on the association between blood group and HLA phenomena and worm burdens, along with behavioural studies of human contact with infective stages or vectors.

3. Measurement of density-dependent constraints on parasite establishment, survival, and fecundity within the human host is a major priority, given their significance as determinants of population stability and resilience. At present we know a little about density-dependent fecundity, but even here our knowledge is inadequate. For example, most studies of the relationship between worm burden and egg output record the latter quan-

tity as eggs per gram of faeces (Fig. 21); the appropriate measure, however, is total egg output per female worm per unit time. The transformation of eggs per gram to eggs per unit time period requires data on age-related changes in daily faecal output per person. This information is rarely recorded in epidemiological surveys. Our knowledge of density-dependent factors in worm establishment and survival within man is nonexistent at present. Unfortunately it is difficult to see how such information could be acquired except by extrapolation from results obtained within experimental laboratory hosts.

4. Mathematical models make clear the significance of an overall measure of transmission or reproductive success (R_0) to observed patterns in parasite prevalence and intensity. Estimates of the magnitude of the basic reproductive rate within defined communities are very few at present (Table 8). More information, however, could be easily acquired from reinfection data (where both prevalence and intensity are recorded) accumulated over periods of, say, 1–2 years following chemotherapeutic treatment.

5. Age-related changes in the rate at which people come into contact with infection can have great significance in determining observed patterns of age–prevalence or age–intensity. Quantitative data on these aspects of infection are extremely limited, although for schistosomiasis good data are now becoming available from behavioural studies of water contact (see Jordan and Webbe, 1982). Similar studies are required for man-biting habits in the case of vector-transmitted infection, and for contact with directly transmitted helminth eggs or infective larvae. Behavioural work on the latter topic is beset with many practical problems, but such work is urgently required (Dunn, 1979). Age-related changes in parasite establishment within man may also be of great importance, but here too there are obvious difficulties in such investigations. At present it may be more appropriate to focus on indirect measures of such age-specific changes; for example, data on the age and size distributions of intestinal nematodes within different age classes in human communities would be of great value.

6. Currently our estimates of the life expectancies of adult worms in man are based more on guesswork than accurate measurement (Table 5). More information could be acquired from studies of the decay in parasite prevalence following a cessation in transmission (i.e., movement of people out of areas of contact with infective stages). However, ethical problems arise in work of this nature, because those under observation must remain untreated for the data to be of value.

In addition to improvements in the epidemiological data base, there is an associated need for extensions to the mathematical framework cur-

rently available for the study of helminth transmission. It should be noted, however, that such needs are probably of lesser significance at present, in comparison with the inadequacies in the available empirical information. With this caveat in mind we suggest three areas for further mathematical study:

a. The estimation of the basic reproductive rate R_0 from epidemiological data is dependent, to a degree, on the assumptions that are made in the model being used. Work is required on the sensitivity of such estimates to assumptions relating both to the type and severity of density-dependent constraints on population growth, and to the significance of heterogeneity in exposure to infection.

b. Heterogeneity in exposure to infection is also relevant to the dynamic properties of mathematical models, due to its role as a determinant of the distribution of parasite numbers per host. Tractable stochastic models, whose assumptions generate probability distributions of parasite numbers per host and which also incorporate heterogeneous exposure, are clearly a desirable extension to the existing body of theoretical work.

c. Linked to the need for models which generate parasite distributions, there is an associated need for mathematical work on the impact of selective treatment on the temporal dynamics of parasite transmission. Targeted chemotherapy clearly has an impact on the distribution of parasites within human communities. Models are required which treat this distribution as a dynamic, as opposed to a static, entity.

Finally, we wish to emphasize the belief that simple mathematical models for helminth transmission can be valuable tools in the design of policies for parasite control, provided they are used sensibly. The dangers of oversimplification in constructing models are widely appreciated. However, there is a converse danger which is less widely understood: the complexities of helminth life cycles and population behaviour are such that intuition will not always yield accurate insights into the long-term consequences of a specific control programme or intervention. The sensible use of models can help to remedy this situation, provided the construction and analysis of models are based on collaboration between people who understand the epidemiology and people who appreciate the strengths and weaknesses of the mathematical methods employed.

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REFERENCES

Abdel-Salam, E., and Abdel-Fattah, M. (1977). Prevalence and morbidity of *Schistosoma haematobium* in Egyptian children. A controlled study. *American Journal of Tropical Medicine and Hygiene*. **26,** 463–469.

Anderson, R. M. (1974). Mathematical models of host-helminth parasite interactions. *In* "Ecological Stability" (M. B. Usher and M. H. Williamson, eds.), pp. 43–70. Chapman & Hall, London.

Anderson, R. M. (1978). Population dynamics of snail infection by miracidia. *Parasitology* **77,** 201–224.

Anderson, R. M. (1980). The dynamics and control of direct life cycle helminth parasites. *Lecture Notes in Biomathematics* **39,** 278–322.

Anderson, R. M., ed. (1982a). "Population Dynamics of Infectious Diseases: Theory and Applications." Chapman & Hall, London.

Anderson, R. M. (1982b). Epidemiology. *In* "Modern Parasitology" (F. E. G. Cox, ed.), pp. 204–251. Blackwell, Oxford.

Anderson, R. M., and Crombie J. (1984). Experimental studies of age prevalence curves for *Schistosoma mansoni* infections in populations of *Biomphalaria glabrata*. *Parasitology* **89,** 79–105.

Anderson, R. M., and Gordon, D. M. (1982). Processes influencing the distribution of parasite numbers within host populations with special emphasis on parasite-induced host mortalities. *Parasitology* **85,** 373–398.

Anderson, R. M., and May, R. M. (1978). Regulation and stability of host-parasite populations interactions. I. Regulatory processes. *Journal of Animal Ecology* **47,** 219–249.

Anderson, R. M., and May, R. M. (1979a). Prevalence of schistosome infections within molluscan populations: Observed patterns and theoretical predictions. *Parasitology* **79,** 63–94.

Anderson, R. M., and May, R. M. (1979b). Population biology of infectious diseases: Part I. *Nature* (*London*) **280,** 361–367.

Anderson, R. M., and May, R. M. (1982a). Population dynamics of human helminth infections: Control by chemotherapy. *Nature* (*London*) **287,** 557–563.

Anderson, R. M., and May, R. M. (1982b). Directly transmitted infectious diseases: Control by vaccination. *Science* **215,** 1053–1060.

Anderson, R. M., and May, R. M. (1983). Vaccination against rubella and measles: Quantitative investigations of different policies. *Journal of Hygiene* **90,** 259–325.

Anderson, R. M., Mercer, J. G., Wilson, R. A., and Carter, N. P. (1982). Transmission of *Schistosoma mansoni* from man to snail: Experimental studies of miracidial survival and infectivity in relation to larval age, water temperature, host size and host age. *Parasitology* **85,** 339–360.

Augustine, D. L. (1923a). Investigations on the control of hookworm disease. XVI. Variation in length of life of hookworm larvae from the stools of different individuals. *American Journal of Hygiene* **3,** 127–137.

Augustine, D. L. (1923b). Investigations on the control of hookworm disease. XXIII. Experiments on the factors determining the length of life of infective hookworm larvae. *American Journal of Hygiene* **3,** 420–443.

Augustine, D. L. (1926). Studies and observations on soil infestation with hookworm in southern Alabama from October 1923–September 1924. *The American Journal of Hygiene (Suppl.)* **6,** 63–79.

Bailey, N. T. J. (1975). "The Mathematical Theory of Infectious Diseases and Its Applications," 2nd Ed. Griffin, London.

Barbour, A. D. (1978). Macdonald's model and the transmission of bilharzia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **72,** 6–15.

Barbour, A. D. (1982). Schistosomiasis. *In* "Population Dynamics of Infectious Diseases: Theory and Applications" (R. M. Anderson, ed.), pp. 180–208. Chapman & Hall, London.

Bartlett, M. S. (1960). "Stochastic Population Models in Ecology and Epidemiology." Methuen, London.

Bliss, C. A., and Fisher, R. A. (1953). Fitting the negative binomial distribution to biological data and a note on the efficient fitting of the negative binomial. *Biometrics* **9,** 176–200.

Bodmer, W. F. (1980). The HLA system and diseases. *Journal of the Royal College of Physicians* **14,** 43–50.

Bossche, H., van den (1978). Chemotherapy of parasitic infections. *Nature (London)* **273,** 626–630.

Botero, R. D. (1975). Epidemiology and public health importance of intestinal nematode infections in Latin America. *In* "Progress in Drug Research" (E. Jucker, ed.), Vol. 19, pp. 64–69. Birkhauser, Basel.

Bradley, D. J. (1972). Regulation of parasite populations: A general theory of the epidemiology and control of parasitic infections. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **66,** 697–708.

Bradley, D. J., and May, R. M. (1978). Consequences of helminth aggregation for the dynamics of schistosomiasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **72,** 262–273.

Bundy, D. A. P., Harland, E., Potter, I., Stennett, M. A., Thompson, D., and Foreman, J. (1982). Paediatric trichuriasis in urban Jamaica. *In* "Parasites—their world and ours." (D. F. Mettnick and S. S. Desser, eds.), pp. 282–283. *Molecular and Biochemical Parasitology* Supplement 1982.

Cabera, B. D., Arambulo, P. V., III, and Portillo, G. P. (1975). Ascariasis control and/or eradication in a rural community in the Philippines. *Southeast Asian Journal of Tropical Medicine and Public Health* **6,** 510–518.

Chai, J.-Y., Cho, S.-Y., Kang, S.-Y., and Seo, B.-S. (1976). Frequency distribution of *Enterobius vermicularis* in a highly endemic population. *Korean Journal of Parasitology* **14,** 103–108.

Chandler, A. C. (1925). The rate of loss of hookworms in the absence of re-infections. *Indian Journal of Medical Research* **13,** 625–634.

Chandler, A. C. (1927). The prevalence and epidemiology of hookworm and other helminthic infections in India. Part XI: Madras residency and southern states. *Indian Journal of Medical Research* **15,** 159–180.

Cheever, A. W. (1968). A quantitative post-mortem study of *Schistosomiasis mansoni* in man. *American Journal of Tropical Medicine and Hygiene* **17,** 38–64.

Cheever, A. W., Kamel, J. A., Elui, A. M., Mosimann, J. E., and Danner, R. (1977). *Schistosoma mansoni* and *S. haematobium* infections in Egypt. II. Quantitative parasitological findings at necropsy. *American Journal of Tropical Medicine and Hygiene* **26,** 702–716.

Cheke, R. A., Garms, R., and Kerner, M. (1982). The fecundity of *Simulium damnosum s.l.* in northern Togo and infections with *Onchocerca* spp. *Annals of Tropical Medicine and Parasitology* **76,** 561–568.

Chowdhury, A. B., and Schiller, E. L. (1968). A survey of parasitic infections in a rural community near Calcutta. *American Journal of Epidemiology* **87,** 299–312.

Christensen, B. M. (1978). *Dirofilaria immitis:* Effect of longevity of *Aedes trivittatus*. *Experimental Parasitology* **44,** 116–123.

Chu, K. Y., Massoud, J., and Sabbaghian, H. (1966). Host-parasite relationship of *Bulinus truncatus* and *Schistosoma haematobium* in Iran. 3. Effect of water temperature on the ability of miracidia to infect snails. *Bulletin of the World Health Organisation* **34,** 131–133.

Clegg, J. A., and Smith, M. A. (1978). Prospects for the development of dead vaccines against helminths. *Advances in Parasitology* **16,** 165–218.

Cohen, J. E. (1973). Selective host mortality in a catalytic model applied to schistosomiasis. *American Naturalist* **107,** 199–212.

Cohen, J. E. (1977). Mathematical models of schistosomiasis. *Annual Review of Ecology and Systematics* **8,** 209–233.

Cook, J. A., Jordan, P., and Bartholomew, R. K. (1977). Control of *Schistosoma mansoni* transmission by chemotherapy in St. Lucia. I. Results in man. *American Journal of Tropical Medicine and Hygiene*. **26,** 887–893.

Cort, W. W. (1922). A graphic analysis of certain factors in hookworm control. *American Journal of Tropical Medicine* **2,** 449–463.

Coutinho, F. A. B., Griffin, M., and Thomas, J. D. (1981). A model of schistosomiasis incorporating the searching capacity of the miracidium. *Parasitology* **82,** 111–120.

Crofton, H. D. (1971a). A quantitative approach to parasitism. *Parasitology* **62,** 179–194.

Crofton, H. D. (1971b). A model of host-parasite relationships. *Parasitology* **63,** 343–364.

Croll, N. A., Anderson, R. M., Gyorkos, T. W., and Ghadinan, E. (1982). The population biology and control of *Ascaris lumbricoides* in a rural community in Iran. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **76,** 187–197.

Crompton, D. W. T., Keymer, A. E., and Arnold, S. E. (1984). Investigating overdispersion: *Moniformis* (Acanthocephala) and rats. *Parasitology* **88,** 317–331.

Cross, J. H., Gunawan, S., Gaba, A., Watten, R. H., and Sulianti, J. (1970). Survey for human intestinal and blood parasites in Bojolali, Central Java, Indonesia. *Southeast Asian Journal of Tropical Medicine and Public Health* **1,** 354–360.

Dalton, P. R., and Pole, D. (1978). Water contact patterns in relation to *Schistosoma haematobium* infection. *Bulletin of the World Health Organization* **56,** 417–426.

Davis, A., Biles, J. E., and Ulrich, A-M. (1979). Initial experiences with praziquantel in the treatment of human infections due to *Schistosoma haematobium*. *Bulletin of the World Health Organisation* **57,** 773–779.

Dietz, K. (1980). Models for vector-borne parasitic diseases. *Lecture Notes in Biomathematics* **39,** 264–277.

Dietz, K. (1982a). The population dynamics of onchocerciasis. *In* "Population Dynamics of Infectious Diseases: Theory and Applications" (R. M. Anderson, ed.), pp. 209–241. Chapman & Hall, London.

Dietz, K. (1982b). Overall population patterns in the transmission cycle of infectious disease agents. *In* "Population Biology of Infectious Diseases" (R. M. Anderson and R. M. May, eds.), pp. 87–102. Springer-Verlag, Berlin.

Docherty, J. F. (1926). Hookworm infestation and reinfestation in Ceylon. A study of high incidence with a moderate degree of infestation. *American Journal of Hygiene* **6,** 160–171.

Domingo, E. O., Tiu, E., Peters, P. A., Warren, K. S., Mahmoud, A. A., and Haiser, H. B. (1980). Morbidity in *Schistosomiasis japonica* in relation to intensity of infection: Study of a community in Leyte, Philippines. *American Journal of Tropical Medicine and Hygiene* **29,** 858–867.

Dunn, F. L. (1976). Human behavioural factors in the epidemiology and control of *Wuchereria* and *Brugia* infections. *Bulletin Public Health Society, Malaysia* **10,** 34–44.

Dunn, F. L. (1979). Behavioural aspects of the control of parasitic diseases. *Bulletin of the World Health Organisation* **57,** 499–512.

Fernando, M. A., and Balasuriya, S. (1976). Prevalence of soil-transmitted helminths in the Hindagala community health project area. *Ceylon Medical Journal* **22,** 177–183.

Fine, P. E. M., and Lehman, J. S. (1977). Mathematical models of schistosomiasis: Report of a workshop. *American Journal of Tropical Medicine and Hygiene* **26,** 500–504.

Fisher, R. A. (1930). "The Genetical Theory of Natural Selection." Clarendon, Oxford.

Fushimi, J. (1959). A consideration on the correlation between the so-called egg positive rate and the genuine infection rate of the unisexual parasitism on the mean number of infected worms in the case of ascarid infection I. The examination of the fundamental materials for the construction of the theoretical model II. The construction of the theoretical model. *Japanese Journal of Parasitology* **8,** 108–114, 166–173.

Goddard, M. J. (1978). On Macdonald's model for schistosomiasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **72,** 123–131.

Hadeler, K. P., and Dietz, K. (1983). Nonlinear hyperbolic partial differential equations for the dynamics of parasite populations. *Comparative Mathematics and Applications* **9,** 415–430.

Hairston, N. G. (1962). Population ecology and epidemiological problems. *Ciba Foundation Symposium on Bilharziasis* (G. E. W. Wolstenholme and M. O'Connor, eds.). pp. 36–80. J. and A. Churchill, London.

Hairston, N. G. (1965a). On the mathematical analysis of schistosome populations. *Bulletin of the World Health Organisation* **33,** 45–62.

Hairston, N. G. (1965b). An analysis of age-prevalence data by catalytic models. *Bulletin of the World Health Organisation* **33,** 163–175.

Hairston, N. G., and Jackowski, L. A. (1968). Analysis of the *Wucheria bancrofti* population in the people of American Samoa. *Bulletin of the World Health Organisation* **38,** 29–59.

Hamer, W. H. (1906). Epidemic disease in England. *Lancet* **1,** 733–739.

Hill, R. B. (1926). The estimation of the number of hookworm harboured by the use of the dilution egg count method. *American Journal of Hygiene* **6,** 19–41.

Hliang, T., Than-Saw, Htay-Htay-Aye, Myrint-Lwin, and Thein-Maung-Myint (1983). Epidemiological transmission dynamics of *Ascaris lumbricoides* in Okpo village, rural Burma, *Transactions of the Royal Society of Hygiene and Tropical Medicine* **78,** 497–504.

Hoagland, K. E., and Schad, G. A. (1978). *Necator americanus* and *Ancylostoma duodenale:* Life history parameters and epidemiological implications of two sympatric hookworms of humans. *Experimental Parasitology* **44,** 36–49.

Hossain, M., Glass, R. I., and Black, R. E. (1981). The prevalence of *Ascaris,* hookworm and *Trichuris* in patients attending a rural diarrhoea treatment centre in Bangladesh. *Southeast Asian Journal of Tropical Medicine and Public Health* **12,** 539–543.

Hsieh, H. C. (1970). Studies on endemic hookworm: I. Survey and longitudinal observation in Taiwan. *Japanese Journal of Parasitology* **19,** 508–522.

Jones, R. M. (1981). A field study of the Morantel sustained release bolus in the seasonal control of parasite gastroenteritis in grazing calves. *Veterinary Parasitology* **8,** 237–251.

Jordan, P. (1977). Schistosomiasis—research to control. *American Journal of Tropical Medicine and Hygiene* **26,** 877–886.

Jordan, P., and Webbe, G. (1969). "Human Schistosomiasis." Heinemann, London.

Jordan, P., and Webbe, G. (1982). "Schistosomiasis: Epidemiology, Treatment and Control." Heinemann, London.

Katz, N., Rocha, R. S., and Chaves, A. (1979). Preliminary trials with praziquantel in human infections due to *Schistosoma mansoni. Bulletin of the World Health Organisation* **57,** 781–785.

Kendrick, J. F. (1934). The length of life and the rate of loss of the hookworms, *Ancylo-*

stoma duodenale and *Necator americanus*. *American Journal of Tropical Medicine* **14,** 363–379.

Kermack, W. O., and McKendrick, A. G. (1927). Contributions to the mathematical theory of epidemics. *Proceedings of the Royal Society Series A* **115,** 700–721.

Keymer, A. (1982). Density-dependent mechanisms in the regulation of intestinal helminth populations. *Parasitology* **84,** 573–587.

Khan, S. M., and Anuar, A. K. (1977). Prevalence of intestinal helminths among patients admitted to the Balik Pulau District Hospital on Penang Island. *Southeast Asian Journal of Tropical Medicine and Public Health* **8,** 260–264.

Kirkwood, B., Smith, P., Marshall, T., and Prost, A. (1983a). Variations in the prevalence and intensity of microfilarial infections by age, sex, place and time in the area of the onchocerciasis control programme. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **77,** 857–861.

Kirkwood, B., Smith, P., Marshall, T., and Prost, A. (1983b). Relationships between mortality, visual acuity and microfilarial load in the area of the onchocerciasis control programme. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **77,** 862–868.

Kostitzin, V. A. (1934). "Symbiose, Parasitism et Evolution." Hermann, Paris.

Krupp, I. M. (1961). Effects of crowding and of superinfection on habitat selection and egg production in *Ancylostoms caninum*. *Journal of Parasitology* **47,** 957–961.

Lee, K. L., and Lewis, E. R. (1976). Delay time models of population dynamics with application to schistosomiasis control. *IEEE Transactions of Biomedical Engineering* **BME-23,** 225–233.

Lewart, R. M., Yogore, M. G., and Blas, B. L. (1979). Schistosomiasis japonicum in Bario San Antonio, Basey, Samar, the Philippines. *American Journal of Tropical Medicine and Hygiene* **28,** 1010–1025.

Lewis, T. (1975a). A model for the parasitic disease bilharziasis. *Advances in Applied Probability* **7,** 673–704.

Lewis, T. (1975b). Threshold results in the study of schistosomiasis. *Statistics Reports and Preprints* No. 23, 1–10.

Leyton, M. K. (1968). Stochastic models in populations of helminthic parasites in the definitive Host. II. Sexual mating functions. *Mathematical Biosciences* **3,** 413–419.

Lloyd, S. (1981). Progress in immunization against parasitic helminths. *Parasitology* **83,** 225–242.

Lotka, A. J. (1923). Contributions to the analysis of malaria epidemiology. *American Journal of Hygiene* **3,** 1–21.

Lyons, G. R. (1972). Guineaworm infection in the Wa district of north-western Ghana. *Bulletin of the World Health Organization* **47,** 601–610.

Macdonald, G. (1965). The dynamics of helminth infections, with special reference to schistosomes. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **59,** 489–506.

Mahmoud, A. A. F., and Warren, K. S. (1980). Control of infection and disease in *Schistosomiasis mansoni* by targeted chemotherapy. *Clinical Research* **28,** 474.

Maizels, R. M., Partono, F., Rioemijati, S., and Ogilvie, B. M. (1983). Antigenic analysis of *Brugia timori*, a filarial nematode of man: Initial characterization of surface radioiodination and evaluation of diagnostic potential. *Clinical Experimental Immunology*, **51,** 269–277.

Mansour, N. S., Higashi, G. I., Schinski, V. D., and Murrell, K. D. (1981). A longitudinal study of *Schistosoma haematobium* infection in Qena Governorate, Upper Egypt. *American Journal of Tropical Medicine and Hygiene* **30,** 795–805.

Martin, J., and Keymer, A. (1983). The prevalence and intensity of helminth infections in children from rural Bangladesh. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **77,** 702–706.

May, R. M. (1974). "Stability and Complexity in Model Ecosystems." Princeton Univ. Press, Princeton, New Jersey.

May, R. M. (1977a). Togetherness among schistosomes: Its effects on the dynamics of the infection. *Mathematical Biosciences* **35,** 301–343.

May, R. M. (1977b). Dynamical aspects of host-parasite associations-Crofton's model revisited. *Parasitology* **75,** 259–276.

May, R. M., and Anderson, R. M. (1978). Regulation and stability of host-parasite population interactions. II. Destabilizing processes. *Journal of Animal Ecology* **47,** 249–267.

May, R. M., and Anderson, R. M. (1979). Population biology of infectious diseases. Part II. *Nature (London)* **280,** 455–461.

Maynard-Smith, J. (1968). "Mathematical Ideas in Biology." Cambridge Univ. Press, London and New York.

Miller, M. J., Krupp, I. M., Little, M. D., and Santos, C. (1974). Mebendazole. An effective anthelmintic for trichuriasis and enterobiasis. *Journal of the American Medical Association* **230,** 1412–1414.

Miller, T. A. (1978). Industrial development and field use of the canine hookworm vaccine. *Advances in Parasitology* **16,** 333–342.

Minchella, D. J., and Loverde, P. T. (1983). Laboratory comparison of the relative success of *Biomphalaria glabrata* stocks which are susceptible and insusceptible to infection with *Schistosoma mansoni*. *Parasitology* **86,** 335–344.

Mitchell, G. F. (1979). Responses to infection with metazoan and protozoan parasites in mice. *Advances in Immunology* **28,** 451–511.

Muench, H. (1959). "Catalytic Models in Epidemiology." Harvard Univ. Press, Cambridge, Massachusetts.

Muller, R. (1975). "Worms and Disease. A Manual of Medical Helminthology." Heineman, London.

Nåsell, I. (1976a). A hybrid model of schistosomiasis with snail latency. *Theoretical Population Biology* **10,** 47–69.

Nåsell, I. (1976b). On eradication of schistosomiasis. *Theoretical Population Biology* **10,** 133–143.

Nåsell, I. (1977). On transmission and control of schistosomiasis, with comments on Macdonald's model. *Theoretical Population Biology* **12,** 335–365.

Nåsell, I., and Hirsch, W. M. (1972). A mathematical model of some helminthic infections. *Communications on Pure and Applied Mathematics* **25,** 459–477.

Nåsell, I., and Hirsch, W. M. (1973). The transmission dynamics of schistosomiasis. *Communications on Pure and Applied Mathematics* **26,** 395–453.

Nwosu, A. B. C., Ifezulike, E. O., and Anya, A. O. (1982). Endemic dracontiasis in Anambra State of Nigeria: Geographical distribution, clinical features, epidemiology and socioeconomic impact of the disease. *Annals of Tropical Medicine and Parasitology* **76,** 121–131.

Papasarathorn, T., Chularerk, P., Chearanai, S., Chularerk, U., Kiarttivuti, B., Viboolyanvatna Krrttivuti, A., and Vongtangswad, S. (1967). Study on ecology and prevalence of intestinal parasites with special reference to the intensity of human hookworms infection and apisthorhiasis in health development area, Bantard Udoin Province. *Journal of the Medical Association of Thailand* **50,** 423–445.

Payne, F. K. (1924). Investigations on the control of hookworm disease. XXXI. The relation of the physiological age of hookworm larvae to their ability to infect the human host. *American Journal of Hygiene* **3,** 584–597.

Pesigan, T. P., Farooq, M., Hairston, N. G., Jauregui, J. J., Garcia, E. G., Santos, A. T., Santos, B. C., and Besa, A. A. (1958). Studies on *Schistosoma japonicum* infection in the Philippines. 1. General considerations and epidemiology. *Bulletin of the World Health Organisation* **18,** 345–455.

Pichon, G., Prod'hon, J., and Rivière, F. (1980). Filarioses: Surdispersion parasitaire et

surinfection de l'hôte invertébré. *Cahiers O.R.S.T.O.M., Entomologie Medicale et Parasitologie* **18,** 27–47.

Rosenfield, P. (1975). "Development and Verification of a Schistosomiasis Transmission Model." Ph.D. dissertation. John Hopkins University, Baltimore.

Rosenfield, P. L., Smith, R. A., and Wolman, M. G. (1977). Development and verification of a schistosomiasis transmission model. *American Journal of Tropical Medicine and Hygiene* **26,** 505–516.

Ross, R. (1911). "The Prevention of Malaria" (2nd Ed.). Murray, London.

Ross, R. (1915). Some a priori pathometric equations. *British Medical Journal* **1,** 546–547.

Rougemont, A., Thylefors, B., Ducam, M., Prost, A., Ranque, Ph., and Delmont, J. (1976). Traitement de l'onchocercose par la suramine à faiblesses progressives dans les collectivités hyperendémiques d'Afrique occidentale. 1. Resultats parasitologiques et surveillance ophtalmologique en zone de transmission non interronpue. *Bulletin of the World Health Organization* **58,** 917–922.

Sawyer, W. A. (1925). Factors that influence the rate of increase of hookworm infection. *American Journal of Hygiene* **5,** 790–817.

Schacher, J. F., and Danaraj, T. J. (1960). Intestinal helminths in relation to eosinophilic lung (tropical eosinophilia) in Singapore. *American Journal of Tropical Medicine and Hygiene* **9,** 616.

Schad, G. A., and Rozeboom, L. E. (1976). Integrated control of helminths in human populations. *Annual Review of Ecology and Systematics* **7,** 393–420.

Schad, G. A., and Anderson, R. M. (1985). Predisposition to hookworm infection in man *Science* (in press).

Scott, D., Senker, K., and England, E. C. (1982). Epidemiology of human *Schistosoma haematobium* infection around Volta Lake, Ghana, 1973–75. *Bulletin of the World Health Organization* **60,** 89, 100.

Seo, B. S., Cho, S. Y., and Chai, J. Y. (1979). Frequency distribution of *Ascaris lumbricoides* in rural Korea with special reference on the effect of changing endemicity. *Korean Journal of Parasitology* **17,** 105–113.

Seo, B. S., Cho, S.-Y., Chai, J.-Y., and Hong, S.-T. (1980). Comparative efficacy of various interval mass treatment on *Ascaris lumbricoides* infection in Korea. *Korean Journal of Parasitology* **18,** 145–151.

Smillie, W. G. (1924). Control of hookworm disease in south Alabama. *Southern Medical Journal* **17,** 494–502.

Smith, M. A., Clegg, J. A., Snary, D., and Trejdosiewicz, A. J. (1982). Passive immunization of mice against *Schistosoma mansoni* with an IgM monoclonal antibody. *Parasitology* **84,** 83–92.

Smithers, S. R., and Terry, R. J. (1969). Immunity to schistosomiasis. *Annals of the New York Academy of Science* **160,** 836–840.

Soper, H. E. (1929). Interpretation of periodicity in disease-prevalence. *Journal of the Royal Statistical Society* **92,** 34–73.

Stoll, N. R. (1923). Investigations on the control of hookworm disease. XVIII. On the relation between the number of eggs found in human faeces and the number of hookworms in the host. *American Journal of Hygiene* **3,** 103–117.

Sturrock, R. F. (1973). Field studies on the transmission of *Schistosoma mansoni* and on the bionomics of its intermediate host, *Biomphalaria glabrata,* on St. Lucia, West Indies. *International Journal of Parasitology* **3,** 175–194.

Sturrock, R. F., and Webbe, G. (1971). The application of catalytic models to schistosomiasis in snails. *Journal of Helminthology* **14,** 189–200.

Sturrock, R. F., Cohen, J. E., and Webbe, G. (1975). Catalytic curve analysis of schistosomiasis in snails. *Annals of Tropical Medicine and Parasitology* **69,** 133–134.

Tallis, G. M., and Leyton, M. (1966). A stochastic approach to the study of parasite populations. *Journal of Theoretical Biology* **13,** 251–260.

Teesdale, C. (1962). Ecological observations on the molluscs of significance in the transmission of bilharziasis in Kenya. *Bulletin of the World Health Organization* **27,** 759–782.

Wagner, W. H. (1980). Drugs for tropical diseases in the third world. *Interdisciplinary Science Reviews* **5,** 186–203.

Wakelin, D. (1978a). Immunity to intestinal parasites. *Nature (London)* **273,** 617–620.

Wakelin, D. (1978b). Genetic control of susceptibility and resistance to parasitic infection. *Advances in Parasitology* **16,** 219–284.

Wakelin, D. (1984). "Immunity to Parasites" Arnold, London.

Walsh, J. A., and Warren, K. S. (1979). Selective primary health care: An interim strategy for disease control in developing countries. *New England Journal of Medicine* **301,** 967–974.

Warren, K. S. (1973). Regulation of the prevalence and intensity of schistosomiasis in man. Immunology or ecology? *Journal of Infectious Diseases* **127,** 595–609.

Warren, K. S. (1979). Diseases due to helminths. *In* "Principles and Practice of Infectious Diseases" G. L. Mandel, R. G. Douglas, Jr., and J. E. Bennet, eds.). Wiley, New York.

Warren, K. S. (1981). The control of helminths: Nonreplicating infectious agents of man. *Annual Reviews in Public Health* **2,** 101–115.

Warren, K. S., and Mahmoud, A. A. F. (1976). Targeted mass treatment: A new approach to the control of schistosomiasis. *Transactions of the Association of American Physicians* **89,** 195–204.

Warren, K. S., and Mahmoud, A. A. F. (1980). Targeted mass treatment: A new approach to the control of schistosomiasis. *Clinical Research* **28,** 195–204.

Warren, K. S., Arap Siongok, T. K., Houser, H. B., Ouma, J. H., and Peters P. A. (1978). Quantification of infection with *Schistosoma haematobium* in relation to epidemiology and selective population chemotherapy. I. Minimal number of daily egg counts in urine necessary to establish intensity of infection. *Journal of Infectious Diseases* **138,** 849–855.

Webber, R. H. (1975). Theoretical considerations in the vector control of filariasis. *Southeast Asian Journal of Tropical Medicine and Public Health* **4,** 544–548.

Wenlock, R. W. (1978). Age variation in prevalence of parasitic diseases in rural communities. *Medical Journal of Zambia* **12,** 13–15.

Wilkins, H. A. (1977). *Schistosoma haematobium* in a Gambian community. I. The intensity and prevalence of infection. *Annals of Tropical Medicine and Parasitology* **71,** 53–58.

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Anorexia: Occurrence, Pathophysiology, and Possible Causes in Parasitic Infections

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I. Introduction

This review examines the occurrence, physiological effects, and possible causes of voluntary reduction of food consumption in parasitic infections with protozoa and helminths. Parasitologists use the terms *anorexia* or *inappetence* in place of the longer expression. Either is acceptable, as the common definition of both is loss or lack of appetite. Because the word *anorexia* is more frequently used, and because there is a subjective connotation to the word *inappetence* and I cannot know whether this is experienced by animals other than man, I have used *anorexia* throughout this review. Anorexia is taken to refer to any reduction in food consumption, whether slight or complete.

The occurrence of anorexia in secondary infections, i.e., in the immune host, is not reported in this review largely because I have almost solely

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studied the pathophysiology of primary infections. Although anorexia may occur in secondary infections, it is unlikely that the causes and effects are qualitatively different from those of primary infections.

A study of anorexia is justified by its widespread occurrence in protozoal infections and helminthiases, particularly of the gastrointestinal tract (GIT), and its association with poor growth or loss of weight of the host. What the connection is between the physiological responses to parasitism and anorexia is a question that must be answered. Viral, bacterial, and noninfectious diseases of man and domestic animals are also mentioned briefly because anorexia in these and protozoal and helminthic infections may have common causes and responses.

So little is known about the causes of anorexia that a summary of what is known of the regulation of eating and satiety in normal animals is included in this review. Much work in recent years on regulation in the normal animal raises the question whether the mechanisms of eating and satiety have any basis for an explanation of anorexia in parasitized animals. Present work to answer this question is at a preliminary stage. Necessary future work on the causes of anorexia and of its relevance to pathophysiology of parasitism is described where appropriate in the text, rather than collected in a section at the end of this article.

II. Occurrence of Anorexia

Reports of the occurrence of anorexia in protozoal and helminthic infections are listed in Tables 1 and 2, respectively. These lists are not exhaustive and include only those infections for which I have found some statement that anorexia occurs. The hosts cover most groups of animals, including man. They show that anorexia may occur with infections in different parts of the GIT or in other organs and tissues. In some instances there are a number of reports of the presence of anorexia, but I have included only one representative in each instance in the tables. In a number of papers and text books the descriptions of symptoms such as listlessness or malaise indicate that anorexia almost certainly occurs although it is not specifically mentioned (e.g., by Soulsby, 1982). These infections are not included in the tables. These reports of the occurrence of anorexia are expanded in the following text.

A. PROTOZOAL INFECTIONS

Coccidia infect the mucosa, usually the epithelial cells, from the duodenum to the caecum of a number of species. Coccidiosis is well documented.

TABLE 1
Reports of anorexia in protozoal infections

Parasite	Hosts	Site of infection	References
Eimeriidae			
Eimeria spp.	Sheep	Duodenal epithelium	Pout and Catchpole (1974)
E. tenella	Chickens	Caecal epithelium	Symons and Jones (1977)
E. acervulina	Chickens	Small intestinal epithelium	Michael and Hodges (1971)
E. necatrix	Chickens	Small intestinal epithelium	Michael and Hodges (1972)
E. adenoides	Turkey poults	Entire intestinal epithelium	Clarkson and Gentles (1958)
E. meleagrimitis	Turkey poults	Small intestinal epithelium	Clarkson and Gentles (1958)
Cryptosporidium spp.	Piglets	Small intestinal epithelium	Tzipori *et al.* (1981)
	Man	Small intestinal epithelium	Tzipori *et al.* (1983a)
	Calves	Small intestinal epithelium	Tzipori *et al.* (1983b)
Plasmodiidae			
Haemoproteus columbae	Pigeons, doves, etc.	Endothelium of blood vessels	Soulsby (1982, p. 700)
Leucocytozoon simondi	Ducks and geese	Sundry tissues	Soulsby (1982, p. 704)
Babesiidae			
Babesia bigemina	Calves	Erythrocytes	Knowles *et al.* (1982)
B. bovis	Calves	Erythrocytes	Knowles *et al.* (1982)
B. equi	Horses	Erythrocytes	Soulsby (1982, pp. 706–718)
B. canis	Dogs	Erythrocytes	Soulsby (1982, pp. 706–718)
Sarcocystidae			
Sarcocystis cruzi	Calves	Endothelium of blood vessels	Dubey (1976)
S. ovicanis	Sheep	Endothelium of blood vessels	Dubey (1976)
S. hominis	Man	Endothelium of blood vessels	Dubey (1976)
S. porcihominis	Man	Endothelium of blood vessels	Dubey (1976)

Soulsby (1982, p. 605) stated that mixed infections of young sheep and goats are common and that anorexia is a feature of symptomatic infections. Pout and Catchpole (1974) infected newborn lambs with mixed species of coccidia (50, 500, 5000, and 50,000 cysts day^{-1} in the first, second, third, and fourth weeks, respectively). Two of the infected lambs were fed a constantly adjusted mixture of milk and grass nuts so that they had a growth rate of 350 g day^{-1} (high plane), and two were fed the diet adjusted so that their growth rate was 190 g day^{-1} (low plane). Anorexia, diarrhoea, and loss of weight began after 3 weeks on both planes of nutrition, but animals on the high plane had more severe anorexia and recovered more slowly than those on the low plane.

Table 1 includes a number of species of *Eimeria* infecting chickens and turkeys. These infections can be severe diseases, of which one of the most notorious is the infection of *E. tenella* in the caeca of chickens. Although food consumption was not measured in the experiment listed in Table 1, it was obvious from the behavior of the birds that they ate very little after one dose of 25,000 oocysts (Symons and Jones, 1977). Michael and Hodges (1971, 1972) found that anorexia was directly related to the dose rate of oocysts of *E. acervulina* and *E. necatrix*, whether administered in single or multiple doses. Clarkson and Gentles (1958) reported that turkey poults infected with *E. adenoides* and *E. meleagrimitis* may cease to eat altogether.

Tzipori and colleagues (1981, 1983a,b) reported that anorexia occurred in infections with *Cryptosporidium* spp. in both adults and children. Milk intake was reduced in calves, and piglets were anorectic when infected with protozoa isolated from calves.

Anorexia may also occur in some protozoal infections in tissues other than the GIT. In acute infections of pigeons, the schizonts of *Haemoproteus columbae* are located in the endothelial cells of blood vessels. In the infections of ducks and geese with *Leucocytozoon simondi*, schizonts are present in parenchymal cells of the liver and megaloschizonts are in brain, liver, lungs, kidneys, intestinal tissue, and lymphoid cells.

In babesiosis the protozoa are present in erythrocytes and leukocytes. Knowles *et al.* (1982) did not give any quantitative data for a naturally occurring infection in calves, but stated that the animals became anorectic 17 days after importation from the United States to the island of St. Lucia in the Caribbean. These cattle were also infected with *Anaplasma marginale* (a rickettsia) but, as they did not exhibit any symptoms until 5 months after importation, this infection could not have been responsible for the earlier anorexia due to babesiosis.

Sarcocystis spp. occur in a number of vertebrate species. Dubey (1976) stated that anorexia occurred in acute infections of calves, sheep, and man.

Soulsby (1982) has described a number of protozoal infections in which the symptoms suggest that anorexia probably occurs. Although infections of man with *Giardia* sp. are usually symptomless, there are reports of clinical cases with diarrhoea, malaise, abdominal cramps, and weight loss, which indicate that anorexia may also be present (Meyer and Radulescu, 1979).

B. HELMINTHIASES

Infections with helminths well illustrate the fact that anorexia occurs in infections with a variety of parasitic species (trematodes, nematodes, and even cestodes), which are located in a variety of organs and tissues.

TABLE 2
Reports of anorexia in helminthiases

Parasite	Hosts	Site of infection	References
Trematodes			
Fasciola hepatica	Sheep	Liver	Berry and Dargie (1976)
	Cattle	Liver	Cawdery *et al.* (1977)
Schistosoma mattheei	Sheep	Sundry veins	Preston *et al.* (1973)
Echinostoma paraulum	Ducks, pigeons, and man	Small intestine	Soulsby (1982, p. 57)
Cestodes			
Davainea proglottina	Poultry	Duodenal loop	Soulsby (1968, p. 108)
Nematodes			
Hyostrongylus rubidus	Pigs	Stomach	Castelino *et al.* (1970)
Ostertagia circumcincta	Sheep	Abomasum	Sykes and Coop (1977)
Haemonchus contortus	Sheep	Abomasum	Abbott (1982)
Trichostrongylus colubriformis	Sheep	Small intestine	Steel *et al.* (1980)
Nematodirus battus	Sheep	Small intestine	Rowlands and Probert (1972)
Cooperia pectinata	Calves	Small intestine	Keith (1967)
Ascaris suum	Pigs	Small intestine	Forsum *et al.* (1981)
Ascaridia galli	Chickens	Small intestine	Ikeme (1971)
Ancylostoma duodenale *A. ceylonicum* *Necator americanus*	Man	Small intestine	Miller (1979)
Capillaria philippinensis	Man	Small intestine	Whalen *et al.* (1969)
Trichuris suis	Pigs	Caecum	Powers *et al.* (1960)
Oesophagostomum radiatum	Cattle	Distal ileum and colon	Bremner (1961)
Chabertia ovina	Sheep	Colon	Herd (1971)
Bulbodacnitis ampullastoma	Rainbow trout	Gut	Hiscox and Brocksen (1973)
Strongylus spp.	Foals	Blood vessels or liver	Soulsby (1982, pp. 176–177)
Stephanurus dentatus	Pigs	Kidney	Soulsby (1982, p. 194)
Dirofilaria spp.	Dogs	Circulation	Atwell and Farmer (1982)

1. *Trematodes*

Infection of sheep and cattle, particularly the former, with the liver fluke *Fasciola hepatica* has been investigated extensively. The detailed study of the disease in sheep by Berry and Dargie (1976) (Table 2) found that those animals with relatively high fluke numbers (greater than about 200 per liver) were anorectic. Anorexia was most pronounced between the seventh and tenth week of infection and again during the weeks preceding death. It was also greater in animals fed about 6% crude protein (CP) than in those on a supplemented diet of 13% CP. Berry and Dargie (1976) infected their sheep with one dose of 1000 metacercariae, whereas

Sykes *et al.* (1980) infected sheep with 3, 8, and 14 metacercariae on 5 days a week for 22 weeks. The latter team reported anorexia in what they described as subclinical infections. Cawdery *et al.* (1977) reported that cattle were anorectic when given a single dose of 1000, but not when given 600, metacercariae of *F. hepatica*.

Schistosomiasis of the blood vessels of man and many other species is another trematode infection that has been reported extensively. Preston *et al.* (1973) measured consumption in sheep after infection with 10,000 metacercariae of *Schistosoma mattheei* and reported that anorexia occurred after about 7–8 weeks and was most severe for the next 10–14 days. Anorexia has been reported in pigeons infected with *Echinostoma paraulum*. In addition, the symptoms for infections of other species with schistosomes described by Soulsby (1982) suggest strongly that anorexia occurs, even if not specifically mentioned.

2. *Cestodes*

Tapeworm infections of vertebrates are commonly symptomless, but a noteworthy exception is that of the duodenal loop of poultry and other birds with *Davainea proglottina*. Birds frequently show loss of appetite.

3. *Nematodes*

There are many accounts of anorexia as a symptom of roundworm infection. These may be divided conveniently into infections of different parts of the GIT and of other viscera.

(*a*) *Stomach and abomasum*. Growing pigs with infection of the stomach with *Hyostrongylus rubidus*, as described by Castelino *et al.* (1970), were anorectic after massive doses of 200,000 and 500,000 infective larvae, but not after 150,000 (Lean *et al.*, 1972).

In Scotland, Sykes and Coop (1977) found consumption reduced by 20% in 4-month-old sheep dosed daily for 14 weeks with 4000 larvae (28,000 week^{-1}) of *Ostertagia circumcincta*. Subsequently, Steel *et al.* (1980) in Australia reported the physiological responses of Merino × Border Leicester lambs dosed for 24 weeks with up to 120,000 larvae week^{-1} divided into three equal doses on alternate days. Larval doses up to 37,500 week^{-1} did not affect consumption, whereas 120,000 week^{-1} reduced intake by 20% during the first 12 weeks. Calves that were diarrhoeic and lost weight rapidly after infection with *Ostertagia ostertagii* probably became anorectic (Armour *et al.*, 1973).

Anaemia due to ingestion of blood is the predominant effect of infection of the abomasum of sheep with *Haemonchus contortus*. However, there are conflicting reports as to whether anorexia also occurs. Dargie (1973) found that 1-year-old Merinos infected with 10,000 larvae increased their

intake of nitrogen during the first 5 weeks of infection. On the other hand, Evans *et al.* (1963) and Pradhan and Johnstone (1972) reported anorexia. The last two authors reported that anorexia appeared after 9–10 weeks following dosing with 3500 infective larvae $week^{-1}$ or 500 day^{-1}, and was more severe with continuous than with intermittent weekly dosing.

An interesting and important study of the pathophysiology of ovine haemonchosis was made by Abbott (1982). She compared lambs fed a high-protein diet of 169 g crude protein (CP) per kilogram dry matter (DM) with a low-protein diet of 88 g CP kg^{-1} DM. The diets were equal in energy content. In one experiment, lambs of 24–25 kg were infected with a single dose of 350 larvae per kilogram body weight (about 9000 larvae per sheep). Abbott found that when all sheep were fed 1000 g of pellets day^{-1} the high-protein group ate all of the food, whereas the low-protein group were anorectic. This group ate only about 600 g day^{-1}, except for one lamb whose intake was only about 100 g day^{-1}. It is not clear from her report whether the high-protein group would have shown some degree of anorexia had they been fed *ad libitum* instead of the 1000 g day^{-1}, which represented about 90% of their earlier intake. In other experiments Abbott found that anorexia occurred in some lambs fed the low- but not the high-protein diet, but no quantitative figures were given.

The report by Dargie (1973) is one of the rare occasions when food intake has been increased, not decreased, by a nematode infection of the GIT. The reason for the difference between this finding and the other three reports is uncertain, but there were experimental differences that may have been relevant.

Severe experimental infection of four camels with 300–400 larvae of *Haemonchus longistipes* per kilogram body weight undoubtedly resulted in marked and progressive anorexia. The camels almost stopped feeding over the last days preceding death (Arzoun *et al.*, 1984).

(b) Small intestine. Small intestinal nematode infections of ruminants with accompanying anorexia have also been widely reported. Steel *et al.* (1982) infected Merino × Border Leicester and Merino lambs with weekly doses of *Trichostrongylus colubriformis* by the method described above for *O. circumcincta*. The degree of anorexia was directly related to larval doses of 3000, 9500, and 30,000 $week^{-1}$, the last dose reducing consumption by about 55%. Lambs were considerably more affected in a number of metabolic indicators, including consumption, by *T. colubriformis* than by *O. circumcincta*, despite the fact that four times the number of larvae of the latter species were used. In a third experiment of this series, concurrent infections of these parasites reduced consumption, whereas monospecific infections at the same dose levels did not. The results showed clearly that the additive effect on the concurrent infection was not

due to the greater total number of parasites (Steel *et al.* 1982). A number of other authors have also reported anorexia in infections with *T. colubriformis*.

Other infections of the small intestine of ruminants that produce anorexia are included in Table 2.

Forsum *et al.* (1981), in experiments investigating the effect of *Ascaris suum* on growth, food intake, nitrogen and fat utilization, and intestinal function, found that young pigs fed a low protein diet of 7.8% were anorectic after three doses of 200 eggs, each 2 days apart. Pigs on low protein given one dose of 300 eggs ate no less than uninfected animals on the same diet, but the difference between the two experiments may have been due to severity of infection. The mean number of worms recovered from the pigs receiving one dose of eggs was 31 (±25, SE), whereas in those receiving three doses it was 130.5 (±23.2) worms.

No quantitative figures were given for the following three infections in which anorexia was reported to occur. Ikeme (1971) found that *Ascaridia galli* reduced consumption of chickens fed 10% protein when dosed with 1000 parasitic eggs, but not of birds fed 12.5 or 15% protein. In his review of hookworm infection of man, Miller (1979) stated that anorexia with abdominal pain may occur in the intestinal phase in acute infections. Patients infected with *Capillaria philippinensis* were also said to be anorectic.

(c) Caecum and colon. Trichuris spp. are parasites of the caecum and colon of a number of species. *Trichuris suis* in the caecum of pigs caused anorexia about 26 days after the commencement of dosing over 19–22 days with a total of 34,500–39,700 ova (Powers *et al.*, 1960).

Oesophagostomum radiatum is a parasite of the colon and, in more acute infections, of the distal ileum of cattle. When calves were infected with 7000 larvae, anorexia began by the third to fifth weeks, but intake had returned to normal by about the fourteenth week (Bremner, 1961). *Chabertia ovina* is another parasite of the colon. In the experimental infection described by Herd (1971), infection of sheep extended the time taken to consume a maintenance ration from 2 to 8 hours.

(d) Fish. Infection of rainbow trout with *Bulbodacnitis ampullastoma* illustrates that anorexia in nematode infections is not confined to mammals and birds.

(e) Other viscera. Although adult *Strongylus* spp. are parasites of the caecum and colon of equines, infection of foals may cause anorexia at the time of larval migration through blood vessels or liver.

Although they gave no quantitative figures, Atwell and Farmer (1982)

reported anorexia as a symptom of canine dirofilariasis in northern Australia. *Dirofilaria* spp. are found in the blood circulation. *Stephanurus dentatus,* the "kidney worm" of pigs, may cause anorexia.

The symptoms of severe infections with *Dictyocaulus* spp. and *Metastrongylus* spp. in the bronchi or lungs of ruminants and pigs, respectively, *Syngamus trachea* in the trachea of turkeys, and *Dirofilaria immitis* in the circulation of canines and felines suggest that anorexia may occur (see Soulsby, 1982).

An important conclusion of this survey of anorexia in protozoal infections and helminthiases is that it may occur in poorly fed but not in well fed animals. There is some evidence that this is related to dietary protein intake. For instance, anorexia occurred in sheep infected with *F. hepatica* and *H. contortus,* in pigs with *A. suum,* and in chickens with *A. galli,* when fed low-protein diets, but not when these animals received adequate protein. On the other hand, in an experiment with coccidiosis of lambs, those fed a high plane of nutrition (milk and grass nuts) suffered more severely than those on a low plane (Pout and Catchpole, 1974). Unfortunately, there were only two lambs on each plane of nutrition and the authors expressed the planes in terms of available dry matter without giving the proportion of protein. However, it is unlikely that the levels of protein would have been significant in this experiment as the proportion would have been about the same in each plane and relatively constant throughout the weeks of the experiment.

As pointed out in this survey, anorexia is also related to the severity of infection, or at least to the number of larvae administered. There may, therefore, be an interaction between this and nutritional standards. Careful studies of the possible interaction between anorexia, nutrition, and number of parasites must be undertaken for more protozoal infections and helminthiases before the importance of nutrition in this respect can be understood.

C. NONPARASITIC DISEASES

Anorexia is also a symptom of some viral, bacterial, and noninfectious diseases. These are included in this section because it is not known whether the mechanisms of anorexia in these diseases are the same as in protozoal infections and helminthiases. Even if the precipitating peripheral causes differ, it is reasonable to suggest that mechanisms in the central nervous system (CNS) may be the same.

For anorexia in viral and bacterial infections of domestic animals, including the bacterial species *Salmonella, Escherichia, Streptococcus, Staphylococcus,* and *Corynebacterium,* Blood *et al.* (1979) may be consulted. They include infections of both the GIT and other viscera.

T. K. S. Mukkur and G. H. McDowell (personal communication) found that with rising body temperature unimmunized sheep infected with *Salmonella typhimurium* were anorectic 14 days after infection and lost about 20% of their body weight.

As an example of a noninfectious disease, Gent and Creamer (1968) found that in coeliac disease of man weight loss was related more to anorexia than to steatorrhoea.

III. Pathophysiology and Anorexia

Because of the widespread occurrence of anorexia, particularly in infections of the GIT, its importance to the pathophysiology of disease is often either emphasized or taken for granted. Anorexia and poor growth or loss of weight are often associated, but sometimes it has been assumed without critical assessment that there is a causative relationship between the two. The following sections examine the relevance of anorexia to the physiological responses to infection.

A. Assessment of the Relevance of Anorexia

As a general rule there is a direct relationship between the severity of infection and the degree of anorexia; for example, in trichostrongylosis and ostertagosis the degree of anorexia was related to the size of the larval dose (Steel *et al.*, 1980; Symons *et al.*, 1981).

Anorexia obviously restricts the availability of nutrients to the host, but one can argue, as has Sykes (1982), that if skeletal growth and its supporting musculature are reduced so that weight falls, then the need for intake to support this is also reduced. On the other hand, whole-body flux of tyrosine per gram protein ingested, and hence protein synthesis, in anorectic lambs infected with *T. colubriformis* was higher than in uninfected animals fed *ad libitum* (Jones and Symons, 1982), suggesting that consumption needed to be increased. These two contradictory examples indicate that expressing food intake during infection in absolute terms may be misleading. Sykes (1982) collated food intake per kilogram body weight from experiments at the Moredun Institute, Edinburgh, and McMaster Laboratory, CSIRO, Sydney, for sheep with trichostrongylosis and ostertagosis. He showed that there was then a close similarity of intake by infected and noninfected animals, but agreed that food intake may be significantly reduced in acute infections and during the first weeks after initial dosing. In support of this latter contention Michael and Hodges (1971, 1972) reported that consumption per unit of body weight fell abruptly between days 3 and 4, followed by a similar rise about days 6–8

after infection with the coccidia *E. acervulina* and *E. necatrix*. These examples indicate that the relationship between consumption and body weight may be important in any assessment of the significance of anorexia in the physiological responses to infection.

The relative significance of anorexia in physiological responses is frequently assessed by the pair-feeding technique. The responses of infected hosts fed *ad libitum* are compared with those of uninfected animals paired with them and fed the weight of food consumed by the former group the preceding day. Whenever possible the responses of infected and pair-fed animals are compared in all that follows.

B. IS ANOREXIA EVER BENEFICIAL?

Must anorexia always be harmful? Murray *et al.* (1978), when proposing that anorexia has an evolutionary and ecological significance, asked whether the old adage "Feed a cold and starve a fever" arose from observations of the value of starvation in the early stages of infection. They proposed that anorexia may have a beneficial role in the "preliminary skirmish" of a host with infection, but agreed that if prolonged it must adversely affect the host. They listed a number of theoretical possibilities when reduced food intake, particularly in intracellular viral and bacterial infections, may stimulate defense against infecting agents or suppress inflammation and oncogenesis. These included the direct or indirect deprivation of the availability of macro- and micronutrients to the infecting agent and effects on the functions of cells or on immunological responses. Subsequently, Murray and Murray (1979) reported that mortality increased and survival time decreased in anorectic mice force-fed when infected with the bacterium *Listeria monocytogenes*.

This hypothesis requires further investigation, especially in protozoal and helminthic infections. Nevertheless, because anorexia is common to so many forms of infection the possibility that it may be beneficial, particularly early in disease, should not be ignored.

C. PRODUCTIVITY

There are many instances when it has been shown by pair-feeding that anorexia was not the sole factor accounting for poor growth or loss of weight of infected animals. In coccidiosis of chickens, for example, pair-fed birds did not lose as much weight and recovered more rapidly than did those infected with *E. acervulina* or *E. necatrix* (Michael and Hodges, 1971, 1972). Sheep infected with *S. mattheei* began losing weight at the time of oviposition at about the sixth or seventh week of infection, whereas pair-feeding had little effect (Preston *et al.*, 1973). Berry and

Dargie (1976) found by pair-feeding that anorexia in sheep infected with *F. hepatica* contributed substantially, but not entirely, to weight loss and hypoalbuminaemia.

It has also been well established that anorexia in nematode infections of different parts of the GIT does not entirely explain poor productivity. For instance, weight gain during abomasal infection with *O. circumcincta* was only 80% of that of pair-fed animals. Reduction of the deposition of body fat and skeletal calcium and phosphorus was greater in the infected than in the pair-fed group (Sykes and Coop, 1977).

In an infection of sheep with *T. colubriformis*, loss of weight appeared to be due to anorexia (Symons and Jones, 1975). When a more detailed examination was made of this infection in guinea pigs, it was confirmed that loss of weight was directly related to food consumption. The greater the anorexia, the greater the loss of weight and, although the mean loss of weight by the pair-fed animals was less than that of the infected group, the difference was not statistically significant. However, as the degree of anorexia increased so did the rate of weight loss by the infected group, whereas there was a constant relationship between loss of weight and consumption by the pair-fed animals (Symons and Jones, 1978). Subsequently, in a third experiment, it was found that the mean rate of loss of weight by lambs with trichostrongylosis was 0.02 kg week^{-1} contrasted with gains of 0.38 and 0.68 kg week^{-1} by uninfected lambs pair-fed or fed *ad libitum*, respectively (Jones and Symons, 1982). Such differences between the results of experiments are not uncommon and are referred to again in this review. They may be due to a number of factors such as differences in the hosts' age or nutritional state or to experimental procedures. For instance, infective larvae may be administered in one dose or given over several days or weeks, or the sophistication of measuring procedures may differ. Some of these differences occurred between the three experiments described here. In this instance it was concluded that in trichostrongylosis, as in other infections, anorexia does not entirely account for loss of weight.

Wool production was lower by about 40% in year-old sheep initially infected with 20,000 larvae of *T. colubriformis* followed by 4000 week^{-1} for 6 weeks, than in pair-fed sheep (Barger *et al.*, 1973). Daily dosing for 14 weeks with larvae of *O. circumcincta* or *T. colubriformis* reduced the skeletal growth of lambs. Pair-feeding indicated that some of this may have been due to anorexia in ostertagosis, but this was unlikely in trichostrongylosis (Sykes *et al.*, 1975 and 1977, respectively).

Anorexia with infection of the lower bowel is exemplified by infection of the distal ileum and large intestine of calves with *O. radiatum*. The rate of weight gain by calves infected with a single dose of 7000 larvae was appreciably lower than in pair-fed animals. Diarrhoea, hypoproteinaemia,

and normochromic, normocytic anaemia occurred only in the infected animals (Bremner, 1961).

In rats infected with the bacterium *S. typhimurium*, anorexia was not the sole factor responsible for loss of weight. Infected animals lost more weight and excreted more urinary nitrogen than pair-fed rats (McGuire *et al.*, 1968).

If anorexia is not the sole factor responsible for poor growth or loss of weight, etc., what other derangements may be involved, and is anorexia responsible for any part of them?

D. MALABSORPTION AND ENDOGENOUS PROTEINS

When discussing weight loss by chickens infected with *E. acervulina*, Michael and Hodges (1971) suggested that malabsorption might add to the effect of anorexia. They quoted Preston-Mafham and Sykes (1970), who found poor absorption of glucose and histidine from the proximal small intestine in this infection. Although malabsorption of ingesta may occur in the infected region of the intestinal tract (often the proximal small intestine in helminth infections), it was concluded that malabsorption, at least of the major constituents of the diet, is not an important factor exacerbating anorexia (Symons, 1976). There is apparently sufficient functional reserve in the parasite-free ileum to compensate for malabsorption in the duodenum and jejunum. This presumably operates in most coccidial infections as it has been shown to do in some nematode infections. Exceptions to this may occur in infections of the ileum and large intestine, e.g., in calves infected with *O. radiatum*. In this infection plasma proteins lost by colonic leakage cannot be reabsorbed and this adds to the effect of anorexia, leading to hypoproteinaemia (Bremner, 1969).

Increased loss of endogenous proteins released into the lumen of the GIT is significant in many infections of the tract and has been reviewed for trichostrongylosis and ostertagosis by Steel and Symons (1982). Unless it is reabsorbed, protein lost from plasma and in exfoliated epithelial cells and mucus will be an additional drain on available protein. Its resynthesis almost certainly diverts available amino acids from skeletal muscle and, in sheep, from wool. It has been shown in sheep with trichostrongylosis that about 70% of endogenous protein is reabsorbed, but about 30% must pass into the caecum and large bowel (Poppi *et al.*, 1981). That this loss is not confined to ruminants is shown in the rat infected with *Nippostrongylus brasiliensis*, in which loss of exfoliated cells occurs in the worm-free distal ileum and large intestine (Symons, 1978; Cheema and Scofield, 1982).

Ingestion of large quantities of whole blood by the parasites and marked catabolism of albumin in haemonchosis is a form of endogenous protein

loss. As reported above, Dargie (1973) found that although sheep infected with *H. contortus* lost weight they were not anorectic, but actually increased their intake of nitrogen. He explained this weight loss by proposing that there was considerable diversion of amino acids from liver, bone marrow, and muscle in an attempt to maintain physiological levels of plasma proteins and haemoglobin. On the other hand, as mentioned earlier anorexia may also occur in ovine haemonchosis.

E. PROTEIN SYNTHESIS AND UTILIZATION

1. *Protein synthesis and anorexia in trichostrongylosis*

Except for infection of sheep with *T. colubriformis*, protein synthesis and catabolism have been examined only to a limited extent in nematode infections. Because I am familiar and involved with much of this work on trichostrongylosis, I have reviewed it in this section and drawn some conclusions about the relevance of anorexia to protein metabolism.

There was a series of experiments at McMaster Laboratory, CSIRO, on protein synthesis and one on catabolism. Tyrosine flux, as a measure of whole-body protein synthesis, was not affected by trichostrongylosis when expressed in terms of body weight, but was higher in terms of protein intake than in uninfected sheep fed *ad libitum*. But neither of these responses was due to anorexia as pair-feeding reduced flux per kilogram body weight and tended to reduce flux per gram protein intake (Jones and Symons, 1982).

There was some conflict as to whether protein synthesis was reduced in skeletal muscle of pair-fed as well as infected sheep. First experiments appeared to show clearly that anorexia reduced muscle protein synthesis in infected and pair-fed sheep and guinea pigs (Symons and Jones, 1975, 1978). In the later experiment with tyrosine the fractional synthetic rate (FSR) and protein synthesized per day by the semitendinosus muscle of lambs were not reduced by pair-feeding, whereas infection reduced both (Jones and Symons, 1982). As suggested earlier in this review, the differences between the earlier and later experiments may have been due to the greater sophistication of the last experiment when incorporation following infusion of tyrosine over 6 hours was measured, compared with incorporation of leucine after a single injection. On the other hand, the differences may have been due to the greater anorexia in the earlier experiments in which infected sheep ate very little, compared with a reduction of intake of only about 50% in the tyrosine experiment. When the results of these experiments were compared in detail it was concluded that although anorexia may reduce the rate of skeletal muscle protein synthesis, it was not the sole factor responsible.

The rate of synthesis of structural proteins of the liver, including en-

zymes, was increased in each of the three experiments referred to above, but again there was some uncertainty as to whether anorexia was responsible. When synthesis was measured in sheep by incorporation of leucine per unit of tissue nitrogen the rate in the infected animals was higher than in the pair-fed group, which, in turn, exceeded that of the uninfected animals fed *ad libitum* (Symons and Jones, 1975). But pair-feeding did not increase the rate of protein synthesis in the tyrosine experiment (Jones and Symons, 1982). Again, the difference between experiments could have been due to differences in technique or degree of anorexia.

Amino acid incorporation into membrane-bound ribosomes isolated from the liver measures synthesis of circulating proteins, particularly albumin. When incorporation of leucine by these ribosomes isolated from the livers of guinea pigs infected with *T. colubriformis* was measured, the rate was almost doubled and was independent of anorexia (Symons *et al.*, 1974). There was no significant increase in synthesis by free ribosomes that synthesize intracellular proteins. The increase in the rate of synthesis of circulating proteins is undoubtedly stimulated by leakage of plasma proteins.

The FSR and protein synthesized daily by the kidney cortex, a tissue unlikely to be directly affected by leakage of plasma proteins, are reduced by trichostrongylosis. This, too, is independent of anorexia (Jones and Symons, 1982).

For technical reasons intestinal protein synthesis in trichostrongylosis was measured in guinea pigs, not sheep (Symons and Jones, 1983). Infection had no effect on the FSR in either the infected or parasite-free sections of the small intestine, but the amount of protein synthesized daily by the entire small intestine exceeded that in uninfected guinea pigs fed *ad libitum* (Symons and Jones, 1983). This increase was presumably due to the greater protein content of the infected intestines. Both the FSR and daily protein synthesis were appreciably increased in the large intestine of the infected animals, the latter by over 70%. None of these changes was due to anorexia, as reducing the rations of uninfected guinea pigs reduced both the FSR and daily protein synthesis in the small intestine without affecting the large intestine. The increase in protein synthesis in the large intestine is an instance of infection changing function in a part of the intestinal tract harboring no parasites.

On the other hand, anorexia did account for the fall in the rate of skeletal muscle protein catabolism in guinea pigs with trichostrongylosis (Jones and Symons, 1978). This is consistent with the observations of Young *et al.* (1973) that muscle protein catabolism was depressed in man when starved. Millward *et al.* (1976) also found that the rate of muscle protein catabolism, together with synthesis, fell in rats starved or fed protein-deficient diets. Loss of skeletal muscle nitrogen in infection is clearly due to greater reduction of synthesis rather than of catabolism.

Protein synthesis by homogenates of wool follicles from sheep with trichostrongylosis was depressed by over 50%, but it was not known whether this was due to anorexia (Symons and Jones, 1975). This had been made clear by Barger (1973) who found that poor wool growth in this infection was due to poor protein utilization rather than anorexia. Similarly, it has been shown that poor skeletal growth in chronic infections with *O. circumcincta* and *T. colubriformis* was due to poor utilization of energy and protein rather than to anorexia (Sykes, 1982).

Whether alterations in hormonal concentrations are responsible in any way for changes in protein synthesis or utilization is not known, but nevertheless it has been speculated that this may be so. Prichard *et al.* (1974) reported that plasma concentration of corticosteroids rose, whereas that of insulin fell, in growing sheep infected with *T. colubriformis*. Because plasma concentration of corticosteroids also rose in pair-fed sheep, but not as high as in infected animals, whereas there was a similar fall of insulin in both groups, it was concluded that anorexia may explain the fall in the latter, but does not entirely explain the rise in corticosteroids. Alternatively, it could be asked whether these hormonal changes explain anorexia.

It is not possible to construct balance sheets of protein synthesis or amino nitrogen movement in the whole-body and different organs of sheep infected with *T. colubriformis*. However, it is possible to summarize with a schematic diagram the changes in protein synthesis and intestinal leakage of endogenous proteins, to show whether anorexia was responsible for the changes. This has been done in Fig. 1 in which little attempt has been made to show the interrelationships between all organs or tissues; e.g., the sources of amino nitrogen that account for increases in whole-body or intestinal protein synthesis are not illustrated. Nevertheless, it is clear that amino nitrogen is diverted from productive tissues such as skeletal muscle and wool to intestinal and plasma proteins. Presumably the increase in whole-body protein synthesis per unit of food ingested is largely explained by the increase in synthesis of these intestinal and plasma proteins (see Symons and Jones, 1983). From the point of view of this review it is clear that anorexia explains very little of this with any certainty, apart from the fall in the rate of muscle protein catabolism. In fact, as has already been stated, had anorexia been responsible, the rate of small-intestinal protein synthesis would have fallen and the rate in the large intestine would have been unchanged.

2. *Protein synthesis in other parasitic infections*

Protein synthesis has been measured in very few other infections. Skeletal muscle protein synthesis is depressed in chickens infected with the coccidium *E. tenella*, and in guinea pigs with the bacterium *Yersinia*

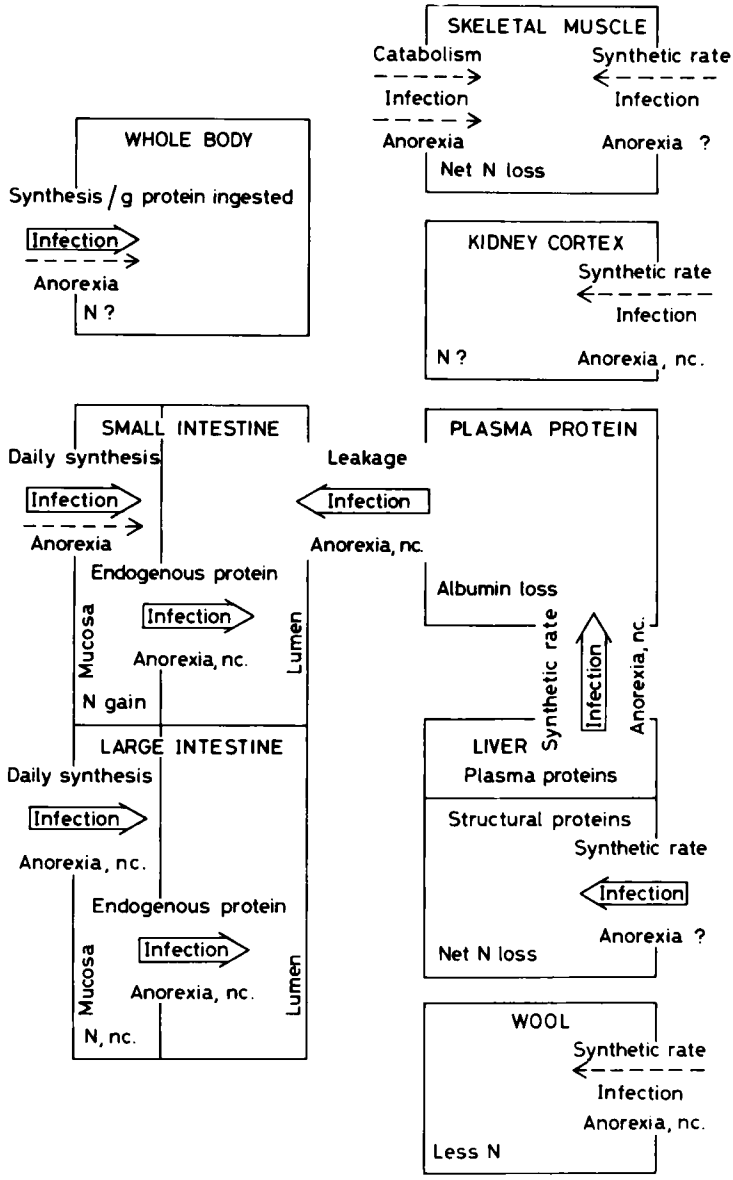

FIG. 1. Schematic summary of the effects of infection of sheep with *Trichostrongylus colubriformis* and the symptom of anorexia on protein synthesis and intestinal leakage of plasma proteins. Wide arrow denotes an increase; dotted arrow, a decrease; nc, no change; N, nitrogen.

pseudotuberculosis (Symons and Jones, 1971). The hosts in both infections, particularly the former, were anorectic, but as there was no pair-feeding it is impossible to say whether this affected the rate of synthesis. Similarly, the rate of liver protein synthesis was increased in piglets infected with *Strongyloides ransomi* (Dey-Hazra *et al.*, 1979). As no statement was made about food consumption and there was no pair-feeding, it is not known whether anorexia affected this measurement of synthesis.

3. *Utilization*

If poor protein synthesis in infection cannot be explained by anorexia, what other metabolic changes are there, and is anorexia responsible?

In an experiment with trichostrongylosis of lambs infected by daily dosing with 2500 infective larvae for 14 weeks and using pair-feeding, Sykes and Coop (1976) concluded that poor gain of empty body weight was due in part to reduced intake (about 70–85% of that of uninfected sheep fed *ad libitum*), but largely to poor food utilization. Retention of nitrogen was reduced due to increased urinary excretion. Use of metabolizable energy was reduced by about 50% in the infected lambs, but not in the pair-fed group. On the other hand, Sykes and Coop (1977) found that in lambs infected daily with 4000 larvae of *O. circumcincta* for 14 weeks, anorexia rather than inefficient nitrogen retention accounted for poor growth. Reduction of the use of metabolized energy in the infected lambs was again found to be unrelated to anorexia. Symons *et al.* (1981) also found that retention of nitrogen was unaffected in lambs continuously dosed with this parasite, but could not say whether this was due to anorexia as pair-feeding was not used.

Another nematode infection in which utilization of food has been examined in relation to pair-fed animals was that of calves infected with a single dose of 7000 infective larvae of *O. radiatum* (Bremner, 1961). Utilization in infected calves was 0.039 lb per pound of feed compared with 0.095 lb in the three pair-fed animals. Food intake was reduced after 3–4 weeks of infection by about 50%. It was concluded that poor utilization contributed more to the pathogenesis of the infection than did anorexia.

Utilization has also been examined in trematode infections. Dargie *et al.* (1979) compared pair-fed 9-month-old sheep with others infected with a single dose of 1000 metacercariae of *F. hepatica*. The sheep were fed the two diets with different levels of protein described earlier in this review. Dry matter intake by those receiving hay fell after about week 7 by about 35%, whereas the intake of those on the supplemented diet fell by 29%. In general, this difference between the responses of infected sheep on the two diets was shown for all quantities measured, but the differences were not always statistically significant. Nitrogen balances fell and became negative in the infected group after about 9–10 weeks, compared with a

falling, but always positive balance in the pair-fed animals. Dargie *et al.* (1979) concluded that poor weight gain was due to both anorexia and reduced nitrogen retention. Because urinary excretion of nitrogen was increased in the infected sheep, these authors suggested that catabolism was increased. This would explain poor nitrogen retention. This suggestion was based in part on early observations I had made, but I now suggest that anorexia may have reduced muscle protein catabolism at least (Jones and Symons, 1978), so that protein loss was probably due to net reductions of both synthesis and catabolism of muscle protein.

Without pair-feeding in their experiment Cawdery *et al.* (1977) also concluded that anorexia and poor utilization accounted for poor growth in heavy infections of calves with *F. hepatica*. However, only poor utilization, and not anorexia, affected growth in lighter infections.

Berry *et al.* (1973) pair-fed four uninfected adult sheep and four infected by immersing one leg in water containing 10,000 cercariae of *S. mattheei* (see Preston *et al.*, 1973). Nitrogen intake by the infected sheep fell markedly after about 6 weeks and nitrogen balances became negative in three of the four animals. Nitrogen balance also fell in the fourth animal, but remained narrowly positive. Nitrogen balances in the pair-fed sheep also tended to fall, but remained positive and exceeded those of the infected group. The lower nitrogen balances in the infected sheep were due to greater excretion in both urine and faeces, exceeding that of the pair-fed animals by 2–5 g day^{-1}. The authors again concluded that weight loss in these sheep with schistosomiasis was due to a combination of anorexia and inefficient use of nitrogen. The low nitrogen balances of the pair-fed sheep indicated that anorexia per se may have had some effect on nitrogen metabolism.

These experiments with a variety of parasites, not all in the intestinal tract, show that poor use of ingested food or, in some instances, its constituent nitrogen, explains part of the poor growth or loss of weight in infected animals. It is reasonable to conclude that part of this poor utilization is due to anorexia, particularly when the latter is marked.

Nevertheless, it is clear that anorexia per se does affect growth rate or the maintenance of body weight, although less severely than does infection as a whole. In the only infection in which it has been measured, whole-body protein synthesis in terms of tyrosine flux per kilogram body weight in sheep with trichostrongylosis was unaffected, whereas had anorexia been the sole factor involved this synthetic rate would have fallen (Jones and Symons, 1982). Whole-body protein synthesis in the infected animal is obviously the net result of increases and decreases in various organs and tissues of the body. Clearly then, anorexia reduced the rate of whole-body synthesis when an increase in, or at least the maintenance of, food consumption was necessary to support the higher rate needed for

productivity in this instance. Furthermore, the effect of anorexia would be exacerbated by malabsorption, or by failure to reabsorb a proportion of the GIT loss of endogenous protein or other substances.

This argument can be developed for only one infection, and cannot be extended critically to other GIT infections without more measurements of whole-body syntheses. Equally obviously, we know very little about the effects of infections of other body systems, apart from the certainty that anorexia restricts the availability of nutrients to the host.

IV. Mechanisms of Anorexia

Because anorexia is a symptom in many different infectious and noninfectious diseases of various organs and tissues of the body, it is reasonable to assume that there are manifold causes. Yet it is probable that even if there are many what might be called precipitating or peripheral causes, there is a common mechanism in the CNS. This section begins with an outline of what is known about regulation of appetite in the normal animal before considering possible mechanisms in parasitic infections.

A. Appetite and Satiety in the Normal Animal

Morley (1980) wrote a useful review of the central regulation of appetite using the rat as a model, but recognized that there were differences between species. This review, which may be consulted for more details, is the source of the following outline.

A simplistic approach is to look upon two centres of the hypothalamus as controlling feeding and satiety. One, in the lateral hypothalamus and known as the feeding centre, initiates feeding and the other, situated ventromedially and known as the satiety centre, terminates the desire to feed. However, these two centres do not act independently; there is a two-way link between them. Furthermore, Morley described the role of the hypothalamus as a transducer which integrates multiple inputs from the *milieu interieur*, and so maintains the nutritional homeostasis of the normal animal. Feeding behaviour is thus activated or inhibited.

Impinging upon these hypothalamic centres is a multitude of neuroendocrine factors from other centres of the brain which produce monaminergic, opiate, and peptidergic regulation of food intake. For instance, hypothalamic injections of serotonin and its agonists result in anorexia, whereas its antagonists stimulate hyperphagia. Feeding may be stimulated or inhibited, respectively, by α-adrenergic and β-adrenergic systems. Dopamine stimulates feeding, whereas its antagonists inhibit

feeding. Endogenous opiates may stimulate eating by acting upon the feeding centre.

Much interest has developed in recent years in the control of appetite by the neuropeptides cholecystokinin (CCK) and the thyrotropin-releasing hormone. Morley stressed that it is often difficult to distinguish between the effects of these peptides acting locally in the hypothalamus as paracrines and those they may produce as circulating hormones.

CCK, originally described as a GIT hormone, has now been found in large amounts in the brain, including the hypothalamus, of a number of species including man (Morley, 1980). It may be looked upon as a neurotransmitter. Morley (1982) reviewed the effects of CCK on the gastrointestinal, pancreatic, hepatobiliary, and central nervous systems. Its effect on the last named includes the regulation of appetite.

Morley (1982) referred to reports showing that intravenous injection of the octapeptide of CCK (CCK-OP) depressed appetite in rats, rhesus monkeys, pigs, and man, but the doses were, in general, large and there were some conflicting results. On the other hand, there is more convincing evidence that centrally administered CCK-OP inhibits feeding.

Della-Fera and Baile (1980) reported that injection of CCK-OP at a rate as low as 0.04 pmol min^{-1} in synthetic cerebrospinal fluid (CSF), given over 3 hours at the rate of 0.1 ml min^{-1} into the lateral ventricles (LV) of the brain of sheep, significantly decreased feeding and 0.638 pmol min^{-1} completely depressed feeding. They claimed that the sheep behaved normally in all other respects. Three times the amount of CCK-33 was required to elicit the degree of inhibition resulting from 0.638 pmol min^{-1} of CCK-OP. Caerulein, an analogue of CCK-OP, had a similar effect as the octapeptide when injected into the LV in equimolar quantities (Della-Fera and Baile, 1981). In support of the effect of CCK-OP was the finding that the continuous injection into the LV of an antiserum developed from desulphated CCK-OP approximately doubled intake by satiated sheep (Della-Fera *et al.*, 1981b). Furthermore, the intraventricular injection over 2 hours of dibutyryl cyclic GMP, a competitive antagonist of CCK-OP, in satiated sheep induced them to eat (Della-Fera *et al.*, 1981a). In this experiment the injection of the antagonist at the rate of 2.9 nmol min^{-1} elicited feeding within the first 15 minutes of the injection, whereas 0.72, 29, and 290 nmol min^{-1} did not. During administration of the two higher doses the sheep were restless and vocalized, and feed intakes were reduced. The authors recognized the possibility that eating by satiated sheep after injection of dibutyryl cyclic GMP was independent of a CCK satiety system.

Miceli and Malsbury (1983) examined the effect in hamsters of the peripheral or central injection of a single dose of CCK-OP in bacterio-

static saline. Peripherally, 0.5, 1.0, 2.0, or 4.0 μg per kilogram body weight was injected intraperitoneally in 0.1 ml. Centrally, 50 or 100 ng in 5 μl was injected via a cannula into the LV. By comparison with the medium only as a control, intake was depressed by both routes of administration of CCK-OP. The threshold of the peripheral dose was above 0.5 $\mu g\ kg^{-1}$, with a maximal effect at 1.0 $\mu g\ kg^{-1}$. A single LV injection of 100 ng CCK-OP was as effective in suppressing food intake as any of the larger peripheral doses.

The results of these experiments do not indicate whether CCK-OP acts on peripheral or central receptors to inhibit feeding, as it is known that CCK delivered into the CNS rapidly appears in the circulation (Passaro *et al.*, 1982). Furthermore, regarding the possible importance of CCK to anorexia in parasitic infections, Morley (1982) has stated that available evidence indicates that CCK is one of a number of factors having a *short-term* role in appetite regulation following the ingestion of a meal. Miceli and Malsbury (1983) also stated that experimental results are consistent with the hypothesis that CCK-OP is related to a short-term satiety mechanism restricting meal size.

The possible role of the liver in the control of appetite has been reviewed by Forbes (1982), who pointed out that as almost all absorbed nutrients pass through this organ it could monitor nutrient flow. He stated that evidence has accumulated over the past decade that food intake in a number of species responds to the energy status of the liver and is relayed to the brain by hepatic branches of the vagus nerve. Russek (1976) also suggested that changes in hepatocyte membrane potential proportional to the flow of metabolites may be relayed by the vagus nerve. Forbes (1982) concluded that evidence supports a multifactorial control of food intake, with the liver playing an important but not overriding part.

Dehydration, which increases fluid osmolarity, may also inhibit food consumption.

There are also a number of mechanisms and changes in the GIT which affect appetite, and which may be relevant to anorexia during infections of the tract. Hall (1975) referred to receptors including chemoreceptors, pH receptors, and osmoreceptors, which may alter neuronal activity in hypothalamic centres. Accumulation of fluid or changes in the propulsion and motility of the intestine may affect appetite, presumably by acting through relevant receptors. For instance, abomasal infusion of 5.336 kg day^{-1} of methylcellulose, a bulk laxative, had little effect on intestinal transit time in sheep, even though faecal output was doubled and the intestines markedly distended. However, consumption of chopped lucerne hay was significantly decreased (Grovum and Phillips, 1978). Inflammation of the tract may interfere with autonomic reflexes and neurological input to the hypothalamus (Hall, 1975). Pain may also reduce

eating. Leng (1981) suggested that a major factor affecting food consumption in ruminants was the amount and whereabouts of absorption of amino acids.

Most if not all the mechanisms or factors mentioned above, whether initiated in the CNS or peripherally, may cause anorexia in one or other of the parasitic infections listed in Section II of this review.

B. ANOREXIA IN PARASITIC INFECTION

Although pain in animals is difficult to assess objectively, it is possible that it is responsible for anorexia, at least in some instances. There are occasional subjective statements that pain was the cause, or part of the cause, of anorexia. For instance, Andrews (1939) stated that lambs with fatal infections of *Trichostrongylus* appeared depressed and in pain and were unable to eat all the food given to them. Gibson (1955) had no doubt that severe abomasitis in infection with *Trichostrongylus axei* was accompanied by considerable pain. Neither of these authors described the signs of pain. The statement of Miller (1979) that abdominal pain accompanied anorexia in hookworm disease in man must be one instance based upon objective evidence.

The physical condition of the GIT in infection is frequently and readily obvious as soon as the abdominal cavity is opened, e.g., in sheep infected with *T. colubriformis*. The small intestine, particularly the infected region, may be dilated with fluid. The dilated jejunum of rats infected with *N. brasiliensis* is partly explained by a considerable increase in the volume of fluid in the small intestine (Symons, 1957). Similarly, the "ballooning" of the jejunum of chickens infected with *E. necatrix* is due to an accumulation of fluid and debris (Michael and Hodges, 1972). The rate of propulsion through the intestinal tract may be affected by infection. In one instance, the rate of passage of a meal was slower through the proximal two-thirds and faster through the distal one-third of the small intestine of rats with nippostrongylosis (Symons, 1966). In another example, transit was hastened throughout the small intestine of rats infected with *Trichinella spiralis* (Castro *et al.*, 1976).

The GIT may be inflamed at the site of infection. The histological changes, commonly including villous atrophy, have been so frequently described, as summarized by Symons (1969), that there is no need to repeat them here.

The pH of the abomasal contents of sheep infected with *O. circumcincta* (McLeay *et al.*, 1973) and with *T. colubriformis* (Titchen, 1982) has been found to rise, frequently above pH 4. Intestinal pH may change in other infections.

Whether or not any of these anatomical, physical, or chemical re-

sponses to infection adversely affects appetite is unknown. This needs to be investigated. Techniques are now available to enable the activity of nervous pathways from the GIT to hypothalamic centres to be examined.

As already pointed out, Leng (1981) proposed that any derangement of digestion and absorption of amino acids by ruminants might affect appetite. Leng stated that any change in the availability of amino acids for absorption in infections of sheep with *O. circumcincta* or *T. colubriformis* would change the protein to energy ratio of absorbed nutrients, and so reduce food intake as well as the efficiency of utilization of absorbed amino acids. Furthermore, any change in the region of the small intestine from which amino acids are absorbed may also affect appetite. For instance, the absorption of many substances, including amino acids, is reduced at the site of infection, but may be compensatorily increased in the more distal worm-free regions (Symons, 1976). In trichostrongylosis, rumen fermentation is reduced by 30% (Steel, 1972) so that the amount of organic material leaving the rumen is possibly reduced. In this regard, it is known that the amount of nonammonia nitrogen flowing from the abomasum is increased in infections of *O. circumcincta* (Steel, 1978). This may be due to a higher abomasal pH ensuring that proteins are unchanged by pepsin, or due to release of more endogenous protein into this organ. Another factor possibly changing amino acid absorption could be an increase in deamination due to increases in the number of bacteria in any part of the GIT. This would reduce the availability of amino acids for absorption, thereby depressing appetite. Leng (1981) suggested that the number of bacteria in the small intestine may increase if, as in ostertagosis, poor pepsin activity ensures that protein remains longer in the digestive tract. He also proposed that reduced fermentation in the rumen in trichostrongylosis may be followed by greater fermentation in the caecum and proximal colon, from which the amino acids released are not absorbed.

Unfortunately little work on bacteria in parasitic infections of the GIT has been reported. Jennings *et al.* (1966) found up to about a 40-fold increase in the number of viable aerobic bacteria in abomasal fluid in calves infected with *O. ostertagi*. However, it is anaerobic bacteria that are responsible for fermentation. Conversely, Mettrick (1971) reported that the numbers of aerobic and anaerobic bacteria in the small intestinal contents of rats were markedly reduced in infection with the cestode *Hymenolepis diminuta*.

As part of any future study of the relevance of bacteria to anorexia, it is necessary to know whether the numbers of aerobic and anaerobic organisms in the contents and on the mucosa of all parts of the GIT are affected in several helminthic and protozoal infections. Does abnormal fermentation occur in these infections, what are the relative degrees of fermenta-

tion in different regions of the tract, and is appetite affected by any regional differences?

More knowledge is required of the nitrogenous material passing through the tract in infections of the GIT in both ruminants and monogastric animals. How much is there, in what form is it present, and where is this nitrogen absorbed? The answers to these questions may be relevant to anorexia in infection.

Although it may be relevant to the central control of appetite in parasitic infection, there is no report of CCK concentration in the hypothalamus or CSF of infected animals. The plasma concentration of a substance, which in a bioassay contracted gallbladder tissue of the guinea pig and was believed at the time to be CCK, increased by about 65% in sheep almost completely anorectic when infected with *T. colubriformis*. The concentration returned to normal when food consumption returned after removal of the parasites with an anthelmintic. In addition, the intravenous injection of CCK-OP reduced the food intake of uninfected lambs (Symons and Hennessy, 1981). However, later measurements by radioimmunoassay failed to show any increase in plasma CCK in anorectic sheep with trichostrongylosis (D. A. Titchen and L. E. A. Symons, unpublished results). Whether the bioassay with strips of gallbladder measured CCK or some other substance is being investigated at present.

Investigation of the significance of CCK to anorexia in infection of the GIT is obviously at a preliminary stage. Has it any significance at all? As mentioned previously, Morley (1982) has suggested that CCK is one of a number of factors that have a short-term effect on appetite regulation following the ingestion of a meal, and CCK may have no relation to the relatively long-lasting anorexia in parasitic infections.

In my opinion it is essential that any study of the causes of anorexia in parasitic infection should recognize that CCK is only one part of a complex mechanism in the regulation of eating. Nevertheless, much more must be done before it is discarded as irrelevant to anorexia in these infections. Do the levels of CCK in brain tissue or CSF rise in infected animals? What effect on eating by anorexic infected animals has intraventricular or peripheral administration of CCK antiserum or inhibitors such as dibutyryl cyclic GMP? Even if it is shown that CCK is relevant to anorexia, other substances and/or pathways in the brain may be involved. On the other hand, is the release of CCK from the intestine stimulated by the presence of parasites? If so, is CCK relevant only to intestinal parasitism?

This section has looked almost exclusively at possible causes of anorexia in GIT infections, particularly in ruminants. Although very little is known about the causes of anorexia in these infections, even less is known about its causes in infections of other organs. Are the initiating

causes entirely different in the latter? Are the mechanisms of central regulation of appetite in these infections the same as those for GIT infections? The summary of the regulation of eating and satiety in the normal animal indicates that a complete understanding of anorexia in parasitized animals is certainly complex and may be difficult to unravel. I can only conclude by saying that present explanations for anorexia in parasitic infections are so rudimentary that this is a most interesting and fruitful field for future study.

References

Abbott, E. M. (1982). "Dietary Influences on the Pathophysiology of Ovine Haemonchosis." Ph.D. thesis. Faculty of Veterinary Medicine, University of Glasgow.

Andrews, J. S. (1939). Experimental trichostrongylosis in sheep and goats. *Journal of Agricultural Research* **58,** 761–770.

Armour, J., Jennings, F. W., Murray, M., and Selman, I. (1973). Bovine ostertagiasis. Clinical aspects, pathogenesis, epidemiology and control. *In* "Helminth Diseases of Cattle, Sheep and Horses in Europe" (G. M. Urquhart and J. Armour, eds.), pp. 11–20. University Press, Glasgow.

Arzoun, I. H., Hussein, H. S., and Hussein, M. F. (1984). The pathogenesis of experimental *Haemonchus longistipes* infection in camels. *Veterinary Parasitology* **14,** 43–53.

Atwell, R. B., and Farmer, T. S. (1982). Clinical pathology of the "Caval Syndrome" in canine dirofilariasis in Northern Australia. *Journal of Small Animal Practice* **23,** 675–685.

Barger, I. A. (1973). Trichostrongylosis and wool growth. 1. Feed digestibility and mineral absorption in infected sheep. *Australian Journal of Experimental Agriculture and Animal Husbandry* **13,** 42–47.

Barger, I. A., Southcott, W. H., and Williams, V. J. (1973). Trichostrongylosis and wool growth. 2. The wool growth response of infected sheep to parental and duodenal cystine and cysteine supplementation. *Australian Journal of Experimental Agriculture and Animal Husbandry* **13,** 351–359.

Berry, C. I., and Dargie, J. D. (1976). The role of host nutrition in the pathogenesis of ovine fascioliasis. *Veterinary Parasitology* **2,** 317–332.

Berry, C. I., Dargie, J. D., and Preston, J. M. (1973). Pathophysiology of ovine schistosomiasis. IV. Effects of experimental *Schistosoma mattheei* infection on the nitrogen status and digestive efficiency of the host. *Journal of Comparative Pathology* **83,** 559–568.

Blood, D. C., Henderson, J. A., and Radostits, O. M. (1979). "Veterinary Medicine." 5th Ed. Baillière Tindall, London.

Bremner, K. C. (1961). A study of pathogenetic factors in experimental bovine oesophagostomosis. I. An assessment of the importance of anorexia. *Australian Journal of Agricultural Research* **12,** 498–512.

Bremner, K. C. (1969). Pathogenetic factors in experimental bovine oesophagostomosis. IV. Exudative enteropathy as a cause of hypoproteinaemia. *Experimental Parasitology* **25,** 382–394.

Castelino, J. B., Herbert, I. V., and Lean, I. J. (1970). The liveweight gain of growing pigs experimentally infected with massive doses of *Hyostrongylus rubidus* (Nematoda) larvae. *British Veterinary Journal* **126,** 579–582.

Castro, G. A., Badial-Aceves, F., Smith, J. W., Dudrick, S. J., and Weisbrodt, N. W. (1976). Altered small bowel propulsion associated with parasitism. *Gastroenterology* **71,** 620–625.

Cawdery, M. J. H., Strickland, K. L., Conway, A., and Crowe, P. J. (1977). Production effects of liver fluke in cattle. I. The effects of infection on liveweight gain, food intake and food conversion efficiency in beef cattle. *British Veterinary Journal* **133,** 145–159.

Cheema, K. J., and Scofield, A. M. (1982). Scanning electron microscopy of the intestines of rats infected with *Nippostrongylus brasiliensis*. *International Journal for Parasitology* **12,** 199–205.

Clarkson, M. J., and Gentles, M. A. (1958). Coccidiosis in turkeys. *Veterinary Record* **70,** 211–214.

Dargie, J. D. (1973). Ovine haemonchosis. Pathogenesis. *In* "Helminth Diseases of Cattle, Sheep and Horses in Europe" (G. M. Urquhart and J. Armour, eds.), pp. 63–71. University Press, Glasgow.

Dargie, J. D., Berry, C. I., and Parkins, J. J. (1979). The pathophysiology of ovine fasciolia-sis: Studies on the feed intake and digestibility, body weight and nitrogen balance of sheep given rations of hay or hay plus a pelleted supplement. *Research in Veterinary Science* **26,** 289–295.

Della-Fera, M. A., and Baile, C. A. (1980). CCK-octapeptide injected in CSF and changes in feed intake and rumen motility. *Physiology and Behaviour* **24,** 943–950.

Della-Fera, M. A., and Baile, C. A. (1981). Peptides with CCK-like activity administered intracranially elicit satiety in sheep. *Physiology and Behavior* **26,** 979–983.

Della-Fera, M. A., Baile, C. A., and Peikin, S. R. (1981a). Feeding elicited by injection of the cholecystokinin antagonist dibutyryl cyclic GMP into the cerebral ventricles of sheep. *Physiology and Behaviour* **26,** 799–801.

Della-Fera, M. A., Baile, C. A., Schneider, B. S., and Grinker, J. A. (1981b). Cholecystoki-nin antibody injected in cerebral ventricles stimulates feeding in sheep. *Science* **212,** 687–689.

Dey-Hazra, A., Sallmann, H.-P., Enigk, K., and Harisch, G. (1979). Protein synthesis changes in the liver of piglets infected with *Strongyloides ransomi*. *Veterinary Parasitol-ogy* **5,** 339–351.

Dubey, J. P. (1976). A review of *Sarcocystis* of domestic animals and of other coccidia of cats and dogs. *Journal of the American Veterinary Medical Association* **169,** 1061–1078.

Evans, J. V., Blunt, M. H., and Southcott, W. H. (1963). The effects of infection with *Haemonchus contortus* on the sodium and potassium concentrations in the erythrocytes and plasma in sheep of different haemoglobin types. *Australian Journal of Agricultural Research* **14,** 549–558.

Forbes, J. M. (1982). The role of the liver in the control of food intake. *Proceedings of the Nutrition Society* **41,** 123–125.

Forsum, E., Nesheim, M. C., and Crompton, D. W. T. (1981). Nutritional aspects of *Ascaris* infection in young protein-deficient pigs. *Parasitology* **83,** 497–512.

Gent, A. E., and Creamer, B. (1968). Faecal fats, appetite and weight loss in the coeliac syndrome. *Lancet* **1,** 1063–1064.

Gibson, T. E. (1955). Studies on *Trichostrongylus axei*. IV. Factors in the causation of pathogenic effects by *T. axei*. *Journal of Comparative Pathology and Therapeutics* **65,** 317–324.

Grovum, W. L., and Phillips, G. D. (1978). Factors affecting the voluntary intake of food by sheep. 1. The role of distension, flow-rate of digesta and propulsive motility in the intes-tines. *British Journal of Nutrition* **40,** 323–336.

Hall, R. J. C. (1975). Progress report. Normal and abnormal food intake. *Gut* **16,** 744–752.

Herd, R. P. (1971). The pathogenic importance of *Chabertia ovina* (Fabricius, 1788) in experimentally infected sheep. *International Journal for Parasitology* **1,** 251–263.

Hiscox, J. I., and Brocksen, R. W. (1973). Effects of a parasitic gut nematode on consump-tion and growth in juvenile rainbow trout (*Salmo gairdneri*). *Journal of the Fisheries Research Board of Canada* **30,** 443–450.

Ikeme, M. M. (1971). Observations on the pathogenicity and pathology of *Ascaridia galli*. *Parasitology* **63,** 169–179.

Jennings, F. W., Armour, J., Lawson, D. D., and Roberts, R. (1966). Experimental *Ostertagia ostertagi* in calves: Studies with abomasal cannulas. *American Journal of Veterinary Research* **27,** 1249–1257.

Jones, W. O., and Symons, L. E. A. (1978). Protein metabolism. 6. *Trichostrongylus colubriformis*: Skeletal muscle protein catabolism in primary and secondary infections of the guinea pig. *Experimental Parasitology* **44,** 92–99.

Jones, W. O., and Symons, L. E. A. (1982). Protein synthesis in the whole body, liver, skeletal muscle and kidney cortex of lambs infected by the nematode *Trichostrongylus colubriformis*. *International Journal for Parasitology* **12,** 295–301.

Keith, R. K. (1967). The pathogenicity of experimental infections of *Cooperia pectinata* Ransom 1907 in calves. *Australian Journal of Agricultural Research* **18,** 861–864.

Knowles, R. T., Montrose, M., Craig, T. M., Wagner, G. G., and Long, R. F. (1982). Clinical and serological evidence of bovine babesiosis and anaplasmosis in St. Lucia. *Veterinary Parasitology* **10,** 307–311.

Lean, I. J., Herbert, I. V., and Castelino, J. B. (1972). Studies on the pathogenesis of infection with *Hyostrongylus rubidus* (Nematoda). The effects of levels of infection up to 150,000 infective stage larvae on the growing pig. 1. Nutritional studies. *British Veterinary Journal* **128,** 138–145.

Leng, R. A. (1981). Nutrition and metabolism of parasitized and non-parasitized ruminants. *Isotopes and Radiation in Parasitology* **4,** 191–206.

McGuire, E. A., Young, V. R., Newberne, P. M., and Payne, B. J. (1968). Effects of *Salmonella typhimurium* infection. *Archives of Pathology* **86,** 60–68.

McLeay, L. M., Anderson, N., Bingley, J. B., and Titchen, D. A. (1973). Effects on abomasal function of *Ostertagia circumcincta* infections in sheep. *Parasitology* **66,** 241–257.

Mettrick, D. F. (1971). *Hymenolepis diminuta*: The microbial fauna, nutritional gradients, and physiochemical characteristics of the small intestine of uninfected and parasitized rats. *Canadian Journal of Physiology and Pharmacology* **49,** 972–983.

Meyer, E. A., and Radulescu, S. (1979). *Giardia* and giardiasis. *Advances in Parasitology* **17,** 1–47.

Miceli, M. O., and Malsbury, C. W. (1983). Feeding and drinking responses in the golden hamster following treatment with cholecystokinin and angiotensin II. *Peptides* **4,** 103–106.

Michael, E., and Hodges, R. D. (1971). The pathogenic effects of *Eimeria acervulina*: A comparison of single and repeated infections. *Veterinary Record* **89,** 329–333.

Michael, E., and Hodges, R. D. (1972). The pathogenic effects of *Eimeria necatrix*: A comparison of single and repeated infections. *Veterinary Record* **91,** 258–262.

Miller, T. A. (1979). Hookworm infection in man. *Advances in Parasitology* **17,** 315–384.

Millward, D. J., Garlick, P. J., James, W. P. T., Sender, P. M., and Waterlow, J. C. (1976). Protein turnover. *In* "Protein Metabolism and Nutrition" (D. J. A. Cole, K. N. Boorman, P. J. Buttery, D. Lewis, R. J. Neal, and H. Swan, eds.), pp. 49–69. Butterworths, London.

Morley, J. E. (1980). The neuroendocrine control of appetite: The role of the endogenous opiates, cholecystokinin, TRH, gamma-amino-butyric acid and the diazepam receptor. *Life Sciences* **27,** 355–368.

Morley, J. E. (1982). The ascent of cholecystokinin (CCK) from gut to brain. *Life Sciences* **30,** 479–493.

Murray, J., Murray, A., and Murray, N. (1978). Anorexia: Sentinel of host defense? *Perspectives in Biology and Medicine* **22,** 134–142.

Murray, M. J., and Murray, A. B. (1979). Anorexia of infection as a mechanism of host defense. *American Journal of Clinical Nutrition* **32,** 593–596.

Passaro, E., Debas, H., Oldendorf, W., and Yamada, T. (1982). Rapid appearance of intraventricularly administered neuropeptides in the peripheral circulation. *Brain Research* **241,** 335–340.

Poppi, D. P., MacRae, J. C., and Corrigall, W. (1981). Nitrogen digestion in sheep infected with intestinal parasites. *Proceedings of the Nutrition Society* **40,** 116A.

Pout, D. D., and Catchpole, J. (1974). Coccidiosis of lambs. V. The clinical response to long term infection with a mixture of different species of coccidia. *British Veterinary Journal* **130,** 388–399.

Powers, K. G., Todd, A. C., and McNutt, S. H. (1960). Experimental infections of swine with *Trichuris suis*. *American Journal of Veterinary Research* **21,** 262–268.

Pradhan, S. L., and Johnstone, I. L. (1972). *Haemonchus contortus*—the effect on lambs of prolonged exposure to daily and weekly doses of infective larvae. *Parasitology* **64,** 143–152.

Preston, J. M., Dargie, J. D., and MacLean, J. M. (1973). Patho-physiology of ovine schistosomiasis. 1. A clinico-pathological study of experimental *Schistosoma mattheei* infections. *Journal of Comparative Pathology* **83,** 401–415.

Preston-Mafham, R. A., and Sykes, A. H. (1970). Changes in body weight and intestinal absorption during infections with *Eimeria acervulina* in the chicken. *Parasitology* **61,** 417–424.

Prichard, R. K., Hennessy, D. R., and Griffiths, D. A. (1974). Endocrine responses of sheep to infection with *Trichostrongylus colubriformis*. *Research in Veterinary Science* **17,** 182–187.

Rowlands, D., apT., and Probert, A. J. (1972). Some pathological changes in young lambs experimentally infected with *Nematodirus battus*. *Research in Veterinary Science* **13,** 323–329.

Russek, M. (1976). A conceptual equation of intake control. *In* "Hunger: Basic Mechanisms and Clinical Implications" (D. Novin, W. Wyrwicka, and G. A. Bray, eds.), pp. 327–347. Raven, New York.

Soulsby, E. J. L. (1968). "Helminths, Arthropods and Protozoa of Domesticated Animals (6th Ed. of Mönnig's Veterinary Helminthology and Entomology)." Baillière, Tindall & Cassell, London.

Soulsby, E. J. L. (1982). "Helminths, Arthropods and Protozoa of Domesticated Animals" (7th Ed.). Baillière, Tindall, London.

Steel, J. W. (1972). Effects of the intestinal nematode *Trichostrongylus colubriformis* on ruminal acetate metabolism in young sheep. *Proceedings of the Australian Society of Animal Production* **9,** 402–407.

Steel, J. W. (1978). Inter-relationships between gastrointestinal helminth infection, nutrition and impaired productivity in the ruminant. *In* "Recent Advances in Animal Nutrition" (D. J. Farrell, ed.), pp. 98–109. Univ. of New England Publ. Unit, Armidale.

Steel, J. W., and Symons, L. E. A. (1982). Nitrogen metabolism in nematodosis of sheep in relation to productivity. *In* "Biology and Control of Endoparasites" (L. E. A. Symons, A. D. Donald, and J. K. Dineen, eds.), pp. 235–256. Academic Press, New York.

Steel, J. W., Symons, L. E. A., and Jones, W. O. (1980). Effects of level of larval intake on the productivity and physiological and metabolic responses of lambs infected with *Trichostrongylus colubriformis*. *Australian Journal of Agricultural Research* **31,** 821–838.

Steel, J. W., Jones, W. O., and Symons, L. E. A. (1982). Effects of a concurrent infection of *Trichostrongylus colubriformis* on the productivity and physiological and metabolic responses of lambs infected with *Ostertagia circumcincta*. *Australian Journal of Agricultural Research* **33,** 131–140.

Sykes, A. R. (1982). Nutritional and physiological aspects of helminthiasis in sheep. *In* "Biology and Control of Endoparasites" (L. E. A. Symons, A. D. Donald, and J. K. Dineen, eds.), pp. 217–234. Academic Press, New York.

Sykes, A. R., and Coop, R. L. (1976). Intake and utilization of food by growing lambs with parasitic damage to the small intestine caused by daily dosing with *Trichostrongylus colubriformis* larvae. *Journal of Agricultural Science (Cambridge)* **86,** 507–515.

Sykes, A. R., and Coop, R. L. (1977). Intake and utilization of food by growing sheep with abomasal damage caused by daily dosing with *Ostertagia circumcincta* larvae. *Journal of Agricultural Science (Cambridge)* **88,** 671–677.

Sykes, A. R., Coop, R. L., and Angus, K. W. (1975). Experimental production of osteoporosis in growing lambs by continuous dosing with *Trichostrongylus colubriformis* larvae. *Journal of Comparative Pathology* **85,** 549–559.

Sykes, A. R., Coop, R. L., and Angus, K. W. (1977). The influence of chronic *Ostertagia circumcincta* infection on the skeleton of growing sheep. *Journal of Comparative Pathology* **87,** 521–529.

Sykes, A. R., Coop, R. L., and Rushton, B. (1980). Chronic subclinical fascioliasis in sheep: Effect on food intake, food utilization and blood constituents. *Research in Veterinary Science* **28,** 63–70.

Symons, L. E. A. (1957). Pathology of infestation of the rat with *Nippostrongylus muris* (Yokogawa). 1. Changes in the water content, dry weight and tissues of the small intestine. *Australian Journal of Biological Sciences* **10,** 374–383.

Symons, L. E. A. (1966). Digestion and absorption of maltose in rats infected by the nematode *Nippostrongylus brasiliensis*. *Experimental Parasitology* **18,** 12–24.

Symons, L. E. A. (1969). Pathology of gastrointestinal helminthiases. *International Review of Tropical Medicine* **3,** 49–100.

Symons, L. E. A. (1976). Malabsorption. *In* "Pathophysiology of Parasitic Infection" (E. J. L. Soulsby, ed.), pp. 11–21. Academic Press, New York.

Symons, L. E. A. (1978). Epithelial cell mitosis and morphology in worm-free regions of the intestines of the rat infected by *Nippostrongylus brasiliensis*. *Journal of Parasitology* **64,** 958–959.

Symons, L. E. A., and Hennessy, D. R. (1981). Cholecystokinin and anorexia in sheep infected by the intestinal nematode *Trichostrongylus colubriformis*. *International Journal for Parasitology* **11,** 55–58.

Symons, L. E. A., and Jones, W. O. (1971). Protein metabolism. 1. Incorporation of ^{14}-C-L-leucine into skeletal muscle and liver proteins of mice and guinea pigs infected with *Nematospiroides dubius* and *Trichostrongylus colubriformis*. *Experimental Parasitology* **29,** 230–241.

Symons, L. E. A., and Jones, W. O. (1975). Skeletal muscle, liver and wool protein synthesis by sheep infected by the nematode *Trichostrongylus colubriformis*. *Australian Journal of Agricultural Research* **26,** 1063–1072.

Symons, L. E. A., and Jones, W. O. (1977). Protein metabolism. IV. Altered protein synthesis in hosts infected with *Eimeria tenella* or bacteria compared to synthesis in hosts infected with intestinal nematodes. *Experimental Parasitology* **42,** 194–202.

Symons, L. E. A., and Jones, W. O. (1978). Protein metabolism. 5. *Trichostrongylus colubriformis*: Changes of host body mass and protein synthesis in guinea pigs with light to heavy infections. *Experimental Parasitology* **44,** 7–13.

Symons, L. E. A., and Jones, W. O. (1983). Intestinal protein synthesis in guinea pigs infected with *Trichostrongylus colubriformis*. *International Journal for Parasitology* **13,** 309–312.

Symons, L. E. A., Jones, W. O., and Steel, J. W. (1974). Protein metabolism. III. Relationship between albumin metabolism and elevated liver protein synthesis in the guinea pig infected with *Trichostrongylus colubriformis*. *Experimental Parasitology* **35,** 492–502.

Symons, L. E. A., Steel, J. W., and Jones, W. O. (1981). Effects of level of larval intake on the productivity and physiological and metabolic responses of lambs infected with *Ostertagia circumcincta*. *Australian Journal of Agricultural Research* **32,** 139–148.

Titchen, D. A. (1982). Hormonal and physiological changes in helminth infestations. *In* "Biology and Control of Endoparasites" (L. E. A. Symons, A. D. Donald, and J. K. Dineen, eds.), pp. 257–275. Academic Press, New York.

Tzipori, S., McCartney, E., Lawson, G. H. K., Rowland, A. C., and Campbell, I. (1981). Experimental infection of piglets with *Cryptosporidium*. *Research in Veterinary Science* **31,** 358–368.

Tzipori, S., Smith, M., Birch, C., Barnes, G., and Bishop, R. (1983a). Cryptosporidiosis in hospital patients with gastroenteritis. *American Journal of Tropical Medicine and Hygiene* **32,** 931–934.

Tzipori, S., Smith, M., Halpin, C., Angus, K. W., Sherwood, D., and Campbell, I. (1983b). Experimental cryptosporidiosis in calves: Clinical manifestations and pathological findings. *Veterinary Record* **112,** 116–120.

Whalen, G. E., Strickland, G. T., Cross, J. H., Rosenberg, E. B., Gutman, R. A., Watten, R. H., Uylangco, C., and Dizon, J. J. (1969). Intestinal capillariasis: A new disease in man. *Lancet* **1,** 13–16.

Young, V. R., Haverberg, L. N., Bilmazes, C., and Munro, H. N. (1973). Potential use of 3-methyl-histidine excretion as an index of progressive reduction in muscle protein catabolism during starvation. *Metabolism* **22,** 1429–1436.

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Argasid and Nuttalliellid Ticks as Parasites and Vectors[1]

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I. INTRODUCTION

A. BACKGROUND

Ticks are highly specialized obligate parasites of a wide variety of terrestrial and flying vertebrates and a few marine snakes and lizards. During the one to several long periods that most tick species spend off the host and on the ground, their survival depends on a delicate interplay between physiological and structural properties and functions and ecological factors. Thus, tick–host and tick–environmental factors are both of paramount importance in understanding the role of the individual tick species as a parasite and a vector.

The vast literature regarding ticks has centered mostly around about 40 species of medical and veterinary significance. About 40 other species most obviously involved in human and animal disease epidemiology have received much more biomedical attention than the remaining ~720 species in the world fauna of slightly more than 800 tick species (Fig. 1). However, the epidemiological role of "important" species, and methods for controlling them and preventing diseases they spread, are best clarified when specialists comprehend the biological and physiological similarities and differences between all species, genera, and families in relation to their hosts and to the environment. It should be added parenthetically that virtually every species having a role in veterinary medicine also transmits infectious agents to man. Basic and applied scientists need to recognize the biological models of tick parasitism of wildlife and the factors that have permitted less than 10% of all ticks to become economically

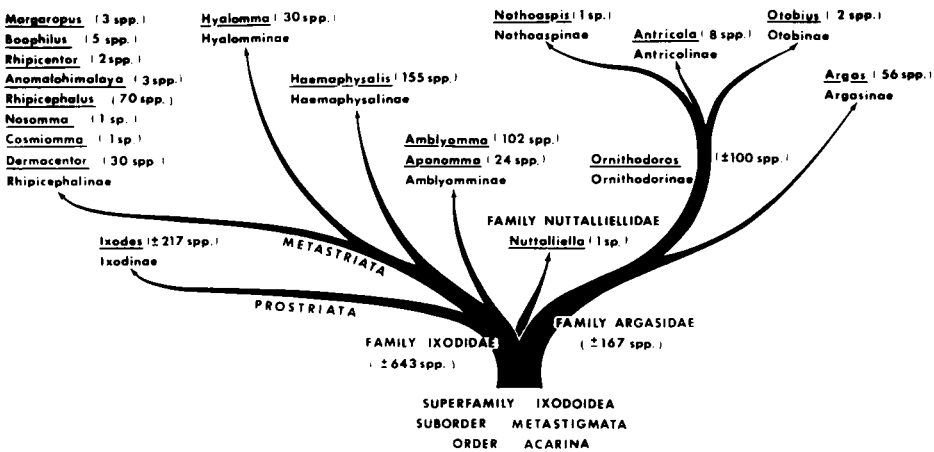

FIG. 1. Dendogram of the superfamily Ixodoidea showing families, subfamilies, genera, and number of species.

important pests and vectors of disease agents to livestock and man (Hoogstraal, 1978).

As contemporary biologists become increasingly specialized they are often said to lose sight of the organism (species) as a whole and of relationships between organisms. Some species constituting the family Argasidae have been intensively investigated, others are poorly known, and others are virtually unknown. (The family Nuttalliellidae is in the last-named category.) No overview of these families has been published. To furnish the student and contemporary researcher with an appreciation of the level of knowledge of the primary affinities and differences in biological phenomena in the Argasidae and Nuttalliellidae, this article is a simple presentation of the basic natural history of each argasid subfamily and genus, the hosts they parasitize, and the infectious agents they transmit. This material and the references cited serve as indices to more specialized literature listed in bibliographies on ticks and tick-borne diseases and in recent authoritative books reviewing tick structures and physiology (cited in the next section).

B. ESSENTIAL LITERATURE

The following literature, dealing chiefly with Ixodidae but also comparatively with Argasidae, is essential for understanding the biology, structures, physiology, and behavior of individual species of the superfamily Ixodoidea in relation to parasitism and disease–agent transmission. Balashov (1972) reviewed information on tick biology, especially of economically and medically important ixodid species in temperate Eurasia. My concept of the fundamental factors in tick biology has appeared in condensed form (Hoogstraal, 1978). The description of the ultrastructure of *Hyalomma asiaticum* Schulze (Ixodidae) and other tick species by Balashov (1983) is a primary source for recognizing relationships between external and internal structures, the environment, and infectious agents transmitted to hosts. Equally important is a book on tick physiology containing reviews by a number of outstanding experts (Obenchain and Galun, 1983). This book deals with the tick cuticle; humidity relationships and water balance; the sensory basis of feeding behavior, attachment and feeding (role of the mouthparts, feeding apparatus, salivary gland secretions, and host response); immunological basis of host resistance; blood digestion; ion and water balance during feeding and mechanisms of excretion; reproduction (sperm development, cytogenetics, oogenesis, and oviposition); structure and functions of the circulatory, nervous, and neuroendocrine systems; endocrine mechanisms (effects of insect hormones and their mimics on development and reproduction); pheromone mechanisms; and diapause and biological rhythms. A more up-to-date authorita-

tive review of tick pheromones is given by Sonenshine (1984). Only bits and pieces from the wealth of detail in these significant, easily available publications will be mentioned herein. The book on ticks and diseases by Arthur (1962) is regrettably incomplete.

A basis for understanding the often moot parameters of tick–host specificity and parasitism models (and tick life cycles) in relation to individual vertebrate host groups was presented by Hoogstraal and Aeschlimann (1982), and bibliographic references to ticks and tick-borne diseases were collated by Hoogstraal (1970–1984). Subject index bibliographies of tick species, distribution, hosts, and tick-borne diseases are included in 70 of the numerous volumes of the Index Catalogue of Medical and Veterinary Zoology published between 1932 and 1983 by the United States Department of Agriculture (USDA), Washington, D.C. These bibliographies are available in biomedical libraries throughout the world. Therefore, the references cited herein are only those of critical importance or which list other important literature on the subject under discussion. When authors are mentioned without a literature citation, the pertinent reference can easily be found in the USDA or Hoogstraal bibliographies.

II. Phylogeny and Evolution

Conclusions regarding tick phylogeny derive from comparative structural and biological data for contemporary species. There is some literature on "fossil species" (Chodziesner, 1924; Schulze, 1929; Weidner, 1964) but no truly fossil ticks have been proven.

The tick superfamily Ixodoidea Banks contains three families (Fig. 1). Some acarine systematists (Krantz, 1978) refer this superfamily of the class arachnida and subclass Acari to the suborder Ixodida, which together with the suborders Gamasida, Holothyrida, and Opilioacardia constitute the order Parasitiformes. Others name the order Metastigmata, or use Metastigmata at the suborder level. The basic relationships between ticks and mites are generally agreed upon by specialists but schemes and terminology for representing them are controversial, as mentioned by Krantz.

The three families of ticks are postulated to have evolved from a single branch of the Parasitiformes as parasites of Reptilia in the warm, humid climate of the late Paleozoic or early Mesozoic (Hoogstraal, 1978). When Paleozoic–Mesozoic Reptilia radiated into numerous bizarre forms filling a variety of aquatic and terrestrial niches, their more conservative tick parasites evolved along three lines.

One phylogenetic line, the Argasidae ("soft ticks"), was originally represented by the genera *Argas* (Argasinae) and *Ornithodoros* (Ornithodori-

nae) partially as we know them today and partially by different species which have become extinct. The other contemporary genera of argasids, *Otobius, Antricola,* and *Nothoaspis* (Fig. 1), evolved in the Tertiary with Chiroptera, Lagomorpha, and Artiodactyla (Hoogstraal and Aeschlimann, 1982).

The second major phylogenetic line, the Ixodidae ("hard ticks"), was originally represented by (1) the genus *Ixodes* (Ixodinae), which has been poorly studied phylogenetically, (2) species of the genera *Aponomma* and *Amblyomma* (Amblyomminae), probably much like those we know today, and (3) species related to the 17 structurally primitive members of the genus *Haemaphysalis* (Haemaphysalinae) (Hoogstraal, 1978; Hoogstraal and Kim, 1985). The genus *Hyalomma* (Hyalomminae) is also structurally primitive but may have appeared later, close to the Cretaceous period of late Mesozoic environmental stresses and reduction of reptile lines to the Rhynchosauria and ancestors of modern birds and mammals. *Dermacentor, Rhipicephalus, Boophilus,* and related genera of Rhipicephalinae did not evolve until the Tertiary, when mammals and birds replaced reptiles as dominant vertebrates.

Another phylogenetic line, the Nuttalliellidae, represented only by the excessively rare South African *Nuttalliella namaqua* Bedford, combines structural features of both other families with characters unique to itself. This relict evolutionary line has probably remained quite stable since the late Mesozoic or early Tertiary.

The phylogenetic relationships between Argasidae, Ixodidae, and Nuttalliellidae are illustrated by basic structural and biological properties common to the three families. In each family these basic properties are more or less distinctively modified in relation to the particular behavior patterns and life-style(s) associated with certain hosts and environments. We usually tend to emphasize the differences between these families and to treat lightly the common basic properties that constitute the rationale for classifying the Argasidae, Ixodidae, and Nuttalliellidae as a superfamily (Ixodoidea).

Biological or physiological adaptations for parasitism in the evolution of the argasid line, in contrast to those of the ixodid line, are expressed chiefly by the rapid feeding of nymphs and adults and some larvae (versus slow feeding in virtually all ixodids), several nymphal bloodmeals and instars (one nymphal bloodmeal and instar in ixodids), excess water and ion excretion via coxal glands (versus this excretion via salivary fluids in ixodids), mating off the host (on the host in ixodids, except some *Ixodes* spp.), several adult bloodmeals and relatively small egg batches (single adult bloodmeal and single larger egg batch in ixodids), and parasitism chiefly of hosts which more or less regularly visit a discrete shelter site (versus more common parasitism of wandering hosts by many adult or

immature and adult ixodids). Various adaptations for existence during the long periods most ticks spend off the host are equally important for tick survival. Argasids are absent from arctic, antarctic, and colder zones of temperate regions, where one or two *Ixodes* species are associated chiefly with marine birds. Nuttalliellid biological adaptations are obviously highly specialized but field and laboratory data are scanty.

III. Argasid and Nuttalliellid Ticks as Parasites (Biosystematics)

In this age of molecular biology, a flippant attitude to the species and to species differentiation (taxonomy and systematics) is commonplace. No outlook is more damaging to the so-called "cutting edge of science" than to disregard the biological uniqueness of the individual species and its component biological races or strains. I employ the term *biosystematics* to embody the integral interrelationships between systematics (including taxonomy) and biology. Only by emphasizing this biological individuality can we understand the role of the tick as a parasite and a vector.

A. Family Argasidae Murray

1. *Introduction*

(*a*) *Biological characteristics and biosystematics*. The leathery Argasidae are highly specialized structurally, physiologically, and biologically for (1) maintaining a favorable water balance in inclement arid or semiarid environments, (2) rapid feeding by nymphs and adults (and larvae of certain species) on hosts which regularly remain near the argasid shelter for only a few weeks annually or which irregularly return to the shelter area for short periods, (3) sheltering in narrow crevices or cracks of rock or wood, or close to the soil surface, or on the soil surface under stones or debris, and (4) surviving for months or years when hosts are absent from the shelter sites.

Argasid adaptations to certain hosts, especially to those which return irregularly or for limited periods to a certain nesting or resting site, are expressed most clearly in unusual feeding and life cycle phenomena in a few species of the subfamilies Argasinae and Ornithodorinae, and also structurally in each species of Otobinae, Antricolinae, and Nothoaspinae.

As a result of dominating biological and structural adaptations, the external structure is relatively uniform within each argasid species group or subgenus. Structural criteria for argasid species classification are usually based on properties of both larvae and adults reared from known

females. Reliable, constant criteria for argasid species identity have long been elusive but are now easily determined with the aid of scanning electron microscopy (SEM) of adults and larvae, preferably those reared from known females. Once established by SEM, most diagnostic characters are discernible under the light microscope and are easily applied to field samples.

Another boon to argasid biosystematics, in addition to the SEM, has been a recent worldwide exploration program for tick-borne viruses. Viruses were isolated from samples collected from numerous biotopes and zoogeographical regions and the living ticks remaining in the collections were reared in the laboratory for species identification. The presence or absence of certain viruses often provided initial clues to different tick species before they could be fully studied taxonomically. Coordinated studies enabled us to resurrect incorrectly synonymized taxons and to designate new species within groups of closely related species. The validity of a number of newly elevated or proposed taxons was confirmed by results of cross-breeding investigations (summarized by Khalil *et al.*, 1980). Beginning with the *Argas* subgenus *Persicargas*, knowledge of the entire genus *Argas* has been particularly enriched by the virological–biosystematic approach (Hoogstraal *et al.*, 1979b). The *Ornithodoros* (*Alectorobius*) *capensis* group has benefited similarly (see below). During these biosystematic investigations much has been learned about the biology of *Argas* and *Ornithodoros* ticks and their disease relationships, and knowledge of *Nuttalliella* has also increased, though not to the level we had hoped for.

Phylogenetic indicators in the Argasidae are provided chiefly by host and distribution data and by integumental characteristics of each genus or subgenus. Certain sensory structures (Haller's organ roof and anterior pit setae) also provide phylogenetic clues. Chaetotaxy is useful especially at the species level and for larvae, but classification systems based only on chaetotaxy are counterproductive.

The isolated American argasid genera that parasitize leporids and ungulates (*Otobius*) of the Nearctic arid environment and Neotropical–Nearctic cave-dwelling bats (*Antricola* and *Nothoaspis*) (Fig. 1) are remarkably specialized structurally and biologically.

(*b*) *Life cycle and feeding patterns*

(i) *Argasid patterns*. The multihost feeding pattern (Fig. 2) characterizes the argasid life cycle (Hoogstraal, 1978; Hoogstraal and Aeschlimann, 1982). Exceptions are the two-host *Ornithodoros* (*Alveonasus*) *lahorensis*, the one-host *Otobius megnini* and *O. lagophilus*, and possibly the unstudied genera *Antricola* and *Nothoaspis*. The hosts of these few argasids with exceptional life cycles are wandering mammals (see the next section on ixodid life cycles and the biosystematics sections for these

Stage	Hosts	Remarks
Egg		All on ground
Larva (one rapid or slow feeding)	Host 1	Rapid feeders usually on land mammals; slow feeders usually on birds or bats
	molt/ground	
Nymph (one rapid feeding on each host)	Host 2	Generally 3–4 nymphal instars and hosts; may be more (5–8)
	molt/ground	
	Host 3	
	molt/ground	
	Host 4	
	molt/ground	
Adult (one rapid feeding on each host)	Host 5	Adults feed and mate several times (3-5/6), do not moult. Females deposit several relatively small egg batches, usually one after each meal. Mating is off the host
	Host 6	
	Host 7	

FIG. 2. Multihost feeding and life cycle pattern typical of Argasidae (revised from Hoogstraal and Aeschlimann, 1982). *Argas* (*Microargas*) *transversus*, the two-host *Ornithodoros* (*Alveonasus*) *lahorensis*, and the one-host *Otobius* spp. are exceptions (see text). In the subgenus *Ornithodoros*, larvae do not feed. In the subgenus *Alectorobius*, the first-instar nymph does not feed. The few other life cycle pattern modifications in the Argasidae are, as always, important biologically but fall within the frame of the pattern illustrated here. The genera *Antricola* and *Nothoaspis* are unstudied biologically. The life cycle of Nuttalliellidae is unknown; the single species may be parthenogenetic.

genera and species, Section III,A,3–6). Notably, *O.* (*A.*) *lahorensis* and *Otobius megnini* have become economically and medically important pests of domestic animals. On the other hand, most *Alectorobius* species [except *O.* (*A.*) *lahorensis*] are surviving poorly in the contemporary world; these species parasitize wandering ungulates, porcupines, or

hedgehogs and are highly adapted for existence in dry habitats but are not known to have specialized life cycles.

Rapidly feeding larval and adult argasids usually engorge in about 30 minutes or within an hour. Slowly feeding larvae require 3–10 days to complete the bloodmeal, depending on species, host, and a variety of other factors. A single nymphal instar may feed twice before molting if the first meal has been interrupted or provides insufficient energy for continuing developmental processes. In general, rapidly feeding argasid larvae parasitize land mammals and slowly feeding argasid larvae parasitize birds and bats; the exceptions to this generalization are of special biological interest.

(ii) *Ixodid patterns*. The three-host cycle characterizes 11 of the 13 ixodid genera (all except *Boophilus* and *Margaropus*) and over 620 of the 650 ixodid species (Hoogstraal, 1978). Two-host or one-host ixodid cycles occur only in more recently evolved tick relationships with migrating birds (*Hyalomma marginatum* group) or wandering mammals (mostly Artiodactyla and Perissodactyla) with extensive home ranges, small herds or flocks, and irregular or long intervals between returning to a certain resting site. These specialized ixodids, which originally coexisted with wandering hosts, often in biotopes with long dry seasons or long winters, have prospered more than many others in the environments created by man and his mobile domestic animal herds and flocks. (Wild and domestic hosts almost invariably belong to the same or closely related families or genera.) Most ixodid species that are specific for wild wandering hosts in inclement environments and have specialized life cycle adaptations are important pests of livestock and vectors of infectious agents. With the notable exception of the larva of *Haemaphysalis* (*Alloceraea*) *inermis* Birula and males of some *Ixodes* species, all studied ixodid species, in each stage, feed for several days.

(*c*) *Collecting methods*. A number of argasid species that parasitize only wildlife, especially birds and bats, are known only or chiefly from larvae. Adults of these species have not been sought for in or near nests or in caves or other shelters. If, for various reasons, one does not wish to disturb or destroy a potential host, much can still be learned from collecting argasids from nesting and resting sites. Notably, argasids are found in these sites the year around, whether hosts are present or not. Most argasids are rather easily reared in the laboratory; this effort provides valuable data for studies on identity and biology. Difficulty in rearing argasids provides clues to unusual physiological properties. However, the problem of rearing long-feeding larval parasites of insectivorous bats remains to be solved, possibly by modifications of rearing techniques mentioned in the following section. (Frugivorous bats are more easily maintained as hosts in the laboratory.)

The tiny argasid larvae localize on the host's body, head, and neck, or

in the wing axillae, and require careful search among fur or feathers and exceedingly careful removal and preservation for subsequent identification. Nymphs and adults, and sometimes also fed larvae, are found either in crevices of wood or rock in or within 1 m of the resting or nesting site of the host, or close to the soil surface under the shade of trees or rocks, or in caves where hosts shelter. In many situations a pickax, chisel, or other sharp tool is useful for opening crevices to reveal argasid nymphs and adults. For burrow-dwelling species, a shovel and sieve are useful and a highly successful "tick sucker" (vacuum-collecting machine) has been developed (Butler *et al.*, 1984). A method for collecting *Ornithodoros* (*S.*) *coriaceus* by attracting the ticks to CO_2 gas (from dry ice) (Garcia, 1962, 1964) has also been used for *Ornithodoros* (*O.*) *savignyi* (Nevill, 1964) and *Dermacentor* spp. (Garcia, 1965, 1969), and has been modified for collecting ixodids and argasids (Hair *et al.*, 1972).

(*d*) *Rearing techniques.* A standardized technique for rearing *Argas* was reported by Kaiser (1966a). For experimental studies, argasids can be fed through membranes (Avivi *et al.*, 1968; Tawfik and Guirgis, 1969). The mass rearing method described by Kohls (1937) for ixodids includes certain techniques useful for argasids. A simple field or laboratory method for holding tick-infested vertebrates alive until the ticks drop, so that they can be reared in the laboratory, was described by Kaiser and Hoogstraal (1968).

2. *Genus* Argas *Latreille*

(*a*) *Introduction.* The 56 species and seven subgenera constituting the genus *Argas,* with their distribution, hosts and habitats, viruses and other infectious agents, and cross-breeding studies, were summarized by Hoogstraal *et al.* (1979b). Subsequently, results of crossing the African *A.* (*Persicargas*) *arboreus* and the Asian–Australian *A.* (*P.*) *robertsi* were reported (Khalil *et al.*, 1980). Results of this and other attempted crossings [*A.* (*P.*) *arboreus* × *A.* (*P.*) *persicus, A.* (*P.*) *arboreus* × *A.* (*P.*) *walkerae, A.* (*P.*) *persicus* × *A.* (*P.*) *radiatus, A.* (*P.*) *persicus* × *A.* (*P.*) *sanchezi, A.* (*P.*) *sanchezi* × *A.* (*P.*) *radiatus*] indicate weak or distant relationships. If oviposition occurred, the eggs did not hatch or the progeny did not develop to the adult stage. Cytogenetic studies of 11 *Argas* species (Oliver, 1977) showed a diploid (2*n*) number of 26 chromosomes (two long sex chromosomes in the female, one long and one shorter in the male), but 24 in *A.* (*Ogadenus*) *brumpti* Neumann and 20 in *A.* (*Carios*) *vespertilionis* (Latreille).

(*b*) *Subgenus* Argas *Latreille.* This subgenus contains 21 described species from the Palearctic (9), Neotropical (7), Nearctic (2), Australian (2), and Ethiopian (1) regions (Hoogstraal *et al.*, 1979b). One species from Egypt remains to be described. Adult and immature morphological char-

acters are recorded for each species except *A.* (*A.*) *himalayensis* Hoogstraal and Kaiser (larva only known) and *A.* (*A.*) *dulus* Keirans, Clifford, and Capriles (larva unknown). *Argas* (*Argas*) species have been collected from sea level to 4300 m altitude; the high altitude record is *A.* (*A.*) *himalayensis* from the snow partridge, *Lerwa lerwa* (Hodgson), above timberline in Nepal.

The definitive structural and biological properties of the subgenus *Argas* were reviewed by Clifford *et al.* (1984). Four Neotropical species have distinctive characters indicating structural and biological evolutionary trends in this region. The fifth Neotropical species, *A.* (*A.*) *dalei* Clifford, Keirans, Hoogstraal, and Corwin, a Peruvian parasite of the Nearctic–Neotropical burrowing owl, *Speotyto,* is more closely related to Nearctic than to Neotropical *Argas* species.

All species of the subgenus *Argas* parasitize birds in nesting colonies or resting groups. Most of the 21 species shelter in crevices of rock ledges or in stony ground near the birds. However, two Neotropical species (*A. monachus* group) infest arboreal nests of birds: *A.* (*A.*) *dulus* parasitizes the palm chat, *Dulus dominicus* (L.), in the Dominican Republic; and *A.* (*A.*) *monachus* Keirans, Radovsky, and Clifford parasitizes the monk parakeet, *Myiopsitta monachus* (Boddaert), in Argentina. One Nearctic species, *A.* (*A.*) *brevipes* Banks, inhabits holes in trees and treelike cacti and parasitizes various birds nesting in these shelters. The host specificity of most *Argas* (*Argas*) species is strictly or relatively limited but somewhat more extensive for widely distributed species. Examples of the chief hosts of certain species are the rock pigeon, *Columba livia* Gmelin (and the domestic pigeon derived from it), and the already-mentioned snow partridge, burrowing owl, palm chat, and monk parakeet, as well as the crested cormorant and cliff swallow, mentioned below. Two Neotropical species are thus far known only from domestic chickens.

The structure of Haller's organ is less constant in the subgenus *Argas* than in *Persicargas*. The capsule roof structure in *Argas* (*Argas*) differs rather greatly between individual species and species groups, as well as within some species; the nine typical anterior pit setae also vary in number and are reduced to three or four in Neotropical species (Clifford *et al.*, 1984). The biological, behavioral, and phylogenetic implications of these variations and differences remain to be determined.

Two *Argas* (*Argas*) species parasitize marine birds and are structurally and biologically distinctive. *Argas* (*A.*) *macrostigmatus* Filippova infests wet nests of the crested cormorant, *Phalacrocorax aristotelis* (L.), on islands in the Black Sea (Ukrainian SSR) and the Mediterranean (Corsica) (Hoogstraal *et al.*, 1984). This is the only *Argas* recorded from a damp habitat; one wonders whether its unusually large spiracular plates are associated functionally with this exceptional environment. This is also the

only *Argas* known to occur together with an *Ornithodoros* tick—*O.* (*Alectorobius*) *maritimus* Vermeil and Marguet. The second marine bird parasite, *A.* (*A.*) *cucumerinus* Neumann, inhabits barren Peruvian cliffs facing the Pacific and feeds on birds (and human visitors) occasionally resting (not nesting) on ledges where the ticks shelter (Clifford *et al.*, 1978). In this chancy host-encountering situation, the ticks literally run during daytime, their bodies elevated high over hot sand on long, spidery legs, to reach a host. No other *Argas* is known to venture voluntarily into sunlight or to feed during daytime and no other has spidery legs except some cave-dwelling bat parasites of the subgenera *Carios* and *Chiropterargas*. Also, no other *Argas* larva is known to feed rapidly. *Argas* (*A.*) *cucumerinus* larvae feed to repletion within 7–25 minutes (on pigeon and man in the laboratory) and become large (~4–5 mm long). This rapid larval feeding pattern probably also reflects irregular host visits of a few hours to the rock ledge.

Both marine bird parasites are notable for unusual Haller's organ features in larvae, nymphs, and adults (Clifford *et al.*, 1984). The Haller's organ capsule of *A.* (*A.*) *macrostigmatus* lacks a roof, a presumably primitive character shared in the entire genus only with *A.* (*A.*) *polonicus* Siuda, Hoogstraal, Clifford, and Wassef (of Palearctic rock pigeons, *Columba livia* Gmelin, and domestic pigeons in Poland and Czechoslovakia) and *A.* (*A.*) *cooleyi* Kohls and Hoogstraal (of Nearctic cliff swallows, *Hirundo pyrrhonota* subspp., western United States and Mexico). In *A.* (*A.*) *cucumerinus*, the capsule roof is merely an open, corraline-reticulate cuticular net and the anterior pit setae number only three, rather than the 7–11 characteristic of most *Argas* species. The functional and behavioral associations of these distinctive structural modifications are unknown.

The life cycle of the southern Palearctic, northwestern Oriental *A.* (*A.*) *hermanni* Audouin (see Khalil and Metwally, 1974) and of the Ethiopian *A.* (*A.*) *africolumbae* Hoogstraal, Kaiser, Walker, Ledger, and Converse, when reared under comparable conditions, are practically identical with regard to larval and nymphal cycles (two or three, sometimes four, nymphal instars), sex ratio, fecundity, preoviposition and oviposition periods, and nondiapause behavior (Kraiss and Gothe, 1982). When hosts are constantly available, two or three generations develop annually and form dense populations. The few studied species of the subgenera *Argas* and *Persicargas* conform closely to these patterns except where diapause lengthens the development of populations in zones with a definite winter season (such as Egypt, southern Europe and USSR, and southern United States). Relevant reports are listed by Kraiss and Gothe (1982). Life cycle details obviously differ distinctly from those of species mentioned already at altitudes above timberline [*A.* (*A.*) *himalayensis*], or where hosts are

absent for many months [*A.* (*A.*) *falco* Kaiser and Hoogstraal] or return irregularly to the *Argas* shelter [*A.* (*A.*) *cucumerinus*].

The arboviruses infecting *Argas* (*Argas*) species are listed in Table 1, and together with human irritation, tick paralysis, *Borrelia anserina*, and *Aegyptianella pullorum*, are discussed in Section IV.

TABLE 1
Argasid species and virus associations

Argasid	Virus associations
Family Argasidae Murray	
Subfamily Argasinae Canestrini	
Argas (*Argas*) *cooleyi* Kohls and Hoogstraal	Reoviridae, *Orbivirus* (Kemerovo serogroup)
	Sixgun City, USA (Texas, Colorado, New Mexico, South Dakota)
	Mono Lake, USA (California)
	Bunyaviridae, *Nairovirus* (Hughes serogroup)
	Sapphire II, USA (Texas, New Mexico, Montana, South Dakota)
	Bunyaviridae "possible member" (serologically ungrouped)
	Sunday Canyon, USA (Texas)
Argas (*Argas*) *reflexus* (Fabricius)	Bunyaviridae, *Uukuvirus*
	Grand Arbaud, France
	Ponteves, France
Argas (*Argas*) *hermanni* Audouin	Togaviridae, *Flavivirus* (RSSE serogroup)
	Royal Farm, Afghanistan
	Togaviridae, *Flavivirus*
	West Nile, Egypt
	Reoviridae, *Orbivirus* (Kemerovo serogroup)
	Chenuda, Egypt
	Bunyaviridae, *Uukuvirus*
	Grand Arbaud, Afghanistan
	Bunyaviridae, *Nairovirus* (Dera Ghazi Khan serogroup)
	Abu Hammad, Egypt, Iran
	Unclassified (Nyamanini serogroup)
	Nyamanini, Nepal
	Unclassified (Quaranfil serogroup)
	Quaranfil, Egypt, Afghanistan, Nepal
Argas (*Argas*) *vulgaris* Filippova	Unclassified (Quaranfil serogroup)
	Quaranfil, Iran (Khorasan)

TABLE 1 (*continued*)

Argasid	Virus associations
Argas (*Argas*) *africolumbae* Hoogstraal, Kaiser *et al.*	Bunyaviridae, *Nairovirus* (Dera Ghazi Khan serogroup) Pretoria, South Africa
Argas (*Persicargas*) *arboreus* Kaiser, Hoogstraal, and Kohls	Unclassified (Quaranfil serogroup) Quaranfil, Egypt, Nigeria, South Africa Unclassified (Nyamanini serogroup) Nyamanini, Egypt, Nigeria, South Africa
Argas (*Persicargas*) *streptopelia* Kaiser, Hoogstraal, and Horner	Bunyaviridae, *Nairovirus* (Dera Ghazi Khan serogroup) Abu Mina, Egypt
Argas (*Persicargas*) *robertsi* Hoogstraal, Kaiser, and Kohls	Bunyaviridae, *Nairovirus* (Dera Ghazi Khan serogroup) Kao Shuan, Taiwan, Indonesia (Java), Australia Pathum Thani, Thailand, Sri Lanka Unclassified (Nyamanini serogroup) Nyamanini, Thailand, Sri Lanka Unclassified (serologically ungrouped) Lake Clarendon, Australia (Queensland)
Argas (*Persicargas*) *persicus* (Oken)	Bunyaviridae, *Nairovirus* (Crimean-Congo H. F. serogroup) Crimean-Congo hemorrhagic fever, USSR (Uzbek SSR) ("Slovakia virus": not an arbovirus)
Argas (*Persicargas*) *abdussalami* Hoogstraal and McCarthy	Bunyaviridae, *Uukuvirus* (Uukuniemi serogroup) Manawa, Pakistan (Lahore area) Bunyaviridae ("possible member") (Bakau serogroup) Bakau, Pakistan (Lahore area)
Argas (*Carios*) *vespertilionis* (Latreille)	Togaviridae, *Flavivirus* Sokuluk, USSR (Kirgiz SSR) Unclassified (serologically ungrouped) Issyk Kul, USSR (Kirgiz SSR) (? identical to *Keterah*)
Argas (*Carios*) *pusillus* Kohls	Unclassified (serologically ungrouped) Keterah, Malaysia (? identical to Issyk Kul)
Subfamily Ornithodorinae Pospelova-Shtrom	

TABLE 1 (*continued*)

Argasid	Virus associations
Ornithodoros (*Alectorobius*) *boliviensis* Kohls and Clifford	Unclassified (serologically ungrouped) Matucare, Bolivia
Ornithodoros (*Alectorobius*) *tadaridae* Černy and Dusbabek	Unclassified (serologically ungrouped) Estero Real, Cuba
NOTE: All following members of the subgenus *Alectorobius* are part of the "*O.* (*A.*) *capensis* group"	
Ornithodoros (*Alectorobius*) *amblus* Chamberlin	Reoviridae, *Orbivirus* (Kemerovo serogroup) Huacho, Peru Bunyaviridae, *Nairovirus* (Hughes serogroup) Punta Salinas, Peru
Ornithodoros (*Alectorobius*) *capensis* Neumann	Togaviridae, *Flavivirus* Saumarez Reef, Australia (Queensland) Bunyaviridae, *Nairovirus* (Hughes serogroup) Hughes, Trinidad Soldado, Trinidad, USA (Texas), Ethiopia, Senegal, Seychelles Bunyaviridae (possible member) (Upolu serogroup) Upolu, Australia (Queensland) Aransas Bay, USA (Texas) Unclassified (Quaranfil serogroup) Johnston Atoll, Central Pacific Ocean, Australia, New Zealand, Namibia Unclassified (Nyamanini serogroup) Midway, Central Pacific Ocean, Japan (N Honshu)
Ornithodoros (*Alectorobius*) *denmarki* Kohls, Sonenshine, and Clifford	Bunyaviridae, *Nairovirus* (Hughes serogroup) Hughes, USA (Florida), Cuba, Trinidad Soldado, Trinidad Raza, Mexico (Baja California), USA (California) Unclassified (Quaranfil serogroup) Johnston Atoll, Central Pacific Ocean
Ornithodoros (*Alectorobius*) *denmarki* (species near)	Bunyaviridae, *Nairovirus* (Hughes serogroup)

TABLE 1 (*continued*)

Argasid	Virus associations
	Farallon, USA (California, Oregon), Mexico (Baja California)
Ornithodoros (*Alectorobius*) *maritimus* Vermeil and Marguet	Togaviridae, *Flavivirus* Meaban, France (S. Brittany) West Nile, USSR (Azerbaijan SSR) (from "*O. capensis*") Bunyaviridae, *Nairovirus* (Hughes serogroup) Soldado, Ireland, France Puffin Island, Britain (Wales) Bunyaviridae (serologically ungrouped) (from "*O. capensis*") Caspiy, USSR (Azerbaijan SSR)
Ornithodoros (*Alectorobius*) *muesebecki* Hoogstraal	Bunyaviridae, *Nairovirus* (Hughes serogroup) Zirqa, Abu Dhabi
Ornithodoros (*Alectorobius*) *coniceps* (Canestrini)	Bunyaviridae, *Flavivirus* West Nile, USSR Bunyaviridae (serologically ungrouped) Caspiy, USSR (Turkmen SSR) Reoviridae, *Orbivirus* (Kemerovo serogroup) Baku, USSR (Uzbek SSR)
Ornithodoros (*Pavlovskyella*) *marocanus* Velu	Iridoviridae, *Iridovirus* African swine fever, Spain
Ornithodoros (*Pavlovskyella*) *sonrai* Sautet and Witkowski	Bunyaviridae, *Nairovirus* (Qalyub serogroup) Bandia, Senegal
Ornithodoros (*Pavlovskyella*) *erraticus* (Lucas) (= "*O. alactagalis*" Issakjan)	Bunyaviridae, *Nairovirus* (Qalyub serogroup) Qalyub, Egypt Bunyaviridae (serologically ungrouped) Artashat, USSR (Armenian SSR)
Ornithodoros (*Pavlovskyella*) *tartakovskyi* Olenev	Unclassified (serologically ungrouped) Chim, USSR (Uzbek SSR)
Ornithodoros (*Pavlovskyella*) *tholozani* (Laboulbene and Megnin) (= "*O. papillipes*" Birula)	Togaviridae, *Flavivirus* Karshi, USSR (Uzbek SSR) West Nile, USSR (Turkmen SSR)

TABLE 1 (*continued*)

Argasid	Virus associations
	Unclassified (serologically ungrouped) Chim, USSR (Uzbek SSR)
Ornithodoros (*Ornithodoros*) *porcinus porcinus* Walton [Also known as *O.* (*O.*) *moubata porcinus* Walton]	Iridoviridae, *Iridovirus* (?) African swine fever, Kenya, Uganda, Tanzania, South Africa
Ornithodoros (*Proknekalia*) *peringueyi* Bedford and Hewitt	Reoviridae, *Orbivirus* (Kemerovo serogroup) Chenuda, South Africa
Ornithodoros (*Ornamentum*) *coriaceus* Koch	Two unidentified viruses, one a Togavirus, isolated during studies on epizootic bovine abortion in California (Wada *et al.* 1976; McKercher *et al.* 1980)
Ornithodoros (*Reticulinasus*) *chiropterphila* Dhanda and Rajagopalan	Togaviridae, *Flavivirus* (RSSE serogroup) Kyasanur Forest disease, India (Karnataka)
Ornithodoros (*Reticulinasus*) *piriformis* Warburton	Unclassified (serologically ungrouped) Muroor, India (Karnataka)
Ornithodoros (*Reticulinasus*) sp.	Unclassified (serologically ungrouped) Chobar Gorge, Nepal
Ornithodoros (*Alveonasus*) *lahorensis* Neumann	Bunyaviridae, *Nairovirus* (Crimean-Congo H. F. serogroup) Crimean-Congo hemorrhagic fever, Iran
Subfamily Otobinae Pospelova-Shtrom	
Otobius lagophilus Cooley and Kohls	Reoviridae, *Orbivirus* (Colorado tick fever serogroup) Colorado tick fever, USA (Nevada, Utah)

(*c*) *Subgenus* Persicargas *Kaiser, Hoogstraal, and Kohls.* This subgenus contains 15 described species originating in the Ethiopian (5), Palearctic (2), Nearctic (4), Netropical (1), Oriental (2), and Australian (1) regions. Four *Persicargas* species range into a second region and one species has been widely distributed by human transport of domestic chickens (see below). Two species await description, one from South Africa and one from Madagascar. The adult, nymph, and larva of each taxon have been described, except the nymph and adult of the Nearctic *A.* (*P.*) *giganteus* Kohls and Clifford. The larvae of *A.* (*P.*) *giganteus* and *A.*

(*A.*) *cucumerinus* are remarkable for their large size. *Persicargas* species are found in lowlands and mountains, generally well below 1800 m altitude.

The definitive structural and biological features of *Persicargas* were reviewed by Hoogstraal *et al.* (1984). Species in this subgenus are relatively uniform biologically and structurally, including the Haller's organ and anterior pit setae. However, as suggested by the gigantic size of the larval *A.* (*P.*) *giganteus*, this species may have an unusual feeding and life cycle pattern.

All *Persicargas* species parasitize birds, all (with one exception) in arboreal nests. Specific hosts are vultures, doves or pigeons, storks, herons, or ibises, or various medium-sized birds. The exception, *A.* (*P.*) *zumpti* Hoogstraal, Kaiser, and Kohls, has been found only in rock ledge crevices near nests of the South African Cape vulture *Gyps coprotheres* (Forster). Six of the 15 *Persicargas* species have successfully adapted to domestic chickens. Larvae of the poorly studied *A.* (*P.*) *giganteus* are recorded from both ground-nesting and arboreal-nesting hosts [screech owl, *Otus:* burrowing owl, *Speotyto*;; thrasher (several species), *Toxostoma* and *Oreoscoptes*; towhee (two species), *Pipilo*; Oregon junco, *Junco*; Gambel quail, *Lophortyx*; fox sparrow, *Passerella*; white-crowned sparrow, *Zonotrichia*; piñon jay, *Cynocephalus*; etc.]. It is amazing that the adults and biology of *A.* (*P.*) *giganteus* remain unknown in a wide area where parasitologists and ornithologists abound. Notably, *Persicargas* species characteristically shelter in wood crevices in contrast to *Argas* (*Argas*) species, which usually do so in rock or stone crevices.

Four *Persicargas* species occur in two faunal regions, undoubtedly as a result of migrating bird transport of feeding larvae. *Argas* (*P.*) *streptopelia* Kaiser, Hoogstraal, and Horner, an Ethiopian parasite of tree-nesting doves (*Streptopelia* spp., *Turtur* spp.), ranges through much of sub-Saharan Africa but also extends into the Palearctic (Egypt, western and eastern Arabia, Cyprus, and probably Tadzhik SSR). *Argas* (*P.*) *robertsi* Hoogstraal, Kaiser, and Kohls, an Oriental parasite of herons (*Ardea, Ardeola, Bubulcus, Nycticorax*), egrets (*Egretta*), open-billed storks (*Anastomus*), ibises (*Threskiornis, Plegadis*), cormorants (*Phalacrocorax*), and other birds, is distributed from India and Sri Lanka to Java and Taiwan and to the Australian region (Queensland and Northern Territory), where it also infests domestic chickens as it occasionally does in Oriental localities. *Argas* (*P.*) *arboreus* Kaiser, Hoogstraal, and Kohls, the Ethiopian counterpart of *A.* (*P.*) *robertsi* and much like it structurally and biologically, is widely distributed south of the Sahara and extends into the Palearctic, but only in the narrow Nile Valley and Delta and nearby oases and Red Sea coastal areas of Egypt (Khalil *et al.*, 1980). *Argas* (*P.*) *miniatus* Koch, a Neotropical parasite of smaller birds and

domestic chickens, occurs in small foci in the Nearctic (southeastern United States). A fifth species, *A.* (*P.*) *persicus* (Oken), a Central Asian (Palearctic) parasite of arboreal nesting birds such as sparrows (*Passer* spp.), rooks (*Corvus frugilegus* L.), and rollers (*Coracias garrulus* L.), has successfully adapted to coexistence with domestic chickens, turkeys, and other fowl, and has been carried to many parts of the world where it survives practically exclusively in associations with domestic fowl. Numerous pre-1966 *A.* (*P.*) *persicus* records are invalid; they concern recently resurrected and designated taxons.

The life cycle patterns of studied *Argas* (*Argas*) and *Argas* (*Persicargas*) species are quite similar (Kraiss and Gothe, 1982). These authors listed the literature on the life cycles of *A.* (*P.*) *persicus*, *A.* (*P.*) *arboreus*, *A.* (*P.*) *walkerae*, *A.* (*P.*) *robertsi*, *A.* (*P.*) *miniatus*, and *A.* (*P.*) *radiatus*.

The arboviruses that infect *Persicargas* species are listed in Table 1 and, together with human irritation, tick paralysis, *Borrelia*, *Aegyptianella pullorum*, *Wolbachia persica*, and other microorganisms, are discussed in Section IV.

(*d*) *Subgenus* Microargas *Hoogstraal and Kohls*. The single species, *A.* (*M.*) *transversus* Banks, is among the smallest of all ticks (male 1.5 mm long, 2.3 mm broad) and is unique in spending its entire life cycle, including the egg stage, in tight clusters on the leathery skin below the carapace of the Galapagos giant tortoise, *Geochelone elephantopus* subspp. This minute tick is also notable for various groups of odd body setae similar to those of pterygosomatid mite parasites of reptiles (Hoogstraal and Kohls, 1966; Hoogstraal *et al.*, 1974). Practically all reptile-infesting argasid and ixodid species (and mites) bear specialized setae but no other tick setae are like those of *A.* (*M.*) *transversus*. The sensory functions of these distinctive setae are unstudied, as is the matter of convergent evolution of the body setae of this single tick species and those of pterygosomatid mites. The solid, sloping Haller's organ roof has a circular aperture surrounded by a few small perforations; the anterior pit setae, arranged as in *Persicargas*, number only eight (the serrate seta is lacking) (Hoogstraal *et al.*, 1984). Unfortunately, little is known about the biology of this remarkable parasite.

(*e*) *Subgenus* Carios *Latreille*. Six *Carios* species parasitize cave-dwelling insectivorous bats (Microchiroptera) (Hoogstraal *et al.*, 1979b). *Argas* (*C.*) *vespertilionis* (Latreille) is widely distributed in the Ethiopian region and is scattered in the Palearctic to Britain, USSR, Korea, and Japan, as well as into parts of India (Oriental). Elsewhere in the Oriental region (Bangladesh to Malaysia and the Philippines), *A.* (*C.*) *vespertilionis* is replaced by the smaller *A.* (*C.*) *pusillus* Kohls. The chief host genera of these parasites are *Pipistrellus* and *Tadarida*; other hosts are *Otonycteris*, *Scotophilus*, *Taphozous*, etc. In Australia, four *Carios* species (*C. austra-*

liensis, daviesi, dewae, and *macrodermae*), described by the author and colleagues, parasitize certain insectivorous bats in different environmental zones.

The definitive structural characters of *Carios* were described by Hoogstraal (1958) and reviewed, together with definitive biological characters, by Roshdy *et al.* (1984). The Haller's organ roof is solid with a slitlike aperture, and the anterior pit has 10 setae. *Argas* (*C.*) *vespertilionis* larvae attach to bats for 14–31 (usually 17–19) days. Nymphs and adults feed to repletion in about 30 (20–50) minutes. Males and females usually appear after the first and second nymphal instars, respectively (Hoogstraal, 1956). *Argas* (*C.*) *macrodermae* Hoogstraal *et al.* (1977a) of Queensland is distinctive for its large size, long, spiderlike legs, numerous setae on the body and legs, and parasitism of the rare false vampire, *Macroderma gigas,* which roosts at least 14 m above the cave floor. Biological, sensory receptor, and behavioral investigations of this specialized species have been thwarted by the rarity of the host and the enormous size of the cave habitat. The one or two arboviruses infecting *A.* (*C.*) *vespertilionis* and *A.* (*C.*) *pusillus* (Table 1) and their possible role in human disease are discussed in Section IV.

(*f*) *Subgenus* Chiropterargas *Hoogstraal.* The four species of *Chiropterargas* also parasitize cave-dwelling Microchiroptera. *Argas* (*C.*) *boueti* Roubaud and Colas-Belcour is extraordinarily widely distributed; our records are from throughout the Ethiopian region and in the Palearctic (Morocco, Egypt, Arabia, Iran, Afghanistan) and Oriental (India, Malaysia, Korea) regions. The generally rare *A.* (*C.*) *confusus* Hoogstraal of the Ethiopian region extends only into Egypt and in and near Jerusalem (Palearctic). *Argas* (*C.*) *cordiformis* Hoogstraal and Kohls appears to be confined to eastern and southern Africa. *Argas* (*C.*) *ceylonensis* Hoogstraal and Kaiser is recorded only from Sigiriya Rock, Sri Lanka (Oriental).

Bat host genera are *Asellia, Nycteris, Rhinolophus, Rhinopoma, Tadarida,* and *Taphozous* [for *A.* (*C.*) *boueti*], *Asellia, Chaerophon, Eptesicus, Mermopterus, Otonycteris, Pachyotus, Pipistrellus, Rhinopoma,* and *Scotophilus* [for *A.* (*C.*) *confusus*], *Hipposideros,* and *Nycteris* [for *A.* (*C.*) *cordiformis*], and *Taphozous* [for *A.* (*C.*) *ceylonensis*].

The definitive structural characters of *Chiropterargas* were described by Hoogstraal (1955) and reviewed, together with distinctive biological characters, by Roshdy *et al.* (1984). The Haller's organ roof has a large aperture through which one or two sensilla characteristically protrude and the anterior pit setae number 10 or 11. The specialized function of the protruding sensilla, as well as that of certain exceptionally long setae on *Chiropterargas* legs, should be investigated. The *A.* (*C.*) *boueti* capitulum is borne on a membranous "neck" which is retracted when the tick is resting but greatly extended when feeding, thus resembling a miniature

elephant trunk. I have seen nothing like this "neck" in other tick species. Internal structures of *Carios* and *Chiropterargas* are much alike but externally the *Chiropterargas* integument lacks the lateral suture characteristic of all other *Argas* subgenera. Larvae feed for days or weeks; nymphs and adults feed in an hour or less (Hoogstraal, 1956). Remarkable differences recorded in nymphal feeding (or nonfeeding) and instar numbers in each species point to the need for investigating *Chiropterargas* feeding, life cycle, and physiological phenomena more intensively. Females "brood" the egg batches and may transport newly hatched larvae to roosting bats for feeding (phoresy).

Chiropterargas and *Carios* probably evolved from a parasite of birds nesting among rocks. In the evolutionary process, *Chiropterargas* has diverged more markedly from the typical *Argas* than has *Carios*. The spiderlike legs characterizing *A.* (*Carios*) *macrodermae* also occur in some but not all populations of *A.* (*Chiropterargas*) *boueti*. *Chiropterargas* species are not known to be associated with microorganisms infecting wildlife or man.

(*g*) *Subgenus* Secretargas *Hoogstraal*. This subgenus, defined for a single African species (Hoogstraal, 1957), now contains two other species from Madagascar (Hoogstraal *et al.*, 1967). The African species, *A.* (*S.*) *transgariepinus* White, occurs in dry habitats from South Africa and Namibia to Egypt and Morocco, and also in Spain, Italy, Switzerland, Greece, Israel, and Afghanistan. This wide distribution undoubtedly results from transport of feeding larvae by migrating bats. Recorded host genera are *Eptesicus, Otonycteris, Pipistrellus, Platymops, Rhinolophus, Rhinopoma,* and *Taphozous*. In Egypt, we find this tick chiefly associated with solitary bats or small colonies of bats in desert hillside clefts and caves, infrequently with large colonies in humid caves. Geckos sheltering in crevices together with these secretive ticks are occasional hosts. In Greece, I found *A.* (*A.*) *transgariepinus* in cracks of the window woodwork of a school dormitory where *Rhinolophus ferrumequinum* roosted between the roof and ceiling. Both species found in Madagascar are restricted to the hot, semiarid savanna zone south of Tananarive (Hoogstraal *et al.*, 1967). *Argas* (*S.*) *hoogstraali* Morel and Vassiliades shelters under stones and infests three species of *Opulurus* lizards resting under these stones. *Argas* (*S.*) *echinops* Hoogstraal, Uilenberg, and Blanc shelters under larger stones and infests the small Madagascar hedgehog. *Echinops telfairi*.

A comparative morphological and biological study of *Secretargas* and *Ogadenus* (see below) in relation to other *Argas* subgenera, and showing stages of convergent evolution of these two subgenera and the genus *Ornithodoros*, is in preparation. Associations between these ticks and human and animal diseases have not been investigated.

(h) Subgenus Ogadenus *Pospelova-Shtrom.* This monotypic subgenus is represented by *A. (O.) brumpti* Neumann, chiefly in low rainfall areas, from Namibia and South Africa through East Africa into Egypt and northwestern Africa (northern Nigeria). As evidenced by the presence of a lateral suture and peripheral striations of the body integument, this is a true *Argas* species despite the unusual depressions and ridges on the integumental surface and the habit of sheltering in loose soil (rather than crevices in wood or rock). These and other characters show convergent evolution of *Ogadenus* and *Ornithodoros.* The rock hyrax, *Procavia capensis* subspp., is frequently parasitized. Various other mammals (but apparently not bats), lizards, and birds also serve as hosts. Data on the hosts, habitats, and life cycle of *A. (O.) brumpti,* reviewed by Hoogstraal (1956), are being brought up to date (Hoogstraal, 1985).

The bruiselike lesions following *A. (O.) brumpti* bites on man (Condy *et al.,* 1980) and the probable transmission of a piroplasm of the hyrax by this tick are reviewed in Section IV.

(i) Unnamed subgenera. Argas bureschi Dryenski was collected in Bulgaria from the burrow of a suslik, *Citellus citellus.* From the meager description and illustrations, this very unusual *Argas* is unassignable to any standing subgenus. *Argas* larvae from an *Agama* lizard at Herat, Afghanistan, represent an undescribed species also unassignable to subgenus.

3. *Genus* Ornithodoros *Koch*

(a) Introduction. The genus *Ornithodoros* consists of about 100 species in eight subgenera; the subgenera are uncertain for one Nearctic and six Neotropical species. The initial subgeneric review by Clifford *et al.* (1964) was followed by keys to larvae of the Western Hemisphere (Kohls *et al.,* 1965) and of the Eastern Hemisphere (Sonenshine *et al.,* 1966), descriptions of larvae of eight new species from the Western Hemisphere (Kohls *et al.,* 1969), and a revision of the 1965 key with seven new Western Hemisphere species based on larval characters (Jones and Clifford, 1972). A comprehensive study of the Soviet argasid fauna (Filippova, 1966) presents many biological and taxonomic data. A review of the argasids of Kazakh SSR and Soviet Middle Asia (Kusov, 1973) is also important for information on biology and natural history. More recently described subgenera and species are mentioned here.

In contrast to the relative numerical uniformity of *Argas* diploid chromosomes, the 12–32 and occasionally 34 of *Ornithodoros* represent the least and greatest numbers recorded for any tick genus (Oliver, 1977). The Y and X chromosomes differ only in that the Y arms are slightly shorter, but Y is longer than any autosome. Oliver recognized five groups of autosomes in the 11 studied species of *Ornithodoros.*

Biomedical specialists are acquainted chiefly with the *Ornithodoros* parasites of rodents and other nonflying mammals inhabiting burrows, dens, or caves, and of marine birds nesting or resting in large colonies on or near the ground. There are about 66 *Ornithodoros* species in this general category, which also includes two species specific for birds nesting in tree holes or caves and three species specific for reptiles (African tortoise and Galapagos iguanid lizards). The 34 described species of *Ornithodoros* associated with bats, in three subgenera consisting entirely or largely of these parasites, are mostly poorly known but are of considerable phylogenetic, zoogeographical, and biological interest. Certain life cycle adaptations characterize *Ornithodoros* species which are specific for wandering hosts or for hosts which spend only a limited period of the year in nesting or resting sites. The more extreme evolutionary developments of exceptional life cycle patterns, including unique morphological characters and reduction of the adult feeding apparatus to a nonfunctional vestige, are represented by the phylogenetically more recent genera *Otobius, Antricola,* and *Nothoaspis* (Fig. 1).

(*b*) *Subgenus* Ornithodoros *Koch.* Eight species of large ticks constitute the subgenus *Ornithodoros*. Where the life cycle has been studied, it is exceptional in that larvae molt to the first nymphal instar, without feeding, shortly after hatching from the egg (reviewed and illustrated by Hoogstraal, 1956). This unique adaptation places the subgenus *Ornithodoros* among the more recent, biologically advanced groups of argasids. Six of the eight species shelter in dens or burrows. Nymphs and adults are rapid feeders.

The sand tampan, *O.* (*O.*) *savignyi* (Audouin), one of the two *Ornithodoros* species with eyes [see also *O.* (*Ornamentum*) *coriaceus*], rests in dry soil shaded by trees, fences, or buildings. It feeds nocturnally, often in tremendous numbers, on tethered livestock, sleeping human beings, and wildlife in desert or semidesert environments, or savannas with long dry seasons, and is the only widely distributed species of this subgenus (much of Africa, also Arabia, India, and Sri Lanka) (Hoogstraal, 1956). Intense irritation, and sometimes paralysis and death, follow the enormous blood loss or toxemia suffered by hosts of the sand tampan. However, this tick is not recorded as being infected by arboviruses or spirochetes.

Three species are known only by single collections in the Palearctic, Nearctic, and Oriental regions, respectively. *Ornithodoros* (*O.*) *procaviae* Theodor and Costa infests the rock hyrax, *Procavia capensis syriaca,* in its dens in the Negev desert. *Ornithodoros* (*O.*) *eremicus* Cooley and Kohls is recorded from a nymph taken from a deer mouse, *Peromyscus maniculatus,* in Utah. *Ornithodoros* (*O.*) *indica* Rau and Rao is represented by a female reared (through seven nymphal instars on laboratory

mice over a 21-month period) from a nymph from a Himalayan barking deer, *Muntiacus muntjak vaginalis,* in northeastern India. The seven nymphal instars possibly resulted from feeding on an inappropriate host [but see also *O.* (*Ornamentum*) *coriaceus*]. Notably, this is the only species of this subgenus from a wandering, humid forest artiodactyl which does not shelter in a den or burrow.

The African *O.* (*O.*) *moubata* "superspecies," according to Walton (1962), consists of *O.* (*O.*) *apertus* Walton (Kenya, Ghana, Botswana), *O.* (*O.*) *porcinus porcinus* Walton (Kenya to South Africa), *O.* (*O.*) *porcinus domesticus* Walton (Kenya, Tanzania, Mozambique, Angola), *O.* (*O.*) *compactus* Walton (South Africa), and *O.* (*O.*) *moubata* (Murray) ("domestic" and "wild" races) (East and South Africa). *Ornithodoros* (*O.*) *moubata* and *O.* (*O.*) *porcinus domesticus* inhabit human habitations. *Ornithodoros* (*O.*) *compactus* parasitizes tortoises, *Testudo* spp., in their scrapes south of the Zambezi River. The other species frequent burrows of large mammals, especially the warthog [*Phacochoerus aethiopicus* (Pallas)], porcupine (*Hystrix africaeaustralis* Peters), and antbear [*Orycteropus afer* (Pallas)], and may be carried into houses on game animals or by men investigating these burrows. Peirce (1974) lucidly described the ecology, populations, behavior, and distribution of *"O. moubata porcinus"* in East African burrows.

Walton's (1962) pioneer biosystematic conclusions require intensive experimental confirmation. These conclusions, based largely on anecdotal events and observations and on more or less clearly definable structural criteria, point to the need for an extensive, well-funded, long-term integrated biomedical, microbiological, and taxonomic investigation, with precise controls, by a variety of collaborating specialists having access to living population samples from numerous localities south of the Sahara. The structure, reproduction, physiology, and other properties of *O.* (*P.*) *"moubata"* (or *porcinus*) have been intensely investigated in numerous laboratories in Kenya, Europe, and the United States. However, often the exact identity of the source materials will remain in limbo until the biosystematic questions are answered.

Ornithodoros (*O.*) *porcinus porcinus* [and possibly *O.* (*O.*) *moubata*] is the chief if not the only reservoir and vector of African swine fever virus south of the Sahara. *Ornithodoros* (*O.*) *moubata* [and probably *O.* (*O.*) *porcinus domesticus*] serves as the reservoir and vector of *Borrelia duttoni,* the agent of African relapsing fever in humans.

(*c*) *Subgenus* Pavlovskyella *Pospelova-Shtrom.* The 32 species in the subgenus *Pavlovskyella* occur in all regions, but two in the Oriental (limited to the northwestern area) are chiefly Palearctic in distribution. All species inhabit caves, dens, or burrows except the two described from Australia (see below); some species are partial to rock ledge shelters. All

species (except the Australian bird parasite) parasitize mammals. Domestic mammals in stables are infested by eight species. Reptiles are also parasitized by five species and birds by four. Notably, *Pavlovskyella* larvae, as well as nymphs and adults, are rapid feeders [but nymphal and adult *O.* (*P.*) *tartakovskyi* may remain on the host for many days in winter].

Ornithodoros (*P.*) *tholozani* (Laboulbène and Mégnin) (= *O. papillipes* Birula of certain Soviet workers and *O. crossi* Brumpt of certain Indian workers), the type species of the subgenus, ranges from southwestern China and southern USSR to northwestern India, the Middle and Near East and northern Arabia, and Greece, to northwestern Egypt and northeastern Libya, and also Cyprus and other eastern Mediterranean islands (Filippova, 1966; Avivi *et al.*, 1973). This notorious vector of *Borrelia persica*, the agent of Persian relapsing fever, inhabits caves, burrows, and ruins; in southern USSR, Iran, and eastward it also thrives in stables, barns, clay and stone fences, storerooms, and human habitations where domestic animals are quartered in hamlets, old and new towns, and cities in semidesert, steppe, and Mediterranean-climate environments. The ticks are often transported with household or commercial goods and easily survive eradication attempts. Man, sheep, goats, porcupines (*Hystrix*), hedgehogs (*Hemiechinus, Paraechinus*), foxes (*Vulpes*), badgers (*Meles*), jackals (*Canis*), and rodents (*Rhombomys, Meriones, Pallasiomys, Mesocricetus*, etc.) are commonly reported hosts; camels and cattle are also hosts. Birds, including chickens, are less often infested and a blunt-nosed viper (*Vipera lebetina* L.) bloodmeal is said to be toxic to these ticks. Three arboviruses have been isolated from *O.* (*P.*) *tholozani* (Table 1). There is an extensive literature on the biology and medical and veterinary relationships of *O.* (*P.*) *tholozani*, chiefly by Soviet workers (as *O. papillipes*), but also by French and Israeli researchers.

Ornithodoros (*P.*) *tartakovskyi* Olenev is employed in many European and American biomedical laboratories for experimental studies on the pathogenicity and immunology of the filarial parasite *Dipetalonema viteae* (Section IV,K). In the USSR, *O.* (*P.*) *tartakovskyi* occurs in each southern Republic east of the Caspian Sea; elsewhere it occurs in Iran, Afghanistan, and China (Sinkiang). The northern boundary is 44° N to 47° N (Filippova, 1966). The tick ranges from sea level to 2660 m altitude (our unpublished data from Afghanistan) and inhabits chiefly small, permanent burrows of rodents and small carnivores, but also resting places of hedgehogs, tortoises and other reptiles, and less often shelters of other wildlife (including burrow-nests of birds) and livestock. Unlike most other argasid nymphs and adults, those of *O.* (*P.*) *tartakovskyi* may remain on the host for several hours or days or even through much of the winter. The shelters of this tick and its hosts are in hills, mountains, floodplains, irrigation

ditches, wells, tombs, and other human structures with a rather high degree of relative humidity and temperature generally not exceeding 30°C; winter temperatures may be as low as 0°C. Nymphal instars number two or three. The life cycle may be completed in 3 or 4 months or extended to 2 or more years. *Ornithodoros* (*P.*) *tartakovskyi* has also been associated with Chim virus (Table 1), human relapsing fever caused by *Borrelia latyshevi*, plague, Q fever, and a pathogenic strain of *Leptospira*.

Shelters and hosts of *O.* (*P.*) *erraticus* (Lucas) are similar to those of *O.* (*P.*) *tartakovskyi*, but generally are in lowland deserts, semideserts, and dry tracts in cultivated zones, and infrequently at higher altitudes [*O.* (*R.*) *alactagalis* Issakjan (Armenian SSR and Azerbaijan SSR) and *O.* (*P.*) *neerensis* Pavlovsky (Turkmen SSR) are probably junior synonyms of *O.* (*P.*) *erraticus* (see Filippova, 1966)]. *Ornithodoros* (*P.*) *erraticus* occurs in southwestern USSR, Iran, Turkey, northern Arabia, and Egypt to Tunisia. In the Ethiopian region (Kenya), it is recorded from burrows of the white-fronted bee-eater, *Merops* (*Melittophagus*) *bullockoides* (Smith), and of the pygmy gerbil, *Gerbillus bottai* Lataste. Larvae, nymphs, and adults complete feeding within 30 minutes; nymphs undergo three to five instars. There may be two generations annually. Hyperparasitism, chiefly of larger fed females by unfed females, males, and nymphs, appears to be a common phenomenon in this species (Helmy *et al.*, 1983), and also in *O.* (*P.*) *tartakovskyi* (Votava *et al.*, 1974) and *O.* (*P.*) *tholozani* (Rao and Kaira, 1949). *Ornithodoros* (*P.*) *erraticus* is the reservoir and vector of *Borrelia crocidurae*, the agent of North African relapsing fever, and also of two arboviruses (Table 1). In Kenya, *O.* (*P.*) *erraticus* has been circumstantially associated with mass mortalities of bee-eaters, *M. bullockoides*, in cliffside burrow nests (S. T. Emlen, personal communication), and *Borrelia crocidurae* (= *B. dipodilli*) has been isolated from the gerbil-infesting populations.

Other Palearctic species parasitize chiefly cricetid rodents burrowing in deserts, semideserts, and dry areas in cultivated zones. These species are *O.* (*P.*) *asperus* Warburton[2] (southwestern USSR and Iraq), *O.* (*P.*) *cholodkovskyi* Pavlovsky (Iran, Uzbek SSR, Turkmen SSR), *O.* (*P.*) *arenicolous* Hoogstraal (Egypt to Algeria), *O.* (*P.*) *normandi* Larrousse (Tunisia), and *O.* (*P.*) *marocanus* Velu (*erraticus* group) (northwestern Africa and southwestern Europe). *Ornithodoros* (*P.*) *marocanus* is somewhat more adaptable than the other species and is frequently reported from pigsties;

[2] *Ornithodoros* (*P.*) *asperus* Warburton, 1918, is referred to *O.* (*A.*) *verrucosus* Olenev, Zasukhin, and Fenyuk, 1934 (tentatively a junior synonym) in much Soviet biomedical literature. Filippova (1966) indicated the complexity of this taxonomic and biological question, which has not yet been adequately addressed.

in Spain, it serves as a reservoir and vector of African swine fever virus (Table 1).

Three *Pavlovskyella* species are confined to the Ethiopian region. *Ornithodoros* (*P.*) *sonrai* Sautet and Witkowski (*erraticus* group) of Senegal infests chiefly the grass rat *Arvicanthis* (Muridae); *O.* (*P.*) *sonrai* is the reservoir and vector of Bandia virus, which is closely related to Qalyub virus of *O.* (*P.*) *erraticus* infesting *Arvicanthis* in Egypt (Table 1). *Ornithodoros* (*P.*) *zumpti* Heisch and Guggisberg inhabits burrows of the striped mouse, *Rhabdomys pumilio* (Muridae), in Cape Province, South Africa. *Ornithodoros* (*P.*) *graingeri* Heisch and Guggisberg lives in soil on the floors of coastal caves in Kenya. Man and the porcupine, *Hystrix africaeaustralis* Peters, are reported to be hosts and a spirochete, *Borrelia graingeri,* infects this tick.

In Madagascar, *O.* (*P.*) *grenieri* Klein is known only from burrows of a rare cricetid rodent, *Hypogeomys antimena*, in a single central eastern lowland forest area. The rodent host is nearing extinction because of deforestation and *O.* (*P.*) *grenieri* will probably disappear with it (Uilenberg *et al.*, 1980). *Ornithodoros* (*P.*) *grenieri* appears to be a distant member of the Palearctic-Ethiopian *O.* (*P.*) *erraticus* group.

In Australia, three *Pavlovskyella* species inhabit hot, sparsely wooded regions (Roberts, 1970). *Ornithodoros* (*P.*) *gurneyi* Warburton shelters in dry soil under trees and parasitizes several species of kangaroos resting in the shade. People who also rest under the trees and are bitten by these ticks suffer severe local and systemic disturbances. Larvae become replete in about 3 days (exceptionally slow feeding for larval *Pavlovskyella*), and nymphs and adults within 2 hours. A closely related, undescribed species infesting wallabies (species undetermined) sheltering in caves probably represents the prototype of these two species. *Ornithodoros* (*P.*) *macmillani* Hoogstraal and Kohls is unique in this subgenus for inhabiting tree holes (hollow *Eucalyptus* branches) and feeding on the galah cockatoo, *Kakatoe roseicapilla* Vieillot, rather than mammals. Larval, nymphal, and adult feeding is completed in 15–30 minutes.

In the Americas, four of the eight *Pavlovskyella* species are reservoirs and vectors of four *Borrelia* agents of relapsing fevers (for biomedical studies on these ticks, see papers by G. E. Davis, unlisted). These species characteristically parasitize certain burrowing or shelter-seeking rodents but three have a wider range of hosts and habitats. *Ornithodoros* (*P.*) *sparnus* Kohls and Clifford is a nest parasite of the wood rat, *Neotoma* spp., and also of the deer mouse, *Peromyscus maniculatus* (Wagner), to at least 2100 m altitudes in the western United States (Utah, Nevada, Arizona, California). *Neotoma* nests on the ground against rocks or trees. *Peromyscus* nests in burrows, logs, or buildings. Laboratory and field

studies suggest that *O.* (*P.*) *sparnus* may have two generations annually. Another parasite of *Neotoma*, *O.* (*P.*) *nicollei* Mooser, is recorded from nine States of Mexico; it also infests caves, rural houses, and burrows of other animals (Hoffman, 1962). The wood rat (*Neotoma* spp.), ground squirrel (*Citellus* spp.), sidewinder rattlesnake (*Crotalus cerastes* Hallowell), dog, and man are recorded hosts. The biology of *O.* (*P.*) *sparnus* and *O.* (*P.*) *nicollei* is virtually unstudied. The rickettsial agent of Rocky Mountain spotted fever has been isolated from *O.* (*P.*) *nicollei* in Mexico.

Ornithodoros (*P.*) *turicata* (Dugès) occurs throughout the drier regions of Mexico (Hoffman, 1962) and southwestern United States, and as far north and east as southern Kansas and Florida. Reports of *O.* (*P.*) *turicata* from Canada and from Guatemala to Argentina are probably incorrect. Wood rats, ground squirrels, and other burrowing and cave-dwelling vertebrates, including various birds (owls), snakes, and the gopher (land) turtle [*Gopherus polyphemus* (Daudin)], are among the reported wild hosts. *Ornithodoros* (*P.*) *turicata* also infests huts and stables and feeds on domestic animals, especially swine. Man is parasitized indoors and outdoors near burrows and in caves. Larvae and nymphs become replete in 30 minutes or less; adults may remain on the host for several to 48 hours. This tick is the reservoir and vector of *Borrelia turicatae*, and in Mexico is associated with diseases of swine. Subcutaneous nodules and intermittent itching follow the initially painful bites of *O.* (*P.*) *turicata* on man, and gangrene has been associated with bites by these ticks from filthy pigsties.

Ornithodoros (*P.*) *parkeri* Cooley is a burrow parasite of the ground squirrel (*Citellus*), prairie dog (*Cynomys*), and burrowing owl (*Speotyto*) in western United States (California, Colorado, Idaho, Montana, Nevada, Oregon, Utah, Washington, Wyoming) and Mexico (Baja California). Man, rabbits (*Sylvilagus* spp.), various smaller rodents, and the desert tortoise [*Gopherus agassizii* (Cooper)], are occasionally reported hosts, but seldom if ever are domestic animals. As with other *Pavlovskyella* species, each stage, including the larva, feeds rapidly; there are two to five nymphal instars. *Ornithodoros* (*P.*) *parkeri* is the reservoir and vector of *Borrelia parkeri*, which apparently is seldom transmitted to man.

Ornithodoros (*P.*) *hermsi* Wheeler, Herms, and Meyer infests nests of the chipmunk (*Eutamias*), wood rat (*Neotoma*), pine squirrel (*Tamiasciurus*), and other rodents in hollow logs, tree stumps, and log cabins in forests to about 2500 m altitude in British Columbia, Washington, Oregon, California, Idaho, and Nevada. Tourists, boy scouts, woodsmen, and residents of log cabins and other buildings in wooded areas are not infrequently bitten by *O.* (*P.*) *hermsi* and may experience a severe relapsing fever caused by *Borrelia hermsi*.

In the Neotropical region, *O.* (*P.*) *furucosus* Neumann parasitizes man

and domestic animals in Colombia, Ecuador, and Peru. *Ornithodoros (P.) braziliensis* Aragão parasitizes the peccary (*Tayassu*) and skunk (*Conepatus*) in Brazil and is a pest of man and domestic animals when it inhabits soil under houses and around sheds. Each species has been reported to be infected by *Borrelia* but the status of these organisms in disease epidemiology is uncertain. *Ornithodoros (P.) rostratus* Aragão is more widely distributed (southern Brazil, Bolivia, Paraguay, northern Argentina) and also infests peccaries, livestock, man, and dogs in nature and in villages. This species is a vector of *Rickettsia rickettsi* (Rocky Mountain spotted fever) but has not been associated with relapsing fever spirochetes. Biomedical investigations of Neotropical *Pavlovskyella* species have been perfunctory. Their hosts and habitats apparently differ widely from those of Nearctic species.

(*d*) *Subgenus* Ornamentum *Clifford, Kohls, and Sonenshine (1964).* *Ornithodoros (O.) coriaceus* Koch, the pajaroello, the sole member of this subgenus, possibly evolved from the subgenus *Pavlovskyella*. The pajaroello is remarkable for having four eyes and ornate integumental mammillae and is notorious for irritating deer, cattle, and people resting on "deer beds" under trees in hillside scrub oak forests from Humboldt County, California, to Chiapas, Mexico. The presence of four eyes is associated with the habitat of ground surface deer beds, which are visited diurnally, more or less regularly, by the host. This tick is active in summer in cool zones and throughout the year in warmer zones. Fed adults can survive for 3–5 years. The life cycle is said to require 1 or 2 years and five to seven nymphal instars, the first two nonfeeding. Adults and nymphs feed rapidly but larvae engorge in 5–18 days. This life pattern, suggestive of that characterizing the subgenus *Alectorobius*, is reported from studies using common laboratory animal hosts [as with *O. (Ornithodoros) indica*, also taken from a deer], but should be reinvestigated using deer as hosts. Whether *Ornithodoros* parasites of deer characteristically develop with more nymphal instars than generally required by those specific for other hosts is a challenging question. One also wonders whether the structure and function of certain sensilla common to *Ornithodoros* are modified as a result of dependence on four eyes for host finding. *Ornithodoros (O.) coriaceus* transmits an uncharacterized agent causing epizootic bovine abortion in California (Table 1).

(*e*) *Subgenus* Alectorobius *Pocock.* The 40 *Alectorobius* species shelter almost invariably in rock crevices or stony situations. About 30 species are Neotropical; 3 others occur in both the Neotropical and Nearctic, 2 only in the Nearctic and 5 are derived from the Neotropical–Nearctic marine bird parasite *O. (A.) capensis* (which is also present in each region) and are localized in certain island groups of the Palearctic (4) and Oriental (1) regions. Hosts of *Alectorobius* are bats (20 species), birds

(chiefly oceanic) (11), Galapagos iguanid lizards (2), or "miscellaneous" (either mammals, or reptiles, birds, and mammals) (7).

Larval *Alectorobius* feed for several days; feeding nymphal instars and adults engorge in an hour or less. However, there may be a distinct, host-dependent dichotomy in *Alectorobius* first instar nymph feeding and molting patterns: the first instar feeds if bats are the hosts but does not feed if birds or land mammals are the hosts. The life cycle is unstudied for the two *Alectorobius* species parasitizing lizards and for many species parasitizing bats and land mammals.

The 20 species of *Alectorobius* parasitizing bats, most known only by a few larvae collected by several enthusiasts, occur in the Neotropical (15 species) and Nearctic (2) regions, or in both (3). Neotropical species described by Jones and Clifford (1972) are *A. clarki* and *A. knoxjonesi* from Nicaragua and *A. tiptoni* from Venezuela. Kohls *et al.* (1969) described *A. mimon* (Bolivia, Uruguay), *A. eptesicus* (Venezuela), *A. setosus* (Brazil, Venezuela, Mexico), *A. peruvianus* (Peru), and *A. peropteryx* (Colombia). Černý (1967) described *A. dusbabeki* and Černý and Dusbabek (1967) described *A. tadaridae*, both from Cuba; the latter is infected by Estero Real virus (Table 1). Other Neotropical species are *A. hasei* (Schulze) (Mexico to Panama, Trinidad, Bolivia, Brazil), *A. azteci* Matheson (Mexico, Cuba, Jamaica, Panama, Trinidad, Colombia), *A. boliviensis* Kohls and Clifford (Bolivia), and *A. brodyi* Matheson (Mexico, Guatemala, Panama).

Neotropical–Nearctic *Alectorobius* bat parasites are *A. kelleyi* Cooley and Kohls (Cuba, 22 of the United States, and Canada), *A. yumatensis* Cooley and Kohls (much of Mexico, California, Arizona, Texas, and Florida), and *A. dyeri* Cooley and Kohls (El Salvador, Mexico, Arizona, California). Nearctic species are *A. rossi* Kohls, Sonenshine, and Clifford (Arizona, New Mexico) and *A. stageri* Cooley and Kohls (Texas, Oklahoma, Arizona, New Mexico, California). Subsequent records of *A. rossi* and *A. stageri* from the Neotropical region would not be surprising.

Of these 20 *Alectorobius* species infesting bats, the structure of both immatures and adults and the biology of only *O.* (*A.*) *kelleyi*, *O.* (*A.*) *boliviensis*, and *O.* (*A.*) *tadaridae* have been studied. *Ornithodoros* (*A.*) *boliviensis*, the vector of Matucare virus (Table 1), parasitizes *Myotis* in houses; adults also bite man. The cave-dwelling *O.* (*A.*) *kelleyi* parasitizes *Myotis*, *Eptesicus*, *Pipistrellus*, and other bats and is frequently found in buildings where hosts roost. Larvae feed on bats for 15 (9–20) days; nymphs (including the first instar) and adults engorge within 30–135 minutes (Sonenshine and Anastos, 1960). *Ornithodoros* (*A.*) *tadaridae* parasitizes *Mormopterus minutus* (Miller) and *Tadarida laticauda yucatanica* (Miller), which rest in clusters of dry leaves of the palm tree *Copernicia vespertilionum* Leon in Cuba (Honzáková *et al.*, 1983). Cuban specimens

reared in Czechoslovakia on dark laboratory mice (albino mice were rejected as hosts and bats were not available for experimental use) underwent a life cycle fairly typical of bat-infesting *Alectorobius* species, with feeding in the first nymphal instar. Feeding on mice was shorter for larvae (6–13 days) and longer for adults (10 hours) than recorded for *O.* (*A.*) *kelleyi* (on bats). Adults of other *Alectorobius* species should be sought in bat caves, reared in the laboratory, and investigated for biological and biomedical properties. Host data for most bat-parasitizing species are too limited to merit repeating here.

The *Alectorobius* parasites of iguanid lizards in the Galapagos are *O.* (*A.*) *darwini* and *O.* (*A.*) *galapagensis*, both described as larvae by Kohls, Clifford, and Hoogstraal and later (Keirans *et al.*, 1980) from nymphs and adults. Both species occur on several islands. *Ornithodoros* (*A.*) *darwini* parasitizes the land lizards *Conolophus subcristatus* and *C. pallidus*. *Ornithodoros* (*A.*) *galapagensis* parasitizes chiefly the marine lizard *Amblyrhynchus cristatus*; a few specimens have been recorded from *Conolophus* spp. and from the larva lizard *Tropidurus albemarlensis*. Both tick species shelter in rock crevices and under debris in burrows where the lizards rest. The Galapagos finch, *Geospiza fuliginosa*, preys on the feeding ticks. We were unable to rear these ticks in the laboratory and virus could not be isolated from field samples. The thick or expanded setae of the larval body reflect their association with reptile hosts. Both lizard-parasitizing species of those of the *O.* (*A.*) *capensis* group (below) probably evolved from a common base. Among the 100 *Ornithodoros* species, mostly confined to dry ecosystems, the humid habitats of *O.* (*A.*) *galapagensis* [and *O.* (*A.*) *sawaii*; see below] are noteworthy.

The *O.* (*A.*) *capensis* group of 10 species has been the subject of continuous study since 1966. Eight of the 10 species parasitize ground- or shrub-nesting marine and wading birds on islands or shores of tropical and subtropical oceans and East African lakes. One Palearctic–Ethiopian parasite of rock pigeons and other ground- and rock-nesting birds also extends into the Indian subregion of the Oriental region. The only strictly Oriental species infests nests of the cave swiftlet on the coasts of Java.

Ornithodoros (*A.*) *capensis* Neumann, postulated to represent the Neotropical progenitor of this group of 10 species and originally described from St. Paul's Rocks in the Atlantic off Brazil, has a wide distribution: the coasts of Texas, California, and Oregon; many tropical, subtropical, and warmer temperature islands of the Pacific, southern Atlantic, and Indian oceans; coasts of Australia, New Zealand, and southern Africa (Kohls *et al.*, 1965); and the Rift Valley lakes of East Africa (Hoogstraal *et al.*, 1976a). [Records of *O.* (*A.*) *capensis* from the USSR and Europe are based on misidentified *O.* (*A.*) *maritimus*.] More localized Neotropical species are *O.* (*A.*) *amblus* Chamberlin (coasts and guano islands of Peru)

(Clifford *et al.*, 1980), *O.* (*A.*) *yunkeri* Keirans, Clifford, and Hoogstraal (1984) (Galapagos), and *O.* (*A.*) *denmarki* Kohls, Sonenshine, and Clifford (1965) (Trinidad, Jamaica, Mexico, Florida, Hawaii). The only Nearctic member is *O.* (*A.*) sp. (near *O. denmarki*) (Baja California, California, Oregon).

Four Palearctic species represent the *O.* (*A.*) *capensis* group. *Ornithodoros* (*A.*) *maritimus* Vermeil and Marguet (Hoogstraal *et al.*, 1976b; Chastel *et al.*, 1983) occurs on islands in Britain, France (including Corsica), northwestern Africa, and southern USSR (Black, Caspian, and Aral seas). (See also Soldado virus in Section IV,F,2,b.) *Ornithodoros* (*A.*) *muesebecki* Hoogstraal is found on islands in the Arabian Sea and Arabian Gulf (Hoogstraal *et al.*, 1970) and *O.* (*A.*) *sawaii* Kitaoka and Suzuki (1973) in the Amami Islands, Japan. Notably, *O.* (*A.*) *sawaii* has been taken only from wet sand in nesting burrows of the streaked shearwater and is smaller and paler than the *O.* (*A.*) *capensis* which parasitize other marine birds nesting in dry situations in the Amami Islands. *Ornithodoros* (*A.*) *coniceps* Canestrini, an atypical member of this group, parasitizes domestic and wild pigeons, swallows, and other birds nesting among rocks and in buildings from southern Europe to Egypt and southern Africa (Botswana), the Near and Middle East, southern USSR, northern India, and southwestern Nepal (Hoogstraal *et al.*, 1979a). Migratory pigeon hosts of *O.* (*A.*) *coniceps* probably account for its distribution through much of the southern Palearctic and into the southeastern Ethiopian region and Indian subregion of the Oriental region.

The only truly Oriental species, *O.* (*A.*) *collocaliae* Hoogstraal, Kadarsan, Kaiser, and Van Peenen, infests mud nests of the cave swiftlet, *Collocalia esculenta linchi* Horsfield, on the coasts of Java.

The hosts of the first eight species of the *O.* (*A.*) *capensis* group include a large variety of marine birds nesting on or near the ground, usually on barren shores. For instance, penguins are common hosts of *O.* (*A.*) *capensis* in southern Africa [*Spheniscus demersus* (L.)] and Australia [*Eudyptula minor* (Forster)] and in Peru *O.* (*A.*) *amblus* and an undescribed species parasitize the Humboldt penguin, *Spheniscus humboldti* Meyer. These and/or other *O.* (*A.*) *capensis* group members parasitize gulls (*Larus*), cormorants (*Phalacrocorax*), boobies (*Sula*), albatrosses (*Diomedea*), ospreys (*Pandion*), terns (*Sterna*), shearwaters (*Puffinus*), pelicans (*Pelecanus*), murres (*Uria*), etc. Counterpart ixodid parasites of marine birds are *Amblyomma loculosum* of tropical oceans near and south of the equator, and the *Ixodes* subgenera *Scaphixodes* and *Ceratixodes* of arctic, antarctic, and northern and southern temperate regions.

Members of the *O.* (*A.*) *capensis* group have been found to be infected by one or several arboviruses (Table 1) and to produce irritation and illness when biting man; they also may cause mass mortalities of marine

birds, especially when tick population numbers increase greatly (see Section IV). In buildings infested by *O.* (*A.*) *coniceps*, man suffers from allergic reactions and toxemia following bites.

The eleventh species of *Alectorobius* parasitizing birds, *O.* (*A.*) *concanensis* Cooley and Kohls, is related to the bat parasite *O.* (*A.*) *kelleyi* and the "miscellaneous-host" *O.* (*A.*) *talaje* (see below). *Ornithodoros* (*A.*) *concanensis* inhabits cliffs, caves, and buildings where the cliff swallow (*Hirundo pyrrhonota* subspp.), phoebe (*Sayornis phoebe* subspp.), and other birds nest or rest and various bats (*Eptesicus, Myotis*, etc.) roost in the United States (Kansas to California). The importance of bats in supporting certain *O.* (*A.*) *concanensis* populations is unclear. Ongoing biological studies and earlier literature on this species are reviewed by Hopla and Loye (1984). The chief bat hosts of *O.* (*A.*) *kelleyi* should also be determined; in buildings where bats roost, this tick also feeds on people and causes irritating welts and pruritus.

Among the seven *Alectorobius* species with "miscellaneous" hosts, little information is available for the four described (from larvae) by Jones and Clifford (1972): *A. casebeeri* [Costa Rica; rodent (*Ototylomys*)], *A. chironectes* [Nicaragua; marsupial (*Chironectes*) and rodent (*Sigmodon*)], *A. marmosae* [Venezuela and Colombia; marsupial (*Marmosa*) and rodents (*Oryzomys* and *Rhipidomys*], and *A. tuttlei* [Venezuela; tapir, *Tapirus terrestris* (L.), and rodent, *Agouti paca* (L.)], or for *A. echimys* Kohls, Clifford, and Jones [Venezuela; rodent (*Echimys*) and marsupial (*Marmosa*)]. *Ornithodoros* (*A.*) *talaje* (Guérin-Meneville) and *O.* (*A.*) *puertoricensis* Fox have been recorded more frequently, but precise biomedical investigations of both species are necessary. *Ornithodoros* (*A.*) *talaje* infests numerous reptiles, birds, and mammals from Argentina to the United States (Kansas and California), but many pre-1950 literature references to this taxon are in error. *Ornithodoros* (*A.*) *puertoricensis* parasitizes commensal and wild rodents (*Sigmomys, Proechimys, Zygodontomys, Dasyprocta*), rabbits (*Sylvilagus*) and marsupials (*Marmosa* and *Monodelphis*), and other mammals in Puerto Rico, Virgin Islands, Guadeloupe, Jamaica, Colombia, Panama, Venezuela, and Trinidad. *Ornithodoros* (*A.*) *talaje* and *O.* (*A.*) *puertoricensis* are structurally similar in the adult and nymphal stages but differ distinctly in the larval stage. Both species feed on humans, especially where associated with commensal rodents in towns and cities. Larval *O.* (*A.*) *puertoricensis* feed for 4–7 days; the first nymphal instar does not feed but subsequent instars and adults feed rapidly. Experimentally, this species can support and transmit African swine fever virus. Relapsing fever spirochetes, *Borrelia mazzottii*, have been reported from Mexican and Panamanian populations of *O.* (*A.*) *talaje* but knowledge of the tick–spirochete interrelationships is equivocal.

(*f*) *Subgenus* Proknekalia *Keirans, Hoogstraal and Clifford.* This is a distinctive group of three parasites of swallows, *Hirundo* spp., and a few other birds nesting in caves and rock walls adjacent to mud nests of swallows (Keirans *et al.*, 1977a). *Ornithodoros* (*P.*) *vansomereni* Keirans, Hoogstraal, and Clifford occurs in eastern Kenya and in Botswana, *O.* (*P.*) *peringueyi* Bedford and Hewitt in Transvaal and Cape Province, South Africa, and *O.* (*P*). *peusi* (Schulze) in Greece. The long, narrow north–south axis of *Proknekalia* distribution, from Greece to South Africa, suggests a single migratory swallow-parasitizing prototype for these three species. *Proknekalia* and *Alectorobius* have been linked taxonomically but I am uncertain that this linkage represents the phylogenetic history of these subgenera. *Proknekalia* biology is unstudied. Chenuda virus has been isolated from *O.* (*P.*) *peringueyi* in South Africa (Table 1).

(*g*) *Subgenus* Subparmatus *Clifford, Kohls, and Sonenshine.* Three *Subparmatus* species parasitize at least four mormoopid and phyllostomatid bat genera from southern Central America to northern South America and in Cuba (Clifford *et al.*, 1964). The hosts roost in caves, often with other genera of bats. *Ornithodoros* (*S.*) *viguerasi* Cooley and Kohls is recorded from *Phyllonycteris, Brachyphylla, Pteronotus,* and *Mormoops* in Cuba, Trinidad, and Costa Rica. *Ornithodoros* (*S.*) *marinkellei* Kohls, Clifford, and Jones is recorded from *Pteronotus personata* and *P. purnellii* in Panama and Colombia and *O.* (*S.*) *mormoops* Kohls, Clifford, and Jones from *Mormoops* sp. in Curaçao. *Ornithodoros* (*S.*) *marinkellei* and *O.* (*S.*) *mormoops* are known only from larvae. *Ornithodoros* (*S.*) *viguerasi* adults and nymphs have unique sclerotized plates on the venter, a small, flattened hypostome in the shape of an inverted V, and pulvilli on all tarsi (Cooley and Kohls, 1941). (Pulvilli are present in only a few cave-dwelling, bat-infesting *Ornithodoros* species.) Whether adult *O.* (*S.*) *viguerasi* feed is unknown. The nymph and larva each have a long, pointed hypostome and the larva has unique projections on the basis capituli.

Subparmatus and the genera *Antricola* and *Nothoaspis* may have evolved as two separate branches from a common base in the subgenus *Alectorobius,* with the latter two groups (genera) differing more distinctively from typical *Ornithodoros* than does the subgenus *Subparmatus.* The hosts and habitats of each species in these three Neotropical supraspecific categories are much alike and Cuba is a common locality record for each group. Otherwise, *Subparmatus* geographic records are from the southern range of, or to the south of, those of the other two groups.

(*h*) *Subgenus* Alveonasus *Schulze.* The six large *Alveonasus* species, each with distinctive integumental sculpturing, constitute a specialized but diverse branch of *Ornithodoros* comparable to the subgenera *Secretargas* and *Ogadenus* of the genus *Argas. Alveonasus* is sometimes ranked as a full genus, a conclusion reasonably rejected by Clifford *et al.*

(1964). Hosts are medium- to large-sized mammals in the Palearctic (four species) and eastern Ethiopian (two species) regions. Habitats are in soil in caves and in or near rock crevices or (one species) porcupine burrows. Notably, life cycle patterns differ distinctly among studied *Alveonasus* species.

Ornithodoros (*A.*) *lahorensis* Neumann, originally a parasite of the Asiatic mouflon, *Ovis orientalis arkal* Eversmann, and other wandering ungulates resting beside cliffs, is now a notorious parasite of sheep, camels, and cattle, especially in primitive stables and dwellings in steppe and mountain deserts from sea level to 2900 m altitude in Tibet, Kashmir, southern USSR and southwest Asia [northern Pakistan to Saudi Arabia (unpublished observations)] and southeast Europe (Turkey, Bulgaria, Yugoslavia, Greece) (Filippova, 1966).

The two-host life cycle of *O.* (*A.*) *lahorensis* (Brumpt, 1936a; Filippova, 1966) is exceptional among argasids. The larva remains on the host for 3–6 weeks and detaches as an engorged third-instar nymph which rests in a crevice and molts to an adult. After mounting another host, the adult feeds within an hour or two but can ingest as much as 228 mg of blood. However, third-instar nymphal feeding may be sufficient for the unfed female to deposit two viable egg batches. The larva attaches during fall or winter, when hosts often remain in stables; the final nymph molts to an adult in spring. Mated fed or unfed females deposit batches of 300–500 eggs (only during warm months) but unfed females require bloodmeals to produce third and subsequent egg batches. The egg incubation period is 2–6 weeks. Unfed larvae can survive for a year, and unfed adults for 18 years. Tremendous population densities often develop between bricks and stones, under plaster, and in cracks of roof supports of stables. I rapidly determine whether a stable is heavily infested by searching for nymphal pelts entangled in cobwebs on walls, in corners, and over windows. The success of *O.* (*A.*) *lahorensis* in this artificial environment, with a regular supply of hosts, results from its exceptional original life cycle adaptation associated with parasitizing small flocks or herds of wandering wild ungulates. This tick causes anemia, toxic reactions, and paralysis in hosts and transmits the agents of tularemia, Q fever, brucellosis, and piroplasmosis.

Ornithodoros (*A.*) *canestrinii* (Birula) is recorded from Iran and Turkmen SSR. Other records are incorrect or questionable. Wild sheep [such as the Pamir Argal, *Ovis ammon* (L.)], goats, and possibly gazelles were the original hosts. Most specimens are from caves and stables sheltering sheep and goats; cattle and other domestic animals are also parasitized. The only reliable biological studies were reported by Kusov (1973) from Turkmen SSR. Larvae feed for 10–31 days; second to fifth nymphal instars and adults feed more rapidly. The first nymphal instar (as in *Alec-*

torobius) does not feed. In cold zones or where hosts rarely appear in the ticks' habitat, the life cycle may require 10–16 years to complete. *Ornithodoros* (*A.*) *canestrinii* can survive in the laboratory without feeding for 10 years. This tick tolerates extraordinarily low atmospheric humidity. Its saliva contains a toxin which causes the host skin to swell and become bluish.

The extremely desert-adapted *O.* (*A.*) *foleyi* Parrot inhabits dry sandy ground shaded by rock ledges, and also rodent burrows, in southeastern Arabia (Oman) and Egypt to Algeria and Niger (Hoogstraal, 1981a). Hosts are the thar (*Hemitragus jayakeri* Thomas), gazelle (*Gazella gazella* subspp., *G. dorcas* subspp.), Barbary sheep [*Ammotragus lervia* (Pallas)], hyena [*Hyaena hyaena dubbah* (Meyer)], jackal [*Canis aureus lupaster* (Hemprich and Ehrenberg)], gerbil (*Meriones crassus* subsp.), camel, cow, goat, and man. Larvae feed for several days; each of the four or five nymphal instars, and the adults, complete feeding in less than 30 minutes. Chancre-like lesions and fever follow *O.* (*A.*) *foleyi* bites on man but we have not recovered viruses or spirochetes from Egyptian samples.

Ornithodoros (*A.*) *delanoei* Roubaud and Colas-Belcour is found only in small numbers in arid caves, rock crevices, and burrows where it parasitizes hedgehogs (*Paraechinus*) and small to large rodents [*Gerbillus* (gerbils) to *Hystrix* (porcupines)] in scattered desert localities from Egypt to Morocco. This large, handsome species is difficult to rear. Larvae feed for 5 to 15–21 days; the three to seven nymphal instars and adults feed rapidly. The biological peculiarities of *O.* (*A.*) *delanoei* deserve more study.

In the Ethiopian region, the huge *O.* (*A.*) *acinus* Whittick is recorded from a few caves sheltering large mammals in Somalia. Life history data for this species, which is also difficult to rear, are similar to those of *O.* (*A.*) *delanoei. Ornithodoros* (*A.*) *eboris* Theiler, remarkable for its ivory color, is known only from a few adults, nymphs, and laboratory-reared larvae from a porcupine burrow in Pretoria District, South Africa.

(*i*) *Subgenus* Reticulinasus *Schulze.* Nine *Reticulinasus* species have been described (six in The Oriental, one each in the Malagasy, Palearctic, and Ethiopian regions). At least three others, two from New Guinea and one from Thailand, await description. Criteria for identifying *Reticulinasus* species are inadequately developed. Most samples from "remote" localities are too limited or poorly preserved for proper study. Hosts are cave-dwelling bats, usually of the frugivorous genus *Rousettus.* In Malaysia, the frugivorous *Eonycteris* and insectivorous *Hipposideros* and *Rhinolophus* are recorded hosts of *O.* (*R.*) *batuensis* Hirst; in Mindanao, Philippines, the host of this species is *Rousettus.* Hosts recorded for *O.* (*R.*) *faini* Hoogstraal are *Rousettus* in Zaire, Uganda, Tanzania, Zambia, and South Africa but *Hipposideros* in coastal caves of Kenya. Hosts of *O.*

(*R.*) *piriformis* Warburton in India are *Rousettus* and of this or a closely related species in Nepal are *Miniopterus*. In Papua, Dr. D. Moorhouse has collected two undescribed *Reticulinasus* species from separate "rooms" housing two different bat species in a large cave system.

Nymphal and adult *O.* (*R.*) *salahi* Hoogstraal, a parasite of *Rousettus aegyptiacus* in North Africa and the Near East, feed to repletion within 30 minutes on bats and man. During this time, they lunge into the host at 4-second intervals. Nymphs and adults rest under debris of the cave floor until about 1100 hours, when they start climbing up the walls to reach bats clinging to the roof (Hoogstraal, 1953). Females "brood" the egg batch, of 22–54 eggs, until larvae hatch. An Indian species, *O.* (*R.*) *chiropterphila* Dhanda and Bhat, has been found to be infected by Kyasanur Forest disease virus and bites of *O.* (*R.*) *salahi* are irritating to man. The other species of *Reticulinasus* are *R. steini* (Schulze) (Timor), *R. solomonis* Dumbleton (Solomon Islands), *R. rennellensis* Clifford and Sonenshine (Solomon and Admiralty Islands), and *R. madagascariensis* Hoogstraal (Madagascar).

(*j*) *Subgenera uncertain.* Seven poorly known *Ornithodoros* species (one Nearctic, six Neotropical) of uncertain subgeneric affiliations (Kohls *et al.*, 1965) are listed in the hope of stimulating investigations of their biomedical properties. These are *O. cooleyi* McIvor (United States: Nevada, Arizona; chiefly carnivores), *O. elongatus* Kohls, Clifford and Sonenshine (probably Dominican Republic; host unknown), *O. natalinus* Černý and Dusbabek (Cuba; bats), *O. nattereri* Warburton (Brazil; host uncertain), and *O. rudis* Karsch (= *O. venezuelensis* Brumpt) (Paraguay, Ecuador, Colombia, Venezuela, Panama; rodent nests, chicken coops, buildings). *Ornithodoros rudis* has been taken from beds in houses of Rocky Mountain spotted fever patients in Colombia.

4. *Genus* Otobius *Banks*

The two species of *Otobius* (Otobinae: see Fig. 1) are highly specialized biologically and structurally for coexisting with two kinds of roaming mammals in arid and semiarid biotopes of western North America. *Otobius megnini* (Dugès) parasitizes mule deer [*Odocoileus hemionus* (Rafinesque)], Virginia deer [*O. virginianus* (Zimmerman)], pronghorn antelope [*Antilocapra americana* subsp.], and mountain sheep, [*Ovis canadensis* subspp.] from western Canada southward into Mexico (Cooley and Kohls, 1944). This species has adapted to domestic cattle, horses, sheep, and goats, and also parasitizes man and dogs. Feeding deeply in the ears of the host, larval and nymphal *O. megnini* have been widely transported with domestic animals and the species is established in western South America, Galapagos, Cuba, Hawaii, India, Madagascar, and southeastern Africa. The second species, *Otobius lagophilus* Cooley

and Kohls, feeds on the faces of rabbits (*Sylvilagus*) and jack rabbits (*Lepus*), in approximately the same geographical area as *O. megnini*. Herrin and Beck (1965) reported on *O. lagophilus* structure, biology, and vector relationships.

Otobius adults have nonfunctional mouthparts, do not feed, and mate on the ground. Female *O. megnini* may survive for more than 20 months. They deposit as many as 1500 eggs within 2 weeks. The one-host life cycle, with the larva and two nymphal instars feeding on a single host, is completed in 2–4 months, chiefly in winter and spring; there may be two or more generations annually. The similar life cycle of *O. lagophilus* is apparently accomplished chiefly in summer. Both *Otobius* species begin spermatogenesis and spermiogenesis several days before the second nymphal instar molts and continue during and after the molt. Male *O. megnini* can inseminate females 2 days or possibly sooner after molting from the nymphal stage. Diploid chromosomes number 20 in both species (Oliver and Osburn, 1977).

As mentioned in Section IV, severe irritation to man and animals, economic losses, secondary infections by screw worms, tick paralysis, and Q fever are associated with *O. megnini*. The agents of Rocky Mountain spotted fever, Colorado tick fever, and tularemia have been isolated from *O. lagophilus*, which appears to be a cul-de-sac or blind alley in the epidemiology of these microorganisms.

5. *Genus* Antricola *Cooley and Kohls*

The Neotropical *Antricola* are highly specialized for parasitizing mormoopid, phyllostomid, and a few other bats, usually where roosting in large numbers, often with related species, in hot, humid chambers of large cave systems. The chief hosts are the genera *Chilonycteris, Phyllonycteris, Mormoops, Brachyphylla,* and *Pteronotus. Antricola* adults have a nonfunctional, short, spatulate hypostome (denticulate in some species) and do not feed. Numerous adults are often found on bat guano, sometimes together with other *Antricola* species and with *Nothoaspis reddelli*. Nymphs and larvae each have a long, pointed hypostome with many denticles. Only larvae have been taken from bats; larvae probably feed for a longer period than nymphs, which have been recovered from guano.

The subgenus *Antricola* contains seven species: *A.* (*A.*) *coprophilus* McIntosh [United States (Texas, Arizona), Mexico (Nuevo Leon, Chiapas, Colima)], *A.* (*A.*) *mexicanus* Hoffman [Mexico (Guerrero, Tabasco, Yucatan), Guatemala, Panama], *A.* (*A.*) *silvai* Černý (Cuba), *A.* (*A.*) *martelorum* de la Cruz (Cuba), and *A.* (*A.*) *naomiae* de la Cruz (Cuba). (Cuban species are discussed by de la Cruz, 1978a,b.) The subgenus *Parantricola* Černý (1966) contains *A.* (*P.*) *marginatus* (Banks) (Cuba, Puerto Rico).

6. *Genus* Nothoaspis *Keirans and Clifford*

Nothoaspis reddelli Keirans and Clifford, the single *Nothoaspis* species, is represented by three males, 11 nymphs, and two tentatively associated larvae from hot, deep caves in Tabasco, Campeche, and Yucatan, Mexico (Keirans *et al.*, 1977b). *Antricola mexicanus* and *A. marginatus* were taken from *N. reddelli* from bat guano in some caves. The probable host is the insectivorous bat *Mormoops megalophylla* (Mormoopidae). Adult and nymphal *Nothoaspis* differ from those of the closely related genus *Antricola* in having a "false shield" over the anterior half of the body. The adult hypostome (minute, broadly rounded, denticulate, apparently nonfunctional) is similar to those of adult *Antricola* spp. (some of which are nondenticulate). The *Nothoaspis* nymph (except for the dorsal shield) and the tentatively associated larva are also much like those of *Antricola*.

B. FAMILY NUTTALLIELLIDAE SCHULZE

Genus Nuttalliella *Bedford*

The phylogenetic affiliations of this remarkable monotypic family have been the subject of conjecture by biologists and invertebrate zoologists for half a century. The single species, *Nuttalliella namaqua* Bedford, is known only by 18 females and three nymphs (one molted to a female; two died) from scattered semiarid areas in Namaqualand, Cape Province, South Africa, and from crevices of large granite boulders in a higher rainfall area of Tanzania (Keirans *et al.*, 1976; and unpublished observations). Single specimens have been taken from a rodent (Otomyidae), small carnivore (Viverridae), and two rock-clinging mud nests of the striped swallow (Hirundinidae). Circumstantial evidence leads me to suspect that the rock hyrax, *Procavia capensis* (Hyracoidea), may be the principal or an important host. *Agama* and other lizards should be considered as candidate hosts. Living nymphs and females did not feed on proffered pigeons, chickens, mice, rats, hamsters or rabbits in my laboratory at NAMRU-3 or at Onderstepoort (J. B. Walker, personal communication).

In the original description of *N. namaqua,* Bedford suggested that this species represents a "missing link" between the families Argasidae and Ixodidae. From the studies of our group (cited herein), I believe that this species is an independent branch, albeit truncated, from the common basic stock of the superfamily Ixodoidea (Fig. 1). Scanning electron microscopy of the external surfaces reveals an argasid-like tick (with a peculiar Haller's organ), certain generalized ixodid-like characters, and other characters unique to *Nuttalliella* (organs of unknown function, three-

segmented palpi, pseudoscutum, and ball-and-socket leg joints) (Keirans *et al.*, 1976). Some internal structures are like those in Argasidae, others are like those in Ixodidae, and others appear to be modifications unique to *Nuttalliella* (El Shoura *et al.*, 1984). Nuttalliellid spiracles also combine features of both other families but the fenestrated plate surfaces are unique to this family (Roshdy *et al.*, 1983).

The absence of male specimens suggests that (1) *Nuttalliella* is parthenogenetic, or (2) males are more secretive and less mobile than females and remain to be discovered, or (3) the sex ratio is unusually disproportionate.

IV. Argasid Ticks as Vectors

A. Tick-Borne Infections as Zoonoses

Ticks transmit a greater variety of infectious agents than any other group of hematophagous arthropods. Many of these agents cause zoonoses, diseases that are intertransmissible between other animals and man. However, *Borrelia duttoni* (African tick-borne relapsing fever), a symbiont of the *Ornithodoros* (*O.*) *moubata* group, is known from no vertebrate other than man (Section IV,I). Zoonoses were recently reviewed in volumes edited by Stoenner *et al.* (1980) (bacterial, rickettsial, and mycotic diseases), Beran (1981) (viral diseases), and Jacobs and Arambulo (1982) (parasitic zoonoses).

Infectious agents transmitted to livestock and man are of primary concern in health and economics. To clarify the biological background and bring these agents into a biological perspective, I discuss the roles of ticks as amplifiers and reservoirs separately and adopt the unconventional scheme of discussing each group of agents (infections) first in terms of wildlife and livestock hosts and then in terms of human hosts.

B. Ticks as Reservoirs and/or Amplifiers

1. *Introduction*

Toxins (Section IV,E) and most infectious agents (Section IV,F–J) are transmitted to vertebrates chiefly via salivary fluids inoculated while the parasite feeds. The structure and functioning of argasid and ixodid salivary glands (reviewed by Balashov, 1972, 1983; Obenchain and Galun, 1983) are therefore of considerable importance to the student of ticks as parasites and vectors.

Many infectious agents survive transstadially within an individual tick,

from the larval to nymphal to adult stage. In this case, the term *transmission* is biologically incorrect. Transstadial survival is a common phenomenon in tick-associated viruses, rickettsiae, bacteria, and protozoa. The tick's internal molting pattern contributes fundamentally to the ability of the large number and variety of microorganisms to replicate in and be transmitted by tick amplifiers and reservoirs. In holometabolous insects, the extensive internal changes during molting appear to be deleterious to survival of most infectious agents. In molting ticks, ectodermal derivatives and certain muscle groups undergo histolysis and only salivary gland alveoli are completely replaced. Most internal cells and organs change gradually throughout the tick lifetime (Balashov, 1972, 1983; Obenchain and Galun, 1983).

Agents may also be transmitted within an argasid population or from argasids to vertebrates by contamination with infected coxal fluid, body fluids (when the body is broken), or fecal deposits, by aerosol inhalation, by consumption of living or dead infected tick bodies, or by venereal or hyperparasitic routes.

2. *The agent–tick amplifier system*

In this system, an agent replicates in the tick, survives transstadially, and is transmitted to one or several vertebrate hosts by the feeding tick. The agent may be inherent to ticks (when the tick is also a reservoir) or to vertebrates (when the tick is only or chiefly an amplifier). The epidemiologically critical distinction between the intrinsic arthropod or vertebrate host of the agent, discussed in the following sections, can be determined only for adequately investigated agents. Agents intrinsic to vertebrates are apparently not (or seldom?) transovarially transmitted by ticks. Usually, only agents intrinsic to ticks and a few of those intrinsic to insects are transovarially transmitted by ticks. This hypothesis must be accepted with caution until the life cycles of more viruses have been investigated. Some intrinsic agents of vertebrates may have evolved a life pattern in which the agent replicates in both a vertebrate and a tick and transovarial transmission also occurs in the tick. However, conclusive evidence for this phenomenon, if it exists, is lacking.

When two or more infected and uninfected tick amplifier species simultaneously parasitize a host within a period of a few weeks, or longer, an uninfected tick may acquire one or more agents if it feeds while the agent(s) is replicating in the vertebrate. (Two or more tick reservoir species seldom if ever infest the same host.) A susceptible tick becomes infected when feeding on a host in which the agent is circulating at or above an infective threshold titer (periods of viremia, rickettsemia, spirochetemia, bacteremia).

The structural, physiological, biochemical, genetic and microbiological

factors that permit different agents to multiply in certain tick species but not in others need more definitive investigation. A case in point is why *Argas (Argas)* spp. and *A. (Persicargas)* spp. are commonly infected by arboviruses but the otherwise unusually adaptable *A. (P.) persicus* is apparently resistant to most or all arboviruses.

3. *The agent–tick reservoir system*

The agent in this system has evolved as a harmless symbiont during eons of coexistence with the tick. Survival of the agent population depends solely on tick population survival. The agent undergoes several or many replicative cycles within the tick. Whether the agent does or does not replicate in the vertebrate host of the tick may affect its own prevalence, density, and possibly virulence for the vertebrate, but is not essential for survival. Transovarial transmission (see below) is a primary phenomenon characterizing the agent–tick reservoir system. Unfortunately, most of the numerous arboviruses infecting argasids (Table 1) are poorly studied or unstudied in this respect.

4. *Examples of agent and amplifier or reservoir systems*

The agent–amplifier system is represented among argasids by Quaranfil (QRF) virus in *Argas (P.) arboreus*, other *Argas* species, and birds (Section IV,F) and by the filaria *Dipetalonema viteae* in *Ornithodoros (P.) tartakovskyi* (Section IV,J). Examples of this system among ixodids are Kyasanur Forest disease (KFD) virus (Boshell-M., 1969) and Colorado tick fever (CTF) virus (Hughes *et al.*, 1974) in several tick and mammal species.

Prolonged survival of these three agents in ticks, and of KFD and CTF viruses in vertebrates, assures that after winter, or after a dry season or monsoon season, new developmental stages or generations of the same or another tick species parasitizing the infected host acquire the agent and transmit it to the same or different kinds of vertebrates.

The agent–tick reservoir system, in which an agent is transovarially transmitted by its specific tick host (and possibly by other tick species), is represented in the Argasidae by African swine fever virus in the *O. (O.) moubata* group and *Borrelia* spirochetes and "rickettsia-like" *Wolbachia* in *Argas* spp. and *Ornithodoros* spp.

Rickettsia spp. may infect argasids but appear to be original symbionts only of ixodid ticks (reservoirs). The limited research on *Rickettsia*–argasid interrelationships is mentioned in Section IV,G.

5. *Other (unconventional and uncertain) agent–tick systems*

Coxiella burneti, the rickettsial agent of Q fever (Section IV,G), survives and multiplies in a variety of abiotic and biotic environments and

microhabitats. The unconventional ("atypical") *C. burneti* may have evolved (escaped) from an agent–tick cycle into a wider biotic and abiotic world.

The tortured history of research on Omsk hemorrhagic disease virus, first considered to be an ixodid-borne agent and now to be disseminated among mammals chiefly by water (reviewed by Hoogstraal, 1981b), exemplifies conceptual changes of inherent properties of an agent when either environmental factors change and/or research efforts become more sophisticated. If new epidemiological data for an agent contradict previous data for a well-established system, one must be alert for the presence of a different agent or different genetic strain of the agent or for an unconventional or unrecognized, epidemiologically distinctive system, especially in marginal distribution areas but possibly also in a central area.

A surprising number of recent research developments require us to revise cherished concepts of agent–tick–vertebrate circulation flow patterns. Examples among the Argasidae (see Section IV,F) are African swine fever virus (the transmission role of ticks was earlier disparaged) and Quaranfil virus (new data incriminating ixodids and mammals are a perplexing addition to the much-studied argasid and bird chain of this virus).

Among agents transmitted by ixodids, Russian spring-summer encephalitis (RSSE) virus is an example of how new findings in peripheral zoogeographical or ecological zones oblige us to rethink established concepts and investigate "exotic" epidemiological transmission factors. RSSE virus was long considered to be strictly an agent of *Ixodes persulcatus* and of a few other ixodid species in the geographic range of the *Ixodes* reservoir–vector. Revolutionary recent data demonstrate that in the northern Siberian tundra RSSE virus infects gamasid mites, fleas, and mosquitoes (and mammals). (Except for *Ixodes uriae* and *I. signatus* in colonies of marine birds, ticks have been absent from the northern tundra biotope since the last glacial period but were probably numerous in the luxuriant forests before the last ice age.) Another very recent epidemiological finding is that in Irkutsk Oblast (a geographically and ecologically marginal area for RSSE virus) classic Siberian RSSE strains are partially replaced by a different but epidemiologically significant serotype.

The reader may wish to watch current literature on Colorado tick fever (CTF) virus and ixodids for data leading to changing concepts of agent–tick epidemiological relationships in California, outside the central zone of CTF virus distribution. Tettnang virus infections of ixodids, *Hyalomma* in Egypt and *Ixodes* in Europe, present an exceptionally confusing epidemiological problem still in early stages of investigation.

Agents normally transmitted by insects (but seldom if ever by mites) are occasionally isolated from ticks in which they have survived after an

infected bloodmeal. A few insect agents replicate in ticks and are transmitted transovarially to the next tick generation or in salivary fluids to a vertebrate host. An example is yellow fever virus in the ixodid *Amblyomma variegatum* in West Africa. These biologically interesting phenomena appear to be of little epidemiological importance. Furthermore, few insect viruses survive and multiply in tick tissue cultures and few tick viruses multiply in insect cell cultures (Yunker, 1971), thus providing experimental evidence of agent adaptation to specific arthropod groups. However, some concepts of insect agent dissemination patterns in ticks may be modified by more intensive research.

Little attempt has been made by western investigators to confirm the results of rather many Soviet workers dealing with tick dissemination of *Leptospira* spp., *Brucella* spp., *Pasteurella pestis* (plague), etc. With all due respect to the published results, I tentatively categorize some of the epidemiological conclusions as uncertain.

6. *Transovarial transmission of infectious agents*

Transovarial transmission as mentioned above is a primary phenomenon characterizing the agent–tick reservoir system. In a masterly review of transstadial and transovarial development of disease agents in arthropods, Burgdorfer and Varma (1967) stressed that transovarial development produces two distinct infection rates which may not bear any relation to each other: (1) *transovarial infection rate,* the percentage of females that pass microorganisms to their progeny, and (2) *filial infection rate,* the percentage of infected progeny derived from an infected female. The reviews by Fine (1975, 1981) of transovarial ("vertical") transmission among arthropods should also be consulted.

Much well-intentioned literature regarding transovarial transmission is based on inadequate samples, insensitive techniques, or even unsound experiments. As a single example [for ixodid ticks and Russian spring-summer encephalitis (RSSE) and tick-borne encephalitis (TBE) viruses], I quote the following from Hoogstraal (1981b):

> Hundreds of papers deal with the roles of small-, medium-, and large-sized vertebrate hosts of *Ixodes* (*I.*) *persulcatus* [and *I.* (*I.*) *ricinus*], and the dynamics of these vertebrates, in contributing to the total virus pool and thus to the intensity of virus circulation and annual morbidity rates of human disease. Korenberg (1976, 1979) now rejects almost all data on which these conclusions are based as superficial and incorrect. RSSE and TBE viruses survive as long as the ticks survive, by transstadial passage and by transovarial transmission to following generations, no matter which hosts nourish the ticks. Rodents are important in maintaining larvae and nymphs of these *Ixodes* species, but nymphs also frequently infest medium- or large-sized hosts (which are the chief hosts of adults). The dynamics of human morbidity are determined by complex interactions in ecological processes.

In summary, transovarial transmission is the chief mechanism for disseminating RSSE and TBE viruses among tick populations. The role

of various vertebrates in disseminating this virus is either more limited or nil.

Transstadial survival of an agent (which characterizes both agent–tick systems) is equally as important as transovarial transmission in the epidemiological process but transovarial transmission appears to be confined to the agent–tick reservoir system. The role of each potential vertebrate amplifier of a transovarially transmitted agent of the agent–tick reservoir system in contributing to the agent population in nature must be assessed separately.

Knowledge of the structure, physiology, biochemistry, and functioning of the reproductive system of each tick species or group, and of the species life cycle and reproductive behavior, is necessary to understand the milieu in which transovarial transmission occurs and the factors determining transmission rates. By the same token, it is equally necessary to determine the precise physiological and genetic properties of the agent strain under investigation and to be alert for potential strain differences. For excellent reviews of tick reproduction, see chapter 8 (by Oliver) and chapter 9 (by Diehl *et al.*) in Obenchain and Galun (1983).

An example of the need to know details of reproductive functioning in relation to agent replication and transmission is furnished by the *Borrelia* spirochetes intrinsic to *Argas* and *Ornithodoros* ticks. Spirochetemia in the female argasid must reach a certain level before germinal cells in the ovary are invaded (Diab and Soliman, 1977; Gaber *et al.*, 1984). During the first gonotrophic cycle of females infected as adults, this level is inadequate for the spirochetes to be transmitted transovarially. However, during the second cycle, spirochetes are transmitted to 27 and 47% of the F_1 males and females, respectively. After the first gonotropic cycle of the F_1 generation from these parents, all infected females are able to transmit the spirochetes to 27–73% of the F_2 larvae. Results of these studies, using adequate tick samples over two generations and an easily demonstrable agent, provide clues to the uncertainties of studies using small samples and agents (especially viruses) that may be technically more difficult to demonstrate.

7. *Venereal and hyperparasitic transmission of infectious agents*

Venereal transmission, from the infected male to the female tick via the spermatophore during mating, has been demonstrated for African swine fever virus and *Borrelia* spp. in *Ornithodoros* spp. (Section IV,F and I) and for *Rickettsia rickettsi* in *Dermacentor* (Ixodidae) (Philip and Parker, 1933). Questions such as the means of penetrating the spermatophore or adherence to the spermatophore surface by different agents should be investigated in more detail.

Hyperparasitic transmission of *Borrelia crocidurae* occurs when smaller, infected *O.* (*P.*) *erraticus* feed on engorged females or nymphs

and may be a more common phenomenon among burrow-dwelling argasids than is generally recognized (Helmy *et al.*, 1983).

8. *Agent–tick specificity*

Specificity of the relationship between an agent and the tick species or species group with which it has coexisted harmoniously for eons is easily understood. This specificity may be subject to change or stress under the impact of recent or contemporary environmental changes and gradual movements or rapid transportation of susceptible domestic animals, exotic tick species, and man himself over vast distances intracontinentally and intercontinentally, far beyond original geographic boundaries. We now face a number and variety of man-made problems relating to specificity between agents, ticks and vertebrates which did not exist in the Recent epoch before the dawn of civilization.

We do not understand precisely why certain tick species, closely or distantly related to efficient reservoir–vector species, are either equally efficient or less efficient (secondary) reservoir–vectors of an agent, or are incapable of maintaining and transmitting the agent. Genetic, biochemical, physiological, and histological properties of individual tick species in relation to individual agents remain to be investigated.

African swine fever (ASF) virus and Crimean-Congo hemorrhagic fever (CCHF) virus are examples of two differing contemporary tick–agent relationships. One (ASF virus) involves only a single *Ornithodoros* species in nature but several subgenera of *Ornithodoros* which, experimentally, prove to be efficient reservoir–vectors (Section IV,F). The second (CCHF virus) involves 10 species and subspecies of *Hyalomma* (Ixodidae) and also about 20 species of six different ixodid genera in nature (Hoogstraal, 1979a). Man has extended the geographic range of both ASF and CCHF viruses and therefore made each available to "new" susceptible tick species. ASF virus has been spread chiefly by introduction and movements of domestic swine and airplane transport of infected pork in the residue of passengers' meals, which were fed to swine at the planes' destinations. CCHF virus has been spread with *Hyalomma* and other ticks whose distribution range has been greatly extended by domestic animal movements. However, the extensive distribution and numerous tick reservoir–vectors of CCHF virus result also in part from a variety of natural phenomena (climate, vertebrate population densities, bird migration, etc.) unrelated to human activity.

C. TICKS AS VECTORS

The chief physiological and biological properties that determine the vector capacity of ticks have been mentioned, at least in passing, in pre-

ceding sections (especially Sections III,A,1 and IV,A and B). Here, I succinctly point to other factors, mostly related to the environment and the host, which also determine this capacity.

Argasid shelter-seeking habits and their specialized environments (often devoid of or with little vegetation), coupled with their usual high degree of host specificity, restrict per se the variety of vertebrate hosts they encounter and the infectious agents they transmit. However, Hughes group arboviruses have proliferated and prospered in members of the *Ornithodoros* (*A.*) *capensis* group (Table 1), as have *Borrelia* spp. in a number of *Ornithodoros* species and in several *Argas* species.

It is epidemiologically important that most argasid species feed on man when the hungry tick and man meet. (For details of tick "hunger," see Chapter 3, by Waladde and Rice, in Obenchain and Galun, 1983.) Biologically, however, it is even more important that few vertebrates, other than those specifically associated with most argasids, are usually available to argasids in or near their shelters. When man or other vertebrates foreign to the close tick–specific host community invade the argasid habitat, or when hungry argasids wander into a bedroom after pigeons abandon a household cote, the "foreign" vertebrate may serve as an opportunistic host. However, the atypical bloodmeal is often qualitatively unsuitable for supporting the life cycle, or it may be toxic or lethal to the argasid.

A few *Ornithodoros* species have adapted to domestic mammals and subsist on a wider range of hosts than most of the species. The most successful of the *Ornithodoros* species parasitizing domestic animals also have specialized life cycles.

Feeding ticks may be dislodged from the host for a variety of reasons. Once a certain threshold phase has been reached in the feeding process and the tick is dislodged, even a highly host-specific species indiscriminately seeks to feed on any animal it can reach—insects, man, and reptile eggs included. This phenomenon is epidemiologically important when hunters skin deer and are bitten by dislodged ticks infected by the agents of tularemia or Colorado tick fever, or when milkmaids or herdsmen pull off ticks infected by Crimean-Congo hemorrhagic fever virus. These examples involve ixodids; similar episodes have been observed with feeding argasids.

Other factors that limit vectors mentioned in the preceding text [and reviewed by Balashov (1972) and Hoogstraal (1978) and in Obenchain and Galun (1983)] are the ticks' long life cycle in relation to that of many hosts (especially rodents), the several hosts of most tick species, the ability of species with specialized life cycles to adapt to and prosper in association with domestic animals, the extraordinary capacity for diapause (which carries the tick and agent through seasons of cold, drought, or rain), the multiplicity of tick species with differing biological properties often infest-

ing a single host species, transport on migrating hosts into regions with new susceptible hosts, and many others.

D. HOST IMMUNITY TO TICKS

Host immunity (resistance) to tick feeding can be a determining factor in reducing or preventing agent transmission to vertebrate species, breeds, or age groups. The complex subject of acquired resistance to ticks has been studied most intensively in ixodids (see Wikel and Allen in Obenchain and Galun, 1983; Brown and Askenase, 1983; Wikel, 1983) and other hematophagous arthropods (Allen and Nelson, 1982; Wikel, 1982). Argasids have been studied only slightly. Literature on salivary antigens is reviewed in this section and is also mentioned in Section IV,E.

The pioneer studies of Trager (1940) in Panama showed that after chickens were repeatedly infested by rapidly feeding nymphal and adult *Argas* (*P.*) *persicus* [actually *A.* (*P.*) *miniatus*?] the birds showed no immunity to challenge infestation by these stages. After infestation by larvae, which feed slowly (for at least 4 days), birds exhibited a partial immunity. Guinea pigs exposed to repeated infestations by nymphal and adult *Ornithodoros rudis* (= *O. venezuelensis*), which engorge rapidly, showed no resistance, but exposure to larvae, which feed for 3–5 days, resulted in acquired resistance similar to that induced by larval ixodids.

Experiments on cutaneous basophil-associated resistance in guinea pigs sensitized by infestations of nymphal and adult *Ornithodoros* (*P.*) *tartakovskyi* demonstrated that basophil responses to primary and secondary nymphal and adult *O.* (*P.*) *tartakovskyi* infestations were more intense and occurred earlier than in guinea pigs parasitized by *Rhipicephalus appendiculatus* (Ixodidae) (Brown *et al.*, 1983). These results indicate that the host is more sensitive to the salivary secretions of the argasid than of the ixodid. Basophil levels rose on day 2 or 3 in both primary and secondary hosts of nymphal and adult argasids. Thereafter, basophil levels in primary hosts increased gradually during nymphal feeding, but decreased gradually during adult feeding. Basophil levels in secondary hosts, however, dropped dramatically after peaking at day 2 or 3 in response to both nymphs and adults. Adult challenge feedings resulted in anamnestic-type blood basophil responses, which were evident by 6 hours; maximum elevations were nine times as high as the normal level. Nymphal challenge responses were also anamnestic and were five times as high as the normal level. Sensitized animals did not express acquired resistance when challenged with *O.* (*P.*) *tartakovskyi* or *R. appendiculatus* or exposed to a tertiary feeding by *Ornithodoros*, even when the challenge was at the height of blood basophilia from the previous feeding. Although the ticks probably digested immune, basophil-containing blood, these bloodmeals produced no apparent deleterious ef-

fect, unlike that described in ixodid ticks (Brown *et al.*, 1982a,b). Interestingly, long-feeding argasid larvae are susceptible to host immunity, whereas fast-feeding argasid nymphs and adults are not, even though all stages imbibe basophilemic blood. Therefore, it appears that the primary site of basophil degranulation (in the tissue for long feeders or in the tick gut for fast feeders) may determine the potency of basophil-derived products to act as anti-tick substances.

During studies at NAMRU-3 of *A.* (*P.*) *arboreus* in heronries of the cattle egret, *Bubulcus ibis ibis,* we observed that immature and adult ticks feed readily on nestlings. However, they are rarely found feeding on adult egrets in the laboratory or in the field, presumably owing to an immune response which had developed in younger egrets in the heavily tick-infested breeding colonies. Five-week old chickens and adults of the cattle egret and the American snowy egret, *Leucophoyx t. thula,* developed only low-grade viremia, if any, following inoculation of Quaranfil virus in quantities sufficient to produce death in chicks (Kaiser, 1966b). Thus, it appears that age-dependent immunity of the host is important in the transmission of Quaranfil virus by affecting the ability of the previously tick-infested bird to prevent or minimize establishment of the agent.

Casual observations also suggest that nestling marine birds are more commonly and heavily infested by *O.* (*A.*) *capensis* and related species than are adult birds in the nesting colonies. Nevertheless, when *O.* (*A.*) *capensis* population densities explode, adult birds may be severely irritated by the innumerable biting ticks and abandon large areas of nesting grounds, leaving unhatched eggs and fledglings unattended (Hoogstraal and Feare, 1984). Whether the adult birds had earlier developed any degree of immunity to tick bite is unknown.

E. SALIVARY TOXINS AND SECRETIONS CAUSING PARALYSES AND OTHER ILLNESSES

1. *Introduction*

The volume of host blood lost to numerous feeding ticks, or exsanguination, has generally been considered to be a chief cause of thrift loss or fatality among heavily infested animals. However, contemporary specialists, such as Stone and Wright (1981), believe that toxins in the salivary glands of feeding ticks have a considerable role in causing the variety of systemic disturbances exhibited by hosts of ticks which are not infected by recognized disease-causing agents. The suggestion by Nuttall *et al.* (1908) that argasid salivary toxins may be more important than "exsanguination" to the health of the host has been long overlooked. The processes of production and the nature of tick toxins are poorly understood. This

subject is being most actively investigated in the Australian paralysis tick, *Ixodes* (*Sternalixodes*) *holocyclus* Neumann, with the aim of developing an antitoxin (Stone *et al.*, 1982). Tick paralysis is one of the seven more or less distinct forms of tick toxicosis (Stone and Wright, 1981). Among the paralyses caused by argasids and ixodids, that associated with *I.* (*S.*) *holocyclus* is unique in several respects (Gothe *et al.*, 1979), but, notwithstanding, is useful to study for comparative research on argasid toxins.

Binnington and Kemp (1980) and Kemp *et al.* (Chapter 4 in Obenchain and Galun, 1983) stress the need for caution in interpreting all reactions to tick bites as resulting from salivary toxins. Most of their evidence derives from study of ixodids and is difficult to condense owing to many unanswered questions. Nevertheless, these reports are essential reading for the serious student of host reactions to argasid bites. In a nutshell, as shown by Tatchell (1969), salivary antigens introduced into the host are likely to be potent mediators of host reactions. The immune response may lead to edema, hemorrhage, leukocyte degranulation, tissue damage, and clotting prevention. Argasid salivary secretions are especially important to these rapidly feeding parasites, and their actions are more vigorous and destructive than those of ixodids, which feed slowly. An earlier report of the effects on laboratory animals of bites by a number of argasid species (Lavoipierre and Riek, 1955) is also useful for study.

The oral (salivary) secretion of *Ornithodoros* (*O.*) *savignyi*, which is famous for its irritating bite (Hoogstraal, 1956), has a high nitrogen content, mostly protein nitrogen, and 10 or more protein fractions, only one of which is toxic (Howell *et al.*, 1975). The proteinaceous toxin has an isoelectric point of about pH 5 and a molecular weight of about 15,400, and is heat stable to about 80°C. The nontoxic fractions may have a critical role in the syndrome produced by the secretion. The toxic fraction and some of the nontoxic fractions possibly have enzymatic activities, as in snake venoms. Preliminary investigations showed the presence of proteolytic and cholinesterase activities in the oral secretion.

Virologists are aware that inoculating suckling mice with triturated tick bodies for virus isolation attempts is generally harmless to the mice (except, of course, if an infectious agent is present in the bodies), but that inoculating a minute amount of triturated tick eggs may be lethal to the mice. As with toxic salivary fluids, little attempt has been made to determine the processes of production and the nature of tick egg toxins. In the experience of P. A. Nuttall (personal communication), inoculating *O.* (*O.*) *maritimus* eggs into 2-day-old mice produced no ill effect.

For many years, M. N. Kaiser and I have hypothesized from casual observations in the laboratory that *Argas* (*P.*) *arboreus* infected by the "rickettsia-like" *Wolbachia persica* may produce a salivary toxin causing irritation, paralysis, or death of avian hosts. We have been unable to test

this hypothesis but recommend it to readers of this review. Recently, Bezuidenhout and Malherbe (1981) reported that only rickettsia-infected strains of *Hyalomma truncatum* Koch produce sweating sickness, a toxicosis of cattle. The rickettsia in *H. truncatum* was not identified but the sheep and guinea pig hosts of the ticks had no serologically demonstrable antibodies against *Rickettsia conori, R. prowazeki, R. mooseri,* or *Coxiella burneti.* The implications of this finding in relation to our *Wolbachia* hypothesis are self-evident. The *Wolbachia* of argasids are discussed below (Section IV,G,2).

2. *Wildlife and livestock hosts*

(*a*) *Paralyses.* Fowl paralysis produced by each parasitic stage of *Argas* (*P.*) *arboreus*, *A.* (*P*). *radiatus*, and *A.* (*P.*) *walkerae* has been intensively investigated by Gothe and colleagues and is reviewed by Gothe *et al.* (1979). The *Argas* toxin affects afferent and efferent nerve fibers and influences neuromuscular transmission. Toxic action on motor nerves reduces acetylcholine liberation and receptor sensitivity is altered in the myoneural synapse. The intensity and extent of the flaccid tetraplegia characterizing tick paralysis in birds increase in approximately direct proportion to the tick infestation load. Little if any immunity is produced. There are definite host age-related differences in the degree of infestation necessary to produce various degrees of paresis. Dozens or hundreds of moribund immature birds litter the ground under heronries infested with *A.* (*P.*) *arboreus* during the breeding season in Egypt and elsewhere. We have not had the facilities or personnel to determine the proportions of these bird populations that are lost owing to tick paralysis, virus infections, or various mishaps. Field and laboratory investigation of such losses should be of much biomedical and biological interest.

In addition to the three *Argas* species listed in the preceding paragraph, tick paralysis in birds has been ascribed to *A.* (*P.*) *persicus* (Sharma and Sharma, 1975; Rosenstein, 1976; Gothe *et al.*, 1981a), *A.* (*P*). *sanchezi* (Gothe and Englert, 1978), *A.* (*P.*) *miniatus* (de Magalhaes, 1979; de Serra Freire, 1983), and *A.* (*A.*) *africolumbae* (Gothe *et al.*, 1981a; Kraiss and Gothe, 1982). *Argas* (*A.*) *reflexus* should probably be included in this list but I am uncertain of the correct tick species of paralysis episodes attributed to *A. reflexus* in literature.

Tick paralysis of domestic mammals induced by feeding *Ornithodoros* has been reported for *O.* (*O.*) *savignyi* by Howell (1966) and Howell *et al.* (1975), and for *O.* (*A.*) *lahorensis* by Pavlov (1947), Gavrichenkov (1957), Kusov and Peteshev (1961), Kusov (1962), and numerous others.

Ornithodoros (*A.*) *capensis* may cause paralysis in marine birds, as described by Coles (1941, as "*Argas talaje*") in the South African jackass penguin, *Spheniscus demersus* (L.), and observed by D. C. Duffy (per-

sonal communication) in South African gulls (*Larus*), but the possible role of various agents infecting ticks of this group, rather than toxins, in causing paralysis in these birds must be considered.

(*b*) *Irritation.* Irritation (or "worry") of tethered and stabled domestic mammals and birds and of wildlife, especially birds nesting in large colonies, caused by *Argas* and *Ornithodoros* species, especially those which develop heavy population densities under natural or man-made conditions, has been mentioned in the cited literature on these species and in many other reports. Most information is based on casual observations. I am unaware of controlled qualitative or quantitative investigations of irritation produced by individual argasid species in hosts of different species, age groups, or tick exposure histories.

3. *Human hosts*

Numerous if not all argasid species produce more or less severe irritation when biting man. However, the only instance known to me of an argasid producing human paralysis relates to a nymphal *Otobius megnini* feeding in the ear of a South African child and causing generalized paralysis (Peacock, 1958). Eads and Campos (1984) reviewed the numerous American reports of *O. megnini* infestation of human ears; these caused irritation but no demonstrable serious sequelae. Painful infestations of the ears of boys and men herding sheep in India were reported by Chellappa (1973). In Madagascar, an engorged nymph of *O. megnini* removed from the ear of a girl had caused irritation but no ill effects (Uilenberg *et al.*, 1980).

The accounts by Nuttall *et al.* (1908) of severe irritation to people bitten by the "Miana Tick" [said to be *A.* (*P.*) *persicus*] in Persian villages have been frequently repeated in reviews and textbooks. The culprit in this area is likely to have been *O.* (*A.*) *lahorensis* or possibly *O.* (*P.*) *tholozani* rather than *A.* (*P.*) *persicus* (Hoogstraal, 1956). *Argas* (*P.*) *persicus* may occasionally bite man, and in the laboratory can transmit *Bacillus anthracis* (anthrax) to man (Delpy and Kaweh, 1937). However, authentic records of *A.* (*P.*) *persicus* parasitizing man are rare, especially in view of the wide distribution of this tick and its close association with human activities. Among almost 300 records of ticks biting man in western Siberia, only two (in Omsk) were attributed to *A.* (*P.*) *persicus* (Fedorov, 1968) and the exhaustive review of argasids in the USSR by Filippova (1966) contains no mention of *A.* (*P.*) *persicus* feeding on man.

Near Vichy, France, a teacher who had killed and eaten pigeons living under the roof of a building serving as his family residence and the village school was so badly tormented by *A.* (*A.*) *reflexus* bites over a 5-year period that the family and students had to abandon the building (Bénoit-Bazille, 1910). The students and teacher were bitten; the wife either was

not bitten or did not notice bites. Nowadays, with more effective tick control methods than were available at the turn of the century, argasids are seldom reported to bite people in a residence for more than a few weeks or months. Nevertheless, the probability that the *A.* (*A.*) *reflexus* population in the Vichy teacher's residence successfully adapted to and thrived, probably for several generations, on human hosts is of much biomedical interest.

Anaphylactic shock resulting from allergy to the toxin of *A.* (*A.*) *reflexus* bites in a 59-year-old Italian living in a house where pigeons "crowded the roof" was recently described (Miadonna *et al.*, 1982). In Lodz, Poland, a woman bitten by *A.* (*A.*) *reflexus* suffered from vertigo, headache, palpitations, chills, and perspiration beginning a few minutes after the third attack of the year, and became unconscious for a few hours (Grzywacz and Kuzmicki, 1975). The symptoms had increased in severity after each attack. Pigeons had been removed from the attic of an old house next door and numerous "bugs" appeared on the curtains and windows of the patient's house afterward. There are numerous, less spectacular accounts of human irritation owing to *A.* (*A.*) *reflexus* bites following pigeon eradication from European buildings (Roman *et al.*, 1960).

Bites by *A.* (*A.*) *vulgaris*, the eastern counterpart of *A.* (*A.*) *reflexus* in warmer areas of temperate Eurasia, cause severe pruritus in man (Filippova, 1966).

In 1979, when pigeons were driven from resting places infested by *A.* (*A.*) *polonicus* during repairs to the tower of St. Mary's Cathedral in Krakow, Poland, frequent tick attacks on trumpeters stationed to make the hourly bugle call received wide publicity in the European press. One trumpeter, who was bitten on the eye, developed inflammation with erythema, fever, weakness, and diarrhea (Siuda *et al.*, 1982). [St. Mary's Cathedral is the type locality of *A.* (*A.*) *polonicus* and the "home church" of the present Pope.]

Another Eurasian parasite of pigeons, *Ornithodoros* (*A.*) *coniceps*, also bites people in their houses or when sleeping in caves in which rock pigeons nest. The human hosts experience edema, pain, and chills lasting for a few hours or up to 3 days, and fever to 39°C. Six references describing these episodes were listed by Hoogstraal *et al.* (1979a).

In Peru, people bitten by *A.* (*A.*) *moreli* in houses with chickens may suffer from severe pruritus (Keirans *et al.*, 1979; W. E. Dale, personal communication). Discoloration and pruritus lasting for "a couple of weeks" followed bites on the hand by *A.* (*A.*) *cucumerinus* (Clifford *et al.*, 1978). In northern Chile, *A.* (*A.*) *neghmei* is a severe pest of people residing in houses harboring chickens (Porter, 1929; Kohls and Hoogstraal, 1961).

Houses and caves in which bats roost may be the locale of irritating

bites by *Argas* (*C.*) *vespertilionis* in USSR (Galuzo, 1957) and Africa (Bedford, 1934; Brumpt, 1949; Hoogstraal, 1956).

Soldiers bitten by *Argas* (*O.*) *brumpti* while sleeping in granite caves in Zimbabwe experienced extensive bruiselike lesions afterward (Condy *et al.*, 1980). The Tharaka tribesmen of Kenya fear to shelter under rock ledges during storms or when hunting because of the "ulcerations and sickness" caused by *A.* (*O.*) *brumpti* bites in these situations (Walton, 1950, 1958). In dusty "rolling places" of elephant (*Loxodonta africana*), buffalo (*Syncerus caffer*), eland (*Taurotragus oryx*), and giraffe (*Giraffa* spp.) on the Yatta Plains of Kenya, where *A.* (*O.*) *brumpti* "is always easily obtainable," bites by this *kituñu* are said to cause great pain and sickness (Cunliffe, 1914).

The South American *O.* (*P.*) *rostratus* is notorious for fiercely biting man and livestock in houses, corrals, and stables. In man, pruritus and large inflamed areas, which are often secondarily infected, follow these bites.

It appears to be safe to generalize that most *Ornithodoros* species which have adapted to coexistence with domestic animals or inhabit caves or burrows of large mammals bite man with more or less troublesome sequelae. Individual reactions to these bites are, in my experience, quite variable in degree and duration. Special mention should be made of the pajaroello, *O.* (*O.*) *coriaceus*, which has a reputation for extremely irritating bites on hunters, hikers, and woodsmen who rest on "deer beds" in the mountains of western North America. Some persons bitten, who have suffered little or not at all afterward, claim that earlier accounts were exaggerated. Restrictions on the use of human volunteers make it unlikely that this question will be explored experimentally! The literature on this subject was reviewed by Furman and Loomis (1984).

Both species of *Ornithodoros* that shelter in tree-shaded soil in arid and semiarid environments may cause severe local irritation and systemic disturbances when biting man. These species are the Afro-Asian *O.* (*O.*) *savignyi* (Hoogstraal, 1956) and the Australian *O.* (*P.*) *gurneyi* (Henry, 1938; Roberts, 1970).

Among members of the *O.* (*A.*) *capensis* group, which parasitize colonies of nesting marine birds, the Arabian *O.* (*A.*) *muesebecki* causes blisters, pruritus, and fever in man (Hoogstraal *et al.*, 1970; Hoogstraal and Gallagher, 1982), bites by the Peruvian *O.* (*A.*) *amblus* are claimed to produce symptoms ranging from pain to death (Clifford *et al.*, 1980), and pruritus commonly follows bites by the widely distributed *O.* (*A.*) *capensis* (Hoogstraal and Feare, 1984). It has not been determined whether argasid salivary toxins, other salivary components, or arboviruses are responsible for these episodes.

F. TICK-BORNE VIRUSES

1. *Introduction*

Knowledge of families, genera, and serogroups of viruses in general, and of arboviruses in particular, provides a clearer understanding of arbovirus coexistence with hematophagous arthropods and vertebrates; their evolution and biomedical, geomedical, and epidemiological patterns; and the roles of argasids (and ixodids) as vectors. Contemporary arbovirus systematics are based on virion structure and physicochemical properties. Systematic criteria corroborate the results of the classic work of Casals using serological techniques for arbovirus differentiation at the species and supraspecies (serogroup) levels. These techniques remain essential for arbovirus identification and classification. The broader base of arbovirus systematics has increased immeasurably during the past decade or two. However, a number of argasid- and ixodid-related viruses are still unclassified "orphans" or inadequately investigated biologically.

About 126 arboviruses have been reported from 126 tick species (these equal numbers are purely a coincidence). Several of the 126 arboviruses are still under study and have not yet been formally characterized and named. The 49 arboviruses reported from 34 argasid species are listed in Table 1; about 40 of the 49 definitely or possibly represent unequivocal argasid reservoir or amplifier relationships (see Section IV,B and the following sections). Agents that are less distinctly or less consistently associated with argasids are Royal Farm, West Nile, Kyasanur Forest disease, Crimean-Congo hemorrhagic fever, Colorado tick fever, Manawa, and Quaranfil viruses. Certain other listed arboviruses are inadequately investigated and probably not restricted to argasids. The importance of ticks in the natural history of arboviruses characteristic of mosquitoes and sandflies (*Phlebotomus*) is moot. Some Diptera-related agents, such as yellow fever virus, have been demonstrated to be transovarially transmitted by ixodids, thus greatly enhancing their biological and biomedical interest.

2. *Wildlife and livestock hosts*

Arboviruses associated only with ticks have circulated for eons in a tick—wildlife chain in which the ticks serve as reservoirs and/or amplifiers; for some of these viruses, both ticks and vertebrates may be critical for replication and survival (Section IV,B). With the advent of human civilization, domestic animals, together with wildlife or in place of reduced populations of wildlife, assumed material roles in supporting the survival of certain tick-borne viruses. In the biological sense, man is merely a tangential host of these viruses (although this provides scant comfort for a human victim of these viruses).

(*a*) *Togaviridae* (*genus* Flavivirus). The family Togaviridae comprises four genera (Matthews, 1979). Two genera (*Rubivirus* and *Pestivirus*) are not classified as arboviruses. All species of *Alphavirus* and most species of *Flavivirus* multiply in arthropods as well as in vertebrates. The alphaviruses are associated chiefly with mosquitoes, the flaviviruses with either mosquitoes or ticks. Some flaviviruses for which no vector has been recorded may be disseminated directly by contact with infected saliva, aerosols, milk, or urine, or transplacentally (Varelas-Wesley and Calisher, 1982). Six flaviviruses have been recorded from six argasid species but the role of argasids in the natural history of these agents is uncertain.

Royal Farm (RF) virus commonly infects *A.* (*A.*) *hermanni* which parasitizes pigeons in the Kabul bazaar and nearby farms in Afghanistan (Williams *et al.*, 1972). Technical problems have prevented biological and virological studies of RF virus and no seroepidemiological investigation could be undertaken in Afghanistan. In Pakistan, however, sera of five mammals (two rodents of different genera, two cows, and one domestic buffalo, *Bubalus bubalis*) contained antibodies against RF virus, suggesting that mammals and ixodids or possibly other hematophagous arthropods as well as birds and argasids were participating in the natural history of this virus (Darwish *et al.*, 1983a). Antibodies against RF virus were not detected in 43 human sera tested in Pakistan.

West Nile (WN) virus, distributed in much of Africa and southern Eurasia and generally circulating between culicine mosquitoes and birds, with tangential infections in man (Berge, 1975), is frequently isolated from ixodid ticks in the USSR (reviewed by Darwish and Hoogstraal, 1981). Numerous brief reports deal with WN virus isolations in southern USSR from *O.* (*A.*) *maritimus* (as "*capensis*") (summarized by Mirzoeva *et al.*, 1974), *O.* (*A.*) *coniceps* (Sidorova *et al.*, 1975), and *O.* (*P.*) *tholozani* (L'vov *et al.*, 1975a), all of which parasitize birds. In France, Hannoun and Rau (1970) reported experimental transmission of WN virus by *A.* (*A.*) *reflexus*, but natural infections were not found in this parasite in the Camargue (Rageau and Mouchet, 1970). In Egypt, isolation of WN virus from *A.* (*A.*) *hermanni* from pigeon houses during the winter suggests that this tick may serve as an overwintering virus host (Schmidt and Said, 1964). Experimentally, *O.* (*O.*) *moubata*, *O.* (*A.*) *coniceps*, and *O.* (*P.*) *erraticus* can maintain and transmit WN virus for months after feeding on infected hosts (Vermeil *et al.*, 1958, 1960; Whitman and Aitken, 1960); however, in nature *O.* (*O.*) *moubata* and *O.* (*P.*) *erraticus* do not normally parasitize vertebrates infected by WN virus. Research has been too limited to answer many questions on the role of ticks in WN virus epidemiology.

Kyasanur Forest disease (KFD) has caused much human illness and mortality since it first appeared in 1957 in Karnataka, India. This is an outstanding example of a wildlife infection, widely distributed in India, erupting as an epidemic zoonotic disease owing to contemporary environmental modifications in a certain area (Boshell-M., 1969; Bhat, 1983). KFD virus reproduces in mammals and a number of ixodid genera and species, and has been reported to be transovarially transmitted in one or possibly two ixodid species. (Questions relating to the significance of these transovarial transmission studies in ixodids are outside the scope of this review.) The virus appears to be maintained chiefly by a delicate interplay between different ixodid species and stages feeding on one or several species of viraemic mammals during different seasons.

The argasid *O.* (*R.*) *chiropterphila* and its fruit bat host, *Rousettus rouxi*, are both naturally infected by KFD virus in Karnataka (Dhanda and Bhat, 1971). The significance of this phenomenon in KFD epidemiology is unstudied. Experimentally, transstadial passage and transovarial transmission of KFD virus, including F_1 generation virus transmission when feeding on susceptible hosts, have been demonstrated in *A.* (*P.*) *persicus* (Singh *et al.*, 1971) and *O.* (*P.*) *tholozani* (= *O. crossi*) (Bhat and Goverdhan, 1973). These results are of considerable academic interest; argasids may maintain KFD virus in various Indian environments but are apparently uncommon in Karnataka foci of KFD. The bite of a single nymphal *O.* (*P.*) *tholozani* on a laboratory worker (U. K. M. Bhat) produced typical clinical symptoms of the disease; the identity of the agent was confirmed by virus isolation from an acute phase blood sample of the worker.

Saumarez Reef (SR) virus was isolated in Australia from two pools of *O.* (*P.*) *capensis* from nests of the sooty tern, *Sterna fuscata*, on the Great Barrier Reef off Queensland, and from three pools of *Ixodes* (*Multidentatus*) *eudyptidis* Maskell from dead silver gulls, *Larus novaehollandiae gunni*, in northern Tasmania (St. George *et al.*, 1977). SR virus is related to Tyuleniy virus from *I.* (*Ceratixodes*) *uriae* in the USSR and the United States (Oregon) and to an unnamed virus (CSIRO-122) from this tick on Macquarie Island in the Australian sub-Antarctic, where the vertebrate host is the royal penguin, *Eudyptes schlegeli*. SR virus is even more closely related to Meaban (MEA) virus isolated from *O.* (*A.*) *maritimus* parasitizing gulls on the coast of southern Brittany, France (C. Chastel, personal communication).

Karshi (KSI) virus was isolated from *O.* (*P.*) *tholozani* (= *O. papillipes*) from burrows of the great gerbil, *Rhombomys opimus*, in Uzbeck SSR (L'vov *et al.*, 1976) and from adult *Hyalomma asiaticum* subsp. from a camel in Kazakh SSR (Karimov *et al.*, 1978). Complement fixing and

agglutinating antibodies were detected in 2.1% of 188 human blood sera from Kazakh SSR. Immature *H. asiaticum* commonly infest burrows of *R. opimus*.

Sokuluk (SOK) virus appears to be transmitted by the bat-parasitizing *A.* (*C.*) *vespertilionis* in southern USSR (L'vov *et al.*, 1973). SOK virus has been isolated from bats and birds, and antibodies have been detected in sera from bats, birds, domestic animals and man, but the natural history and pathogenesis of this agent are unstudied.

(*b*) *Bunyaviridae* (*genus* Nairovirus). The family Bunyaviridae contains more than 110 viruses transmitted by ticks, mosquitoes, sandflies, and other hematophagous insects (Bishop *et al.*, 1980). The genus *Nairovirus* (Casals and Tignor, 1980) consists of 30 or more viruses (several unnamed under study), all tick associated, in six serogroups. The Crimean-Congo hemorrhagic fever (CCHF) and Nairobi sheep disease (NSD) serogroups are treated here as separate but evidence is developing to suggest that they may better be considered as a single serogroup. At any rate, the five viruses in these two serogroups are characteristic associates of ixodids (two exceptional reports of CCHF virus from argasids are mentioned in the following paragraph). The Qalyub (QYB) and Hughes (HUG) serogroups, with two and eight viruses, respectively, are associated with argasids. Exceptionally, Soldado virus (HUG serogroup) infects the ixodid *Amblyomma loculosum* Neumann as well as *O.* (*Alectorobius*) *capensis*, in the Seychelles (Hoogstraal and Feare, 1984). The Sakhalin (SAK) serogroup, with six species, is associated only with *Ixodes* parasites of marine birds in northern and southern climes. Five of the six members of the Dera Ghazi Khan (DGK) serogroup are associated with argasids; the sixth (DGK virus) has been isolated only from *Hyalomma* (Ixodidae).

The reported isolation of CCHF virus in Uzbeck SSR from *A.* (*P.*) *persicus*, which feeds only on birds, requires confirmation since birds do not develop CCHF viremia (Hoogstraal, 1979a). A CCHF virus isolate from *O.* (*A.*) *lahorensis* larvae from a horse in Iran was reported with the proviso that it may represent an undigested bloodmeal rather than a true infection of this tick species (Sureau *et al.*, 1980).

The DGK serogroup consists of six viruses in three subgroups (Converse *et al.*, 1975). These viruses are unstudied biologically but their tick hosts have been reasonably or exceptionally well studied. The DGK subgroup contains only DGK virus from the camel-infesting *Hyalomma dromedarii* Koch in Pakistan. The Kao Shuan (KS) subgroup contains two viruses: KS virus in Taiwan, Java, and Northern Australia, and Pathum Thani (PT) virus in Thailand and Sri Lanka. These two agents (KS and PT) are recorded only from *A.* (*P.*) *robertsi*, which parasitizes chiefly wading birds and also domestic chickens (Khalil *et al.*, 1980). The wide distribution of *A.* (*P.*) *robertsi* and its viruses in the Oriental and Austra-

lian regions, like that of *A.* (*P.*) *arboreus* and its viruses in the Ethiopian region, undoubtedly results from movements of migrating bird hosts.

The Abu Hammad (AH) serogroup consists of three viruses associated with *Argas* and birds in the Ethiopian region, one also extending into the southern Palearctic (Iran). AH virus has been isolated from *A.* (*A.*) *hermanni* from pigeon houses in Abu Hammad, Sharqiya (eastern Nile Delta of Egypt) and Dormian (3120 m altitude), Isfahan, Iran (Darwish and Hoogstraal, 1981). However, positive reactions for AH virus (and Abu Mina virus, see below) in sera from Egyptian domestic buffaloes, pigs, sheep, dogs, and *Rattus rattus* suggest that the epidemiological process of these viruses, both associated with birds and bird ticks, is probably more complex and the range of virus reservoirs and vectors is probably wider than realized. Abu Mina (AM) virus was first isolated from a northward-migrating turtledove, *Streptopelia turtur* subsp., in the desert near Alexandria, and afterward from the characteristic parasite of African and Near Eastern doves, *A.* (*P.*) *streptopelia*, found on a date palm in Dakhla Oasis, Egypt (Darwish and Hoogstraal, 1981). AM virus is probably widely distributed in the Ethiopian and southern Palearctic regions. Pretoria (PRE) virus was isolated from *A.* (*A.*) *africolumbae* parasitizing rock doves in a house in Pretoria, South Africa, but has not been searched for in populations of this tick elsewhere in Africa (Hoogstraal *et al.*, 1975, 1977a,b).

The Qalyub (QYB) serogroup consists of two viruses associated with closely related *Ornithodoros* species and with rodents in Palearctic and Ethiopian areas of Africa north of the equator. QYB virus is frequently isolated in Egypt from *O.* (*P.*) *erraticus* from burrows of the Nile grass rat, *Arvicanthis niloticus niloticus*, in cultivated fields of the Nile Valley and Delta; it was originally isolated from this tick from an unused nest, probably of the spiny mouse, *Acomys cahirinus cahirinus*, in a tomb wall on a sandy mound in the Delta (Darwish and Hoogstraal, 1981). Experimentally, individual *O.* (*P.*) *erraticus* nymphs, orally infected as larvae by feeding on infected mice, failed to transmit QYB virus when feeding singly on susceptible mice but did transmit the virus when feeding in groups of 11–20 per mouse (Miller *et al.*, 1985). A number of possibilities remain to be investigated to explain these curious results. The second member of the QYB serogroup, Bandia (BDA) virus, has been isolated only from *O.* (*P.*) *sonrai* and from its burrowing rodent hosts, chiefly multimammate mice (*Praomys*), and also grass gerbils and ground squirrels, in the dry tropical Bandia Forest of Senegal (Brès, 1971; Robin and Le Gonidec, 1972).

The Hughes serogroup, comprising at least eight viruses isolated from seven species of the *O.* (*A.*) *capensis* group, which infest marine birds (Table 1: tick species 14–20), is of considerable virological and biomedical

interest. Interrelationships between Hughes serogroup viruses are being investigated in several institutions but studies have been hampered by the apparently weak antigenicity of these agents. Distribution and tick–host associations of this serogroup have been reviewed by Nuttall (1984), Chastel (1980), and Clifford (1979). Results of serological studies were reported by Gould *et al.* (1983), Chastel *et al.* (1983) and Yunker *et al.* (1979a). Most of these viruses are known from only a few isolations from ticks collected by visitors to marine bird colonies. Their pathogenicity for birds has been demonstrated experimentally and is suggested by observations in marine bird colonies, but their replication in ticks and birds and transmission dynamics have been studied only superficially. Some of the more extensive field and laboratory investigations are reviewed below. (Concepts relating to the Hughes serogroup are changing rapidly; the reader is referred to the most recent papers cited above for "state-of-the-art" information.)

Human illness often follows bites by *O.* (*P.*) *capensis* group ticks (Section IV,E,3) but it is generally unknown whether salivary toxins or viruses cause these episodes. However, in Morocco an ornithologist bitten by *O.* (*P.*) *maritimus* in a sea gull colony experienced a febrile episode and serious persistent rhinitis attributed to a strain of Soldado (SOL) virus (Chastel *et al.*, 1981). These authors consider SOL virus to be a potential public health hazard in Mediterranean and Atlantic urban areas visited by sea gulls.

SOL virus represents a complex of more or less closely related strains ("antigenic variants") (Chastel *et al.*, 1983): (1) an Old World group from *O.* (*P.*) *maritimus*, (2) a New World group from *O.* (*P.*) *capensis* and *O.* (*P.*) *denmarki*, (3) an unassigned group from *O.* (*P.*) *capensis* from southern Africa, and (4) an unstudied group from *O.* (*P.*) *capensis* from the Seychelles and Ethiopia and *Amblyomma loculosum* Neumann (Ixodidae) from the Seychelles. SOL virus strains have been reported from these three argasid species and one ixodid species from marine bird colonies in Trinidad, continental United States (Texas), France, Morocco, Senegal, Seychelles, Ethiopia, Hawaii, and southern Africa; the chief vertebrate hosts of the incriminated ticks were boobies, terns, gulls, and cormorants.

In the Seychelles, SOL virus was isolated from 13 of 23 pools of *O.* (*A.*) *capensis* from nests and chicks of the sooty tern (*Sterna fuscata*), roseate tern (*S. dougallii*), black-naped tern (*S. sumatrana*), masked booby (*Sula dactylatra*), and white-tailed tropic bird (*Phaethon l. lepturus*) on five islands (Hoogstraal and Feare, 1984). Another SOL strain was isolated from a pool of six female *Amblyomma loculosum* taken from dead sooty tern chicks, or found crawling on the collectors, on Farquhar Atoll. A population explosion of virus-infected *O.* (*P.*) *capensis* on Bird Island in

1973 appears to have been directly associated with sooty tern abandonment of a large breeding area, mass mortality of eggs and young birds, and failure to reoccupy the area in 1974. In 1976, the tern population was only one-third of that in 1972; ticks remaining alive in the deserted area were mostly adults, indicating that they had survived but not reproduced between 1973 and 1976. Notably, SOL virus was isolated from a pool of 27 adult and 10 nymphal *O.* (*A.*) *capensis* taken in the deserted area in 1976. The record of a banded immature sooty tern that left Bird Island in October 1973 and was recovered in northern Australia in January 1974 shows the extensive dispersal of these birds, and possibly also of SOL virus and *O.* (*P.*) *capensis*. In the laboratory, naturally infected adult and nymphal *O.* (*P.*) *capensis* from sick sooty tern chicks transmitted the virus when biting domestic chicks, which died 3 and 5 days after the ticks fed; SOL virus was isolated from the dead chicks.

Data on other SOL strains from *O.* (*A.*) *capensis*, *O.* (*A.*) *denmarki*, and *O.* (*A.*) *maritimus* are reviewed in literature cited above. Studies on SOL virus in *O.* (*A.*) *maritimus* in France and Morocco by Chastel and colleagues contributed notably to knowledge of SOL and related viruses, especially their visualization of SOL virus in *O.* (*A.*) *maritimus* tissues by electron microscopy (Chastel *et al.*, 1984).

Puffin Island (PI) virus, previously considered to be SOL virus, was isolated from *O.* (*P.*) *maritimus* parasitizing a variety of marine birds on Puffin Island, northern Wales, and probably also occurs elsewhere in the British Isles, including Ireland (Gould *et al.*, 1983).

Hughes (HUG) virus has been reported from *O.* (*A.*) *capensis* in Trinidad and from *O.* (*A.*) *denmarki* in Trinidad, Cuba, and Florida. Raza and Farallon (FAR) viruses infect *O.* (*A.*) *denmarki* and *O.* (*A.*) sp. near *denmarki*, respectively, on Pacific islands off California and Mexico. Reviews by Clifford (1979) and Yunker *et al.* (1979a) provide more information on these three Hughes serogroup viruses. Punta Salinas (PA) virus infects the *O.* (*A.*) *amblus* parasites of guano-producing marine birds on Pacific islands off Peru and might be a cause of the human illness associated with bites of this tick (Clifford *et al.*, 1980). Zirqa virus infecting *O.* (*A.*) *muesebecki*, a parasite of boobies, cormorants, ospreys, and other marine birds in the Arabian Gulf, is a possible cause of blisters, pruritus, and fevers in people bitten by this tick (Hoogstraal and Gallagher, 1982).

(*c*) *Bunyaviridae* (*genus* Uukuvirus). The genus *Uukuvirus*, with seven virus species, is best known for biological and molecular studies on the prototype Uukuniemi (UUK) virus. UUK virus infects *Ixodes* (*I.*) *ricinus*, rodents, and other small mammals, in Central Europe (Finnoscandia to Austria) and European USSR (as far south as Azerbaijan SSR). Three *Uukuvirus* agents are associated with *I.* (*Ceratixodes*) *uriae* White of marine birds: Zaliv Terpeniya (northeastern USSR), Oceanside (United

States: Oregon, California), and an unnamed strain (RML105,355; United States: Alaska).

Three other *Uukuvirus* agents are associated with three Eurasian *Argas* species. Grand Arbaud (GA) virus, originally isolated from *A.* (*A.*) *reflexus* from a pigeon house in the Camargue, France, can be transmitted when infected nymphs and adults bite laboratory chickens about 14 months after the initial infective feeding (Hannoun and Rau, 1970). GA virus (strain Art 363) also infects *A.* (*A.*) *hermanni* in the Kabul bazaar, Afghanistan (Williams *et al.*, 1972). Ponteves (PTV) virus was isolated from *A.* (*A.*) *reflexus* from a pigeon house on another Camargue farm but has not subsequently been reported from nature and the original strain has been lost. Manawa (MWA) virus was originally isolated from a pool of adult *A.* (*P.*) *abdussalami* from trees supporting nests of the white-backed vulture, *Gyps bengalensis*, in the hot, dry alluvial Indus River plain near Lahore, Pakistan, and later from *Rhipicephalus* (*R.*) *ramachandrai* Dhanda from the burrow of a grass gerbil, *Tatera indica*, in Changa Manga forest near Lahore, and from *R.* (*R.*) *turanicus* Pomerantsev from goats in Hunza District (Begum *et al.*, 1970). These reports of MWA virus-infected argasid and ixodid parasites of birds, rodents, and goats indicate the need to investigate the natural history of this agent. In complement-fixation (CF) tests of 43 human sera from Pakistan, one displayed antibodies to MWA virus (Darwish *et al.*, 1983b).

(*d*) *Bunyaviridae* (*serologically ungrouped*). Little information is available regarding the following two viruses, which were classified in the Bunyaviridae by Poleshchuk *et al.* (1981). Artashat (ART) virus was isolated from *Ornithodoros* (*P.*) *erraticus* (reported as "*O. alactagalis*") in Armenian SSR in 1972 (L'vov *et al.*, 1975b). Caspiy (CAS) virus, isolated from *O.* (*A.*) *maritimus* (reported as "*O. capensis*") and *O.* (*A.*) *coniceps* and from *Larus argentatus* in Azerbaijan SSR and Turkmen SSR, was said to be "enzootic" among herring gulls in the Caspian Sea (L'vov, 1980) but published details are fragmentary.

(*e*) *Bunyaviridae* ("*possible members*"). Bakau (BAK) and MWA viruses were isolated from pooled *A.* (*P.*) *abdussalami* from the same source in Pakistan [see Section IV,F,B,c above]. BAK virus also infects *Culex* mosquitoes in Malaysia, where 20% of the human sera tested showed antibodies to this virus. In Pakistan, CF antibodies against BAK virus were detected in sera of four rodents (*Tatera indica* and *Meriones hurrianae*) of the 157 tested (Darwish *et al.*, 1983b). Much obviously remains to be learned about BAK virus.

Sunday Canyon (SC) virus was isolated from *A.* (*A.*) *cooleyi* infecting a colony of cliff swallows, *Petrochelidon pyrrhonota*, in Texas (Yunker *et al.*, 1977).

The Upolu (UPO) serogroup consists of UPO and Aransas Bay (AB)

viruses from *O.* (*A.*) *capensis* from Upolu Cay, Great Barrier Reef, Australia, and the Caribbean coast of Texas, respectively (Yunker *et al.*, 1979b).

UPO virus was isolated from *O.* (*A.*) *capensis* taken under succulent vegetation in a nesting area of the sooty tern, *Sterna fuscata*, and crested tern, *Thalasseus berghii* (Berge, 1975). In neutralization tests of sera from numerous wild and domestic mammals from Queensland antibodies to UPO virus were detected in samples from a kangaroo and a cow.

AB virus (as well as SOL virus) was isolated from *O.* (*A.*) *capensis* from nests of the brown pelican, *Pelecanus occidentalis*, which had abandoned heavily tick-infested nests at Aransas Bay (Yunker *et al.*, 1979b). On another coastal island of southern Texas, AB virus was isolated from *O.* (*A.*) *capensis* infesting nests of the roseate spoonbill, *Ajaia ajaja*. AB virus is lethal for newborn mice and weanling mice following inoculation intracranially or intraperitoneally.

(*f*) *Reoviridae* (*genus* Orbivirus). The family Reoviridae comprises at least six genera (Gorman, 1979; Matthews, 1979). Five genera infect nonhematophagous insects or are transmitted horizontally (not by vectors). The genus *Orbivirus* (Gorman, 1983), with 17 serogroups, is associated with ticks, mosquitoes, biting midges (*Culicoides*), and phlebotomines. Two of the 17 *Orbivirus* serogroups are tick-borne and have certain relationships with argasids.

The Colorado tick fever (CTF) serogroup consists of CTF virus and a closely related unnamed virus from California, associated chiefly with *Dermacentor andersoni* Stiles and related *Dermacentor* species and small and medium-sized mammals in the western United States, and Eyach virus, associated chiefly with *I.* (*I.*) *ricinus* and mammals in Germany and Central Europe (Hoogstraal, 1981). CTF virus isolations from argasids came from the leporid-infesting *Otobius lagophilus* in Nevada and Utah. Results of current investigations into the roles of ticks other than *D. andersoni* in CTF epidemiology will modify concepts of the natural history of this virus and others closely related to it.

The Kemerovo (KEM) serogroup consists of 21 viruses in four subgroups (subgenera): Chenuda (CNU) (5), Cape Wrath (CW) (10), KEM (4), and Wad Medani (WM) (2) (Main *et al.*, 1976). Three of these subgroups are associated with ixodids but not, as far as is known, with argasids: CW [with *Ixodes* (*C.*) *uriae* and marine birds], KEM [chiefly with *I.* (*I.*) *ricinus*, birds, and small mammals], and WM [with ixodids (especially Rhipicephalinae) parasitizing domestic mammals in Africa and southern Asia].

CNU virus, the prototype of the CNU subgroup, commonly infects *Argas* (*A.*) *hermanni* in Nile Delta pigeon houses but efforts to infect *A.* (*A.*) *hermanni* by feeding on birds and to transmit the virus by these ticks

were inconclusive (Darwish and Hoogstraal, 1981). CF antibodies against CNU virus detected in sera from mammals (camels, buffaloes, pigs, dogs, donkeys, and *Rattus*) in northern Egypt point to the need for more intensive virological and epidemiological investigation. In Omsk, Oblast, Siberia, sera of 7.2% of 304 healthy persons investigated by the indirect hemagglutination test showed antibodies against CNU virus (Lebedev *et al.*, 1975). Near Lake Mamed Kul in Turkmen SSR, Skvortsova *et al.* (1982) isolated CNU virus from *Culex molestus* mosquitoes and suggested that these insects may have been infected by feeding on the numerous migrating turtledoves in this East European waterway bird migration zone. (I understand that other CNU and "CNU-like" strains are under study in the USSR but do not have details.) A number of CNU virus strains have been isolated in South Africa from *Ornithodoros* (*P.*) *peringueyi* from nests of the cliff swallow, *Petrochelidon spilodera*, first in the 1950s (Berge, 1975) and later, during the summer of 1960, while the birds were breeding, and during the winter of 1961, when the birds had migrated to central Africa (Jupp and McIntosh, 1981; ticks incorrectly identified as *A. arboreus*). CNU virus obviously overwinters in *O.* (*P.*) *peringueyi* in South Africa as it does in *A.* (*A.*) *hermanni* in Egypt.

Sixgun City (SG) virus infects *A.* (*A.*) *cooleyi* parasites of the cliff swallow, *Petrochelidon pyrrhonota*, in western United States (Texas, New Mexico, Colorado, South Dakota) (Yunker *et al.*, 1972). Mono Lake (ML) virus was reported from ticks identified as *A.* (*A.*) *cooleyi*, but representing an undescribed species, from nesting areas of the California gull, *Larus californicus*, on an island in the saline Mono Lake, California (Berge, 1975). This habitat is not typical of *A.* (*A.*) *cooleyi*. Huacho (HUA) virus infects *Ornithodoros* (*A.*) *amblus* (*O. capensis* group) in Peru (see also Punta Salinas virus). Baku (BAKU) virus reports are from ticks identified first as *O.* (*A.*) *coniceps* (as in Table 1), but later as *O.* (*A.*) *capensis* [which, however, is replaced by *O.* (*A.*) *maritimus* in the USSR] from Glinyany Island in the Caspian Sea, where many herring gulls, *Larus argentatus*, nest. Several strains were isolated from fledgling gulls and antibodies to the virus were detected in 7 of 78 herring gull sera. One strain was isolated from *Hyalomma marginatum marginatum* (Ixodidae) from a dead saiga antelope, *Saiga t. tatrica* (L.), on the island (Sokolova *et al.*, 1973). Baku virus also infects different bird species nesting on several islands in the Caspian Sea. Isolates from *O.* (*A.*) *coniceps* from pigeon nests in the Chatkal Mountains of Tashkent Oblast, Uzbek SSR, were reported by Sidorova *et al.* (1974). CF antibodies against Baku virus were detected in domestic mammal sera from Osh Oblast, Kirgis SSR (Timofeev *et al.*, 1973). Despite the extensive literature on Baku virus isolates and antibodies, the natural history of this agent remains obscure.

(*g*) *Family Iridoviridae*. African swine fever (ASF) virus, presently classified as a member of the family Iridoviridae (?genus *Iridovirus*), which contains a number of insect and frog viruses (Matthews, 1979), is a symbiont of the African *O.* (*O.*) *porcinus porcinus* (also known as *O. moubata porcinus*). This is the only DNA virus known to be an arbovirus and to infect mammals. The tremendous international economic importance of ASF has led to intensive virological, biomedical, and epidemiological research and to hundreds of publications, which are authoritatively reviewed by Wilkinson (1981), Wilkinson and Wardley (1982), and Wardley *et al.* (1983). In brief, the African warthog, *Phacochoerus aethiopicus* (Pallas), and bush pig, *Potamochoerus porcus* (L.), suffer no ill effects when bitten by infected *O.* (*O.*) *p. porcinus* but the virus causes devastating losses among domestic swine bitten by infected ticks, consuming infected meat products, or exposed to the agent by contagion. Thus, ASF virus has spread from sub-equatorial Africa to much of southern Europe and Mediterranean islands, Brazil, Haiti, Dominican Republic, and Cuba, often as a result of infected meat left uneaten by airline passengers and fed as garbage to pigs maintained near airports. The European wild boar and American feral pigs are as susceptible to ASF as domestic swine. ASF is one of the few viruses failing to induce neutralizing antibodies in mammals; therefore, slaughter and sanitary measures are necessary to prevent its spread. During ASF outbreaks in Europe and Latin America, tens of thousands of swine were slaughtered as a preventive measure.

The literature on interrelationships between ASF virus and *Ornithodoros* has been reviewed by Wardley *et al.* (1983). All examined populations of *O.* (*O.*) *p. porcinus* have been found to be infected by this agent, with higher rates in females than in males. ASF virus survives transstadially in *Ornithodoros* and is transmitted to the next generation transovarially and sexually (venereally). Following its ingestion by ticks in host blood, the virus replicates in the tick gut and then in other tissues, including the reproductive organs. The virus is transmitted to the vertebrate host in saliva or coxal fluid of feeding ticks; tick excreta have also been reported to be infective. Immature warthogs develop a sufficiently high viremia to infect at least some of the ticks parasitizing them after primary infection. In Spain, *O.* (*P.*) *marocanus* (reported as *O. erraticus*) has become a link in ASF virus epidemiology. Experimentally, the American *O.* (*S.*) *coriaceus*, *O.* (*A.*) *puertoricensis*, and possibly other *Ornithodoros* species are efficient vectors. Ixodid ticks are apparently incapable of maintaining ASF virus for a significant period of time and do not transmit this agent. Much remains to be learned about tick and ASF virus interrelationships. Nevertheless, the available data are a significant con-

tribution to parasitological and virological knowledge; anyone concerned with ticks as parasites and vectors should carefully study the literature on ASF virus and *Ornithodoros*.

(*h*) *Unclassified viruses* (*Quaranfil serogroup*). The Quaranfil (QRF) serogroup consists of QRF and Johnston Atoll (JA) viruses. JA virus infects *O.* (*A.*) *capensis* on Johnston Atoll in the Central Pacific, the Great Barrier Reef off northeastern Australia, and South Island of New Zealand (Berge, 1975), Mana Island of Hawaii (Yunker, 1975), and in Africa on the Atlantic coast of Namibia (C. E. Yunker, personal communication). Among the reported bird hosts of infected *O.* (*A.*) *capensis* are the noddy tern (*Anous stolidus*), sooty tern (*Sterna fuscata*), crested tern (*Thalasseus berghii*), Australian-New Zealand gannet (*Sula serrator*), and great cormorant (*Phalacrocorax capensis*). In the Central Pacific, *O.* (*A.*) *denmarki* is also infected. The JA prototype strain was pathogenic for laboratory chicks; JA strains from *O.* (*A.*) *capensis* from a gannet (*S. serrator*) colony in New Zealand multiplied in laboratory chicks but were not pathogenic for them (Austin, 1978). Results of transmission experiments with *O.* (*A.*) *capensis* and the high prevalence of neutralizing antibody among the New Zealand gannets indicate that JA virus is maintained by a tick–gannet cycle. (Transovarial transmission of the virus was not investigated.) Austin (1978) considered the gannet to be a likely source of virus introduction from tropical Pacific islands to temperate New Zealand. The avian host most likely to have transported JA virus from the Pacific or the Australian–New Zealand region to Southwest Africa (Namibia) remains to be determined. *Ornithodoros* (*A.*) *capensis* is considered to be a Neotropical tick which has been widely disseminated by migrating marine birds (Section III,A,3a).

QRF virus was originally considered to circulate in an *Argas*–bird cycle (Kaiser, 1966b,c; Darwish and Hoogstraal, 1981) but "somehow" also to infect man and cause febrile illness. The evidence for this conclusion is first succinctly reviewed, and thereafter recent data suggesting ixodid and mammal involvement in QRF virus epidemiology are mentioned. Human disease aspects are reviewed in Section IV,F,3.

Originally isolated in 1953 from a febrile child in Quaranfil village near Cairo, and from *A.* (*P.*) *arboreus* infesting arboreal heronries of the cattle egret, *Bubulcus ibis ibis*, near Cairo, QRF virus was subsequently isolated from febrile farmers, cattle egrets, a pigeon squab, and the pigeon-parasitizing *A.* (*A.*) *hermanni* near Cairo; from cattle egrets in South Africa; from *A.* (*A.*) *hermanni* infesting pigeon houses in Kabul, Afghanistan, and Katmandu, Nepal; from *A.* (*A.*) *vulgaris* taken from pigeon nests in a deep well in Khorasan Province, Iran; and from *A.* (*P.*) *arboreus* from a cattle egret nesting site in northeastern Nigeria (Darwish and Hoogstraal, 1981). The QRF isolates reported from *A.* (*P.*) *walkerae* from

a Transvaal cattle egret nesting site (Jupp and McIntosh, 1981) were in fact from *A.* (*P.*) *arboreus* (B. M. McIntosh, personal communication).

In the *A.* (*P.*) *arboreus* population infesting cattle egrets in the Nile Barrage Park (the type locality of this tick species) near Cairo, the natural QRF infection index peaks in spring, drops afterward, and remains low to early fall when it rises again (Kaiser, 1966b,c). (Incidentally, this is the only study of the seasonal dynamics of a virus in an argasid population.) This virus infection index is closely correlated with the egret spring breeding and winter migration periods and with *A.* (*P.*) *arboreus* population dynamics and wintertime diapause.

QRF virus becomes widely distributed in the body of *A.* (*P.*) *arboreus* during and after the 44-day extrinsic incubation period, survives transstadially, is transmitted to bird hosts by feeding ticks, and remains viable in overwintering ticks. However, QRF virus is apparently not transovarially transmitted by *A.* (*P.*) *arboreus*. Therefore, a vertebrate host (along with timely availability to hungry infected and uninfected ticks) is necessary to perpetuate virus circulation in nature.

In contrast to the high vector potential of *A.* (*P.*) *arboreus*, the closely related *A.* (*P.*) *persicus* is never infected by QRF virus in nature and, experimentally, is an inefficient vector of this agent (Kaiser, 1966c).

In a recent study of *A.* (*P.*) *arboreus* as a QRF vector, Riad *et al.* (1978) stated that the chromosomal pattern indicated the possibility of parthenogenetic and bisexual races. Sidky *et al.* (1982) reported localization of QRF virus in *A.* (*P.*) *arboreus* salivary glands.

QRF infection in man (Section IV,F,3) and the presence of CF antibodies against QRF virus in Egyptian rodents (*Acomys, Mus, Rattus*), goats, sheep, donkeys, pigs, camels, buffaloes, and dogs suggest ixodid vectors or other transmission routes for QRF virus (Darwish and Hoogstraal, 1981). A step in the direction of involving ixodids and mammals was made by the isolation of five QRF virus strains from *Hyalomma dromedarii* parasitizing camels in Kuwait, Iraq, and Yemen (Converse and Moussa, 1982). Notably, none of the numerous ixodid parasites of Egyptian domestic animals tested for viruses over the years have yielded QRF virus. The riddle of QRF circulation between argasids and ixodids and birds and mammals urgently needs solving to provide an important model of virus–host interrelationships and to permit predicting the hazards of potential cyclic outbreaks of human illness caused by this virus.

(*i*) *Unclassified viruses* (*Nyamanini serogroup*). The Nyamanini (NYM) serogroup consists of NYM virsus and Midway (MID) viruses. These exceptionally large arboviruses may be related to the arenaviruses (see MID virus below).

NYM virus was originally isolated from a cattle heron, *Bubulcus ibis* subsp., from Nyamanini Pan, a subtropical lowland savanna—scrub

woodland area in Natal, South Africa. NYM virus has also been isolated from nestling *B. ibis ibis* in Egypt and on numerous occasions from *A. (P.) arboreus* parasitizing these birds (see below). Elsewhere, NYM virus is recorded from *A. (P.) arboreus* in Nigeria, *A. (P.) robertsi* in Thailand and Sri Lanka, *A. (P.) hermanni* in Nepal, and a gray heron, *Ardea cinerea rectirostris* Gould, in India (Darwish and Hoogstraal, 1981). As with QRF virus, the reported isolation of NYM virus from *A. (P.) walkerae* in South Africa (Jupp and McIntosh, 1981) was based on misidentification of *A. (P.) arboreus*.

In the studies on QRF virus seasonal dynamics in an Egyptian population of *A. (P.) arboreus* (mentioned above), 76 NYM strains and 42 QRF strains were isolated from these ticks. The natural infection index of both viruses peaks in spring but, unlike QRF virus, the NYM index is maintained at a high level through much of the summer, followed by a lower fall peak, and remains fairly high through the winter. No NYM virus was recovered from *A. (P.) persicus*. No NYM viremia resulted from experimental inoculation of baby chicks. NYM virus is postulated (but not proven) to be transovarially transmitted to subsequent generations by *A. (P.) arboreus* (Kaiser, 1966b).

NYM virus also infects mammals. Antibodies to this agent were detected in sera from man, goats, and a donkey in South Africa (Berge, 1975) and from buffaloes, a camel, and a dog in Lower Egypt (Darwish and Hoogstraal, 1981). Migrating birds are obviously responsible for the exceptionally wide distribution of NYM virus (South Africa to Egypt, India, Sri Lanka, and Thailand) and for infections in at least three *Argas* species, but the pathogenicity and routes of virus transmission to man and domestic mammals remain an enigma.

MID virus history and studies were reported by Takahashi *et al.* (1982). MID virus infects *O. (A.) capensis* and *O. (A.) denmarki* in the Central Pacific (Midway, Kure, and Manana Islands), and the former species on Aomatsushima off northern Honshu, Japan, where antibodies are prevalent among nestling black-tailed gulls, *Larus crassirostris*, but scarce among those of the black-crowned night heron, *Nycticorax nycticorax*. MID virus is lethal for newborn mice inoculated intracerebrally but not for those inoculated intraperitoneally. Takahashi *et al.* (1980) considered MID virus (reported as "Hirota" virus) to be morphologically related to the arenaviruses.

(j) Unclassified viruses (serologically ungrouped). Lake Clarendon (LC) virus (strain CSIRO-704), isolated from *Argas (P.) robertsi* infesting heronries of the cattle egret, *Bubulcus ibis coromandus*, 100 km west of Brisbane, and maintained in an Australian laboratory colony of this tick, apparently is not transovarially transmitted (Kemp *et al.*, 1982; St. George *et al.*, 1984). Neutralizing antibodies to LC virus were detected in

each of eight nestling egrets tested but the virus was not isolated from their blood.

Keterah (KTR) virus, isolated from the bat parasite *A.* (*C.*) *pusillus* in Malaysia, and Issyk Kul (IK) virus, isolated from the bat parasites *A.* (*C.*) *vespertilionis* and *Ixodes* (*E.*) *vespertilionis* in Kirgiz SSR, may be identical or very closely related but the neutralization tests needed to determine this have not been performed (Hoogstraal, 1980). Human disease has been attributed to both virus taxons (see following section on human hosts). IK virus has also been isolated from two species of insectivorous bats in Kirgiz SSR and Tadzhik SSR. Antibodies to IK virus were detected in a significant number of human and domestic animal sera tested in Kirgiz SSR (Timofeev *et al.*, 1973) but the source(s) of these infections is unknown. Naturally infected nymphal and adult *A.* (*C.*) *vespertilionis*, in which IK virus survives for at least a year, transmitted the virus when biting baby mice in the laboratory (Vargina *et al.*, 1982). IK virus has also been isolated from gamasid mites and mosquitoes; the latter are considered to be potential vectors in Kirgiz SSR (Bulychev *et al.*, 1979). KTR-IK virus(es) is a riddle challenging virologists and biomedical investigators to answer a variety of biological and epidemiological questions.

Chobar Gorge (CG) virus infects a bat parasite, *O.* (*Reticulinasus*) sp. ("near *piriformis* and *chiropterphila*"), taken by me from the walls and floor of a limestone cave about 11 km southwest of Katmandu, Nepal (Berge, 1975).

Chim (CHIM) virus is known from isolates from argasids and ixodids from burrows of the great gerbil, *Rhombomys opimus*, from different areas of Uzbek SSR. The infected ticks were *O.* (*P.*) *tholozani* and *O.* (*P.*) *tartakovskyi* (Argasidae) and *Rhipicephalus* (*R.*) *turanicus* (Ixodidae) (L'vov *et al.*, 1979).

(*k*) *Miscellaneous viruses*. Two different viruses, one said to be a Togavirus, were reported from *O.* (*S.*) *coriaceus* during studies on epizootic bovine abortion in California (Wada *et al.*, 1976; McKercher *et al.*, 1980). These agents have not yet been characterized.

Infectious bovine rhinotracheitis (IBR) virus (*Herpesvirus*), an important respiratorily transmitted pathogen of cattle, was isolated from three collections of *O.* (*S.*) *coriaceus* taken from deer beds in the Sierra Nevada Mountains of Nevada over a 3-year period (Taylor *et al.*, 1982). IBR virus is believed to be a mammalian virus, not an arbovirus. The source of tick infections by IBR virus is uncertain; the viremic period in cattle and mule deer (*Odocoileus lemionus*) is brief and it is not known whether IBR virus replicates in ticks, how long it remains infectious in ticks, whether ticks become infected from feeding on viremic mammals, or whether the virus can be transmitted, mechanically or after replication, during feeding.

Newcastle disease virus (Paramyxoviridae) remained virulent in *A.* (*P.*) *persicus* for at least 39 weeks, and survived from experimentally infected larvae to first-instar nymphs but was not transmitted during feeding on susceptible chickens (Petrov, 1972). Chickens might become infected from feeding on infected *A.* (*P.*) *persicus*.

Attempts to infect *O.* (*O.*) *savignyi* by allowing them to feed on monkeys infected by Chikungunya (CHIK) virus (Togaviridae, *Alphavirus*) failed (Jupp *et al.*, 1981). CHIK virus isolates have been reported from *O.* (*P.*) *sonrai* from rodent burrows in Senegal (Taufflieb *et al.*, 1968). This disease-producing agent is generally mosquito-borne (Berge, 1975).

3. *Human hosts*

(*a*) *Togaviridae* (*genus* Flavivirus). Sokuluk virus infection of man is indicated by serological findings. Details of the pathogenesis and epidemiology of this agent are unknown. West Nile (WN) virus and Kyasanur Forest disease (KFD) virus are enzootic in Africa and Eurasia and in India, respectively; both cause epidemics of human disease. Mosquitoes usually transmit WN virus and ixodid ticks usually transmit KFD virus. Natural and experimental infections of argasids have been reported. [See Singh *et al.* (1971) for KFD virus in *Argas* (*P.*) *persicus* and Whitman and Aitken (1960) for WN virus in *Ornithodoros* (*O.*) *moubata*.] However, the roles of argasids in enzootic circulation and transmission of both viruses are unstudied.

(*b*) *Bunyaviridae* (*genus* Nairovirus). Reports of Crimean-Congo hemorrhagic fever (CCHF) virus infecting *A.* (*P.*) *persicus* require confirmation. The significance of CCHF virus isolation from *O.* (*A.*) *lahorensis* in relation to circulation of this agent in nature and transmission to man is unstudied.

Persons bitten by *O.* (*A.*) *capensis* group populations infected by various viruses of the Hughes serogroup may suffer from pruritus, blisters, fever, headache, or even more serious disease (Section IV,E,3). Virological investigations of these episodes have thus far been impossible to arrange. The only exception to this situation is the work of Chastel *et al.* (1981) on Soldado (SOL) virus (Morroccan strain) producing febrile illness and serious persistent rhinitis in French ornithologists bitten by *O.* (*A.*) *maritimus* in a sea gull colony. Chastel considered SOL virus to be a potential public health problem where sea gulls feed in urban environments.

Techniques for serological surveys of human infection by viruses are now so simple, inexpensive, and painless that there is little excuse for the dearth of knowledge regarding Hughes serogroup activity and pathogenicity in man. This is especially true for Punta Salinas virus (Hughes serogroup) and Huacho virus (Reoviridae, *Orbivirus*) in Peru (Clifford *et al.*, 1980).

(*c*) *Bunyaviridae* (*genus* Uukuvirus). The detection of CF antibodies against Manawa (MWA) virus in human sera from Pakistan (Darwish *et al.*, 1983b) indicates the need to learn more about the pathogenesis and epidemiology of this argasid- and ixodid-related agent.

(*d*) *Bunyaviridae* (*serologically ungrouped and possible members*). Bakau (BAK) virus, which has been isolated from *A.* (*P.*) *abdussalami* in Pakistan and from *Culex* mosquitoes in Malaysia, was detected in 20% of the Malaysian human sera tested.

(*e*) *Reoviridae* (*genus* Orbivirus). The epidemiological significance of Colorado tick fever virus infections in *Otobius lagophilus* has not been investigated. Seroepidemiological results suggesting human infection by Chenuda (CNU) virus, or a CNU-related virus, in Omsk Oblast of Siberia point to the need for biomedical investigation of this agent(s). Huacho (HUA) virus from *O.* (*A.*) *amblus* in Peru has been mentioned, together with Punta Salinas virus, in the section on Bunyaviridae, *Nairovirus*, Hughes serogroup.

(*f*) *Family Iridoviridae*. African swine fever virus apparently does not cause viremia in man.

(*g*) *Unclassified viruses* (*Quaranfil serogroup*). Of all argasid-associated viruses that are inadequately investigated virologically and biomedically, the still unclassified Quaranfil (QRF) virus is the most glaring example. Many long-standing questions regarding its epidemiology, especially in relation to human illness, remain unanswered. QRF virus was isolated from patients with "fever of unknown origin" in Egypt in the early 1950s, when antibodies to it were detected in the sera of children. Some 20 years later, results of a seroepidemiological survey in the same area showed antibodies to QRF virus only in the 20–30 year age group (range tested, 10–60 years) (Darwish and Hoogstraal, 1981). This suggests that there may have been an epidemic of QRF virus in Lower Egypt two decades earlier, during the initial QRF virus studies. More recent serological and virological results indicating that QRF virus infects a variety of domestic and commensal mammals, and camel-parasitizing *Hyalomma dromedarii* ticks in Arabia, show how little we know about this agent, which has long been considered to be confined to *Argas* ticks and birds, except for unexplained infections in man. Surveillance should be maintained for possible cyclic epidemics of QRF virus in man, and its pathogenesis in mammals should be investigated.

(*h*) *Unclassified viruses* (*Nyamanini serogroup*). The serological evidence for infections of humans and domestic animals in South Africa and of domestic animals in Egypt by the argasid-associated unclassified Nyamanini virus, usually infecting African and Asian birds, presents another virological and biomedical enigma.

(*i*) *Unclassified viruses* (*serologically ungrouped*). Keterah (KTR) virus and Issyk Kul (IK) virus may be two geographical names for one

virus; as definitive tests have not been performed, the literature on each virus taxon is referred to separately. Virus strains isolated from patients suffering from a severe diabetes-like disease in Japan were identified by R. E. Shope at YARU as KTR virus (Miura, 1976). Antibodies to IK virus were detected in a significant number of human, bat, and domestic animal sera in Kirgiz SSR (Timofeev *et al.*, 1973; Gromashevsky *et al.*, 1975) and in Turkmen SSR (Kurbanov *et al.*, 1974). A virus "antigenically related to IK virus" was isolated from the blood of a patient who developed malaise, chills, headache, general weakness, and muscular pains 5 days after trapping bats in southern Tadzhik SSR (L'vov *et al.*, 1980). Antibodies were not detected in CF tests of this patient's serum on day 2 of disease but were detected on days 40 and 68 (titers 1 : 16 and 1 : 8, respectively). On day 103, no antibodies were detected. In another virologically proven case in a worker living in Dushanbe, facial hyperemia, muscular pains, dry cough, single dry rales in lungs, hyptonia, bradycardia, and muffled heart tones were observed.

Kostyukov (1981) reviewed IK virus isolations from four species of bats, acutely febrile persons, five species of migrating birds, *Argas* (*C.*) *vespertilionis*, and *Aedes caspius* and *Anopheles hyrcanus* mosquitoes, and found that 0.7–7.0% of 4186 human blood sera from southern Tadzhik SSR contained antibodies to IK virus by CF tests (titers 1 : 8 to 1 : 64), and postulated that the *Argas* ticks and possibly mosquitoes transmit IK virus to man. Kostyukov *et al.* (1982) demonstrated IK virus transmission to suckling mice from biting *Aedes caspius* mosquitoes which had earlier fed on infected pipistrel bats. This virus or virus complex, presently regarded as associated chiefly with bats and bat-parasitizing *Argas* (*Carios*) and *Ixodes* ticks and also with mosquitoes, may have more serious epidemiological importance than generally appreciated.

G. TICK-BORNE RICKETTSIALES

1. *Order Rickettsiales*

The very small bacteria (0.2–0.5 μm in diameter) of the order Rickettsiales (bacterial class Schizomycetes) (Moulder, 1974; Marchette 1982) are mostly obligate intracellular parasites of animals. Members of the family Chlamydiaceae are not transmitted biologically by arthropods, and members of the family Bartonellaceae are associated only with phlebotomid sandflies. The two other families, Rickettsiaceae and Anaplasmataceae, have some degree of association with argasid ticks, as discussed below.

2. *Family Rickettsiaceae*

In this family of typhus-like and related agents, three (*Rickettsia, Coxiella, Wolbachia*) of the 10 genera are more or less closely associated with

argasids; the other seven genera are associated only with ixodid ticks or insects (*Rochalimaea, Ehrlichia, Cytocetes, Cowdria, Neorickettsia, Symbiotes*) or with parasitic trematodes (*Rickettsiella*).

(*a*) *Genus* Rickettsia. There is an extensive, continuously expanding literature on *Rickettsia* spp. associated with ixodid ticks and human disease, especially Rocky Mountain spotted fever (*R. rickettsi*), boutonneuse fever (African-European tick typhus) (*R. conori*), Siberian tick typhus (*R. siberica*), and a few other species which do or do not infect man (*R. belli, R. canada, R. montana, R. rhipicephali,* etc.). Argasids are seldom reported to be infected by *Rickettsia* spp., possibly owing in part to lack of curiosity by investigators. In addition to the rickettsial–argasid relationships reviewed below, Tang *et al.* (1983) reported that the Chinese Jinghe strain of the Rocky Mountain spotted fever (RMSF) group infected all examined organs and tissues of *O.* (*O.*) *moubata* except the testes and sperm. (I have not yet seen this paper and do not know to which rickettsial species the authors assigned the Jinghe strain.) The report by Parker (1942) on using *Ornithodoros* spp. to transport *Rickettsia* spp. provides clues to survival of these agents in ticks of this genus.

(i) Rickettsia rickettsi *serogroup*. Davis (1942b,c) demonstrated that *O.* (*P.*) *parkeri* can be experimentally infected with *Rickettsia rickettsi* and transmit the RMSF agent when feeding. This tick and the immature stages of the ixodid *Dermacentor andersoni,* the chief RMSF vector in the western United States, both parasitize ground squirrels and have a number of other hosts in common. Davis (1943c) summarized his further studies essentially as follows: larval, nymphal, and adult *O.* (*P.*) *parkeri* transmit the RMSF agents of the United States, Colombia, and Brazil with equal facility. Females that fail to transmit the rickettsia may produce infective progeny. Transovarial transmission to the F_4, F_2, and F_1 generations was observed in *R. rickettsi* strains from the United States, Colombia, and Brazil, respectively. Agent invasiveness was not lessened by continuous tick passage. Ticks that had fasted for 1 year produced typical infections in guinea pigs and progeny of the fasting ticks produced infections resulting in host death. The data suggest that *O.* (*P.*) *parkeri* may be a factor in maintaining spotted fever foci in nature and may occasionally serve as a vector to man.

On Mexican farms with severe clinical RMSF and a high mortality rate, complement-fixing antibodies against *R. rickettsi* in domestic animal sera were commoner than on other farms. The chief vectors were said to be *Rhipicephalus sanguineus* Latreille and *Amblyomma cajennense* (Fabricius), but *O.* (*P.*) *nicollei* and *Otobius lagophilus* were among the ticks infected by *R. rickettsi*. The literature on RMSF in Mexico is listed by Hoogstraal (1967).

Ornithodoros rudis (subgenus unknown) was found in patients' beds during a RMSF outbreak in the Tobia River Valley of Colombia, where 62

of the 65 patients died (Patiño Camargo *et al.*, 1937; Patiño Camargo, 1941; Hoogstraal, 1967). Naturally infected *A. cajennense* and *Dermacentor (Anocentor) nitens* Neumann were found in the area and the latter species was demonstrated to transmit the agent experimentally. *Ornithodoros* (-) *rudis* did not transmit *R. rickettsia* strains from Colombia, Brazil, or the United States, but conserved these agents for about a year in its body tissues and transmitted them transovarially to the F_1 generation (Davis, 1943a).

In research on RMSF (São Paulo typhus) outbreaks in Brazil, *O. (P.) rostratus* transmitted *R. rickettsi* during feeding on day 13 after infection but not on day 28. The rickettsia is retained and apparently multiplies in *O. (A.) turicata* for 28 months but is not transmitted when this tick feeds (Brumpt, 1936b; Davis, 1942b,c, 1943c). For other literature references to Brazilian studies, see Hoogstraal (1967).

There appear to be no reports associating argasids and *Rickettsia conori,* the agent of boutonneuse fever, the RMSF-group tick typhus of Africa and southern Europe (including European USSR). However, a South African strain of *R. conori,* inoculated into *O. (O.) moubata* and shipped to the Rocky Mountain Laboratory in Montana, was recovered from suspensions of the ticks 36 days after shipping and produced typical reactions of infection following inoculation into guinea pigs (Parker, 1942).

Rickettsia slovaca, described by Urvölgyi and Brezina (1978), has been recorded, chiefly by Řeháček and colleagues, from ixodid ticks (*Dermacentor, Ixodes, Haemaphysalis*) and from field rodents, hares, and birds in Central Europe (Czechoslovakia, southern Germany, Austria, Hungary). Řeháček *et al.* (1977) reported the "massive occurrence" of *R. slovaca* in *A. (P.) persicus* from a poultry farm and a private chicken coop in Oktemberyan, Armenian SSR, thus extending the natural relationships of this agent to argasids and the range eastward into a zone where either *R. conori* or *R. siberica,* or both, might be expected to occur. This finding should arouse much microbiological interest.

(ii) Rickettsia prowazeki *serogroup. Rickettsia prowazeki,* the agent of louse-borne or epidemic typhus, has been reported to reproduce in the bodies of *O. (O.) moubata* and *O. (P.) tholozani.* However, in detailed investigations of this agent (and also of *R. canada*) in *O. (P.) tholozani* and two *Hyalomma* species (Ixodidae), Ignatovich and Grokhovskaya (1976a) found that, in contrast to *R. canada, R. prowazeki* is not transmitted during feeding on guinea pigs and is not transovarially transmitted by any of the tick species studied.

Ricksettsia canada, classified in the *R. prowazeki* serogroup but serologically related to both *R. prowazeki* and the RMSF serogroup, is recorded chiefly from *Haemaphysalis, Dermacentor,* and *Amblyomma* ticks in Canada and the United States and is tentatively associated with

human infection (Moulder, 1974). Antibodies against *R. canada* have also been detected in human sera from European USSR (Ignatovich, 1977). Ignatovich and Grokhovskaya (1976a,b) reported a "considerable degree of adaptation" of *R. canada* to *O.* (*P.*) *tholozani* and *O.* (*O.*) *moubata*, which became regularly infected after membrane feeding on infected blood and retained the agent for 24 and 18 months, respectively. Membrane-fed *A.* (*P.*) *persicus* retained *R. canada* for 12 months. In contrast, few tested specimens of *Dermacentor andersoni* and *D. reticulatus* became infected from feeding on infected guinea pigs, and *R. canada* survived in these ticks for only 1 or 8 days, respectively. Transstadial survival and transovarial transmission of *R. canada* occurred in *O.* (*P.*) *tholozani*. After a bloodmeal from an infected guinea pig, *O.* (*P.*) *tholozani* retained *R. canada* for 526 days. However, infected *O.* (*P.*) *tholozani*, *O.* (*O.*) *moubata*, and *O.* (*A.*) *lahorensis* failed to transmit *R. canada* when feeding on guinea pigs.

(iii) Rickettsia belli *serogroup*. *R. belli*, the monotypic member of the *R. belli* serogroup, was found by Philip *et al.* (1983) in 263 isolates from eight tick species from seven of the United States. Two isolates were from the argasids *A.* (*A.*) *cooleyi* and *O.* (*A.*) *concanesis*. The 261 isolates from ixodids were from *Haemaphysalis leporispalustris* (5) and *Dermacentor variablis*, *D. andersoni*, *D. occidentalis*, *D. parumapterus*, and *D. albipictus* (256 in all). As for other tick-borne *Rickettsia* spp., *R. belli* survives transstadially and is transmitted transovarially (studied in *D. andersoni*). There is no evidence that this agent causes human illness. Related rickettsiae and the natural history and epidemiology of the *R. belli* serogroup will probably be reported before long.

(*b*) *Genus* Coxiella. *Coxiella burneti*, the only member of this genus and the agent causing Q fever, may have "escaped" from a primitive tick-borne cycle by becoming highly adapted for survival in a variety of environments and for multiplication in various invertebrates and vertebrates. Daiter (1979) suggested that alternation between vertebrate and invertebrate (tick) hosts is necessary if *C. burneti* is to be preserved as a species. The data supporting this conclusion are more substantial for ixodids (not reviewed herein) than for argasids.

Baca and Paretsky (1983) recently reviewed *C. burneti* as a model for host–parasite interactions. This excellent basic reference, like other summaries and most investigators, pays scant attention to the known and potential roles of ticks as reservoirs and vectors of *C. burneti* and to much epidemiological literature, often involving ticks, from Eastern Europe and USSR and more recently from India. Q fever is a public health problem in many rural and urban areas of the world, as evidenced by the continuing flow of reports describing newly observed signs and symptoms, pathogenic features, and epidemiological factors. The exceptional capacity of

C. burneti for survival in nature and its transmission to man by aerosol infection, contact with infected domestic animals and animal products, and consumption of unpasteurized milk and cheese, highlight epidemiological considerations of Q fever on all continents.

A number of argasid and ixodid ticks have been implicated or suggested as reservoirs and vectors of *C. burneti* in temperate and tropical regions. However, many biological variables determine tick–*C. burneti* relationships and each experimental and field study has left significant epidemiological and transmission questions unanswered. *Argas* (*A.*) "*reflexus*" [stated by Filippova (1961) to be *A.* (*A.*) *hermanni*] from tree sparrow nests in Karshi Oblast of Uzbek SSR was infected with *C. burneti* (cited by Zhmaeva *et al.*, 1966). *Argas* (*P.*) *persicus* population samples maintained *C. burneti* for the 465-day observation period in Uzbek SSR (Lysunkina, 1960). Transmission attempts with *A.* (*P*). *persicus* [and *O.* (*A.*) *lahorensis*] from infected foci in Iran appeared to give negative results (Giroud and Yassemi, 1952). Gil Fernandez (1960) studied virulent and avirulent *C. burneti* strains in *A.* (*P.*) *persicus* from Spain. Living *A.* (*C.*) *vespertilionis* and others that had been dead for 17–25 months yielded viable strains of *C. burneti* (Belashova, 1966; Zhmaeva *et al.*, 1966). The infected ticks were taken in buildings inhabited by pipistrel bats in Chimkent Oblast of Turkmen SSR and in Dzhambul and Alma Ata Oblasts of Uzbek SSR. Several authors from these republics asserted that *A.* (*C.*) *vespertilionis* can be "highly aggressive" toward man and is important in the epidemiology of Q fever.

Ornithodoros (*O.*) *moubata* were reported to be infected by *C. burneti* ("virus des Bashi") in "West" (Central) Africa (cited by Weyer, 1975); the circumstances were ambiguous. Results of pioneer investigations of *C. burneti* in *O.* (*O.*) *moubata* (Davis, 1943b) showed transmission during feeding 428 days after an infective bloodmeal or 670 days after the agent was injected into the tick. An extended study of *C. burneti* and *O.* (*O.*) *moubata* (Weyer, 1975) demonstrated that the agent infects chiefly gut epithelial cells. However, certain factors, possibly related to the immunological status of the tick or of the agent at a certain time, permit *C. burneti* to form more or less dense populations in the coxal organs, salivary glands, rectal ampullae, and ovaries. Thence, transovarial transmission may occur as well as transmission via salivary or coxal fluids during feeding, via excrement, or from the decomposed body after death. *Coxiella burneti* behavior varied considerably in a single tick and in a single experimental series for reasons that were not immediately clear. Data on *C. burneti* longevity in healthy, dying, and dead *O.* (*O.*) *moubata* are prominent in Weyer's studies.

The ease of infecting *O.* (*O.*) *moubata* by feeding on Q fever patients and of maintaining and transmitting the agent by feeding infected ticks on

guinea pigs prompted Burgdorfer (1951a) to suggest using this parasite as a research tool for determining Q fever infection in Switzerland. Daiter (1963) made a similar suggestion for *O.* (*P.*) *tholozani* in the USSR. *Ornithodoros* (*P.*) *tholozani* transmits *C. burneti* transovarially, and when feeding, over a 10-year period (Zhmaeva *et al.*, 1964, 1965). This tick parasitizes man and wild and domestic mammals; thus it is considered to be an important epidemiological element in Q fever foci in warm desert environments of the USSR. Kusov *et al.* (1962) reported natural infections in *O.* (*P.*) *tholozani* from Uzbek SSR. Extensive Soviet investigations of *C. burneti* in *O.* (*P.*) *tholozani* are reviewed in the easily available monograph by Balashov (1972).

Ornithodoros (*P.*) *tartakovskyi* was a source of *C. burneti* isolates in Turkmen SSR (Zhmaeva and Pchelkina, 1957), suggesting an epidemiological role for this tick among burrowing rodents in desert biotopes of southern USSR (Zhmaeva *et al.*, 1964). *Ornithodoros* (*P.*) *hermsi* transmitted American strains of *C. burneti* more than 2 years after an infective feed or about 3 years after the agent was injected into the tick body, and F_1 larvae inoculated into guinea pigs were infective (Davis, 1943b). *Ornithodoros* (*P.*) *turicata*, however, did not transmit the agent when feeding or transovarially, but it remained infective in the tick body for 1001 days as shown by inoculating suspensions into guinea pigs.

Ornithodoros (*P.*) *marocanus* from nests of rabbits, *Oryctolagus cuniculus*, in Nefifik Forest near Casablanca, Morocco, were naturally infected with *C. burneti* and transmitted the agent during feeding on guinea pigs (Blanc and Bruneau, 1955; referred to as "*O. erraticus*, large form"). The Australian cave-inhabiting species related to *O.* (*P.*) *gurneyi* appears to be unable to transmit *C. burneti* when feeding, but suspensions of these ticks inoculated into guinea pigs 129–535 days after an infective bloodmeal were infective (Smith, 1942).

Infection of *O.* (*A.*) *lahorensis* with *C. burneti* by feeding on infected guinea pigs, with transmission by immature and adult ticks, was recorded in detail by Kusov *et al.* (1962). The close association between *O.* (*A.*) *lahorensis* and domestic animals in Q fever foci of Kazakh SSR implicates this tick in the epidemiology of the disease, according to these authors. Natural infections of *O.* (*A.*) *lahorensis* were also recorded in Turkey (Payzin and Akyay, 1952) and in Iran (Saadatezadeh *et al.*, 1973).

When *O.* (*A.*) *canestrinii* were infected with a *C. burneti* strain which was nonpathogenic following prolonged storage in dry culture, virulence was gradually restored over a 140-day period until the strain was equally as virulent as any other (Pautov and Morozov, 1974a,b). *Ornithodoros* (*S.*) *coriaceus* transmitted a possibly mild strain of *C. burneti* in northern California (Enright *et al.*, 1971). Infected hamsters and mice showed antibody responses but no overt sign of illness. *Otobius megnini* from cattle

near Los Angeles, California, were infected with *C. burneti* (Jellison *et al.*, 1948). This finding raised yet unanswered questions regarding transovarial transmission and transmission during feeding by immature forms of this highly specialized argasid.

(*c*) *Genus* Wolbachia. *Wolbachia persica* Suitor and Weiss (1961) [described from an Egyptian population of *A.* (*P.*) *arboreus*, not *A.* (*P.*) *persicus*] is a true symbiont of argasids and is transovarially transmitted from the female to all, or virtually all, individuals of the F_1 generation. The definitive work on this organism, in addition to the original description, is by M. A. Roshdy, whose publications are listed by Marchette (1982, Vol. 1, pp. 26, 27). *Wolbachia persica* (or a closely related, undescribed species) has been demonstrated in *A.* (*P.*) *arboreus*, *A.* (*P.*) *persicus*, *A.* (*C.*) *boueti*, *A.* (*C.*) *vespertilionis*, *A.* (*S.*) *transgariepinus*, *A.* (*O.*) *brumpti*, *O.* (*O.*) *moubata*, *O.* (*O.*) *savignyi*, *O.* (*P.*) *erraticus*, and *O.* (*P.*) *tholozani*. Various more or less similar organisms were recorded by Suitor (1964) from some of the species listed as well as from *A.* (*A.*) *hermanni*, *A.* (*A.*) *lagenoplastis*, *A.* (*A.*) *cooleyi*, *O.* (*P.*) *arenicolous*, and *O.* (*A.*) *delanoei*. *Wolbachia* organisms infect the oocytes and Malpighian tubules. Cells of the tubules, except those close to the rectal sac, are infected in *Argas*, and cells of the anterior half (but not the most anterior) of the tubules are infected in *Ornithodoros*. Undescribed *Wolbachia* or "*Wolbachia*-like" species occur in ixodid ticks, and two *Wolbachia* species have been described from insects.

3. *Family Anaplasmataceae*

(*a*) *Genus* Anaplasma. Reports of argasids and poorly characterized *Anaplasma* species are tentatively referred to *Aegyptianella pullorum* or omitted here. Bityukov (1953) reported that immature *O.* (*A.*) *lahorensis* became infected when feeding on sheep infected with *Anaplasma ovis* and transmitted the agent when feeding on other sheep.

(*b*) *Genus* Aegyptianella. *Aegyptianella pullorum* Carpano is the only definitely established species in the genus *Aegyptianella* (see Ristic and Kreier in Moulder, 1974, pp. 909–910). As reviewed in detail by Gothe and Kreier (1977), *A. pullorum* is the agent of aegyptianellosis, a noncontagious infectious disease of chickens, ducks, geese, quail [*Coturnix coturnix* (L.)], ostriches (*Struthio camelus* L.), and certain other birds. The disease occurs wherever *Argas* ticks parasitize birds in tropical and warmer temperate areas of the world. The more severe avian borreliosis, caused by *Borrelia anserina*, often occurs simultaneously with aegyptianellosis. *Aegyptianella pullorum* infects avian erythrocytes and is transmitted by several if not most species of bird-parasitizing *Argas* ticks. This agent develops in the gut and salivary glands of the larval, nymphal, and adult *Argas* and remains infective for the tick's lifetime. Transovarial

transmission is uncommon in the South African *A.* (*P.*) *walkerae* (Gothe and Kreier, 1977) and in the cosmopolitan *A.* (*P.*) *persicus* (Gothe, 1971). [If transovarial transmission of an agent is rare, one wonders what factors contribute to this phenomenon when it does occur.] *Aegyptianella pullorum* is apparently disseminated chiefly when *Argas* feed on birds which have earlier been fed on by infected *Argas* (Gothe, 1978). Fowl infected as chicks remain infective for ticks for at least 18 months. Uninfected ticks feeding together with infected ticks on fowl become infected within 5 minutes. Clinically healthy birds with drug-suppressed *Aegyptianella* infections can also infect feeding ticks.

Argas (*A.*) *africolumbae* and *A.* (*P.*) *persicus* populations investigated from chicken houses in different localities of Upper Volta showed a high prevalence of *A. pullorum* and *B. anserina* in every collection of both *Argas* species (Gothe *et al.*, 1981b). Each feeding stage of both species transmitted the agents to chickens. *Argas* (*P.*) *walkerae* samples from 10 of 11 areas of Transvaal, South Africa, also yielded both *A. pullorum* and *B. anserina* (Gothe and Schrecke, 1972a,b). Infected nymphal and adult *A.* (*P.*) *walkerae* retain *A. pullorum*, without an additional bloodmeal, for over 700 and 800 days, respectively. The American *A.* (*P.*) *radiatus* and *A.* (*P.*) *sanchezi* act as vectors and reservoirs of *A. pullorum* in the laboratory. Both species commonly infest domestic fowl. The European *A.* (*A.*) *reflexus* is also a vector and reservoir in the laboratory but seldom parasitizes chickens in the field (Gothe, 1978).

H. TICK-BORNE SPIROCHAETALES[3]

1. *Order Spirochaetales, Family Spirochaetaceae*

Members of this order of slender, flexuous, helically coiled, unicellular bacteria (3–500 μm long), with one or more complete turns in the helix, multiply by transverse fission (Smibert, 1974). The single family contains the genera *Spirochaeta, Cristispira, Treponema, Borrelia,* and *Leptospira.* Of the 19 described *Borrelia* species, one (*B. recurrentis*) is louse-borne, one (*B. theileri*) is associated with four ixodid parasites of ruminants and horses, and 16 are associated with argasid species—*B. anserina* with *Argas* spp. and birds, the others with a variety of *Ornithodoros* species and mammals.

The genus *Borrelia* apparently developed as symbionts (*sensu lato*) of ticks, especially Argasidae, but act as parasites in mammals and birds,

[3] The monograph by Felsenfeld (1971) on *Borrelia* strains and vectors, and human and animal borreliosis, which reviews knowledge to the late 1960s, is essential background reading for this section. Few of the 749 references listed in this monograph are repeated here.

which serve as borrelial amplifiers following bites by infected ticks (Hoogstraal, 1979b). Tick borreliae may multiply in lice but *B. recurrentis* has evolved into a species independent of ticks and now associated only with the human louse and man. *Borrelia duttoni* of certain members of the *O.* (*O.*) *moubata* group apparently circulates in nature only between these ticks and man, not between ticks and other vertebrates. The assertion that vertebrates are a source of borreliae for ticks is misleading. Ticks are apparently the unequivocal original source of borreliae. Alternation between tick and vertebrate hosts may be necessary for the long-term vigor and survival of borreliae, although the vertebrate role in this respect requires more precise investigation. Vertebrates can amplify the infection in nature by supplying the borreliae to "clean" feeding ticks, but only after having been primarily infected by infected ticks (or rarely congenitally). Borreliae are transmitted to a vertebrate host in salivary fluids when an infected tick feeds, or in coxal fluids during feeding. The frequency of coxal fluid emission while feeding on the host, in contrast to that after feeding and leaving the host, is epidemiologically important.

Borrelia taxonomy is outside the scope of this review. However, it is necessary to state that methods, techniques, and criteria for characterizing most *Borrelia* taxons (species) are moot and should be improved by combined molecular, biochemical, and biological studies. Meticulous biological investigations on the *B. anserina* cycle in four bird-parasitizing *Argas* species demonstrated that this agent is highly species specific (Diab and Soliman, 1977; Zaher *et al.*, 1977). Comparable studies are needed to define the biological features and taxonomic status of *Borrelia–Ornithodoros* interrelationships, especially in the Americas, and to extend the pioneer investigations of Davis (1942c) on this subject. More sensitive biochemical and molecular techniques for *Borrelia* research must also be investigated.

2. Borrelia anserina *of birds*

Borrelia anserina, the agent of avian borreliosis, causes serious losses of food for man where *Argas* ticks parasitize domestic chickens and other fowl in tropical and warm temperate regions of the world. Worldwide, *A.* (*P.*) *persicus* is the most important vector but much literature before 1966 on this tick and its association with the disease in the Americas, Asia, Africa, and Australia is in fact based on other (misidentified) *Argas* species. The vector capacity of each *Argas* species infesting domestic fowl must be investigated individually.

A major contribution to knowledge of interactions between *Borrelia* and different tick species was the experimental study of *B. anserina* dynamics in *A.* (*P.*) *persicus* from chicken houses, *A.* (*P.*) *arboreus* from a heron (*Bubulcus ibis ibis*) rookery, *A.* (*P.*) *streptopelia* from dove (*Strep-*

topelia) nests, and *A.* (*A.*) *hermanni* from pigeon houses (Diab and Soliman, 1977; Zaher *et al.*, 1977). After adults fed on infected chickens, the borreliae rapidly disappeared from the gut lumen of *A. streptopelia* (days 7–8) but in the three other species they were immobile by days 15–20. The borreliae penetrated the gut wall and were observed in the hemolymph of each species 2 hours after the infective feeding. Numbers in hemolymph increased for 7 days in *A. persicus* and *A. arboreus* but for only 2 days in *A. streptopelia* and *A. hermanni*. Numbers in hemolymph varied throughout the 60-day study period in *A. persicus* and *A. arboreus* but dropped to zero on day 4 and afterward in *A. hermanni* and (with a single exception) in *A. streptopelia*. Borreliae were first seen in other tissues on day 7. The central nerve mass was the most heavily infected organ in *A. persicus* and *A. arboreus*, and remained infected throughout the 60-day period, but was only lightly infected in *A. streptopelia* and *A. hermanni*. Salivary gland infections were heavy until day 60 in *A. persicus* and *A. arboreus*, irregular (slight or nil) in *A. hermanni*, and nil in *A. streptopelia*. Infections in ovaries and testes were heavy until day 60 in *A. persicus* and *A. arboreus*, but nil in *A. streptopelia* and *A. hermanni*.

Borrelia anserina survived transstadially to the adult stage in *A. persicus* and *A. arboreus* developing from experimentally infected larvae; each stage transmitted the borreliae when feeding on chickens. Borreliae survived only to the first and second nymphal instars (N_1, N_2) in *A. hermanni* and not at all in *A. streptopelia*. After experimental infection of *A. persicus* as N_2 and *A. arboreus* as N_3, 84% of *A. persicus* females and 24% of *A. arboreus* females transmitted the infection transovarially to the F_1 generation. Filial infection rates in *A. persicus* and *A. arboreus* were 80–83% for eggs deposited by originally infected females, 83% for N_2 of the F_2 generation, 100% for eggs deposited by F_1 females, and 100% for N_2 of the F_2 generation. There was no transovarial transmission in *A. streptopelia* or *A. hermanni*. Thus, *B. anserina* is highly host specific for *A.* (*P.*) *persicus* and *A.* (*P.*) *arboreus* but *A.* (*P.*) *streptopelia* and *A.* (*A.*) *hermanni* are ineffective reservoirs and vectors.

Available information on *B. anserina* in African populations of *A.* (*P.*) *walkerae* and *A.* (*A.*) *africolumbae* has been mentioned in the section on *Aegyptianella pullorum* (Section IV,G,3,b). In Brazil, *A.* (*P.*) *miniatus* is an important vector of *B. anserina* (Santos, 1982). Da Massa and Adler (1979) demonstrated natural transmission by *A.* (*P.*) *sanchezi* and the existence of different serological and immunological types of *B. anserina* in the United States, where most earlier reports of "*A. persicus*" probably dealt with *A.* (*P.*) *sanchezi* but a few may have concerned *A.* (*P.*) *radiatus*. Virtually all tick data in reports on borreliosis in wild birds, extending so far as penguins and *Ornithodoros* [= *O.* (*A.*) *capensis*] off South Africa, require reevaluation.

3. Borrelia *species of Old World ticks, mammals, and man*

(*a*) *Sub-Saharan Africa. Borellia duttoni,* the agent of African relapsing fever, apparently circulates only in man and in *O.* (*O.*) *porcinus domesticus* or *O.* (*O.*) *moubata* ("domestic race") inhabiting human dwellings (see Section III,A,3 and Felsenfeld, 1971, Chapter 1, for literature). This disease, first reported by Livingstone in 1874 and afterward studied by numerous biomedical savants, was made famous by popular accounts of burning villages to eliminate spirochete-laden ticks and of men inoculating themselves with tick fluids to prevent relapsing fever before traveling far from home to labor in mines.

During World War II, tick-borne relapsing fever morbidity reached epidemic proportions in East Africa but declined after DDT and BHC were introduced (Walton, 1964). However, African foci with appreciable morbidity and mortality are often unreported or mentioned only in passing or in obscure literature. For instance, numerous cases are being treated in the Rundu Hospital, Kavongo, Namibia, and the disease is also prevalent in southern Angola (Hoogstraal, 1981b), but these episodes are not otherwise reported in literature. A brief note in an obscure journal by Chibwana (1983) reported a case of congenital relapsing fever in the Sengerema Hospital, Tanzania. In reply to my query regarding relapsing fever in this region, Dr. Chibwana wrote that the disease, carried by ticks (*papasi* in Swahili), was fairly common; 267 cases (seven fatal) were seen in the Sengerema Hospital in 1982. In Rwanda, tick-borne relapsing fever morbidity appeared to increase between 1959 and 1974; 103 hospital cases (two fatal) were recorded in 1974 (De Clercq *et al.*, 1975). *Borrelia duttoni* is now endemic in Rwanda east, west, and north of Lake Mugesera and is an important cause of abortion and premature birth ("risk of 33%") and of perinatal maternal morbidity (16%) (Goubau and Munyangeyo, 1983).

Borrelia duttoni dynamics in a single generation of *O.* (*O.*) *moubata* and transmission to vertebrates were reported by Burgdorfer (1951b). Coxal fluids of nymphs and adults and salivary fluids of nymphs are the chief vehicles of *B. duttoni* transmission to vertebrates; adult salivary fluids are less constantly infected. Venereal transfer to the female tick via the spermatophore of the mating male also occurs.

The data in literature on transovarial transmission of *B. duttoni* in *Ornithodoros* were reviewed by Burgdorfer and Varma (1967). I venture to suggest that certain discrepancies in these data may derive from employing different "kinds" (species, subspecies, or races) of the *O.* (*P.*) *moubata* group for different experiments and possibly from the (hypothetical) need for an agent to alternate between an invertebrate vector host and a vertebrate host to remain infective for each carrier.

The other *Borrelia* species of sub-Saharan Africa apparently seldom if

ever infect man in nature. *Borrelia graingeri,* from *O.* (*P.*) *graingeri* inhabiting a coastal cave near Mombasa, caused mild infections in laboratory mammals but persisted for over 3 weeks and reappeared fleetingly about 9 weeks after infected ticks fed on a human patient with general paralysis (Heisch, 1953). *Borrelia tillae,* from South African *O.* (*P.*) *zumpti* and burrowing rodents, was postulated to be the evolutionary precursor of *B. duttoni* (Zumpt and Organ, 1961). Borreliae in East African populations of *O.* (*P.*) *erraticus* are tentatively considered to be *B. crocidurae* (see following section).

(*b*) *North Africa, Southern Europe, Southwest and Central Asia*

(i) *Borreliae infecting the* O. (P.) erraticus *group. Borrelia crocidurae* (including the possibly synonymous *B. merionesi, B. microti, B. dipodilli,* and *B. armenica*) infects *O.* (*P.*) *erraticus* (previously termed "small race" of *O. erraticus*) in North Africa, East Africa, the Near East (including southeast Europe), and the Middle East (see Section III,A,3,e). The taxonomic and biological relationships of borrelial populations should be investigated more intensively in the *O.* (*P.*) *erraticus* group [*O.* (*P.*) *erraticus*, *O.* (*P.*) *marocanus*, and *O.* (*P.*) *sonrai*] and the questions of relationships between eastern and western populations of *O.* (*P.*) *erraticus* should be elucidated by obtaining more precise data.

Investigations of *B. crocidurae* and *O.* (*P.*) *erraticus* in Egypt (references listed by Gaber *et al.,* 1984) provided data on hosts, distribution, and ecology of the tick; seasonal dynamics of the tick and agent; *Borrelia* prevalence, localization in the tick, transstadial survival, transovarial transmission, venereal transfer (from male to female tick during mating), transmission during hyperparasitism of unfed ticks on fed ticks; and on other aspects. Human lice, *Pediculus humanus,* biting animals infected with *B. crocidurae,* easily acquire and maintain the infection (Haberkorn, 1963a,b). Thus, louse-infested persons who are bitten by infected *O.* (*P.*) *erraticus* may experience tick-borne relapsing fever and serve as a source of louse-borne relapsing fever. *Borrelia crocidurae* may have been responsible for the epidemic of louse-borne relapsing fever in Egypt and North Africa in the wake of World War II.

Borrelia hispanica infects *O.* (*P.*) *marocanus* (often reported as *O. erraticus* or "large race" of *O. erraticus*) in northwest Africa (Tunisia, Algeria, Morocco), Spain, and Portugal. The question of identity of borreliae in *O.* (*A.*) *sonrai* from Senegal is moot. Until the interrelationships between populations of borreliae and *O.* (*P.*) *erraticus* group ticks can be established by more sensitive techniques, it is pointless to attempt to evaluate the extensive literature on *B. hispanica* and related species or strains. The tentative concept that was outlined in this section is zoogeographically acceptable. Suggestions that *O.* (*P.*) *erraticus* and its specific *Borrelia* were transported by Moslem invaders from east to west,

including Greece, Portugal, and Spain (quoted by Felsenfeld, 1971) bear no credence. Unlike *O.* (*P.*) *marocanus* [and *O.* (*P.*) *tholozani* and *O.* (*A.*) *lahorensis*] which may infest stables and pens of domestic animals, *O.* (*P.*) *erraticus* seldom if ever leaves the immediate vicinity of wild animal burrows and is unlikely to be transported by domestic animals or in commercial cargoes or household effects.

(ii) *Borreliae infecting other Eurasian or northeast African* Ornithodoros *species. Borrelia persica,* the agent of Persian relapsing fever, has been reported in much literature from most of the extensive area—China to eastern Libya—where *O.* (*P.*) *tholozani* occurs. The disease is often severe and sometimes fatal. The vector is notorious in USSR and elsewhere for being transported with household effects and commercial cargoes and for surviving control campaigns in old populated areas and in newly occupied lands (recent literature reviewed by Hoogstraal, 1981b). Civilian and military visitors to tick-infested caves, stables, and caravansaries, as well as residents of villages where domestic animals are quartered, may succumb to Persian relapsing fever.

Borrelia latyschevi, the agent of Central Asian relapsing fever, is transmitted by *O.* (*P.*) *tartakovskyi* infesting gerbils in Iran and Central Asia and causes a mild human illness, presumably because few borreliae are carried in salivary fluids and infected coxal fluids are emitted chiefly after the tick has finished feeding on the host. The claim that "*O. neerensis*" [probably a junior synonym of *O.* (*P.*) *erraticus*] is also infected by *B. latyshevi* should be accepted with caution until the borrelial identity can be established by more sensitive techniques.

Borrelia caucasica (= ? *B. babylonensis*), the agent of Caucasian relapsing fever, is transmitted by *O.* (*P.*) *asperus* [= ? *O.* (*P.*) *verrucosus*] inhabiting rodent burrows in the Caucasus and Iraq, and is said to cause a severe human disease with numerous rapidly recurring relapses. The identity of different geographic populations of the tick is moot; questions regarding the borrelial agent(s) in different geographic areas are obvious.

(iii) Borrelia queenslandica *of Australia. B. queenslandica,* isolated from *Rattus villosissimus* in Queensland, Australia, produced relapsing infections in laboratory rats and mice but did not infect a human volunteer (Carley and Pope, 1962). An attempt to infect *O.* (*P.*) *gurneyi,* the only argasid species recognized in this area, failed.

4. Borrelia *species of New World ticks, mammals, and man*

The pioneer studies of G. E. Davis between 1936 and 1963 should not be overlooked or taken lightly during contemporary attempts to redefine New World borreliae and to understand the epidemiology of human tick-borne relapsing fever. Davis' concepts and findings require updating but provide numerous significant clues to the biological properties of *Borrelia*

species. The French savant E. Brumpt also made notable contributions in this area in the decade preceding World War II.

Borrelia turicatae, the agent of Mexican-American relapsing fever and carried in *O.* (*P.*) *turicata*, is apparently transmitted chiefly in salivary fluids, not in coxal fluids, infects a large proportion of individuals in studied tick populations, and is transovarially transmitted to at least the F_5 generation of the tick. Unlike the usual models (*B. duttoni* and *B. anserina* in their respective tick hosts), the central nerve mass of *O.* (*P.*) *turicata* is apparently not significantly invaded by *B. turicatae*. Few human infections have been recognized in the United States (see *B. hermsi* below), but in prairie states such as Oklahoma, where *O.* (*P.*) *turicata* infests homesteads and sheds, entire families have experienced relapsing fever. The disease has long been well known in much of Mexico but morbidity data are lacking. Of the 280 human relapsing fever cases reported to state health departments in the United States between 1954 and 1978, 250 were attributed to *B. hermsi* and 30 to *B. turicatae* (Burgdorfer, 1980). *Borrelia hermsi*, the agent of Herms' American relapsing fever, which infects *O.* (*P.*) *hermsi*, has received more attention than other American species. The experimental work on *B. hermsi* was reviewed by Felsenfeld (1971). Rural residents, boy scouts, and tourists from many states and foreign countries who sleep in tick-infested buildings when visiting the scenic vacationlands of the western United States are well-documented victims of the infection (see review by Hoogstraal, 1981b).

Borrelia parkeri, associated with *O.* (*P.*) *parkeri* in the western United States and Baja California, seldom if ever infects man; the tick does not usually occur in the vicinity of man and coxal fluid is emitted only after the tick has left the host. So-called variants of *B. parkeri* require further study. *Borrelia braziliensis* of *O.* (*P.*) *braziliensis* is not known to infect man. *Borrelia mazzottii* and human relapsing fever have been reported in association with Mexican and Panamanian populations attributed to *O.* (*A.*) *talaje*, but the agent and tick interrelationships and disease epidemiology require restudy. [Note that *O.* (*A.*) *talaje* is in the subgenus *Alectorobius*; all other ornithodorine vectors of *Borrelia* discussed so far are members of the subgenus *Pavlovskyella*.] *Borrelia venezuelensis* infects *O. rudis* (subgenus uncertain) and causes mild to severe human relapsing fever in Central America and northern South America. The clinical and epidemiological details are poorly documented (Felsenfeld, 1971).

I. MISCELLANEOUS BACTERIA

Soviet workers have suggested that burrow-inhabiting *Ornithodoros* can be used as indicators of the presence of the agent of plague, *Yersinia pestis* (now known as *Y. pseudotuberculosis pestis*), during interepidemic

periods. This agent retains its original properties and virulence after having remained in the body of *O.* (*P.*) *tartakovskyi* for more than 3 years (Bilyalov *et al.*, 1983).

J. TICK-BORNE PROTOZOA

The only piroplasm known to be carried and transmitted by argasids is *Babesia* (*Nuttallia*) *meri* Gunders, which circulates between *O.* (*P.*) *erraticus* and the fat sand rat, *Psammomys obesus* Cretzschmar, in the Jordan Valley (Gunders and Hadani, 1974). Other piroplasms are probably associated with burrow-inhabiting *Ornithodoros* spp. Conclusions regarding the role of *O.* (*A.*) *lahorensis* as a vector of *Theileria* (= *Gonderia*) *ovis* to sheep are discredited by Gunders and Hadani (1974).

K. TICK-BORNE FILARIA

Ornithodoros (*P.*) *tartakovskyi* infesting burrows of Central Asian gerbils (jirds), *Meriones* spp., are hosts of *Dipetalonema viteae* (also known as *D. witei, D. vitaea,* or *D. vitei*). Microfilariae of *D. viteae* develop in the tick body and can be transmitted by the biting tick for at least 200 days after initial infection (Worms *et al.*, 1961). Developing worms invade rodent subcutaneous tissue and external muscle layers, where the adult filariae are found. Hyperparasitism is a secondary means of disseminating this nematode in *O.* (*P.*) *tartakovskyi* populations (Votava *et al.*, 1974). *Ornithodoros* (*O.*) *moubata* is an efficient experimental vector of *D. viteae*. *Dipetalonema viteae* and *O.* (*P.*) *tartakovskyi* have been tools for a large variety of biomedical and immunological investigations (see Johnson *et al.*, 1974; Beaver *et al.*, 1974, and numerous more recent reports in American and European biomedical literature).

REFERENCES

Allen, J. R., and Nelson, W. A. (1982). Immunological responses to ectoparasites. *Fortschritte der Zoologie* **27**, 169–180.

Arthur, D. R. (1962). "Ticks and Disease." Pergamon, Oxford.

Austin, F. J. (1978). Johnston Atoll virus (Quaranfil group) from *Ornithodoros capensis* (Ixodoidea: Argasidae) infesting a gannet colony in New Zealand. *American Journal of Tropical Medicine and Hygiene* **27**, 1045–1048.

Avivi, A., Galun, R., and Warburg, M. (1968). Rearing and irradiation of the tick, *Ornithodoros tholozani*. (*Panel Proceedings Series, FAO/IAEA Division of Atomic Energy in Food and Agriculture, Tel Aviv*), p. 3–6.

Avivi, A., Warburg, M., and Galun, R. (1973). Ecological studies on the cave tick *Ornithodoros tholozani* and its distribution in Israel. *Israel Journal of Entomology* **8**, 109–129.

Baca, O. G., and Paretsky, D. (1983). Q fever and *Coxiella burneti:* A model for host-parasite interactions. *Microbiological Reviews* **47**, 127–149.

Balashov, Yu. S. (1972). Bloodsucking ticks (Ixodoidea)—vectors of diseases of man and animals. *Miscellaneous Publications of the Entomological Society of America* **8,** 161–376.

Balashov, Yu. S. (1983). "An Atlas of Tick Ultrastructure." Entomological Society of America, Washington, D.C.

Beaver, P. C., Orihel, T. C., and Johnson, M. H. (1974). *Dipetalonema viteae* in the experimentally infected jird, *Meriones unguiculatus*. II. Microfilaraemia in relation to worm burden. *Journal of Parasitology* **60,** 310–315.

Bedford, G. A. H. (1934). South African ticks. Part I. *Onderstepoort Journal of Veterinary Science and Animal Industry* **2,** 49–99.

Begum, F., Wisseman, C. L., Jr., and Casals, J. (1970). Tick-borne viruses of West Pakistan. IV. Viruses similar to, or identical with, Crimean hemorrhagic fever (Congo-Semunya), Wad Medani and Pak Argas 461 isolated from ticks of the Changa Manga Forest, Lahore District, and Hunza, Gilgit Agency, W. Pakistan. *American Journal of Epidemiology* **92,** 197–202.

Belashova, V. S. (1966). [*Argas vespertilionis* ticks in Kazakhstan.] *Tezisy Dokladov Pervoe Akarologicheskoe Soveshchanie* pp. 25–26. (In Russian; English translation *NAMRU*3 T629.)

Bénoit-Bazille, H. (1910). L'*Argas reflexus* (Fabr.) et son parasitisme chez l'homme. *Mémoires de la Société Zoologique de France* **22,** 261–280.

Beran, G. W., ed. (1981). *CRC Handbook Series in Zoonoses*, Section B: Viral Zoonoses.

Berge, T. O. (1975). "International Catalogue of Arboviruses Including Certain Other Viruses of Vertebrates," 2nd Ed. Publication No. (CDC) 75-8301, United States Dept. of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Atlanta, Georgia.

Bezuidenhout, J. D., and Malherbe, A. (1981). Sweating sickness: A comparative study of virulent and avirulent strains of *Hyalomma truncatum*. *Proceedings of an International Conference, Tick Research Unit, Rhodes University, Grahamstown* (South Africa), *January* pp. 7–12.

Bhat, H. R. (1983). A brief history of Kyasanur forest disease. *National Institute of Virology, Quarterly Bulletin* New Series **1,** 4–5.

Bhat, U. K. M., and Goverdhan, M. K. (1973). Transmission of Kyasanur forest disease virus by the soft tick, *Ornithodoros crossi*. *Acta Virologica, Prague* (English Ed.) **17,** 337–342.

Bilyalov, Z. A., Sviridov, G. G., Ershova, L. S., Novikov, G. S., and Tleugabylov, Kh. M. (1983). [Effect of long survival in the *Ornithodoros tartakovskyi* (Argasidae) tick body on plague agent properties.] *Parazitologiya, Leningrad* **17,** 75–76. (In Russian; English translation *NAMRU*3 T1721.)

Binnington, K. C., and Kemp, D. H. (1980). Role of tick salivary glands in feeding and disease transmission. *Advances in Parasitology* **18,** 315–339.

Bishop, D. H. L., Calisher, C. H., Casals, J., Chumakov, M. P., Gaidamovich, S. Ya., Hannoun, C., L'vov, D. K., Marshall, I. D., Oker-Blom, N., Pettersson, R. F., Porterfield, J. S., Russell, P. K., Shope, R. E., and Westaway, E. G. (1980). Bunyaviridae. *Intervirology* **14,** 125–143.

Bityukov, P. A. (1953). [Experiments in transmission of theileriasis and anaplasmosis of sheep through *Ornithodoros lahorensis* and *Haemaphysalis sulcata* ticks.] *Trudy Instituta Zoologii, Akademiya Nauk Kazakhskoy SSR* **1,** 30–36. (In Russian; English translation *NAMRU*3 T3.)

Blanc, G., and Bruneau, J. (1955). *Ornithodores* et *Coxiellose* (Q fever). *Comptes Rendus Hebdomadaires des Séance de l'Académie des Sciences* **240,** 129–131.

Boshell-M., J. (1969). Kyasanur forest disease: Ecologic considerations. *American Journal of Tropical Medicine and Hygiene* **18,** 67–80.

Brès, P. (1971). Activités du Centre Régional de Référence O.M.S. pour les arbovirus (1964–1968). *Rapport sur le Fonctionnement Technique de l'Institut Pasteur de Dakar* pp. 81–86.

Brown, S. J., and Askenase, P. W. (1983). Immune rejection of ectoparasites (ticks) by T cell and IgG_1 antibody recruitment of basophils and eosinophils. *Federation Proceedings, Federation of American Societies for Experimental Biology* **42,** 1744–1749.

Brown, S. J., Galli, S. J., Gleich, G. J., and Askenase, P. W. (1982a). Ablation of immunity to *Amblyomma americanum* by anti-basophil serum: Cooperation between basophils and eosinophils in expression of immunity to ectoparasites (ticks) in guinea pigs. *Journal of Immunology* **129,** 790–796.

Brown, S. J., Graziano, F. M., and Askenase, P. W. (1982b). Immune serum transfer of cutaneous basophil-associated resistance to ticks: Mediation by 7S IgG_1 antibodies. *Journal of Immunology* **129,** 2407–2412.

Brown, S. J., Worms, M. J., and Askenase, P. W. (1983). *Rhipicephalus appendiculatus:* Larval feeding sites in guinea pigs actively sensitized and receiving immune serum. *Experimental Parasitology* **55,** 111–120.

Brumpt, E. (J. A.) (1936a). Evolution expérimentale de l'*Ornithodoros lahorensis*. Similitude biologique des stades post-embryonnaires de cet argasiné et de ceux de l'*O. mégnini*. Röle pathogène éventuel. *Annales de Parasitologie Humaine et Comparée* **14,** 632–639.

Brumpt, E. (J. A.) (1936b). Longue conservation de 28 mois du virus du typhus de São Paulo chez l'argasiné *Ornithodorus turicata*. Non transmission par la piqûre de cet acarien. *Annales de Parasitologie Humaine et Comparée* **14,** 621–628.

Brumpt, E. (J. A.) (1949). "Précis de Parasitologie." éd. Masson, Paris.

Bulychev, V. P., Alekseev, A. N., Kostyukov, M. A., Gordeeva, Z. E., and L'vov, D. K. (1979). [Experimental transmission of Issyk Kul virus by mosquito bite *Aedes caspius caspius*.] *Meditsinskaya Parazitologiya, Moscow* **48,** 53–56. (In Russian; English translation *NAMRU3* T1724.)

Burgdorfer, W. (1951a). *Ornithodorus moubata* als Testobjekt bei Q-Fieberfällen in der Schweiz. *Acta Tropica* **8,** 44–51.

Burgdorfer, W. (1951b). Analyse des Infektionsverlaufes bei *Ornithodorus moubata* (Murray) und der natürlichen Uebertragung von *Spirochaeta duttoni*. *Acta Tropica* **8,** 193–262.

Burgdorfer, W. (1980). *Borrelia*. *In* "Manual of Clinical Microbiology" (E. H. Lennette, A. Balows, W. J. Hausler, Jr., and J. P. Truant, eds.), pp. 383–388. American Society for Microbiology, Washington, D.C.

Burgdorfer, W., and Varma, M. G. R. (1967). Trans-stadial and transovarial development of disease agents in arthropods. *Annual Review of Entomology* **12,** 347–376.

Butler, J. F., Holscher, K. H., Adeyeye, O., and Gibbs, E. P. J. (1984). Sampling techniques for burrow dwelling ticks in reference to potential swine fever virus vectors. *In* "Acarology VI" (D. A. Griffiths and C. E. Bowman, eds.), Vol. 2, pp. 1065–1074. *Proceedings of the VI International Congress of Acarology, Edinburgh, Scotland, September 1982.*

Carley, J. G., and Pope, J. H. (1962). A new species of *Borrelia* (*B. queenslandica*) from *Rattus villosissimus* in Queensland. *Australian Journal of Experimental Biology and Medical Science* **40,** 255–262.

Casals, J., and Tignor, G. H. (1980). The *Nairovirus* genus: Serological relationships. *Intervirology* **14,** 144–147.

Černý, V. (1966). *Parantricola* sg. nov., a new subgenus of argasid ticks (Ixodoidea). *Folia Parasitologica* **13,** 379–383.

Černý, V. (1967). Two new species of argasid ticks (Ixodoidea, Argasidae) from Cuba. *Folia Parasitologica* **14,** 141–148.

Chastel, C. (1980). Arbovirus transmis par des tiques et associés à des oiseaux de mer; une revue générale. *Médecine Tropicale, Marseille* **40,** 535–548.

Chastel, C., Bailly-Choumara, H., and Le Lay-Roguès, G. (1981). Pouvoir pathogène naturel pour l'homme d'un variant antigénique du virus Soldado isolé au Maroc. *Bulletin de la Société de Pathologie Exotique* **74,** 499–505.

Chastel, C., Le Goff, F., and Le Lay-Roguès, G. (1983). Antigenic variants of the Soldado virus (*Nairovirus*, Bunyaviridae) isolated in different parts of the world. *Acta Virologica, Prague* (English Edition) **27,** 51–58.

Chastel, C., Guiguen, C., Quillien, M. C., Le Lay-Roguès, G., and Beauco[u]rnu, J. C. (1984). Visualisation du virus Soldado par la microscopie électronique dans les tissus de la tique vectrice *Ornithodoros* (*Alectorobius*) *maritimus* Vermeil et Marguet, 1967. *Annales de Parasitologie Humaine et Comparée* **59,** 1–6.

Chellappa, D. J. (1973). Note on spinose ear tick infestation in man and domestic animals in India and its control. *Madras Agricultural Journal* **60,** 656–658.

Chibwana, J. A. (1983). A case of congenital relapsing fever. *Medicine Digest* **9,** 60–61.

Chodziesner, M. (1924). Beiträge zur Kenntnis der Zecken mit besonderer Berücksichtigung der Gattung *Hyalomma* Koch. *Zoologische Jahrbücher* **47,** 505–572.

Clifford, C. M. (1979). Tick-borne viruses of seabirds. *Proceedings of the 2nd International Symposium on Arctic Arboviruses, Mont Gabriel, Canada, May 1977* pp. 83–100.

Clifford, C. M., Jr., Kohls, G. M., and Sonenshine, D. E. (1964). The systematics of the subfamily Ornithodorinae (Acarina: Argasidae). I. The genera and subgenera. *Annals of the Entomological Society of America* **57,** 429–437.

Clifford, C. M., Hoogstraal, H., Keirans, J. E., Rice, R. C. A., and Dale, W. E. (1978). Observations on the subgenus *Argas* (Ixodoidea: Argasidae: *Argas*). 14. Identity and biological observations of *Argas* (*A.*) *cucumerinus* from Peruvian seaside cliffs and a summary of the status of the subgenus in the Neotropical Faunal Region. *Journal of Medical Entomology* **15,** 57–73.

Clifford, C. M., Hoogstraal, H., Radovsky, F. J., Stiller, D., and Keirans, J. E. (1980). *Ornithodoros* (*Alectorobius*) *amblus* (Acarina: Ixodoidea: Argasidae): Identity, marine bird and human hosts, virus infections, and distribution in Peru. *Journal of Parasitology* **66,** 312–323.

Clifford, C. M., Hoogstraal, H., Roshdy, M. A., Wassef, H. Y., Keirans, J. E., and Corwin, M. D. (1984). Observations on the subgenus *Argas* (Ixodoidea: Argasidae: *Argas*). 18. Haller's organ roof and anterior pit setae. *Journal of Parasitology* **69,** 967–976.

Coles, J. D. W. A. (1941). An epizootic in seabirds: A visit to Dassen and Malagas Islands. *Journal of the South African Veterinary Medical Association* **12,** 23–30.

Condy, J. B., Norval, R. A. I., Blackburn, N. K., and Clemence, P. (1980). The effects of the bites of *Argas brumpti* (Acarina: Argasidae) on humans. *Central African Journal of Medicine* **26,** 212–213.

Converse, J. D., and Moussa, M. I. (1982). Quaranfil virus from *Hyalomma dromedarii* (Acari: Ixodidae) collected in Kuwait, Iraq and Yemen. *Journal of Medical Entomology* **19,** 209–210.

Converse, J. D., Hoogstraal, H., Moussa, M. I., Casals, J., and Kaiser, M. N. (1975). Pretoria virus: A new African agent in the tickborne Dera Ghazi Khan (DGK) group and antigenic relationships within the DGK group. *Journal of Medical Entomology* **12,** 202–205.

Cooley, R. A., and Kohls, G. M. (1941). *Ornithodoros viguerasi*, a new species of tick from bats in Cuba (Acarina: Ixodoidea). *Public Health Reports, United States Public Health Service* **56,** 396–399.

Cooley, R. A., and Kohls, G. M. (1944). The Argasidae of North America, Central America and Cuba. *American Midland Naturalist* (*Monograph*) **1,** 1–152.

Cunliffe, N. (1914). Observations on *Argas brumpti*, Neumann, 1907. *Parasitology* **6,** 379–381.

Daiter, A. B. (1963). [Experimental infection of several arthropods on Q-fever patients.] *In*

"Exanthematous Fever and Infections With Natural Foci" (M. Ya. Nikitin, ed.), Vol. 25, pp. 92–100. Akademiy Meditsinskikh Nauk SSSR, Leningrad. (In Russian; English translation *NIH* No. 8-14-64.)

Daiter, A. B. (1979). Ecology of the agents of obligate- and facultative-transmissive endemic rickettsiosis in respect to their vectors. *Abstracts of the 14th Pacific Science Congress. Committee M: Public Health and Medical Sciences, Khabarovsk, August* p. 24–25.

Da Massa, A. J., and Adler, H. E. (1979). Avian spirochetosis: Natural transmission by *Argas* (*Persicargas*) *sanchezi* (Ixodoidea: Argasidae) and existence of different serologic and immunologic types of *Borrelia anserina* in the United States. *American Journal of Veterinary Research* **40,** 154–157.

Darwish, M. A., and Hoogstraal, H. (1981). Arboviruses infecting humans and lower animals in Egypt: A review of thirty years of research. *Journal of the Egyptian Public Health Association* **56,** 1–112.

Darwish, M. A., Hoogstraal, H., Roberts, T. J., Ahmed, I. P., and Omar, F. (1983a). A seroepidemiological survey for certain arboviruses (Togaviridae) in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **77,** 442–445.

Darwish, M. A., Hoogstraal, H., Roberts, T. J., Ghazi, R., and Amer, T. (1983b). A seroepidemiological survey for Bunyaviridae and certain other arboviruses in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **77,** 446–450.

Da Serra Freire, N. M. (1983). Tick paralysis in Brazil. *Tropical Animal Health and Production* **15,** 124–126.

Davis, G. E. (1942a). The Rocky Mountain spotted fever rickettsia in the tick genus *Ornithodoros*. *Proceedings of the 6th Pacific Science Congress, Berkeley, Stanford and San Francisco, July–August 1939* **5,** 577–579.

Davis, G. E. (1942b). *Ornithodoros parkeri* and relapsing fever spirochetes in southern Idaho. *Public Health Reports, United States Public Health Service* **57,** 1501–1503.

Davis, G. E. (1942c). Species unity or plurality of the relapsing fever spirochetes. *Publications of the American Association for the Advancement of Science* No. 18, 41–47.

Davis, G. E. (1943a). Relapsing fever: The tick *Ornithodoros turicata* as a spirochetal reservoir. *Public Health Reports, United States Public Health Service* **58,** 839–842.

Davis, G. E. (1943b). American Q fever: Experimental transmission by the argasid ticks *Ornithodoros moubata* and *O. hermsi*. *Public Health Reports, United States Public Health Service* **58,** 984–987.

Davis, G. E. (1943c). Experimental transmission of the spotted fevers of the United States, Colombia, and Brazil by the argasid tick *Ornithodoros parkeri*. *Public Health Reports, United States Public Health Service* **58,** 1201–1208.

De Clercq, A. G., Meheus, A. Z., De Pierpont, E., and Nyirashema, C. (1975). Single-dose doxycycline treatment of tick-borne relapsing fever. *East African Medical Journal* **52,** 428–429.

De La Cruz, J. (1978a). Notas adicionales a la fauna de garrapatas (Ixodoidea) de Cuba. VI. Cuatro nuevas especies del genero *Antricola* Cooley et Kohls, 1942 (Argasidae: Ornithodorinae). *Poeyana* No. 184, 1–17.

De La Cruz, J. (1978b). Composición zoogeográfica de la fauna de garrapatas (Acarina: Ixodoidea) de Cuba. *Poeyana* No. 185, 1–5.

Delpy, L., and Kaweh, M. (1937). Transmission de *Bacillus anthracis* à l'homme par *Argas persicus* Oken 1818. *Revue de Pathologie Comparée et d'Hygiène Générale* **37,** 1229–1234.

De Magalhães, F. E. P. (1979). Paralisia em *Gallus gallus* L. induzida por larvas de *Argas* (*Persicargas*) *miniatus* Koch, 1844 (Ixodoidea, Argasidae). *Resumen IV Congreso de la Sociedad Brasiliana de Parasitologia, Campinas, São Paulo* p. 99.

Dhanda, V., and Bhat, H. R. (1971). *Haemaphysalis* (*Herpetobia*) *sundrai* Sharif (Ixodoidea: Ixodidae), a tick parasitizing sheep in the western Himalayas, redescription of

female, description of male, and ecological observations. *Journal of Parasitology* **57,** 646–650.

Diab, F. M., and Soliman, Z. R. (1977). An experimental study of *Borrelia anserina* in four species of *Argas* ticks. 1. Spirochete localization and densities. *Zeitschrift für Parasitenkunde* **53,** 201–212.

Eads, R. B., and Campos, E. G. (1984). Human parasitism by *Otobius megnini* (Acari: Argasidae) in New Mexico, USA. *Journal of Medical Entomology* **21,** 244.

El Shoura, S. M., Hoogstraal, H., and Roshdy, M. A. (1984). *Nuttalliella namaqua* (Ixodoidea: Nuttalliellidae): female internal morphology. *Journal of Parasitology* **70,** 114–120.

Enright, J. B., Behymer, D. E., Franti, C. E., Dutson, V. J., Longhurst, W. M., Wright, M. E., and Goggin, J. E. (1971). The behavior of Q fever rickettsiae isolated from wild animals in northern California. *Journal of Wildlife Diseases* **7,** 83–90.

Fedorov, V. G. (1968). [Ixodoidea ticks on humans in western Siberia.] *Meditsinskaya Parazitologiya, Moscow* **37,** 615–616. (In Russian; English translation *NAMRU*3 T390.)

Felsenfeld, O. (1971). "*Borrelia*. Strains, Vectors, Human and Animal Borreliosis." Warren H. Green, St. Louis, Missouri.

Filippova, N. A. (1961). [Material on ticks belonging to the subfamily Argasinae. Part 1. Adult ticks and larvae of the genus *Argas* Latr., group *reflexus*.] *Zoologicheskii Zhurnal* **40,** 1815–1826. (In Russian; English translation *NAMRU*3 T63.)

Filippova, N. A. (1966). [Argasid Ticks (Argasidae).] *Fauna SSSR, Paukoobraznye* **4,** 1–255. (In Russian; English translation *NAMRU*3 T600.)

Fine, P. E. M. (1975). Vectors and vertical transmission: An epidemiologic perspective. *Annals of the New York Academy of Sciences* **266,** 173–194.

Fine, P. E. M. (1981). Epidemiological principles of vector-mediated transmission. *In* "Vectors of Disease Agents: Interactions with Plants, Animals, and Man" (J. J. McKelvey, Jr., B.F. Eldridge, and K. Maramorosch, eds.), p. 77–91 Praeger, New York.

Furman, D. P., and Loomis, E. C. (1984). The ticks of California (Acari: Ixodida). *Bulletin of the California Insect Survey* No. 25.

Gaber, M. S., Khalil, G. M., Hoogstraal, H., and Aboul-Nasr, A. E. (1984). *Borrelia crocidurae* localization and transmission in *Ornithodoros erraticus* and *O. savignyi*. *Parasitology* **88,** 403–413.

Galuzo, I. G. (1957). ["Argasid Ticks (Argasidae) and their Epizootological Significance. (Systematics Biology, Harmfulness and Control)."] Akademiya Nauk Kazakhskoi SSR, Institut Zoologii, Alma-Ata. (In Russian; English translation of pp. 83–85: *NAMRU*3 T4.)

Garcia, R. (1962). Carbon dioxide as an attractant for certain ticks (Acarina: Argasidae and Ixodidae). *Annals of the Entomological Society of America* **55,** 605.

Garcia, R. (1964). Studies on the ecology of *Ornithodoros coriaceus* Koch (Acarina: Argasidae). *Dissertation Abstracts* **24,** 5621–5622.

Garcia, R. (1965). Collection of *Dermacentor andersoni* (Stiles) with carbon dioxide and its application in studies of Colorado tick fever virus. *Americal Journal of Tropical Medicine and Hygiene* **14,** 1090–1093.

Garcia, R. (1969). Reaction of the winter tick, *Dermacentor albipictus* (Packard), to CO_2. *Journal of Medical Entomology* **6,** 286.

Gavrichenkov, A. I. (1957). [Tick paralysis in sheep.] *Veterinariya* **34,** 70–71. (In Russian; English translation *NAMRU*3 T1687.)

Gil Fernandez, M. del C. (1960). "Cultivo de los Simbiotas del *Argas persicus*." Thesis. Consejo Superior de Investigaciones Cientificas, Instituto Jaime Ferran, Madrid.

Giroud, P., and Yassemi, H. (1952). À propos de la fièvre Q et sa diffusion dans le monde, sa constatation en Iran. *Bulletin de la Société de Pathologie Exotique* **45,** 23–24.

Gorman, B. M. (1979). Variation in orbiviruses. *Journal of General Virology* **44,** 1–15.

Gorman, B. M. (1983). On the evolution of orbiviruses. *Intervirology* **20,** 169–180.

Gothe, R. (1971). Ein Beitrag zum Wirt-Parasit-Verhältnis von *Aegyptianella pullorum* Carpano, 1928, im biologischen Überträger *Argas* (*Persicargas*) *persicus* (Oken, 1818) und im Wirbeltierwirt *Gallus gallus domesticus* L. *Fortschritte der Veterinärmedizin* (*Suppl.*) **16,** 1–144.

Gothe, R. (1978). New aspects of the epizootiology of aegyptianellosis in poultry. *Proceedings of an International Conference, Edinburgh, Sept.–Oct.* 1976 pp. 201–204.

Gothe, R., and Englert, R. (1978). Quantitative Untersuchungen zur Toxinwirkung von Larven neoarktischer *Persicargas* spp. bei Hühnern. *Zentralblatt für Veterinärmedizin Serie B* **25,** 122–133.

Gothe, R., and Kreier, J. P. (1977). *Aegyptianella, Eperythrozoon,* and *Haemobartonella. In* "Parasitic Protozoa" (J. P. Kreier, ed.), Vol. 4, pp. 251–294. Academic Press, New York.

Gothe, R., and Schrecke, W. (1972a). Zur epizootiologischen Bedeutung von *Persicargas*-Zecken der Hühner in Transvaal. *Berliner und Münchener Tierärztliche Wochenschrift* **85,** 9–11.

Gothe, R., and Schrecke, W. (1972b). Zur Epizootiologie der Aegyptianellose des Geflügels. *Zeitschrift für Parasitenkunde* **39,** 64–65.

Gothe, R., Kunze, K., and Hoogstraal, H. (1979). The mechanisms of pathogenicity in the tick paralyses. *Journal of Medical Entomology* **16,** 357–369.

Gothe, R., Buchheim, C., and Schrecke, W. (1981a). *Argas* (*Persicargas*) *persicus* und *Argas* (*Argas*) *africolumbae* als natürliche biologische Überträger von *Borrelia anserina* und *Aegyptianella pullorum* in Obervolta. *Berliner und Münchener Tierärztliche Wochenschrift* **94,** 280–285.

Gothe, R., Buchheim, C., and Schrecke, W. (1981b). Zur Paralyse-induzierenden Kapazität wildstämmiger *Argas* (*Persicargas*) *persicus*- und *Argas* (*Argas*) *africolumbae*-Populationen aus Obervolta. *Berliner und Münchener Tierärztliche Wochenschrift* **94,** 299–302.

Goubau, P. F. J., and Munyangeyo, C. (1983). Fièvre récurrente à tiques et grossesse. Une étude clinique au Rwanda. *Annales de la Société de Médecine Tropicale* **63,** 347–355.

Gould, E. A., Chanas, A. C., Buckley, A., and Varma, M. G. R. (1983). Immunofluorescence studies on the antigenic interrelationships of the Hughes virus serogroup (genus *Nairovirus*) and identification of a new strain. *Journal of General Virology* **64,** 739–742.

Gromashevsky, V. L., Sidorova, G. A., Andreev, V. P., Skvortsova, T. M., Kurbanov, M., and L'vov, D. K. (1975). [New arboviruses in Central Asia.] *Materialy IX Simpoziuma, Tadzhikskaya SSR, g Dushanbe, Oktyabr' G,* pp. 26–27. (In Russian; English translation *NAMRU*3 T1118.)

Grzywacz, M., and Kuźmicki, R. (1975). [A case of *Argas reflexus* (Fabricius 1794) attack on man.] *Wiadomości Lekarskie* **28,** 1571–1577. (In Polish; English translation *NAMRU*3 T1548.)

Gunders, A. E., and Hadani, A. (1974). Transmission of mammalian piroplasm by an argasid tick. *Nature* (*London*) **247,** 225–226.

Haberkorn, A. (1963a). Untersuchungen über das Verhalten von Rückfallfieberspirochaeten insbesondere der *Borrelia crocidurae*-Gruppe in der Kleiderlaus (1. Teil). *Zeitschrift für Tropenmedizin und Parasitologie* **14,** 95–114.

Haberkorn, A. (1963b). Untersuchungen über das Verhalten von Rückfallfieberspirochaeten insbesondere der *Borrelia crocidurae*-Gruppe in der Kleiderlaus (2. Teil). *Zeitschrift für Tropenmedizin und Parasitologie* **14,** 209–239.

Hair, J. A., Hoch, A. L., Barker, R. W., and Semtner, P. J. (1972). A method of collecting nymphal and adult lone star ticks, *Amblyomma americanum* (L.) (Acarina: Ixodidae), from woodlots. *Journal of Medical Entomology* **9,** 153–155.

Hannoun, C., and Rau, U. (1970). Experimental transmission of certain arboviruses by *Argas reflexus* (Fabricius, 1794). *Folia Parasitologica* **17,** 365–366.

Heisch, R. B. (1953). On a spirochaete isolated from *Ornithodoros graingeri*. *Parasitology* **43,** 133–135.

Helmy, N., Khalil, G. M., and Hoogstraal, H. (1983). Hyperparasitism in *Ornithodoros erraticus*. *Journal of Parasitology* **69,** 229–233.

Henry, M. (1938). The kangaroo tick. *Australian Veterinary Journal* **14,** 69–71.

Herrin, C. S., and Beck, D. E. (1965). Observations on the biology, anatomy, and morphology of *Otobius lagophilus* Cooley and Kohls. *Brigham Young University Science Bulletin, Biological Series* **6,** 1–19.

Hoffmann, A. (1962). Monografia de los Ixodoidea de Mexico. I. Parte. *Revista de la Sociedad Mexicana de Historia Natural* **23,** 191–307.

Honzáková, E., Černý, V., and Daniel, M. (1983). The life cycle of *Ornithodoros tadaridae* Černý et Dusbábek (Argasidae) under laboratory conditions. *Folia Parasitologica* **30,** 357–361.

Hoogstraal, H. (1953). *Ornithodoros salahi* sp. nov. (Ixodoidea, Argasidae) from the Cairo Citadel, with notes on *O. piriformis* Warburton, 1918 and *O. batuensis* Hirst, 1929. *Journal of Parasitology* **39,** 256–263.

Hoogstraal, H. (1955). Bat ticks of the genus *Argas* (Ixodoidea, Argasidae). 1. The subgenus *Chiropterargas*. *Fieldiana: Zoology* **37,** 579–600.

Hoogstraal, H. (1956). "African Ixodoidea. I. Ticks of the Sudan (with Special Reference to Equatoria Province and with Preliminary Reviews of the Genera *Boophilus*, *Margaropus*, and *Hyalomma*)." Department of the Navy, Bureau of Medicine and Surgery, Washington, D.C.

Hoogstraal, H. (1957). Bat ticks of the genus *Argas* (Ixodoidea, Argasidae). 2. *Secretargas* new subgenus and *A. transgariepinus* White, 1846, its adult and immature stages; with a definition of the subgenus *Argas*. *Annals of the Entomological Society of America* **50,** 544–549.

Hoogstraal, H. (1958). Bat ticks of the genus *Argas* (Ixodoidea, Argasidae). 3. The subgenus *Carios*, a redescription of *A.* (*C.*) *vespertilionis* (Latreille, 1802), and variation within an Egyptian population. *Annals of the Entomological Society of America* **51,** 19–26.

Hoogstraal, H. (1967). Ticks in relation to human diseases caused by *Rickettsia* species. *Annual Review of Entomology* **12,** 377–420.

Hoogstraal, H. (1978). Biology of ticks. *Proceedings of an International Conference, Edinburgh, Sept.–Oct. 1976* pp. 3–14.

Hoogstraal, H. (1979a). The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. *Journal of Medical Entomology* **15,** 307–417.

Hoogstraal, H. (1979b). Ticks and spirochetes. *Acta Tropica* **36,** 133–136.

Hoogstraal, H. (1980). Established and emerging concepts regarding tick-associated viruses, and unanswered questions. *Zentralblatt für Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene, Abteilung 1, Suppl.* **9,** 49–63.

Hoogstraal, H. (1981a). Ticks (Ixodoidea) from Oman. *Journal of Oman Studies*, Special report No. 2, 265–272.

Hoogstraal, H. (1981b). Changing patterns of tickborne diseases in modern society. *Annual Review of Entomology* **26,** 75–99.

Hoogstraal, H. (1970–1984). "Bibliography of Ticks and Tickborne Diseases from Homer (about 800 B.C.) to 31 Dec. 1969 (to 1983)." 1. Introductory Remarks and Explanations. Authors A–E. 504 pp. (1970). 2. Authors F–M. 495 pp. (1970). 3. Authors N–S. 435 pp. (1971). 4. Authors T–Z. 355 pp. (1972). 5I. To 31 Dec. 1973. 492 pp. (1974). 5II. To 31 Dec. 1976. 455 pp. 6. To 31 Dec. 1979. 407 pp. (1981). 7. To 31 Dec. 1981. 219 pp. (1982). 8. To 31 Dec. 1983. (in press, 1984). *Special Publications, NAMRU3, Cairo.*

Hoogstraal, H. (1985). Manuscript in preparation.

Hoogstraal, H., and Aeschlimann, A. 91982). Tick-host specificity. *Bulletin de la Société Entomologique Suisse* **55,** 5–32.

Hoogstraal, H., and Feare, C. J. (1984). Ticks and tickborne viruses. *In* "Biogeography and Ecology of the Seychelles Islands" (D. R. Stoddart, ed.), pp. 267–280. Junk, The Hague.

Hoogstraal, H., and Gallagher, M. D. (1982). Blisters, pruritis, and fever after bites by the Arabian tick *Ornithodoros* (*Alectorobius*) *muesebecki*. *Lancet* No. 8293, 288–289.

Hoogstraal, H., and Kim, K. C. (1985). Tick and mammal coevolution. *In* "Coevolution of Parasitic Arthropods and Mammals" (K. C. Kim, ed.). Wiley, New York, in press.

Hoogstraal, H., and Kohls, G. M. (1966). *Argas* (*Microargas*) *transversus* Banks (new subgenus) (Ixodoidea, Argasidae), a diminutive parasite of the Galapagos giant tortoise: Redescription of the holotype male and description of the larva. *Annals of the Entomological Society of America* **59,** 247–252.

Hoogstraal, H., Uilenberg, G., and Blanc, C. P. (1967). The *Argas* subgenus *Secretargas* (Ixodoidea, Argasidae) in Madagascar: Description of *A.* (*S.*) *echinops*, new species, and of the adults and nymph of *A.* (*S.*) *hoogstraali*. *Annals of the Entomological Society of America* **60,** 149–162.

Hoogstraal, H., Oliver, R. M., and Guirgis, S. S. (1970). Larva, nymph, and life cycle of *Ornithodoros* (*Alectorobius*) *muesebecki* (Ixodoidea: Argasidae), a virus-infected parasite of birds and petroleum industry employees in the Arabian Gulf. *Annals of the Entomological Society of America* **63,** 1762–1768.

Hoogstraal, H., Clifford, C. M., and Keirans, J. E. (1973). *Argas* (*Microargas*) *transversus* (Ixodoidea: Argasidae) of Galapagos giant tortoises: Description of the female and nymph. *Annals of the Entomological Society of America* **66,** 727–732.

Hoogstraal, H., Kaiser, M. N., Walker, J. B., Ledger, J. A., Converse, J. D., and Rice, R. C. A. (1975). Observations on the subgenus *Argas* (Ixodoidea: Argasidae: *Argas*). 10. *A.* (*A.*) *africolumbae*, n. sp., a Pretoria virus-infected parasite of birds in southern and eastern Africa. *Journal of Medical Entomology* **12,** 194–201.

Hoogstraal, H., Kaiser, M. N., and Easton, E. R. (1976a). *Ornithodoros* (*Alectorobius*) *capensis* Neumann (Ixodoidea: Argasidae) parasitizing a human and birds nesting on islands in East African lakes. *Journal of Medical Entomology* **12,** 703–704.

Hoogstraal, H., Clifford, C. M., Keirans, J. E., Kaiser, M. N., and Evans, D. E. (1976b). The *Ornithodoros* (*Alectorobius*) *capensis* group (Acarina: Ixodoidea: Argasidae) of the Palearctic and Oriental Regions. *O.* (*A.*) *maritimus*: Identity, marine bird hosts, virus infections, and distribution in western Europe and Northwestern Africa. *Journal of Parasitology* **62,** 799–810.

Hoogstraal, H., Moorhouse, D. E., Wolf, G., and Wassef, H. Y. (1977a). Bat ticks of the genus *Argas* (Ixodoidea: Argasidae). *A.* (*Carios*) *macrodermae*, new species, from Queensland, Australia. *Annals of the Entomological Society of America* **70,** 861–870.

Hoogstraal, H., Wassef, H. Y., Easton, E. R., and Dixon, J. E. W. (1977b). Observations on the subgenus *Argas* (Ixodoidea: Argasidae: *Argas*). 12. *Argas* (*A.*) *africolumbae*: Variation, bird hosts, and distribution in Kenya, Tanzania, and South and South-West Africa. *Journal of Medical Entomology* **13,** 441–445.

Hoogstraal, H., Clifford, C. M., and Keirans, J. E. (1979a). The *Ornithodoros* (*Alectorobius*) *capensis* group (Acarina: Ixodoidea: Argasidae) of the Palearctic and Oriental Regions. *O.* (*A.*) *coniceps*: Identity, bird and mammal hosts, virus infections, and distribution in Europe, Africa, and Asia. *Journal of Parasitology* **65,** 395–407.

Hoogstraal, H., Clifford, C. M., Keirans, J. E., and Wassef, H. Y. (1979b). Recent developments in biomedical knowledge of *Argas* ticks (Ixodoidea: Argasidae). *Proceedings of the 5th International Congress of Acarology, Michigan State University, East Lansing, August 1978* **2,** 269–278.

Hoogstraal, H., Clifford, C. M., Roshdy, M. A., and Keirans, J. E. (1984). The subgenus *Persicargas* (Ixodoidea: Argasidae: *Argas*). 38. Haller's organ roof and anterior pit setae in *Persicargas* and *Microargas*. *Journal of Parasitology* **69,** 977–985.

Hopla, C. E., and Loye, J. E. (1984). The ectoparasites and microorganisms associated with cliff swallows in west-central Oklahoma. I. Ticks and fleas. *Bulletin of the Society of Vector Ecology* **8,** 111–121.

Howell, C. J. (1966). Collection of salivary gland secretion from the argasid *Ornithodoros savignyi* Audouin (1827) by the use of a pharmacological stimulant. *Journal of the South African Veterinary Medical Association* **37,** 236–239.

Howell, C. J., Neitz, A. W. H., and Potgieter, D. J. J. (1975). Some toxic, physical and chemical properties of the oral secretion of the sand tampan, *Ornithodoros savignyi* Audouin (1827). *Onderstepoort Journal of Veterinary Research* **42,** 99–102.

Hughes, L. E., Casper, E. A., and Clifford, C. M. (1974). Persistence of Colorado tick fever virus in red blood cells. *American Journal of Tropical Medicine and Hygiene* **23,** 530–532.

Ignatovich, V. F. (1977). Antigenic relations of *Rickettsia prowazekii* and *Rickettsia canada*, established in the study of sera of patients with Brill's disease. *Journal of Hygiene and Epidemiology* **21,** 55–60.

Ignatovich, V. F., and Grokhovskaya, I. M. (1967a). [Use of ticks in determination of ecological differences between *Rickettsia*.] *Tezisy Dokladov na III Vsesoyuznom Soveshchanii po Teoreticheskoy i Prikladnoy Akarologii, Oktyabra, G, Tashkent* pp. 123–124. (In Russian; English translation *NAMRU3* T1712.)

Ignatovich, V. F., and Grokhovskaya, I. M. (1976b). [Inter-relationships between Ixodoidea ticks and *Rickettsia canada*.] *Meditsinskaya Parazitologiya, Moscow* **45,** 313–317. (In Russian; English translation *NAMRU3* T1713.)

Jacobs, L., and Arambulo, P., eds. (1982). *CRC Handbook Series in Zoonoses, Section C: Parasitic Zoonoses* **1.**

Jellison, W. L., Bell, E. J., Huebner, R. J., Parker, R. R., and Welsh, H. H. (1948). Q fever studies in southern California. IV. Occurrence of *Coxiella burneti* in the spinose ear tick, *Otobius megnini*. *Public Health Reports, United States Public Health Service* **63,** 1483–1489.

Johnson, M. H., Orihel, T. C., and Beaver, P. C. (1974). *Dipetalonema viteae* in the experimentally infected jird, *Meriones unguiculatus*. I. Insemination, development from egg to microfilaria, reinsemination, and longevity of mated and unmated worms. *Journal of Parasitology* **60,** 302–309.

Jones, E. K., and Clifford, C. M. (1972). The systematics of the subfamily Ornithodorinae (Acarina: Argasidae). V. A revised key to larval Argasidae of the Western Hemisphere and description of seven new species of *Ornithodoros*. *Annals of the Entomological Society of America* **65,** 730–740.

Jupp, P. G., and McIntosh, B. M. (1981). Ticks and arthropod-borne viruses in South Africa. *Proceedings of an International Conference, Tick Research Unit, Rhodes University, Grahamstown (South Africa), January* pp. 177–180.

Jupp, P. G., McIntosh, B. M., Dos Santos, I., and De Moor, P. (1981). Laboratory vector studies on six mosquito and one tick species with chikungunya virus. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **75,** 15–19.

Kaiser, M. N. (1966a). The subgenus *Periscargas* (Ixodoidea, Argasidae, *Argas*). 3. The life cycle of *A. (P.) arboreus*, and a standardized rearing method for argasid ticks. *Annals of the Entomological Society of America* **59,** 496–502.

Kaiser, M. N. (1966b). Viruses in ticks. I. Natural infections of *Argas (Persicargas) arboreus* by Quaranfil and Nyamanini viruses and absence of infections in *A. (P.) persicus* in Egypt. *American Journal of Tropical Medicine and Hygiene* **15,** 964–975.

Kaiser, M. N. (1966c). Viruses in ticks. II. Experimental transmission of Quaranfil virus by *Argas (Persicargas) arboreus* and *A. (P.) persicus*. *American Journal of Tropical Medicine and Hygiene* **15,** 975–985.

Kaiser, M. N., and Hoogstraal, H. (1968). Simple field and laboratory method for recovering living ticks (Ixodoidea) from hosts. *Journal of Parasitology* **54,** 188–189.

Karimov, S. K., L'vov, D. K., Rogovaya, S. G., Kiryushchenko, T. V., Ukbaeva, T. D., Drobischchenko, N. I., Kondrashina, N. G., Skvortsova, T. M., Gromashevsky, V. L., and Krasnoborodkina, N. I. (1978). [Isolation of Karshi virus from *Hyalomma asiaticum* ticks in the Alma-Ata Oblast, Kazakh SSR.] *Meditsinskaya Parazitologiya, Moscow* **47,** 50–51. (In Russian; English translation *NAMRU3* T1382.)

Keirans, J. E., Clifford, C. M., Hoogstraal, H., and Easton, E. R. (1976). Discovery of *Nuttalliella namaqua* Bedford (Acarina: Ixodoidea: Nuttalliellidae) in Tanzania and redescription of the female based on scanning electron microscopy. *Annals of the Entomological Society of America* **69,** 926–932.

Keirans, J. E., Hoogstraal, H., and Clifford, C. M. (1977a). *Ornithodoros* (*Proknekalia*) *vansomereni*, new subgenus and new species (Acarina: Ixodoidea: Argasidae), a swallow nest parasite in Kenya. *Annals of the Entomological Society of America* **70,** 221–228.

Keirans, J. E., Clifford, C. M., and Reddell, J. R. (1977b). Description of immature stages of *Nothoaspis redelli* (Ixodoidea: Argasidae) from bat caves in Mexico. *Annals of the Entomological Society of America* **70,** 591–595.

Keirans, J. E., Hoogstraal, H., and Clifford, C. M. (1979). Observations on the subgenus *Argas* (Ixodoidea: Argasidae: *Argas*). 16. *Argas* (*A.*) *moreli*, new species, and keys to Neotropical species of the subgenus. *Journal of Medical Entomology* **15,** 246–252.

Keirans, J. E., Clifford, C. M., and Hoogstraal, H. (1980). Identity of the nymphs and adults of the Galapagos iguanid lizard parasites, *Ornithodoros* (*Alectorobius*) *darwini* and *O.* (*A.*) *galapagensis* (Ixodoidea: Argasidae). *Journal of Medical Entomology* **17,** 427–438.

Keirans, J. E., Clifford, C. M., and Hoogstraal, H. (1984). *Ornithodoros* (*Alectorobius*) *yunkeri* new species (Acari: Ixodoidea: Argasidae) from seabirds and seabird nesting sites in the Galapagos Islands. *Journal of Medical Entomology* **21,** 344–350.

Kemp, D. H., St. George, T. D., and McKilligan, N. (1982). Bird ticks and arboviruses in Australia. *Proceedings of the 3rd Symposium, Arbovirus Research in Australia, Brisbane, February* pp. 152–157.

Khalil, G. M., and Metwally, S. A. (1974). Observations on the subgenus *Argas* (Ixodoidea: Argasidae: *Argas*). 8. The life cycle of *A.* (*A.*) *hermanni*. *Journal of Medical Entomology* **11,** 355–362.

Khalil, G. M., Hoogstraal, H., and Oliver, J. H., Jr. (1980). Biological evaluation of the systematic validity of the African *Argas* (*Persicargas*) *arboreus* and the Asian-Australian *A.* (*P.*) *robertsi* (Ixodoidea: Argasidae). *International Journal of Parasitology* **10,** 253–259.

Kitaoka, S., and Suzuki, H. (1973). *Ornithodoros* (*Alectorobius*) *sawaii* sp.n. (Ixodoidea, Argasidae) associated with the streaked shearwater, *Colonectris leucomelas*, from the Amami-oshima islands, Japan. *National Institute of Animal Health Quarterly, Tokyo* **13,** 142–148.

Kohls, G. M. (1937). Tick rearing methods with special reference to the Rocky Mountain wood tick, *Dermacentor andersoni* Stiles. *In* "Culture Methods for Invertebrate Animals" (P. S. Galtsoff, F. E. Lutz, P. S. Welch, and J. G. Needham, eds.), pp. 246–256. Comstock, Ithaca, New York.

Kohls, G. M., and Hoogstraal, H. (1961). Observations on the subgenus *Argas* (Ixodoidea, Argasidae, *Argas*). 4. *A. neghmei*, new species, from poultry houses and human habitations in northern Chile. *Annals of the Entomological Society of America* **54,** 844–851.

Kohls, G. M., Sonenshine, D. E., and Clifford, C. M. (1965). The systematics of the subfamily Ornithodorinae (Acarina: Argasidae). II. Identification of the larvae of the Western Hemisphere and descriptions of three new species. *Annals of the Entomological Society of America* **58,** 331–364.

Kohls, G. M., Clifford, C. M., and Jones, E. K. (1969). The systematics of the subfamily Ornithodorinae (Acarina: Argasidae). IV. Eight new species of *Ornithodoros* from the Western Hemisphere. *Annals of the Entomological Society of America* **62,** 1035–1043.

Korenberg, E. I. (1976). Some contemporary aspects of natural focality and epidemiology of tick-borne encephalitis. *Folia Parasitologica* **23,** 357–366.

Korenberg, E. I. (1979). [Small mammals and problem of natural focality of tickborne encephalitis.] *Zoologicheskiy Zhurnal* **58,** 542–552. (In Russian; English translation *NAMRU3* T1416.)

Kostyukov, M. A. (1981). [Study of ecology of Issyk Kul virus.] *In* "Arboviruses" (S. Ya. Gaidamovich, ed.), pp. 78–82. Akademiya Meditsinskikh Nauk SSSR, Moscow. (In Russian; English translation *NAMRU3* T1569.)

Kostyukov, M. A., Bulychev, V. P., and Lapina, T. F. (1982). [Experimental infection of *Aedes caspius caspius* Pall. mosquitoes on dwarf bats—*Vespertilio pipistrellus* infected with Issyk-Kul virus with subsequent virus transmission to susceptible animals.] *Meditsinskaya Parazitologiya, Moscow* **50,** 78–79. (In Russian; English translation *NAMRU3* T1699.)

Kraiss, A., and Gothe, R. (1982). The life cycle of *Argas* (*Argas*) *africolumbae* under constant abiotic and biotic conditions. *Veterinary Parasitology* **11,** 365–373.

Krantz, G. W. (1978). "A Manual of Acarology," 2nd Ed. Oregon State University, Corvallis.

Kurbanov, M. M., Berezina, L. K., Zakaryan, V. A., Kiseleva, N. V., and Vatolin, V. P. (1974). [Results of serological investigation of human and domestic animal blood sera with 13 arboviruses in the Karakum canal zone and southeastern Turkmen SSR.] *In* "Ecology of Viruses" (D. K. L'vov and K. I. Maisky, eds.), pp. 113–120. Akademiya Meditsinskikh Nauk SSSR, Moscow. (In Russian; English translation *NAMRU3* T778.)

Kusov, V. N. (1962). [Significance of different stages of metamorphosis of sheep-pen ticks in the etiology of tick paralysis.] *Parazity Sel-skokhozyaystvennykh Zhivotnykh Kazakhstana* **1,** 236–246. (In Russian; English translation *NAMRU3* T99.)

Kusov, V. N. (1973). [Ornithodorinae ticks of Kazakhstan and Republics of Central Asia.] *Institut Zoologii, Akademiya Nauk Kazakhskoi SSR, Alma-Ata* (in Russian).

Kusov, V. N., and Peteshev, V. M. (1961). [Contribution to etiology of tick paralysis of sheep in Kazakhstan.] *Trudy IV Konferentsii po Prirodnoy Ochagovosti Bolezney i Voprosam Parasitologii Kazakhstana i Respublik Sredney Azii, Sentyabrya 1959 G* **3,** 529–533. (In Russian; English translation *NAMRU3* T1689.)

Kusov, V. N., Amanzhulov, S. A., and Postricheva, O. V. (1962). [On the problem of Q-fever infection in the genus *Ornithodoros*.] *Parazity Sel-skokhozyaystvennykh Zhivotnykh Kazakhstana* **1,** 229–235. (In Russian; English translation *NAMRU3* T85.)

Lavoipierre, M. M. J., and Riek, R. F. (1955). Observations on the feeding habits of argasid ticks and on the effect of their bites on laboratory animals, together with a note on the production of coxal fluid by several of the species studied. *Annals of Tropical Medicine and Parasitology* **49,** 96–113.

Lebedev, E. P., Karaseva, P. S., Reshetnikov, I. A., and Busygin, F. F. (1975). [Detection of antibody to Tahyna, Chenuda and Uukuniemi viruses in residents of the northern forest-steppe of Omsk Region.] *Tezisy Konferentsii, Voprosy Meditsinskoy Virusologii, Moskva, Oktyabrya, G* pp. 314–315. (In Russian; English translation *NAMRU3* T1194.)

Livingstone, D. (1874). "The last journals of David Livingstone in Central Africa, from 1865 to his death, continued by a narrative of his last moments, etc., by H. Waller." Murray, London.

L'vov, D. K. (1980). Arboviruses in the U.S.S.R. *Zentralblatt für Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene, Abteilung* 1 (*Suppl.*) **9,** 35–46.

L'vov, D. K., Tsirkin, Yu. M., Karas, F. R., Timofeev, E. M., Gromashevsky, V. L., Veselovskaya, O. V., Osipova, N. Z., Fomina, K. B., and Grebenyuk, Yu. I. (1973). "Sokuluk" virus, a new group B arbovirus isolated from *Vespertilio pipistrellus* Schreber, 1775, bat in the Kirghiz S.S.R. *Archiv für die Gesamte Virusforschung* **41,** 170–174.

L'vov, D. K., Timofeeva, A. A., Smirnov, V. A., Gromashevsky, V. L., Sidorova, G. A., Nikiforov, L. P., Sazonov, A. A., Andreev, A. P., Skvortsova, T. M., Berezina, L. K., and Aristova, V. A. (1975a). Ecology of tick-borne viruses in colonies of birds in the USSR. *Medical Biology* **53,** 325–330.

L'vov, D. K., Leonova, G. N., Gromashevsky, V. L., Skvortsova, T. M., Timofeeva, A. A., Sazonov, A. A., Gofman, Y. G., Berezina, L. K., Klimenko, S. M., and Zakaryan, V. A. (1975b). New arboviruses from encephalomyocarditis group, Bunyam-viridae and ungrouped arboviruses isolated in the Far East of the USSR. *International Virology, Abstracts of the 3rd International Congress for Virology, Madrid, September* **3,** 192.

L'vov, D. K., Neronov, V. M., Gromashevsky, V. L., Skvortsova, T. M., Berezina, L. K., Sidorova, G. A., Zhmaeva, Z. M., Gofman, Yu. A., Klimenko, S. M., and Fomina, K. B. (1976). "Karshi" virus, a new flavivirus (Togaviridae) isolated from *Ornithodoros papillipes* (Birula, 1895) ticks in Uzbek S.S.R. *Archives of Virology* **50,** 29–36.

L'vov, D. K., Sidorova, G. A., Gromashevsky, V. L., Skvortsova, T. M., Berezina, L. K., Kondrashina, N. G., and Uralov, A. U. (1979). [Chim virus, a new arbovirus isolated from ixodid and argasid ticks collected in burrows of great gerbils in Uzbek SSR.] *Voprosy Virusologii* **24,** 286–289. (In Russian; English translation *NAMRU3* T1408.)

L'vov, D. K., Kostyukov, M. A., Pak, T. P., and Gromashevsky, V. L. (1980). [Isolation from the blood of a sick person of an arbovirus antigenically related to Issyk-Kul virus.] *Voprosy Virusologii* **25,** 61–62. (In Russian; English translation *NAMRU3* T1442.)

Lysunkina, V. A. (1960). Results of investigation of several species of ticks and Q-rickettsiosis in Uzbekistan. *Journal of Microbiology (London)* **31,** 930 (Annotation).

McKercher, D. G., Wada, E. M., Ault, S. K., and Theis, J. H. (1980). Viral agents recovered from *Ornithodoros coriaceus*, a vector of epizootic bovine abortion. *American Journal of Veterinary Research* **40,** 803–805.

Main, A. J., Shope, R. E., and Wallis, R. C. (1976). Cape Wrath: A new Kemerovo group orbivirus from *Ixodes uriae* (Acari: Ixodidae) in Scotland. *Journal of Medical Entomology* **13,** 304–308.

Marchette, N. J. (1982). "Ecological Relationships and Evolution of the Rickettsiae." CRC Press, Boca Raton, Florida.

Matthews, R. E. F. (1979). Classification and nomenclature of viruses. (Third Report of the International Committee on Taxonomy of Viruses.) *Intervirology* **12,** 129–296.

Miadonna, A., Tedeschi, A., Leggieri, E., Falagiani, P., Nazzari, M., Manzoni, M., and Zanussi, C. (1982). Anaphylactic shock caused by allergy to the venom of *Argas reflexus*. *Annals of Allergy* **49,** 293–295.

Miller, B. R., Loomis, R., Dejean, A., and Hoogstraal, H. (1985). Qalyub virus (Bunyaviridae: *Nairovirus*) replication in the tick *Ornithodoros* (*Pavlovskyella*) *erraticus*. *American Journal of Tropical Medicine and Hygiene* **34,** 180–187.

Mirzoeva, N. M., Sultanova, Z. L., Kanbai, I. G., Obukhova, V. R., Gaidamovich, S. Ya., Sokolova, E. I., and Kulieva, N. M. (1974). [Biological properties of West Nile virus strains isolated in Azerbaijan.] *In* "Arboviruses" (S. Ya. Gaidamovich, ed.), pp. 119–123. Akademiya Meditsinskikh Nauk SSR, Moscow. (In Russian; English translation *NAMRU3* T1159.)

Miura, T. (1976). Serological characteristics of Japan bat viruses and the relation of the viruses to man. *Medicine and Biology, Tokyo* **92,** 135–140.

Moulder, J. W. (1974). The rickettsias. Order I. Rickettsiales Gieszczkiewics 1939. *In* "Bergey's Manual of Determinative Bacteriology" (R. E. Buchanan and N. E. Gibbons, eds.), pp. 882–914. Williams & Wilkins, Baltimore.

Nevill, E. M. (1964). The role of carbon dioxide as stimulant and attractant to the sand tampan, *Ornithodoros savignyi* (Audouin). *Onderstepoort Journal of Veterinary Research* **31,** 59–67.

Nuttall, G. H. F., Warburton, C., Cooper, W. F., and Robinson, L. E. (1908). "Ticks. A Monograph of the Ixodoidea. Part I. The Argasidae." Cambridge Univ. Press, London.

Nuttall, P. A. (1984). Tickborne viruses in seabird colonies. *Seabird* **7,** 31–41.

Obenchain, F. D., and Galun, R., eds. (1983). Physiology of Ticks. *In* "Current Themes of Tropical Science," Vol. 1. Pergamon, Oxford.

Oliver, J. H., Jr. (1977). Cytogenetics of mites and ticks. *Annual Review of Entomology* **22,** 407–429.

Oliver, J. H., Jr., and Osburn, R. L. (1977). Cytogenetics of ticks (Acari: Ixodoidea). 15. Notes on chromosomes and maturation of *Otobius megnini* and *Otobius lagophilus*. *Journal of Parasitology* **63,** 176–178.

Parker, R. R. (1942). *Ornithodoros* ticks as a medium for the transportation of disease agents. *Public Health Reports, United States Public Health Service* **57,** 1963–1966.

Patiño Camargo, L. (1941). Nuevas observaciones sobre un tercer foco de fiebre petequial (maculosa) en el hemisferio americano. *Boletin de la Oficina Sanitaria Pan-Americana* **20,** 1112–1124.

Patiño Camargo, L., Afanador Salgar, A., and Paul, J. H. (1937). A spotted fever in Tobia, Colombia. *American Journal of Tropical Medicine* **17,** 639–653.

Pautov, V. N., and Morozov, Yu. I. (1974a). [Use of argasid ticks in studies of nonpathogenic *Rickettsia burneti*.] *Meditsinskaya Parazitologiya, Moscow* **43,** 176–179. (In Russian; English translation *NAMRU3* T1714.)

Pautov, V. N., and Morozov, Yu. I. (1974b). [A study of reactivation of *Rickettsia burneti* in *Alveonasus canestrinii* ticks.] *Zhurnal Microbiologii* **51,** 29–32. (In Russian; English translation *NAMRU3* T1715.)

Pavlov, P. (1947). Les tiques en Bulgarie et leurs hôtes vecteurs. *Bulletin de la Société de Pathologie Exotique* **40,** 95–98.

Payzin, S., and Akyay, N. (1952). [Natural occurrence of *Coxiella burneti* in *Ornithodorus lahorensis* ticks.] *Türk Ijiyen Ve Tecrübi Biyoloji Dergisi* **12,** 8–19 (in Turkish).

Peacock, P. B. (1958). Tick paralysis or poliomyelitis. *South African Journal of Medical Science* **32,** 201–202.

Peirce, M. A. (1974). Distribution and ecology of *Ornithodoros moubata porcinus* Walton (Acarina) in animal burrows in East Africa. *Bulletin of Entomological Research* **64,** 605–619.

Petrov, D. (1972). [Role of *Argas persicus* in the epidemiology of Newcastle disease.] *Veterinarno Meditsinski Nauki* **9,** 13–17 (in Bulgarian).

Philip, C. B., and Parker, R. R. (1933). Rocky Mountain spotted fever. Investigations of sexual transmission of the wood tick *Dermacentor andersoni*. *Public Health Reports, United States Public Health Service* **48,** 266–271.

Philip, R. N., Casper, E. A., Anacker, R. L., Cory, J., Hayes, S. F., Burgdorfer, W., and Yunker, C. E. (1983). *Rickettsia bellii* sp. nov.: A tick-borne rickettsia, widely distributed in the United States, that is distinct from the spotted fever and typhus biogroups. *International Journal of Systematic Bacteriology* **33,** 94–106.

Poleshchuk, N. N., Gromashevsky, V. L., Skvortsova, T. M., L'vov, D. K., and Klimenko, S. M. (1981). Investigations on the structure and morphogenesis of some arboviruses isolated in the U.S.S.R. *Acta Virologica, Prague (English Edition)* **25,** 144–149.

Porter, C. E. (1929). Notas de parasitologia. V. Sobre *Argas persicus* en Calama. *Revista Chilena de Historia Natural* **32,** 325–327.

Rageau, J., and Mouchet, J. (1970). Les tiques de la Camargue (Acariens: Ixodoidea) et leur rôle éventuel dans l'épidémiologie des arbovirus. *Folia Parasitologica* **17,** 349–353.

Rao, K. N. A., and Kalra, S. L. (1949). Tick-borne relapsing fever in Kashmir. *Indian Journal of Medical Research* **37,** 385–394.

Řeháček, J., Urvölgyi, J., and Kováčová, E. (1977). Massive occurrence of rickettsiae of the spotted fever group in fowl tampan, *Argas persicus*, in the Armenian S.S.R. *Acta Virologica, Prague (English Edition)* **21,** 431–438.

Riad, Z. M., Sidky, H. S. A., and Abdel-Wahab, K. S. E. (1978). Chromosomal pattern of *Argas (Persicargas) arboreus*. *Journal of the Egyptian Society of Parasitology* **8,** 9–15.

Roberts, F. H. S. (1970). "Australian Ticks." Commonwealth Scientific and Industrial Research Organization, Melbourne.

Robin, Y., and Le Gonidec, G. (1972). Activités du laboratoire des arbovirus. *Rapport sur le Fonctionnement Technique de l'Institut Pasteur de Dakar* pp. 37–42.

Roman, E., Battesti, M. R., and Charret, J. (1960). Parasitisme chez un nourrisson de larves héxapodes de l'acarien *Argas reflexus*. *Bulletin de la Société de Pathologie Exotique* **53,** 420–423. (English translation *NAMRU3* T1688.)

Rosenstein, M. (1976). Paralysis in chickens caused by larvae of the poultry tick, *Argas persicus*. *Avian Diseases* **20,** 407–409.

Roshdy, M. A., Hoogstraal, H., Banaja, A. A., and El Shoura, S. M. (1983). *Nuttalliella namaqua* (Ixodoidea: Nuttalliellidae): Spiracle structure and surface morphology. *Zeitschrift für Parasitenkunde* **69,** 817–821.

Roshdy, M. A., Hoogstraal, H., Clifford, C. M., Keirans, J. E., and Corwin, M. D. (1984). Bat ticks of the genus *Argas* (Ixodoidea: Argasidae). 13. Haller's organ roof and anterior pit setae in *Carios* and *Chiropterargas*. *Journal of Parasitology* **70,** 407–411.

Saadatezadeh, H., Hamidi, A. N., and Faghih, M. A. (1973). Q fever in Iran. Part 2. The first isolation of *Rickettsia burneti* from ticks (*Ornithodorus lahorensis*) in Iran. *Bulletin de la Société de Pathologie Exotique* **66,** 506–511.

Santos, S. M. (1982). O combate ao carrapato das aves. *Estado de São Paulo, Supl. Agricola* 5.

Schmidt, J. R., and Said, M. I. (1964). Isolation of West Nile virus from the African bird argasid, *Argas reflexus hermanni*, in Egypt. *Journal of Medical Entomology* **1,** 83–86.

Schulze, P. (1929). Die heutige Verbreitung einzelner Tierarten im Lichte der erdgeschichtlichen Vergangenheit (besonders der Zecken *Dermacentor reticulatus* Auct. und *Hyalomma marginatum* Koch). *Zeitschrift für Morphologie und Ökologie der Tiere* **15,** 735–754.

Sharma, B. D., and Sharma, T. (1975). Tick paralysis in fowl from Kashmir (J & K) India. *Indian Poultry Review, Calcutta* **6,** 804–805.

Sidky, N. A., and Abdel Wahab, K. S. E. (1982). Quaranfil virus in infected *Argas (Persicargas) arboreus* salivary glands. *Journal of the Egyptian Society of Parasitology* **12,** 467–471.

Sidorova, G. A., Zhmaeva, Z. M., Gromashevsky, V. L., Skvortsova, T. M., and Esipov, V. M. (1974). [Isolation of Baku virus from *Ornithodoros coniceps* ticks collected in pigeon nests in Tashkent Oblast.] *In* "Ecology of Viruses" (D. K. L'vov and K. I. Maisky, eds.), pp. 102–105. Akademiya Meditsinskikh Nauk SSSR, Moscow. (In Russian; English translation *NAMRU3* T775.)

Sidorova, G. A., L'vov, D. K., Gromashevsky, V. L., and Andreev, V. P. (1975). [Landscape association of some virus foci in Central Asia.] *In* "Ecology of Viruses" (D. K. L'vov and I. S. Sattarov, eds.), pp. 50–51. Izdatel'stvo "Donish", Dushanbe. (In Russian; English translation *NAMRU3* T1133.)

Singh, K. R. P., Goverdhan, M. K., and Bhat, U. K. M. (1971). Transmission of Kyasanur forest disease virus by soft tick, *Argas persicus* (Ixodoidea: Argasidae). *Indian Journal of Medical Research* **59,** 213–218.

Siuda, K., Jarosz, Z., and Norek, L. (1982). [The case of attack of trumpeters in St. Mary's Church in Kraków by the ticks *Argas (Argas) polonicus* Siuda, Hoogstraal, Clifford et Wassef, 1979 (Acarina, Ixodides, Argasidae.)] Materialy IV Sympozjum Akaroentomologii Medycznej I Weterynaryjnej, 4-6 IX 1980, Gdańsk. *Wiadomości Parazytologiczne* **18,** 57–62. (In Polish; English translation *NAMRU3* T1677.)

Skvortsova, T. M., Gromashevsky, V. L., Sidorova, G. A., Khutoretskaya, N. V., Aristova, V. A., Kondrashina, N. G., Polyakova, A. N., Muradov, Sh. M., Belousov, E. M., and Kurchenko, F. P. (1982). [Results of virological investigation of arthropod vectors in the territory of Turkmenia.] *In* "Ecology of Viruses" (D. K. L'vov, ed.), pp. 139–144. Akademiya Meditsinskikh Nauk SSSR, Moscow. (In Russian; English translation *NAMRU3* T1664.)

Smibert, R. M. (1974). The spirochetes. Order I. Spirochaetales Buchanan 1917. *In* "Bergey's Manual of Determinative Bacteriology" (R. E. Buchanan and N. E. Gibbons, eds.), 8th Ed., pp. 167–168. Williams & Wilkins, Baltimore.

Smith, D. J. W. (1942). Studies in the epidemiology of Q fever. II. Experimental infection of the ticks *Haemaphysalis bispinosa* and *Ornithodoros* sp. with *Rickettsia burneti*. *Australian Journal of Experimental Biology and Medical Science* **20,** 295–296.

Sokolova, E. I., Mirzoeva, N. M., Kulieva, N. M., Sultanova, Z. D., Kanbay, I. G., Obukhova, V. R., and Gaidamovich, S. Ya. (1973). [Islands of Baku Archipelago—natural foci of arboviruses.] *In* "Ecology of Viruses" (D. K. L'vov, ed.). pp. 126–131. Akademiya Meditsinskikh Nauk SSSR, Moscow. (In Russian; English translation *NAMRU3* T715.)

Sonenshine, D. E. (1984). Tick pheromones. *In* "Current Topics in Vector Research" (K. F. Harris, ed.), Vol. 2. Praeger, New York.

Sonenshine, D. E., and Anastos, G. (1960). Observations on the life history of the bat tick *Ornithodoros kelleyi* (Acarina: Argasidae). *Journal of Parasitolog* **46,** 449–454.

Sonenshine, D. E., Clifford, C. M., and Kohls, G. M. (1966). The systematics of the subfamily Ornithodorinae (Acarina: Argasidae). III. Identification of the larvae of the Eastern Hemisphere. *Annals of the Entomological Society of America* **59,** 92–122.

St. George, T. D., Standfast, H. A., Doherty, R. L., Carley, J. G., Fillipich, C., and Brandsma, J. (1977). The isolation of Saumarez Reef virus, a new flavivirus, from bird ticks *Ornithodoros capensis* and *Ixodes eudyptidis* in Australia. *Australian Journal of Experimental Biology and Medical Science* **55,** 493–499.

St. George, T. D., Cybinski, D. H., Main, A. J., McKilligan, N., and Kemp, D. H. (1984). The isolation of a new arbovirus from *Argas robertsi* from a cattle egret colony in Australia. *Australian Journal of Biological Sciences* (in press).

Stoenner, H. G., Torten, M., and Kaplan, W., eds. (1980). *CRC Handbook Series in Zoonoses, Section A: Bacterial, Rickettsial and Mycotic Diseases* pp. 337–352.

Stone, B. F., and Wright, I. G. (1981). Tick toxins and protective immunity. *Proceedings of an International Conference, Tick Research Unit, Rhodes University, Grahamstown, January* pp. 1–5.

Stone, B. F., Cowie, M. R., Kerr, J. D., and Binnington, K. C. (1982). Improved toxin/antitoxin assays for studies on the Australian paralysis tick *Ixodes holocyclus*. *Australian Journal of Experimental Biology and Medical Science* **60,** 309–318.

Suitor, E. C., Jr. (1964). The relationship of *Wolbachia persica* Suitor and Weiss to its host. *Journal of Insect Pathology* **6,** 111–124.

Suitor, E. C., Jr., and Weiss, E. (1961). Isolation of a rickettsialike microorganism (*Wolbachia persica*, n. sp.) from *Argas persicus* (Oken). *Journal of Infectious Diseases* **108,** 95–106.

Sureau, P., Klein, J. M., Casals, J., Digoutte, J. P., Salaun, J. J., Piazak, N., and Calvo, M. A. (1980). Isolement des virus Thogoto, Wad Medani, Wanowrie et de la fièvre hemorragi-

que de Crimée-Congo en Iran à partir de tiques d'animaux domestiques. *Annales de l'Institut Pasteur, Série Virologie* **131E,** 185–200.

Takahashi, M., Nii, S., and Casals, J. (1980). Hirota virus: A new tick-borne arbovirus related to Nyamanini. *Zentralblatt für Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene, Abteilung 1, Suppl.* **9,** 209.

Takahashi, M., Yunker, C. E., Clifford, C. M., Nakano, W., Fujino, N., Tanifuji, K., and Thomas, L. A. (1982). Isolation and characterization of Midway virus: A new tick-borne virus related to Nyamanini. *Journal of Medical Virology* **10,** 181–193.

Tang, S.-Y., Wang, T.-H., and Li, G.-A. (1983). [Distribution of Jinghe strain of spotted fever rickettsiae in *Ornithodoros moubata*.] *Acta Entomologica Sinica* **26,** 185–187 (in Chinese).

Tatchell, R. J. (1969). Host-parasite interactions and the feeding of blood-sucking arthropods. *Parasitology* **59,** 93–104.

Taufflieb, R., Cornet, M., and Camicas, J.-L. (1968). Les vecteurs d'arbovirus au Sénégal. *Cahiers: Office de la Recherche Scientifique et Technique Outre-Mer, Série Entomologie Médicale* **6,** 221–223.

Tawfik, M. S., and Guirgis, S. S. (1969). Biochemical and physiological studies of certain ticks (Ixodoidea). Experimental feeding of *Argas (Persicargas) arboreus* Kaiser, Hoogstraal and Kohls (Argasidae) through membranes. *Journal of Medical Entomology* **6,** 191–195.

Taylor, R. E. L., Seal, B. S., and St. Jeor, S. (1982). Isolation of infectious bovine rhinotracheitis virus from the soft-shelled tick, *Ornithodoros coriaceus*. *Science* **216,** 300–301.

Timofeev, E. M., Shakhgil'dyan, I. V., Rybin, S. N., Grebenyuk, Yu, I., and Karas', F. R. (1973). [Serological examination of blood sera of humans and domestic animals with fifteen arboviruses in southwestern districts of Oshsk Region, the Kirgiz SSR.] *In* "Ecology of Viruses" (D. K. L'vov, ed.), pp. 80–87. Akademiya Meditsinskikh Nauk SSSR, Moscow. (In Russian; English translation *NAMRU3* T694.)

Trager, W. (1940). A note on the problem of acquired immunity to argasid ticks. *Journal of Parasitology* **26,** 71–74.

Uilenberg, G., Hoogstraal, H., and Klein, J. M. (1980). Les tiques (Ixodoidea) de Madagascar et leur rôle vecteur. *Archives de l'Institut Pasteur de Madagascar, Special Number,* pp. 1–153.

Urvölgyi, J., and Brezina, R. (1978). *Rickettsia slovaca*: A new member of spotted fever group rickettsiae. *Proceedings of the 2nd International Symposium on Rickettsiae and Rickettsial Diseases, Smolenice, June 1976* pp. 299–305.

Varelas-Wesley, I., and Calisher, C. H. (1982). Antigenic relationships of flaviviruses with undetermined arthropod-borne status. *American Journal of Tropical Medicine and Hygiene* **31,** 1273–1284.

Vargina, S. G., Kuchuk, L. A., Gershtein, V. I., and Karas', F. R. (1982). [Transmission of Issyk Kul virus by *Argas vespertilionis* ticks in experiment.] *In* "Ecology of Viruses" (D. K. L'vov, ed.), pp. 123–127. Akademiya Meditsinskikh Nauk SSSR, Moscow. (In Russian; English translation *NAMRU3* T1660.)

Vermeil, C., Lavillaureix, J., and Reeb, E. (1958). Infection et transmission expérimentales du virus West Nile par *Ornithodoros coniceps* (Canestrini) de souche tunisienne. *Bulletin de la Société de Pathologie Exotique* **51,** 489–495.

Vermeil, C., Lavillaureix, J., and Reeb, E. (1960). Sur la conservation et la transmission du virus West Nile par quelques arthropodes. *Bulletin de la Société de Pathologie Exotique* **53,** 273–279.

Votava, C. L., Rabalais, F. C., and Ashley, D. C. (1974). Transmission of *Dipetalonema viteae* by hyperparasitism in *Ornithodoros tartakovskyi*. *Journal of Parasitology* **60,** 479.

Wada, E. M., McKercher, D. G., Castrucci, G., and Theis, J. H. (1976). Preliminary characterization and pathogenicity studies of a virus isolated from ticks (*Ornithodoros coriaceus*) and from tick-exposed cattle. *American Journal of Veterinary Research* **37,** 1201–1206.

Walton, G. A. (1950). *Argas brumpti* Neumann, 1907 (Argasidae, Ixodoidea) in Kenya colony. *East African Medical Journal* **27,** 207.

Walton, G. A. (1958). Notes on *Argas brumpti* Neumann 1907 (Argasidae Ixodoidea) in Kenya and Tanganyika. *East African Medical Journal* **35,** 569–572.

Walton, G. A. (1962). The *Ornithodoros moubata* superspecies problem in relation to human relapsing fever epidemiology. *Symposium of the Zoological Society of London* No. 6, 83–156.

Walton, G. A. (1964). The *Ornithodorus "moubata"* group of ticks in Africa, control problems and implications. *Journal of Medical Entomology* **1,** 53–64.

Wardley, R. C. *et al.* (1983). African swine fever. *Archives of Virology* **76,** 73–90.

Weidner, H. (1964). Eine Zecke, *Ixodes succineus* sp. n., im baltischen Bernstein. *Veröffentlichungen aus dem Überseemuseum in Bremen, Serie A* **3,** 143–151.

Weyer, F. (1975). Beobachtungen über das Verhalten des Q-Fieber-Erregers (*Coxiella burneti*) in der Lederzecke *Ornithodoros moubata. Tropenmedizin und Parasitologie* **26,** 219–231.

Whitman, L., and Aitken, T. H. G. (1960). Potentiality of *Ornithodoros moubata* Murray (Acarina, Argasidae) as a reservoir-vector of West Nile virus. *Annals of Tropical Medicine and Parasitology* **54,** 192–204.

Wikel, S. K. (1982). Immune responses to arthropods and their products. *Annual Review of Entomology* **27,** 21–48.

Wikel, S. K. (1983). Host immunity to tick bite. *In* "Current Topics in Vector Research" (K. F. Harris, ed.), Vol. 1, pp. 249–269. Praeger, New York.

Wilkinson, P. J. (1981). African swine fever. *In* "Virus Diseases of Food Animals. A World Geography of Epidemiology and Control: Disease Monographs" (E. P. J. Gibbs, ed.), pp. 767–786. Academic Press, New York.

Wilkinson, P. J., and Wardley, R. C. (1982). The epidemiology of African swine fever. *Proceedings of the 3rd Symposium, Arbovirus Research in Australia, Brisbane, February* pp. 2–9.

Williams, R. E., Casals, J., Moussa, M. I., and Hoogstraal, H. (1972). Royal Farm virus: A new tickborne group B agent related to the RSSE complex. *American Journal of Tropical Medicine and Hygiene* **21,** 582–586.

Worms, M. J., Terry, R. J., and Terry, A. (1961). *Dipetalonema witei,* filarial parasite of the jird, *Meriones libycus.* I. Maintenance in the laboratory. *Journal of Parasitology* **47,** 963–970.

Yunker, C. E. (1971). Arthropod tissue culture in the study of arboviruses and rickettsiae: A review. *Current Topics in Microbiology and Immunology* **55,** 113–116.

Yunker, C. E. (1975). Tick-borne viruses associated with seabirds in North America and related islands. *Medical Biology* **53,** 302–311.

Yunker, C. E., Clifford, C. M., Thomas, L. A., Cory, J., and George, J. E. (1972). Isolation of viruses from swallow ticks, *Argas cooleyi,* in the southwestern United States. *Acta Virologica, Prague (English Ed.)* **16,** 415–421.

Yunker, C. E., Clifford, C. M., Thomas, L. A., Keirans, J. E., Casals, J., George, J. E., and Parker, J. C. (1977). Sunday Canyon virus, a new ungrouped agent from the tick *Argas (A.) cooleyi* in Texas. *Acta Virologica, Prague (English Edition)* **21,** 36–44.

Yunker, C. E., Thomas, L. A., and Cory, J. (1979a). Phenetic relationships of viruses of the Hughes serological group. *Proceedings of the 2nd International Symposium on Arctic Arboviruses, Mont Gabriel, Canada, May 1977* pp. 211–229.

Yunker, C. E., Clifford, C. M., Keirans, J. E., Thomas, L. A., and Rice, R. C. A. (1979b). Aransas Bay virus, a new arbovirus of the Upolu serogroup from *Ornithodoros capensis* (Acari: Argasidae) in coastal Texas. *Journal of Medical Entomology* **16,** 453–460.

Zaher, M. A., Soliman, Z. R., and Diab, F. M. (1977). An experimental study of *Borrelia anserina* in four species of *Argas* ticks. 2. Transstadial survival and transovarial transmission. *Zeitschrift für Parasitenkunde* **53,** 213–224.

Zhmaeva, Z. M., and Pchelkina, A. A. (1957). Domestic birds as carriers of the Q fever *Rickettsia* in the Turkmen SSR. *Journal of Microbiology (London)* **28,** 347–349.

Zhmaeva, Z. M., Petrishcheva, P. A., and Pchelkina, A. A. (1964). (Bloodsucking ticks. Carriers of Q fever in various landscape zones of the U.S.S.R.) *Zhurnal Mikrobiologii* **41,** 28–33. (In Russian; English translation *Joint Publication Research Service* **25,** 29–38.)

Zhmaeva, Z. M., Petrishcheva, P. A., and Pchelkina, A. A. (1965). Ticks—spontaneous vectors of the causative agent of Q fever in different landscape zones of the USSR. *Československá Parazitologie* **12,** 35–40.

Zhmaeva, Z. M., Pchelkina, A. A., and Belashova, V. S. (1966). [Spontaneous infection of *Argas vespertilionis* with *Rickettsia burnetti* in the south of Kazakhstan.] *Meditsinskaya Parazitologiya, Moscow* **35,** 595–596. (In Russian; English translation *NAMRU3* T599.)

Zumpt, F., and Organ, D. (1961). Strains of spirochaetes isolated from *Ornithodoros zumpti* Heisch and Guggisberg, and from wild rats in the Cape Province: A preliminary note. *South African Journal of Laboratory and Clinical Medicine* **7,** 31–34.

Note added in proof

While this manuscript was in press, I received descriptions of two new Chinese *Argas* (*Argas*) species: *A.* (*A.*) *assimilis* from nests of the swallow *Hirundo daurica japonicus*, in Tonggu, Jiangxi; and *A.* (*A.*) *beijingensis* from roosts of the domestic pigeon, *Columba livia*, in Beijing. The former species is related to *A.* (*A.*) *japonicus*, the latter to *A.* (*A.*) *vulgaris* and *A.* (*A.*) *reflexus*.

References

Teng, K. F. (1983). Notes on Chinese ticks of the subgenus *Argas* (Acarina: Argasidae: *Argas*). *Acta Zootaxonomica Sinica* **8,** 255–261. (In Chinese, English translation *NAMRU3* T1775.)

Teng, K. F., and Song, J.-Y. (1983). A new species of *Argas* from Jiangxi, China (Acarina: Argasidae). *Acta Zootaxonomica Sinica* **8,** 153–156. (In Chinese, English translation *NAMRU3* T1776.)

Trichostrongyloid Nematodes and Their Vertebrate Hosts: Reconstruction of the Phylogeny of a Parasitic Group[1]

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I. Introduction

Reconstruction of the evolutionary history of an animal group is generally accomplished by a paleontologist who, beginning with the morphology of fossil forms which can be dated by various means, traces the evolution of the group up to present-day forms. Unfortunately, such a procedure is often not possible since many animal groups lack fossil forms.

Any attempt to retrace the phylogenetic history of a group lacking fossils must be carried out in two stages. First, one must construct a classification which recognizes the different evolutionary lines which make up the group. Each evolutionary line includes forms which have

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reached different levels of evolution and although evolved members of distinct evolutionary lines may be easy to separate, primitive members may resemble each other rather closely. Second, having established such a classification, one must find some means of dating evolutionary lines. In parasitic groups, there is, at least in theory, a means of dating such lines since the host groups are generally represented by fossil forms.

Among nematode parasites of vertebrates, the Trichostrongyloidea are one of the best models with respect to resolving the above difficulties for two reasons. (1) They are one of the richest parasitic groups in terms of the number of species and genera and their superficial homogeneity masks a rich and varied morphology. Thus, the classification involves a great variety of evolutionary lines. Furthermore, we are certain of their free-living ancestors, the rhabditids, and this allows us to define the direction of evolutionary change; the closer a character state is to that in rhabditids, the more primitive it is, the further a character state is from that in rhabditids the more evolved it is. (2) Trichostrongyloids are cosmopolitan and occur in all classes of terrestrial vertebrates. Therefore, a large part of their diversification has occurred in mammals whose evolutionary history is relatively well known.

The three aims of this article are the following: (1) to present and analyze the parasite data upon which the classification is based (this consists mainly of morphological characters and their evolution); (2) to examine the host distributions and try to show how, in collating parasite data with host data, it is possible to piece together the evolutionary history of the superfamily; and (3) to summarize this history and present a phylogenetic tree of the Trichostrongyloidea.

II. Data Concerning the Parasites

A. Morphological Characters and Their Evolution

Contrary to what has been observed in other nematode groups parasitic in vertebrates, the key to understanding morphological evolution of the Trichostrongyloidea lies neither in cephalic structure nor in that of the female reproductive system, but in characters of the caudal bursa and synlophe, the arrangement of cuticular ridges in trichostrongyloids which serve to maintain purchase on the intestinal wall.

1. *Cephalic characters*

The cephalic extremity of primitive trichostrongyloids resembles that of the Strongyloidea (in particular, the Cloacininae and Oesophagostominae) in having a buccal capsule, six lips (or more rarely, a *corona ra-*

diata), and a dorsal oesophageal tooth. The complement of cephalic sense organs is complete, i.e., six internal and six external labial and four cephalic papillae, and two amphids (Fig. 1A and B).

The buccal capsule is atrophied compared to that of the Strongyloidea; this is one of the principal characters used to distinguish the two superfamilies (Dougherty, 1951; Chabaud, 1959). The buccal capsule becomes progressively reduced during the course of evolution and is absent in the most evolved forms. Disappearance of the buccal capsule is generally accompanied by loss of the lips (or of the *corona radiata*) and loss of the

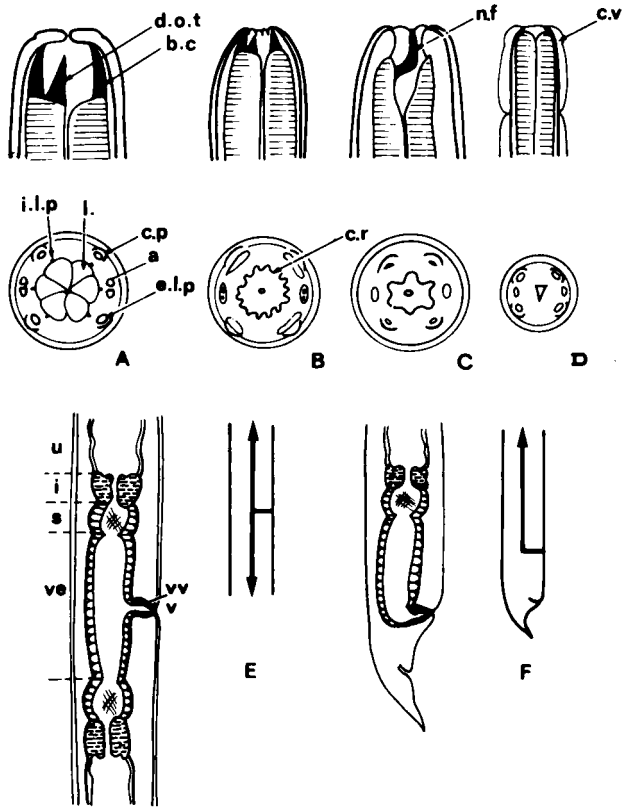


FIG. 1. (A)–(D) Cephalic characters. Cephalic extremities are drawn in left lateral (upper) and apical (lower) views. (A) Primitive head with buccal capsule (b.c), dorsal oesophageal tooth (d.o.t), six lips (l.), six internal and six external labial papillae (i.l.p and e.l.p), four cephalic papillae (c.p), and two amphids (a.). (B) Primitive head with *corona radiata* (c.r). (C) Evolved head with neodont formation (n.f); internal papillae have disappeared. (D) Evolved head with cephalic vesicle (c.v). (E) and (F) Ovejector and its schematic representation: (E) didelphic female; (F) monodelphic female. v, Vulva; vv, *vagina vera;* ve, vestibule; s, sphincter; i, infundibulum; u, uterus.

dorsal oesophageal tooth. A *corona radiata* persists, however, in the highly evolved molineid subfamily, the Nematodirinae. Similarly, the cephalic papillae undergo a simplification during evolution: the circle of inner labial papillae disappears and frequently the externolateral labial papillae fuse with the amphids.

Two highly evolved subfamilies, the Haemonchinae (Trichostrongylidae) and the Nematodirinae (Molineidae), possess a structure which we designate as the neodont formation (Fig. 1C) to distinguish it from the dorsal oesophageal tooth which occurs in primitive forms (Durette-Desset and Chabaud, 1977). The dorsal oesophageal tooth projects into the buccal cavity whereas the neodont formation projects into the oesophageal lumen.

Most trichostrongyloids possess a cephalic vesicle (Fig. 1D) and, as discussed below, its presence is associated with that of the synlophe.

2. *Reproductive tract of the female*

The female reproductive tract is identical primitively to that observed in members of the Strongyloidea. It consists of two branches, usually opposed (amphidelphic), each composed of an ovary, oviduct, and uterus. The two branches unite at an ovejector which empties into the vulva in the midbody region (Fig. 1E). The ovejector functions in copulation and egg laying and is composed of paired infundibula and sphincters, and a common vestibule and *vagina vera* (Seurat, 1920; Chitwood and Chitwood, 1950).

During the course of evolution trichostrongyloids tend to become smaller; the size of the egg diminishes and the number of eggs per female increases. The uteri take up an increasingly greater proportion of the animal and there is a tendency to pass from a didelphic condition to monodelphy, i.e., a reproductive system consisting of a single branch composed of an ovary, oviduct and uterus, and half an ovejector (Fig. 1F). Monodelphy presumably permits more efficient use of space. In the vast majority of cases it is the posterior branch of the reproductive system which atrophies and this is accompanied by migration of the vulva to the anal region.

3. *Reproductive structures of the male*

Three characters have frequently been used above the species level: accessory cuticular pieces, spicules, and the caudal bursa. The accessory cuticular pieces (gubernaculum, telamon, etc.) are simply cuticular thickenings of the lining of the cloaca or spicular pouch; their presence or absence is not associated with a particular degree of evolution. Thus, *Trichoskrjabinia* has a telamon whereas the very closely related genus *Oswaldocruzia* does not. Spicules are of great value at the specific level

but their structure can be appreciated only after they have been dissected from the worm and examined at various angles. Generally, short complex spicules are characteristic of primitive forms; during the course of evolution they become longer and more simplified (Chabaud, 1959). However, within a single genus (e.g., *Viannaia*) spicules may be short and complex or long and simple depending on the species (Durette-Desset, 1968). Thus, morphology of spicules, like that of accessory cuticular pieces, is of little value above the species level.

Characters of the caudal bursa are very important at and above the species level, but can be appreciated only when the bursa is fully extended. The caudal bursa, characteristic of the order Strongylida, consists of two lateroventral lobes and a dorsal lobe which may or may not be fused with the lateroventral lobes.

Caudal sensory structures are situated at the end of long peduncles (bursal rays) which extend into the bursa. The homology between the caudal papillae of free-living rhabditids and bursal rays of the Strongylida was demonstrated by Osche (1958), whose nomenclature was later modified by Chabaud *et al.* (1970). There are 10 pairs of papillae, one papilla which is generally unpaired, and two phasmids. The phasmids are often difficult to see with the light microscope.

Papilla 0, generally unpaired, situated on anterior lip of genital cone.
Papilla 1, prebursal, at end of prebursal ray.
Papilla 2, ventroventral, at end of ray 2.
Papilla 3, lateroventral, at end of ray 3.
Papilla 4, externolateral, at end of ray 4.
Papilla 5, mediolateral, at end of ray 5.
Papilla 6, posterolateral, at end of ray 6.
Papilla 7, on posterior lip of genital cone.
Papilla 8, externodorsal, at end of ray 8.
Papilla 9 and 10, dorsal, at end of dorsal ray.

The disposition of bursal rays and, in particular, the grouping of rays 2–6 is characteristic of a given evolutionary line or a given family. Five principal types of grouping exist (Fig. 2). **Type 2-1-2**: rays 2 and 3 and rays 5 and 6 grouped, ray 4 isolated. **Type 1-3-1**: ray 2 isolated, rays 3 to 5 grouped, and ray 6 isolated. **Type 2-2-1**: rays 2 and 3 and rays 4 and 5 grouped, ray 6 isolated. **Type 3-2**: rays 2–4 and rays 5 and 6 grouped. **Type 2-3**: rays 2 and 3 and rays 4–6 grouped.

Two major evolutionary trends in the caudal bursa are apparent when we consider the Strongylida as a whole: reduction of the dorsal lobe and lengthening of ray 4 (see Fig. 2G). Thus we can speak of a bursa with a short dorsal lobe and long ray 4 as being highly evolved. These trends occur in each type of bursa but, in general, types 2-1-2 and 2-3 (with a long

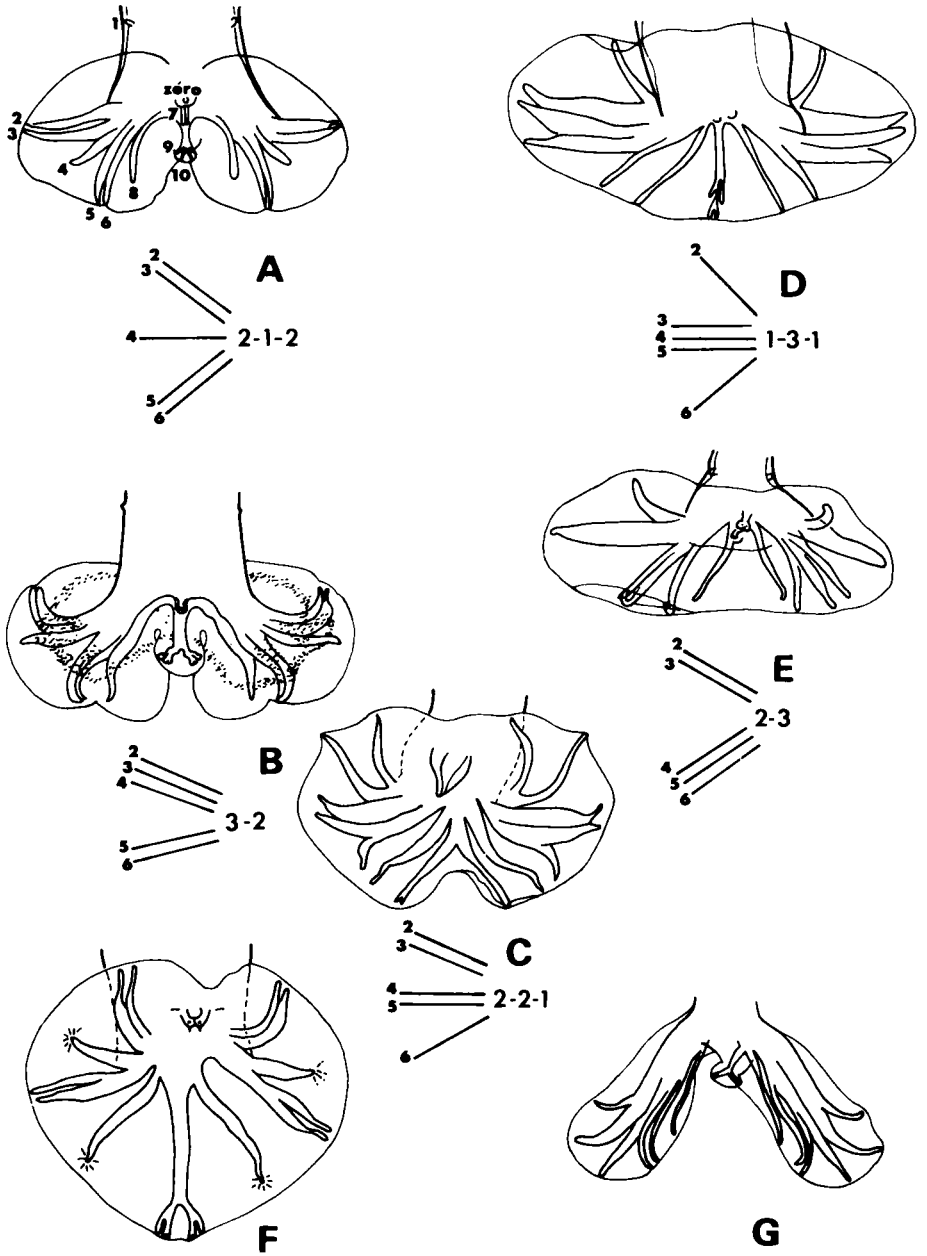


FIG. 2. Bursal characters. Bursal rays are numbered in (A) and the basic bursal types are represented in (A)–(E). (F) represents a primitive bursa with long dorsal ray and short ray 4 and (G) represents an evolved bursa with short dorsal ray and long ray 4.

dorsal lobe and short ray 4, see Fig. 2F) can be considered primitive since they are the types found in the Strongyloidea.

Symmetry, or lack thereof, in the bursa is an easily observed character and many generic diagnoses have been based on it. In fact it is of little value above the species level since asymmetrical bursae have arisen on many occasions in a great number of families. Pronounced asymmetry occurs most commonly in highly coiled species (e.g., members of the Nippostrongylinae). In these forms hypertrophy of one of the lateroventral lobes probably aids in holding the female during copulation.

4. *Synlophe: an apparatus of locomotion and fixation*

The great majority of trichostrongyloids possess longitudinal or obliquely oriented cuticular ridges on the outer surface of the body. In Durette-Desset (1969a), we proposed the term *synlophe* from the Greek "σύν" meaning "together" and "λόφος" meaning "fin" or "that which is salient" to designate the ensemble of these ridges.

The synlophe functions in locomotion or in the attachment of the worm to the host. In the first case, the worms involved live in the ruminant stomach and the ridges presumably allow them to move about without being carried away by the transit of the digestive system. In the second case, the worms involved live in the intestine and the synlophe allows them to attach to the intestinal mucosa (Fig. 3).

Study of the synlophe has revealed its value not only at the species level but also at the generic level and above. Although it is a highly adaptive organ and therefore subject to convergent evolution, a given type of synlophe tends to characterize worms from a particular host group or from a particular biogeographic region. It has thus proved to be the most useful character for distinguishing different evolutionary lines. Furthermore, the synlophe is similar in both sexes and is therefore extremely useful in matching males with corresponding females when, as is relatively frequently the case, several congeneric species occur in the same host (Durette-Desset, 1971).

(a) Methods used in studying the synlophe. The synlophe is best studied in transverse sections generally taken in the midbody region of the worm. These are made free hand using a fragment of a razor blade, and are mounted in lactophenol between slide and coverslip. A piece of paper is inserted between slide and coverslip on either side of the specimen to prevent the section from being squashed and to allow it to be moved around.

It is essential to recognize dorsal, ventral, right, and left sides of the worm. The section is, therefore, taken asymmetrically, i.e., with the anterior surface cut at a right angle and the posterior surface at an oblique angle to the body axis. Since nematodes generally lie on their sides, this

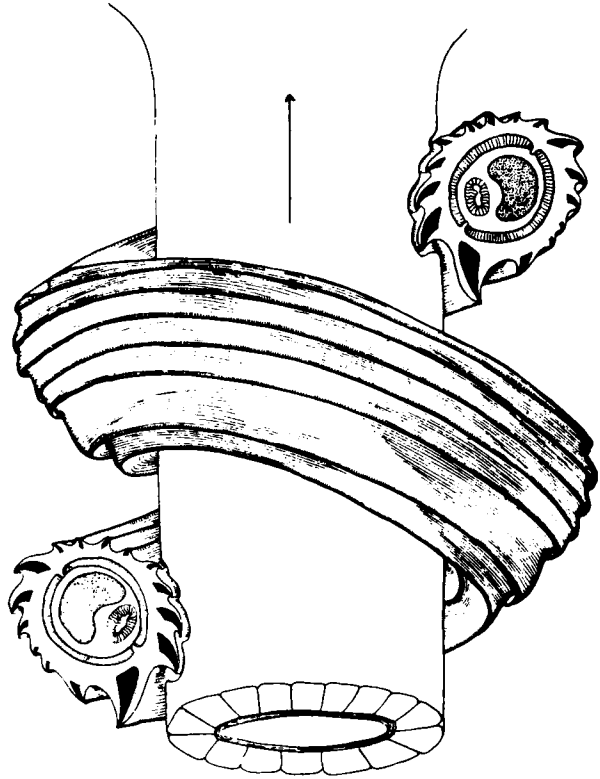


FIG. 3. Schematic representation indicating the coiling of a Nippostrongylinae around an intestinal villus. The arrow points in the direction of the base of the villus and the anterior extremity of the worm. Note that the worm is coiled in a sinistral spiral and that the left ventral ridges occupy an internal position. (After Durette-Desset, 1964.)

procedure usually results in a section which is thicker ventrally than dorsally or vice versa. This asymmetry and the fact that the posterior surface of the section is oblique to the body axis permit recognition of dorsal, ventral, left, and right sides of the worm. Transverse sections herein are drawn so that the anatomical dorsal, ventral, left, and right sides of the animal correspond to top, bottom, left, and right sides, respectively, of the diagram.

(*b*) *Definition of some terms used in studying the synlophe* (*Fig. 4*). Ridges of the synlophe may or may not be supported by an internal cuticular skeleton. Generally they are continuous throughout their length but in certain genera they are discontinuous. Salient portions of adjacent discontinuous ridges may be alternate or nonalternate (Figs. 4E and F).

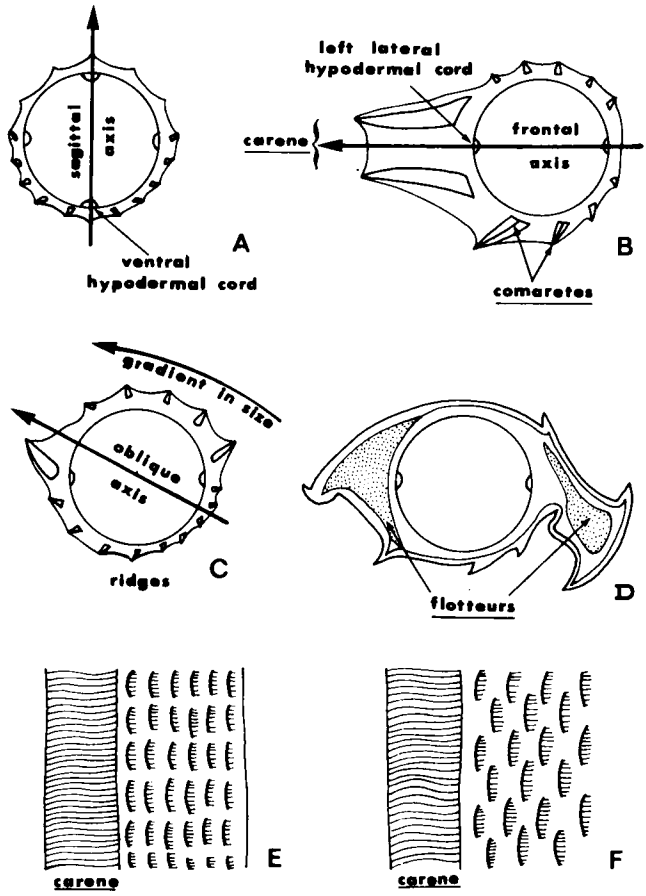


FIG. 4. Characters of the synlophe. (A)–(D) Transverse sections through the body; sections are oriented so that the anatomical dorsal, ventral, left, and right sides of the worm correspond to top, bottom, left, and right sides of the diagram, respectively. (E) and (F) Synlophe with continuous longitudinal ridges supporting the carene and discontinuous ridges on rest of the body. (E) Discontinuous ridges are nonalternate; (F) discontinuous ridges are alternate.

Comarete: highly developed ridge resulting from the fusion of two or more ridges, occurring on ventral (generally ventral left) side of body.
Carene: cuticular longitudinal formation situated on left side of body and appearing in transverse section as a large vesicle, usually supported by two or more hypertrophied ridges. More rarely the two hypertrophied ridges are replaced by a series of small ridges.
Flotteurs: cuticular longitudinal formations situated on right and left

sides of body appearing in transverse section as large fluid-filled vesicles not supported by ridges.

Size gradient: in a transverse section of the body there may be a gradient in size of ridges and this is always described in terms of diminishing size.

Axis of orientation: in a transverse section, the apex of the ridges may be directed perpendicular to, or oblique to, the body surface. In the latter case, an axis of orientation generally exists which separates ridges pointing in opposing directions. This axis passes between ventral right and dorsal left quadrants (the single exception to this, *Vaucherus,* is discussed further on). During the course of evolution it tends to rotate in a counterclockwise direction (when the worm is viewed from behind) and it is generally described in terms of the angle it makes with the sagittal axis. A frontal axis of orientation is one which passes from the right to the left hypodermal cord.

(*c*) *Characteristics of the synlophe and their evolution.* Three characteristics are used to describe the synlophe; the number of ridges, their size, and the axis of orientation.

The synlophe is restricted to the Trichostrongyloidea and therefore we cannot look to their rhabditid and strongyloid ancestors for clues to its origin or evolution. However, it is often present in the fourth-stage larva and its form in the larva can be considered, by definition, more primitive than that in the corresponding adult.

(i) *Ontogenetic information.* Essentially, only two types of synlophe exist: one which is bilaterally symmetrical (Type 1) and one which is not (Type 2). Larval synlophes are known in 30 species representing five of the 14 families and seven of the 24 subfamilies. In each case the larval synlophe will be described and compared with that of the adult. In all but one example (*Batrachonema*), larval and adult synlophes are of the same type. In *Batrachonema* (Nicollinidae), however, the larval synlophe is of type 1 and the adult synlophe of type 2 (Fig. 5).

All the known larval synlophes from the Molineinae, Anoplostrongylinae, and Nematodirinae are of type 1 (Fig. 5). The synlophe is bilaterally symmetrical and the axis of orientation, when present, is sagittal. Larval *Molinostrongylus* (Molineinae) do not have a synlophe. The adult has a small number of dorsal and ventral ridges oriented perpendicular to the body surface. The most primitive larval synlophes in the Anoplostrongylinae occur in *Fontesia* and *Delicata* (Fig. 5) and consist of two lateral ridges perpendicular to the body surface. In the corresponding adults, ventral ridges appear and there is a ventrodorsal axis of orientation. The synlophe of larval *Moennigia* resembles that of adult *Delicata* but dorsal ridges are present in adult *Moennigia*. Larvae of *Rauschia* (Nematodiri-

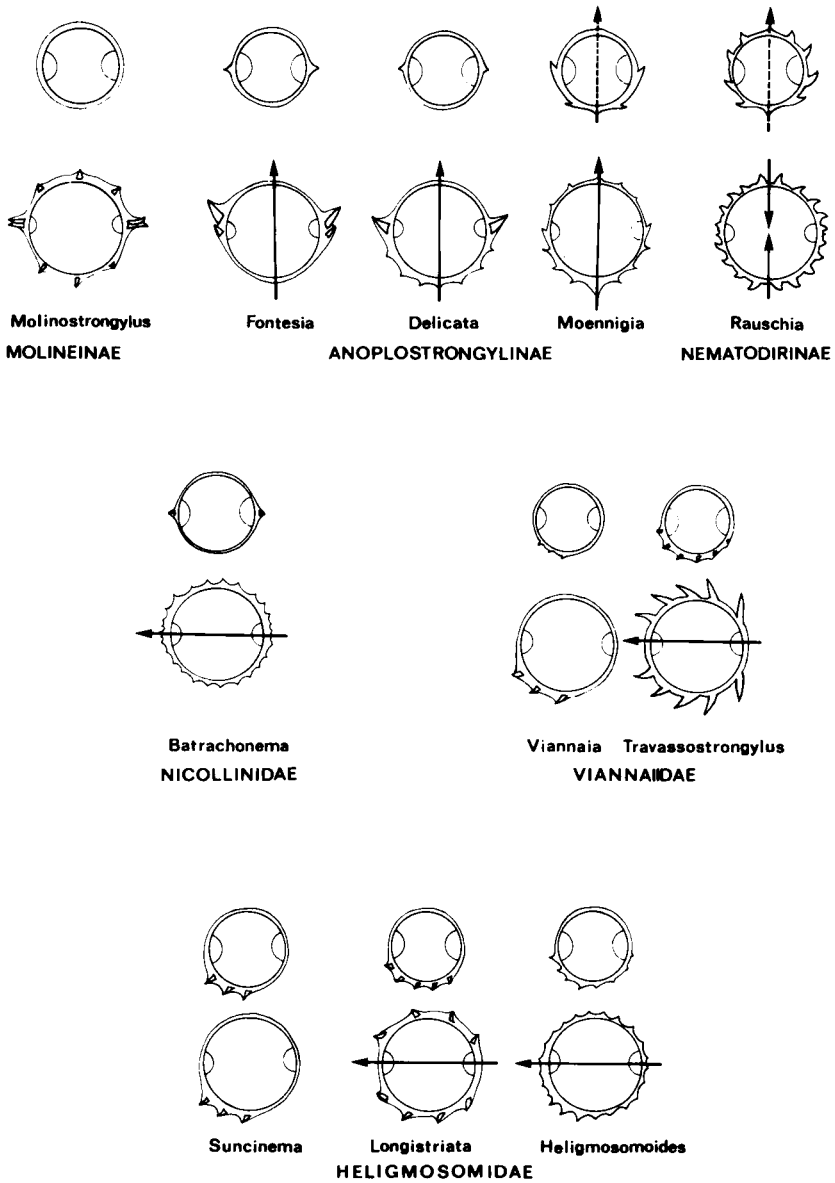


FIG. 5. Larval synlophes (upper section in each pair) with that of corresponding adult (lower section). Arrow indicates axis of orientation. In the Molineinae, Anoplostrongylinae, and Nematodirinae, larval and adult synlophes are of type 1 (bilaterally symmetrical). In the Nicollinidae the larval synlophe is of type 1, and that of the adult is of type 2 (not bilaterally symmetrical). In the Viannaiidae and Heligmosomidae, larval and adult synlophes are of type 2.

nae) have dorsal and ventral ridges with a ventrodorsal axis of orientation. In the adult the number of ridges increases and there is a double axis of orientation: ventrodorsal on the ventral side and dorsoventral on the dorsal side.

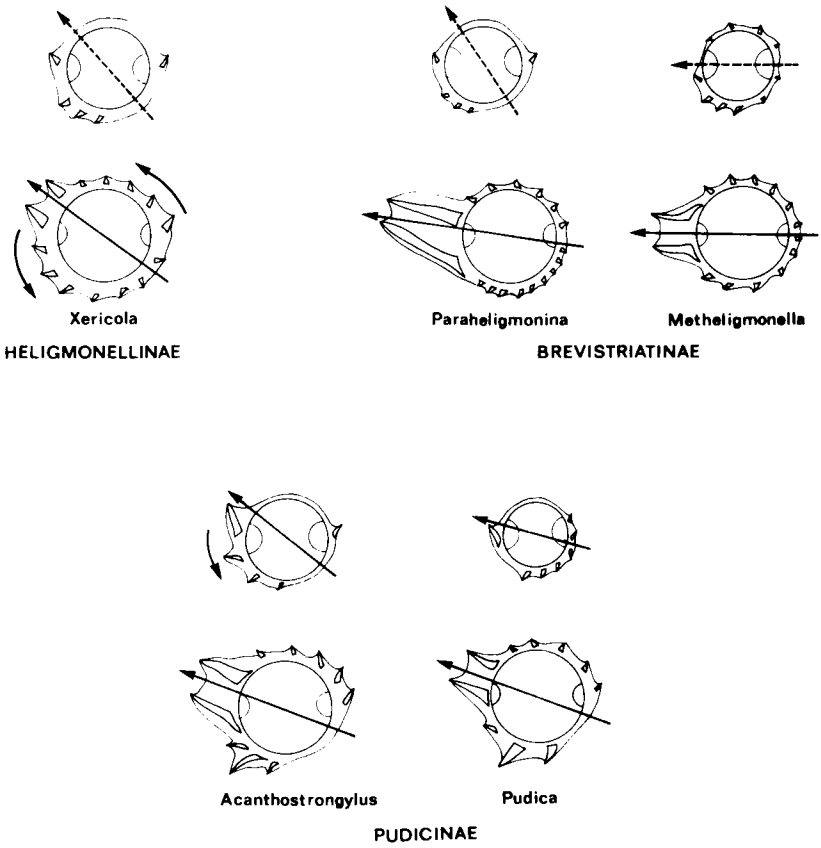
All the other known larval synlophes are of type 2; an asymmetry is immediately established by the presence of ventral left ridges directed to the left side. Larvae can be divided into two groups: in the first (Viannaiidae and Heligmosomidae) (Fig. 5), the synlophe is without ridges adjacent to the lateral hypodermal cords; in the second (Heligmonellidae) (Figs. 6 and 7), there is a ridge adjacent to the right lateral hypodermal cord.

In the most primitive larval synlophes (*Viannaia, Suncinema*) the three ventral left ridges are approximately equal in size. The synlophe of the adult is identical. During the course of evolution, the number of ventral ridges in the larval synlophe increases (*Travassostrongylus, Longistriata*). In the corresponding adults, dorsal ridges appear, which are of about the same size and equal in number to the ventral ridges. The axis of orientation is frontal and in *Travassostrongylus* and most species of *Longistriata,* the synlophe is perfectly symmetrical with respect to this axis. During the last stage in evolution (*Heligmosomoides*), the number of ventral ridges in the larva increases. An axis of orientation appears in the adult but the symmetry is less perfect than in the preceding stage since the ventral ridges, and in particular the ventral left ridges, are often more developed than the dorsal ridges.

The presence in larvae of the Heligmonellidae (Figs. 6 and 7) of a right lateral ridge oriented in a direction opposite to that of the other ridges introduces, as early as the fourth stage, an oblique axis of orientation (with respect to the sagittal axis). The evolution of the synlophe is similar in the four heligmonellid subfamilies. The number of ventral ridges increases; subsequently, lateral and, finally, dorsal ridges appear. At the same time the axis of orientation rotates, becoming subfrontal in the most evolved forms.

The synlophe of larval *Xericola* (Heligmonellinae) has two dorsally directed lateral ridges in addition to the three left ventral ridges. The axis of orientation is inclined about 45° from sagittal. In the corresponding adult, the number of ridges increases and there is a double size gradient: from right to left dorsally and from left to right ventrally. A small carene is present (Fig. 6).

The most primitive larval synlophe in the Brevistriatinae (*Paraheligmonina*) has two dorsally directed lateral ridges and three left ventral ridges. In the corresponding adult the number of ventral ridges increases and dorsal ridges appear. The axis of orientation is almost frontal, a prominent carene is present, and there is no size gradient. In the next stage (*Methe-*



HELIGMONELLIDAE

FIG. 6. Larval synlophes (upper section in each pair) with that of corresponding adult (lower section) in the Heligmonellinae, Brevistriatinae, and Pudicinae (Heligmonellidae). Evolution progresses from left to right. Adults and larvae have type 2 synlophe. Curved arrows indicate size gradient and straight arrows indicate axis of orientation.

ligmonella) the number of ventral ridges increases and dorsal ridges appear in the larval synlophe, the ventral left ridges are the most developed, and the axis of orientation is frontal. In the corresponding adult, the number and size of ridges, including those of the carene, are identical on dorsal and ventral sides of the body (Fig. 6).

The most primitive larval synlophe in the Pudicinae (*Acanthostrongylus*) has two dorsally directed lateral ridges and three ventral left ridges. The left lateral ridge is more developed than the right and there is a size gradient from the left to the ventral side. The axis of orientation is about 45° from sagittal. In the corresponding adult the number of ventral ridges

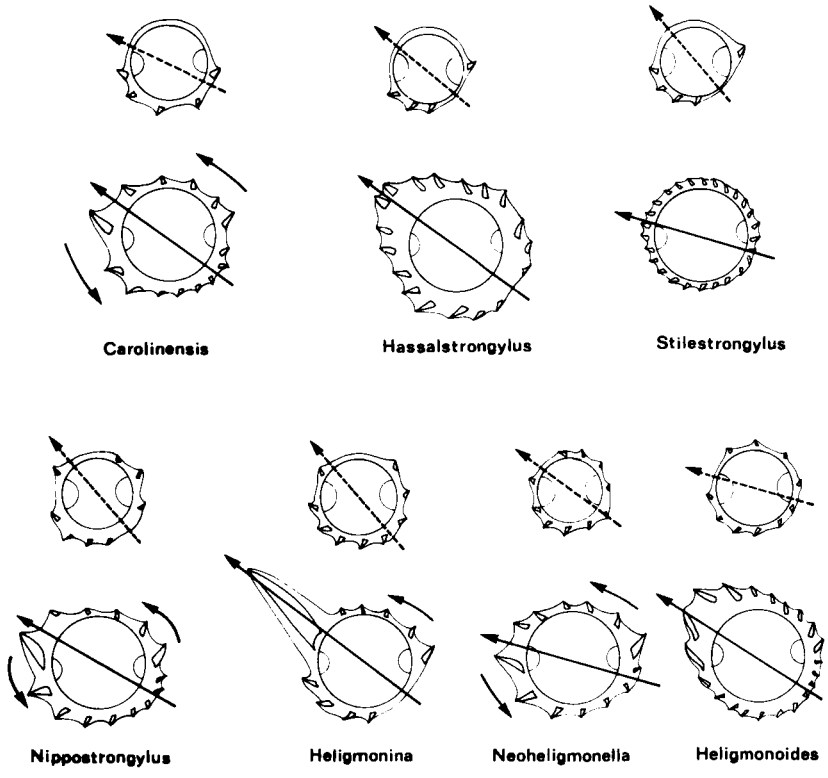


FIG. 7. Larval synlophes (upper section in each pair) with that of corresponding adult (lower section) in the Nippostrongylinae (Heligmonellidae). Evolution progresses from left to right. Curved arrows indicate size gradient and straight arrows indicate axis of orientation.

remains ostensibly the same but some of these can be interpreted as comaretes (two or more fused ridges). Dorsal ridges appear, a large carene is present, and the axis of orientation is rotated further from sagittal. In the next stage (*Pudica*), the number of ventral ridges in the larval synlophe increases (rather exceptionally, by the addition of right ventral ridges), and the axis of orientation is subfrontal. The corresponding adult resembles that of *Acanthostrongylus* (Fig. 6).

Larval synlophes of the Nippostrongylinae can be divided into two groups. In the first, there is no ridge adjacent to the left hypodermal cord; in the second group there is a ridge directly adjacent to or on either side of this cord (Fig. 7). In the first group (*Carolinensis, Hassalstrongylus, Stilestrongylus*), there are three or four left ventral ridges in addition to the

right lateral ridge. The axis of orientation is about 45° from sagittal. Evolution of the synlophe can be traced in the adults beginning with *Carolinensis*, through *Hassalstrongylus*, to *Stilestrongylus*. In *Carolinensis*, dorsal ridges appear and there is a double size gradient: from right to left dorsally and from left to right ventrally. In *Hassalstrongylus*, the number of ridges increases and the size gradient disappears. Ridges in the right ventral quadrant are smaller than the rest and the synlophe is symmetrical with respect to size and orientation of ridges about the axis of orientation. In *Stilestrongylus*, the axis of orientation is subfrontal and the ridges are more numerous, smaller and about equal in size.

Larval synlophes of the second group are found in *Nippostrongylus*, *Heligmonina*, *Neoheligmonella*, and *Heligmonoides*. *Nippostrongylus* displays the most primitive larval synlophe. The axis of orientation is about 50° from sagittal and there are eight ridges: four ventral, one dorsal left and three right. In the adult the axis of orientation is rotated toward the frontal axis and there is a size gradient from right to left dorsally and left to right ventrally.

An additional ventral ridge is present in larvae of *Heligmonina*. The number of ridges is little changed in the adult but the dorsal left ridge is hypertrophied and there is a size gradient from right to left on the dorsal side. The axis of orientation is slightly more frontal.

The addition of a dorsal ridge brings the number of ridges in the larval synlophe of *Neoheligmonella* and *Heligmonoides* to 10. The synlophe of adult *Neoheligmonella* resembles that of *Nippostrongylus* although the size gradient is less marked. In adult *Heligmonoides* the number of ridges increases and the dorsal left ridges become particularly strongly developed.

(ii) *Trends in evolution of the synlophe as revealed by ontogeny*. Evolutionary changes in the synlophe can be summarized as follows.

Number of ridges: The most primitive larval synlophes have two lateral ridges (lateral alae) or three ventral left ridges. During evolution, ridges are added first on the ventral side, then on the dorsal side of the body.

Size of ridges: Primitively, ridges are equal in size. Later, the ventral left ridges become more developed. Subsequent evolution involves acquisition of size gradients (most often lateromedian) and specialized formations such as hypertrophied ridges, comaretes, carenes, or flotteurs. Finally, ridges become smaller, more numerous, and about equal in size.

Axis of orientation: Primitively, the ridges are oriented perpendicular to the body surface. The axis of orientation is thus a secondary acquisition which occurs in one of three ways: (1) The axis of orientation forms along the sagittal axis and thus conserves the primitive bilateral symmetry. (2) The larval synlophe is bilaterally symmetrical with ridges perpendicular to the body surface (i.e., there is no axis of orientation) and the

axis of orientation of the adult is frontal. (3) The axis of orientation is oblique in primitive forms and undergoes a rotation during the course of evolution to become frontal or subfrontal in the most evolved forms.

(iii) *Types of adult synlophes and their phylogenetic classification.* Figures 8–12 illustrate the different types of synlophes found in adult trichostrongyloids classified according to evolutionary trends suggested by ontogeny.

The synlophes can be divided into two major groups. The first consists of the "trichostrongylid" and "molineid" lines. These are generally large uncoiled nematodes. The synlophes are relatively simple and always bilaterally symmetrical. The second corresponds to the "heligmosomid" line. They are generally smaller nematodes and their bodies are tightly coiled in a sinistral spiral about its ventral surface. A great variety of synlophes exists and none is bilaterally symmetrical.

In the trichostrongylid line (Fig. 8), the synlophe is absent in the most primitive subfamilies, and remains relatively undeveloped in most of the others. Its evolution involves an increase in the number of ridges, hypertrophy of lateral ridges, and the appearance in certain Cooperiinae of an axis of orientation, first ventrodorsal and later dorsoventral.

In the molineid line (Fig. 9), a synlophe is present except in the Dic-

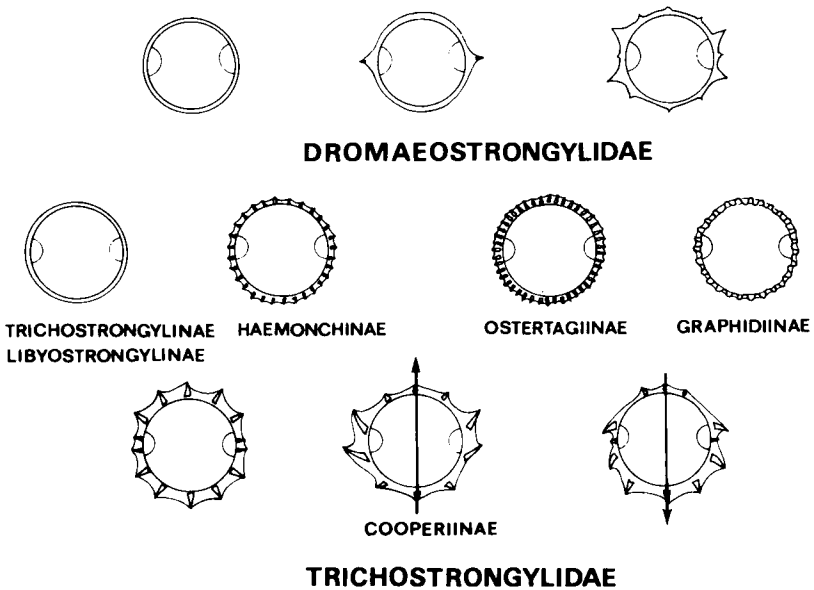


FIG. 8. Representative synlophes of adults of the trichostrongylid line: Dromaeostrongylidae and Trichostrongylidae. The synlophe is absent or with crests oriented perpendicular to body surface. Evolution (progression from left to right in each row of synlophes) involves increase in number of ridges and appearance of sagittal axis of orientation (arrows) in the most evolved forms.

tyocaulidae and its evolution is similar to that described in the trichostrongylid line. In general the synlophe is more highly evolved in this line than in the trichostrongylid line since an axis of orientation is present in most forms.

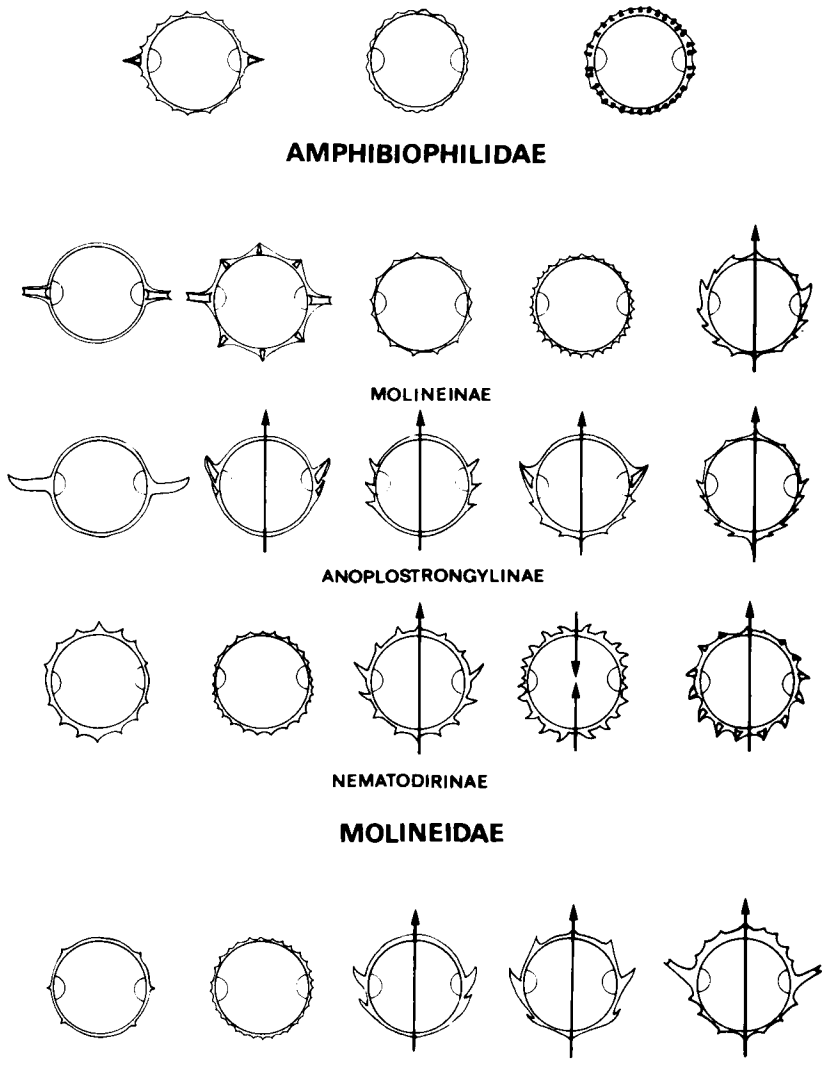


FIG. 9. Representative synlophes of adults of the molineid line: Amphibiophilidae, Molineidae, and Mackerrastrongylidae. Synlophes are bilaterally symmetrical, with ridges oriented perpendicular to body surface in primitive forms. Evolution (progression from left to right in each row of synlophes) involves increase in number of ridges and appearance of sagittal axis of orientation (arrows).

In the heligmosomid line (Figs. 10–12), a synlophe is always present and never bilaterally symmetrical. In the five families illustrated in Fig. 10 (Herpetostrongylidae, Viannaiidae, Heligmosomidae, Nicollinidae, and Ornithostrongylidae), the axis of orientation becomes frontal very rapidly

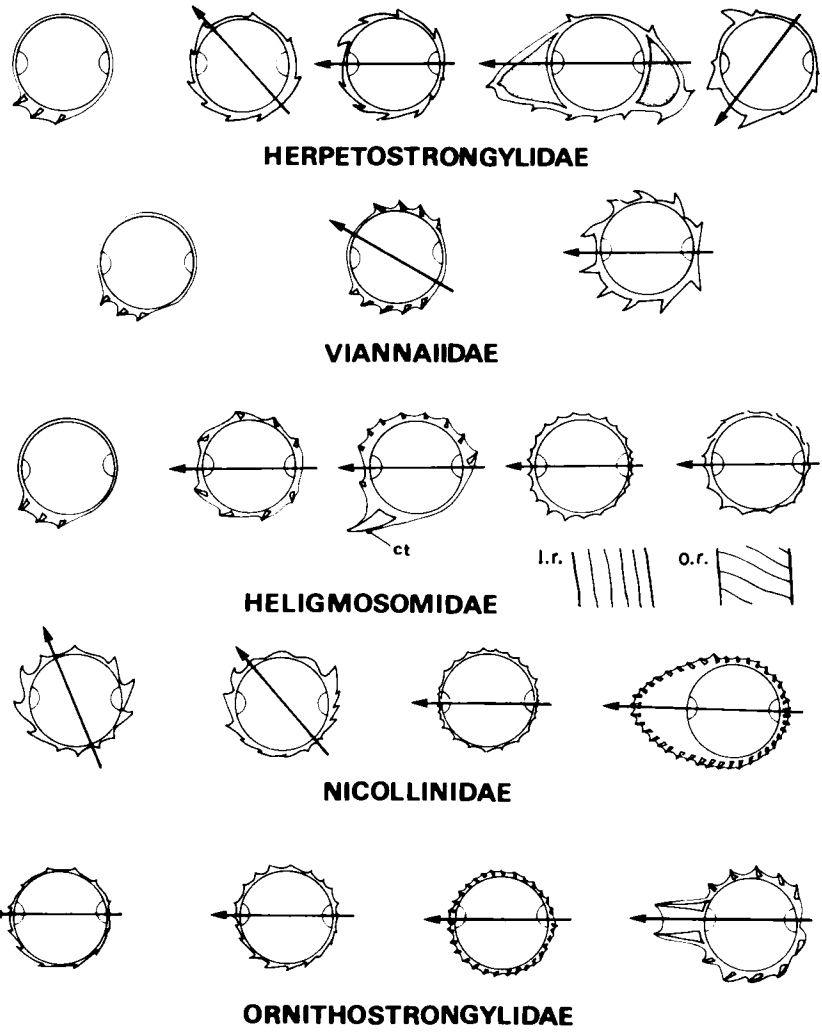


FIG. 10. Representative synlophes of adults of the Heligmosomid line: Herpetostrongylidae, Viannaiidae, Heligmosomidae, Nicollinidae, and Ornithostrongylidae. During evolution (progression from left to right in each row of synlophes), the axis of orientation (arrows) becomes frontal rapidly and the synlophe becomes symmetrical with respect to it. Note the presence of flotteurs in certain Herpetostrongylidae and that the axis of orientation of synlophe at extreme right in the Herpetostrongylidae (genus *Vaucherus*) is postfrontal. Note also comaretes (ct), longitudinal (lr), and oblique ridges (or) in certain Heligmosomidae.

during the course of evolution and the synlophe becomes symmetrical (same number, size, and orientation of ridges) with respect to this axis.

In the Herpetostrongylidae, Viannaiidae, and Heligmosomidae, the synlophe consists primitively of three ventral left ridges. In the first two families the axis of orientation is at first oblique and becomes frontal secondarily; in the Heligmosomidae, it is frontal as soon as it appears. Evolution of the synlophe in the Herpetostrongylidae involves the acquisition of flotteurs; in one genus, *Vaucherus,* the axis of orientation rotates beyond the frontal axis and is directed from dorsal right to ventral left. In the Heligmosomidae, comaretes appear and ridges become oriented obliquely with respect to the long axis of the body. At first this involves only the dorsal ridges but later, all ridges become oblique.

In the Nicollinidae the axis of orientation is primitively about 30° from sagittal. However, within a single genus (*Nicollina*) this axis rotates and becomes frontal. Even the most primitive synlophes in the Ornithostrongylidae are perfectly symmetrical with respect to the frontal axis. A carene appears in the most evolved forms.

In the Heligmonellidae (Figs. 11 and 12), the axis of orientation rotates very slowly during the course of evolution and is frontal only in a few specialized forms. The synlophe is very rarely perfectly symmetrical with respect to the frontal axis. Thus, ridges are generally more numerous on the ventral surface, or they are parallel with respect to the body axis on one side and oblique on the other.

The most primitive synlophe in the Heligmonellinae (Fig. 11) has a small number of relatively large ridges with a size gradient from right to left dorsally and from left to right ventrally. The axis of orientation is inclined about 45° from sagittal. In the most evolved forms the axis of orientation is inclined 55° from sagittal, the size gradient persists, and the number of ridges increases.

In the most primitive synlophe of the Pudicinae (Fig. 11) the axis of orientation is inclined 45° from sagittal and there is a double lateromedian size gradient. Evolution of the synlophe begins with the appearance of a hypertrophied left ridge; at a later stage a large carene appears and subsequently diminishes in size. In certain forms comaretes appear. In the most evolved synlophes, the axis of orientation is frontal but the ventral ridges are smaller and more numerous than the dorsal ridges; furthermore, all ridges except those in the carene are discontinuous and nonalternate with respect to adjacent ridges.

Evolutionary trends observed in the Pudicinae are paralleled and pushed further in the Brevistriatinae (Fig. 11). The axis of orientation is primitively subfrontal and changes little during the course of evolution. Ridges become smaller and more numerous or fuse with one another forming comaretes, and the carene, often prominent, disappears in the

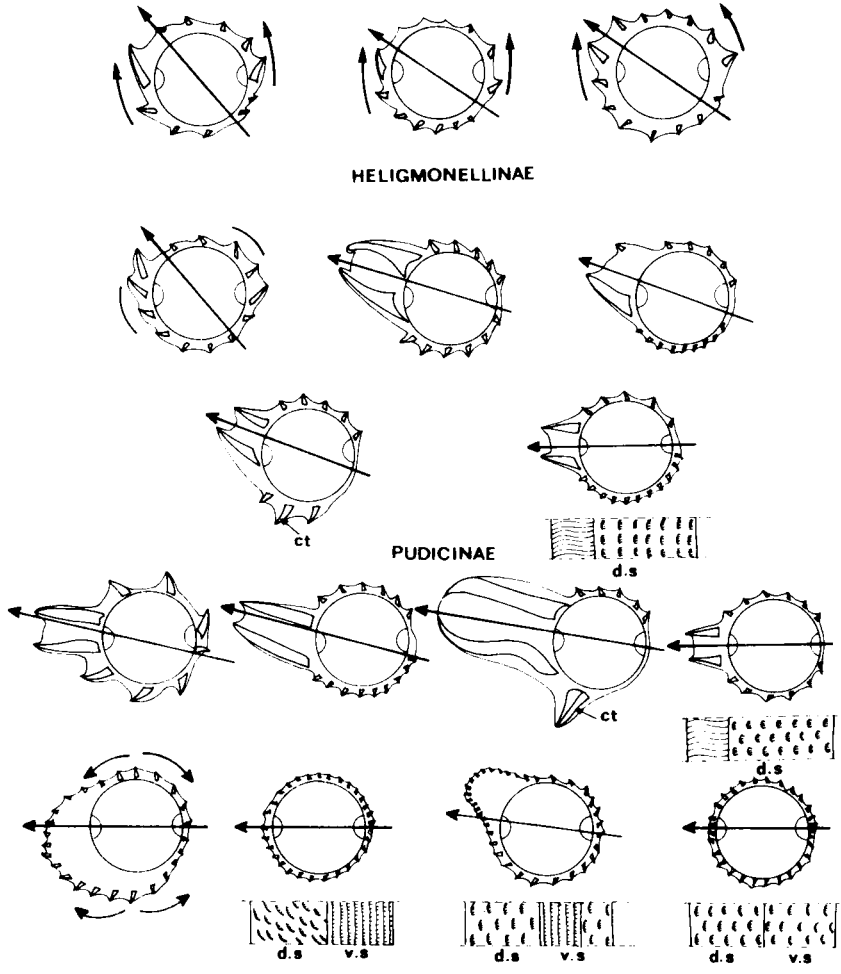


FIG. 11. Representative synlophes of adults of Heligmosomid line: Heligmonellinae, Pudicinae, and Brevistriatinae (Heligmonellidae). Evolutionary progression is from left to right and top to bottom in each subfamily. The axis of orientation (arrows) rotates slowly and is frontal in only a few specialized forms. A carene is commonly present in the Pudicinae and Brevistriatinae. Note the presence of comaretes (ct) in certain Pudicinae and Brevistriatinae, and discontinuous ridges, nonalternate in the Pudicinae and alternate in the Brevistriatinae. Note that ridges may be discontinuous only on the dorsal side (d.s) or on dorsal and ventral side (v.s) of body.

most evolved synlophes. At the same time, ridges except those supporting the carene, become discontinuous and, in general, alternate with respect to adjacent ridges. In spite of their close parallel evolution the Brevistriatinae and Pudicinae are distinct lineages and can be distinguished by the larval synlophe. In the former, the right and left lateral ridges are of the same size whereas in the latter, the left ridge is more developed.

In the Nippostrongylinae (Fig. 12), the axis of orientation is primitively about 45° from sagittal. Its subsequent rotation is much less accentuated than in the Pudicinae and Brevistriatinae and it is subfrontal in only a few highly evolved forms. Ridges on the right and ventral left side are more developed than the rest in all but the most evolved forms. In the latter, the ridges are small, numerous and about equal in size.

The Nippostrongylinae consist of three evolutionary lines whose primitive forms are virtually indistinguishable: dorsal left ridge more developed than other dorsal ridges and axis of orientation 45° from sagittal. However, the evolution of the synlophe is slightly different in each of the three lines. In the Oriental line, evolution sometimes involves reduction in size and increase in number, first of dorsal ridges and later of ventral right ridges; alternatively, dorsal left ridges may hypertrophy and then become smaller and more numerous. In either case, the axis of orientation changes little and is inclined about 50° from sagittal in the most evolved forms. In the Oriental–Australian–Ethiopian line, evolution involves the development of a small carene, or hypertrophy of the left lateral ridge. The axis of orientation rotates to 60° from sagittal. In the Holarctic–Neotropical line, the axis of orientation is at least 50° from sagittal and symmetry is established with respect to it. In the most evolved forms, the axis of orientation rotates to 67° from sagittal, and the ridges are smaller, more numerous, and about equal in size.

Two extremes in the evolution of the synlophe are represented by *Hypocristata,* which has lost its cuticular ridges entirely, and *Mammanidula,* which has a large number of atrophied ridges. These extremes are presumably associated with the biology of the genera. *Mammanidula* occurs in the mammary glands and *Hypocristata,* judging from its long slender body and elongated esophagus, probably also lives in the tissues of its host.

(*d*) *Correlation between synlophe and cephalic vesicle.* A cephalic vesicle is present in all trichostrongyloids in which the synlophe has an axis of orientation. It is absent in forms in which the synlophe is absent or rudimentary. Thus, most members of the molineid line and all members of the heligmosomid line have a cephalic vesicle. The only members of the trichostrongylid line with a cephalic vesicle belong to the Cooperiinae, the subfamily in which the synlophe is most developed (Gibbons, 1981).

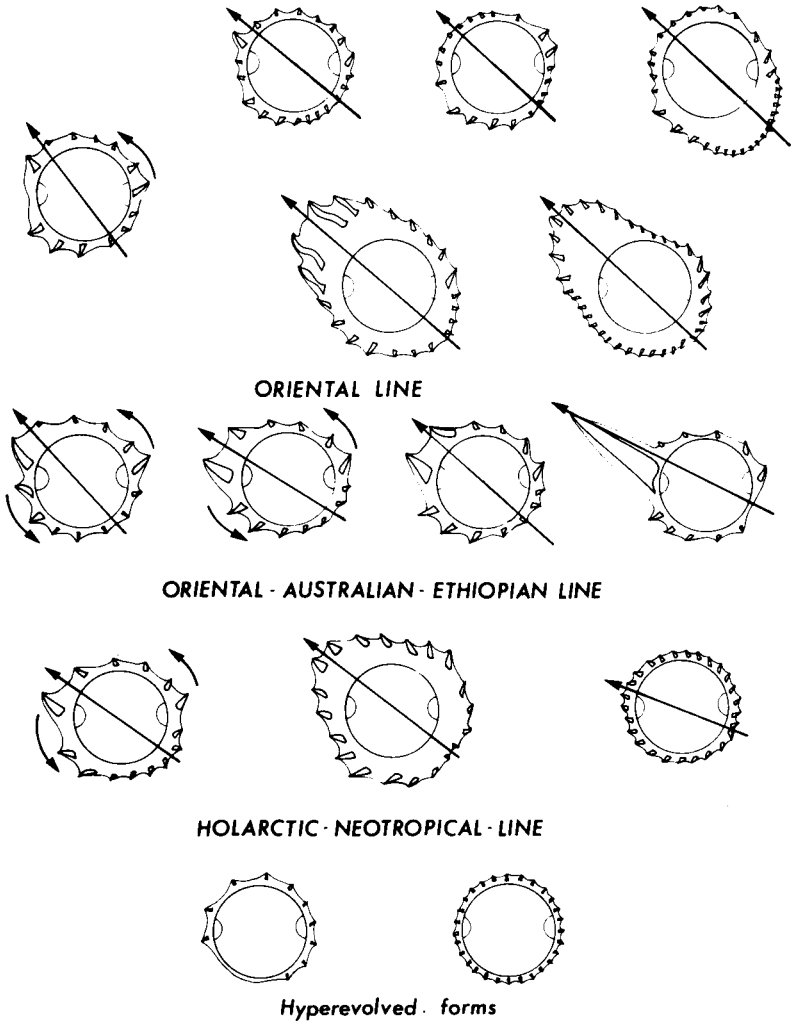


FIG. 12. Representative synlophes of adults of the Heligmosomid line: Nippostrongylinae (Heligmonellidae). Evolutionary progression is from left to right and from top to bottom in each geographical line. Three such lines are indicated. Primitive forms in each are similar, with axis of orientation (arrows) about 45° from sagittal. The axis of orientation rotates slightly but does not become frontal. The two hyperevolved forms are *Hypocristata* (left) and *Mammanidula* (right).

The cephalic vesicle results from the fact that cuticle surrounding the cephalic extremity is separated from that surrounding the rest of the body by a constriction. The extent of this separation is shown by the fact that in living trichostrongyloids of the heligmosomid line, the body cuticle is filled with reddish fluid and that of the cephalic vesicle is filled with clear fluid.

Wright (1975) suggested that the cephalic vesicle might function by transmitting mechanical stimuli from the entire head region to the cephalic papillae. We believe that proper functioning of the synlophe may involve inflation and deflation of the body cuticle. Separation of cephalic and body cuticle into distinct compartments would thus permit the latter to perform its role in attachment and locomotion, leaving the cephalic vesicle free to perform its sensory function.

(*e*) *Possible functional significance of evolutionary trends in the synlophe*. The synlophe undergoes its greatest radiation in the heligmosomid line. These worms coil about the intestinal villi with their ventral surface in contact with the host epithelium. It is therefore not surprising that the most primitive synlophes have three ventral left ridges, since these would allow the worm to grip and move around on the villi. Subsequent changes in the synlophe vary with the subfamily considered, but in all there is a trend toward smaller and more numerous ridges. We believe this is explained by it being in a parasite's best interest to harm its host as little as possible. Spreading the pressure exerted on the villus over a larger number of smaller ridges might allow the same gripping capacity with much less injury to the host epithelium.

B. BIOLOGICAL CHARACTERS

Much remains to be learned about trichostrongyloid biology. I am grateful to Humphrey-Smith (University of Brisbane, South Queensland, Australia), who has reviewed much of the pertinent literature (1984; Ph.D. Thesis, University of Queensland). Most of the studies have involved economically important parasites of domestic animals but two convenient laboratory models, parasites of domestic rat and mouse, respectively, *Nippostrongylus brasiliensis* and *Heligmosomoides polygyrus*, have been used much in biochemical and immunological studies.

The Strongylacanthidae and the Amidostomatidae are morphologically quite distinct from the rest of the Trichostrongyloidea and also have rather particular biologies. The former are parasites of rhinolophoid bats. Larvae develop to the third stage retaining the cuticles of the two previous stages (Seurat, 1920), free-living stages apparently do not feed, and parasitic development has not been examined. The Amidostomatidae parasitize the proventriculus and gizzard of birds. The first two moults occur

in the egg; larvae hatch and become infective in about a week (Cowan, 1955; Kobulei, 1956).

The basic pattern of the life cycle in the rest of the trichostrongyloid families is as follows: eggs are passed with the hosts faeces; larvae hatch and develop to the infective third stage in the external environment. Life cycles can be divided into two major types depending on how the host becomes infected. In the most primitive type, the third larval stage actively penetrates the host, whereas in the evolved type larvae are ingested by the host.

1. *Primitive life history*

In the most primitive trichostrongyloids, the life cycle is comparable to that of the Ancylostomatoidea. The first two larval stages feed in the external environment and the third-stage larva, protected by the second-stage cuticle, is the resistant stage. These larvae actively penetrate the skin of the host and gain access to the circulatory system which carries them to the lungs. They break out of the lungs, are carried up the bronchial "escalator," are swallowed by the host, and settle in the intestine. This type of life cycle is presently known only in *Oswaldocruzia,* essentially parasites of amphibians and lizards (Baker, 1978; Hendrikx, 1983).

2. *Evolved life cycle*

Two major trends are apparent in the evolution of trichostrongyloid life histories.

The free-living larval stage becomes shortened by the existence of moults within the egg (Chabaud, 1955). Larvae become increasingly less dependent on the external environment and increasing more dependent on vitelline reserves for their nourishment. In primitive life cycles, worms hatch from the egg in the first larval stage and undergo two moults in the external environment. Larvae of *Marshallagia marshalli* hatch in the second stage, the first moult occurring in the egg. These second-stage larvae apparently do not feed. In *Nematodirus,* the first two moults take place in the egg. The third-stage larva which hatches is surrounded by the second-stage cuticle and thus does not feed (Boulenger, 1915).

Active skin penetration gives way to oral infection. This change may have been associated with the appearance of early mammals. Since they are homeothermic, mammals must feed a great deal (in the case of small insectivores, almost continuously) and this would have provided the necessary conditions for experimentation with oral routes of infection.

Once successful, oral infection of the host did not immediately supplant skin penetration. Thus, in *Molineus, Nippostrongylus,* and *Hassalstrongylus,* parasites of raccoon, rat, and mouse, respectively, infection

can occur by the oral route or by skin penetration (Gupta, 1961, 1963; Schwartz and Alicata, 1934, 1935). At least in the first two genera, larvae, regardless of the means of infection, undergo an obligatory somatic migration via the circulatory system, lungs, and bronchi before being swallowed and settling in the intestine.

The next stage in the evolutionary sequence from skin penetration to oral infection is illustrated by two rather specialized groups: the Dictyocaulinae and the molineine genus, *Hepatojarakus*. The Dictyocaulinae occur in the lungs of ungulates. Infection is necessarily by the oral route and involves an obligatory somatic migration. *Hepatojarakus* also has an abbreviated life cycle and never reaches the intestine, maturing instead in the bile ducts of the liver (Ow-Yang, 1974).

In the most evolved trichostrongyloid life cycles, infection is necessarily by the oral route and larvae develop to adulthood in the gastrointestinal tract without any somatic migration. Such life cycles are generally characteristic of trichostrongyloids of strictly herbivorous hosts such as lagomorphs, ungulates, and certain rodents (e.g., Arvicolidae). They have been demonstrated in a number of trichostrongylid genera: *Obeliscoides* (Alicata, 1932; Herlich, 1965a,b), *Cooperia* (Andrews, 1939; Herlich, 1965a,b), *Graphidium* (Wetzel and Enigk, 1937), *Hyostrongylus* (Alicata, 1935), *Teladorsagia* (Dikmans and Andrews, 1933), *Ostertagia* (Threlkeld, 1946; Douvres, 1956), *Trichostrongylus* (Douvres, 1957), and *Haemonchus* (Ransom, 1906; Veglia, 1915). Such life cycles are also known in the molineid *Nematodirus* (Boulenger, 1915; Herlich, 1954; Thomas, 1959), the ornithostrongylid, *Ornithostrongylus* (Cuvillier, 1937), and the heligmosomid, *Heligmosomoides* (Bryant, 1973).

3. *Arrested development*

Arrested development in nematodes has been the subject of two lengthy reviews (Michel, 1974; Schad, 1977). The phenomenon is particularly well studied among Trichostrongylidae of lagomorphs and ruminants mainly in temperate regions of the world. In response to one or more factors (environmental, immunological, or genetic), a certain proportion of the infecting larvae temporarily cease development in the early fourth stage and remain in the gastric crypts or encysted in the submucosa of the gastrointestinal tract until other factors stimulate them to resume their development.

The most studied examples of arrested development in trichostrongyloids involve rather highly evolved parasites of ruminants belonging to the Trichostrongylidae. However, there is some indication that developmental arrest is of more general occurrence in the superfamily. Thus, early experiments on *Nippostrongylus brasiliensis* (Heligmonellidae) suggested that some third-stage larvae accumulate and remain in the lungs for a

variable length of time (Schwartz *et al.*, 1931). Chandler (1932) noted a phenomenon resembling developmental arrest in the host intestine in this species.

Our observations on certain heligmonellid parasites of African sciurids belonging to the genus *Paraheligmonina* suggest that developmental arrest occurs here also. Thus, if one opens the intestine taking care not to disturb the mucosa, third-stage larvae cannot be seen. They are present however, and can be seen in histological sections, surrounded by granulomatous capsules in the intestinal submucosa. That these larvae are alive is shown by the fact that if one leaves a dissected intestine for several hours, the larvae break out of their capsules and appear on the mucosal lining. What is interesting in this example (and that of *Nippostrongylus*) is that developmental arrest occurs in the third larval stage, and not the fourth larval stage as has been observed in the Trichostrongylidae.

C. CONGENERIC SPECIES IN THE SAME ORGAN

Problems posed by the coexistence of several congeneric species parasitizing the same organ have been studied in several groups (flagellates of cockroaches, ciliates of perissodactyles, haemosporidians of mammals, monogeneans of fish, etc.). The first nematode examples studied were the Oxyuridae of tortoises (Schad, 1963; Petter, 1966) and the strongyles of horses (Looss, 1901) and elephants (Chabaud, 1956). Such congeneric parasitic faunae were later demonstrated in the Trichostrongyloidea of marsupials (Durette-Desset, 1974; Diaw, 1976), xenarthrans (Durette-Desset *et al.*, 1977), and hystricomorph (Durette-Desset, 1969b, 1971) and sciuromorph (Durette-Desset, 1970, 1971; Kouyaté, 1981) rodents.

1. *The evolutionary problem*

From an evolutionary standpoint, the problem is how such extensive speciation can occur in the colon or intestine in the apparent absence of isolation.

In 1971, I proposed the following hypothesis using as an example the trichostrongyloids of *Funisciurus lemniscatus*. A population of squirrels primitively harbours a single nematode species. Subsequently, the host population becomes divided into two or more isolated subpopulations. This period of isolation is long enough to allow speciation of the nematode populations but insufficient for host speciation. When the host populations come together again, they mix and exchange their parasites. In some cases, certain biological differences allow the parasite species so generated to coexist. Repetition of this phenomenon over the centuries would thus result in the congeneric species associations we observe today.

This hypothesis is consistent with the four principal characteristics of the parasitic faunae (Chabaud and Durette-Desset, 1978):

1. The ancient nature of the host. With the exception of perissodactyles, hosts harbouring these faunae are relatively ancient; i.e., present forms are very similar to fossil forms. Absence of such faunae in recent hosts is explained by the fact that there has not been sufficient time for successive speciations to occur.

2. Monoxenous life cycle. In the great majority of cases, there is no intermediate host in the life cycle. Intermediate hosts are often highly mobile invertebrates and their presence in the life cycle would tend to make isolation of parasitic populations less likely.

3. Close phylogenetic relationship of species comprising the parasitic faunae. The description of these faunae as congeneric is somewhat inexact since species involved may belong to several different genera. However, the genera involved always belong to the same evolutionary line and species parasitizing the same host often resemble each other more closely than they do their congeneric relatives in other host species. Such morphological similarity between parasites in the same host is to be expected if the species arose by successive speciations originating from a single ancestral species.

4. Coexistence of primitive and evolved forms in the same host. Generally these faunae are composed of primitive, evolved, and intermediate forms. This characteristic, like the preceding one, is to be expected if the species are descendents (some recent, others ancient) of a single original species.

2. *The ecological problem*

(*a*) *Niche diversification.* Coexistence of several species in the intestine implies some difference exists in the niche each occupies.

Oxyuroids in the tortoise colon live within or at the periphery of the alimentary bolus. Buccal structures vary considerably from one species to another and Schad (1963) noted that niche diversification involves trophic as well as spatial and seasonal factors. Buccal structures are little varied in trichostrongyloids; diet is probably similar in most species and trophic factors are not likely to play an important role in niche diversification.

The most obvious differences in localization are longitudinal. Thus, a group of species always occurs in the same sequence along the length of the intestine (Durette-Desset, 1971; Kouyaté, 1981). However, this appears to be a case of species dominance (though not necessarily numerical dominance) and not niche diversification. Recent experiments (Sukhdeo and Mettrick, 1983) confirm that the duodenum is the preferred site of

intestinal trichostrongyloids. If we consider a group of species which appear in sequence A, B, C, etc. in the intestine, and if, for example, species A is missing, then the remaining species will occupy a more anterior position.

Radial distribution is probably more important in spatial niche diversification in sympatric trichostrongyloids. These species attach to the intestinal villi and we know of at least one pair of species (*Paraheligmonina quartanuda* and *P. posterior*) in which one (*P. quartanuda*) attaches near the base, and the other near the tip of the villus (Durette-Desset, 1971).

(*b*) *Types of congeneric faunae*. Two major types of faunae occur, which seem to depend on host diet (Chabaud and Durette-Desset, 1978). In monophagous hosts, the diet consists primarily of one food item (e.g., grass, termites, or ants), and the faunae encountered have a relatively large number of species of which a relative abundance of species are very stable and conform to general rules formulated for free-living animals (for example, MacArthur's formulae). In polyphagous hosts, the diet is composed of a great variety of food items, and the parasitic faunae encountered have a relatively small number of species (less than 10), with a relative abundance of species variable and thus without stable equilibrium. The trichostrongyloid faunae of the Myrmecophagidae are of the first type, and those of Hystricidae and Sciuridae are of the second type.

This association between the type of parasite fauna and host diet seems to correspond to general rules of ecology pertaining to stable and unstable environments. The intestinal milieu provided by monophagous hosts would thus correspond to stable environments such as primary forests which harbour species having life history strategies of type K; that provided by polyphagous animals would correspond to unstable environments (burnt grasslands) which favour species with type r strategies.

D. SYSTEMATIC CONCLUSIONS

On the basis of morphological characters and their presumed evolution discussed above, Durette-Desset and Chabaud (1977, 1981a) divided trichostrongyloids into 14 families and 24 subfamilies. Except for the Strongylacanthidae (parasites of rhinolophid bats) and the Amidostomatidae (parasites of birds), which are probably derived from ancylostome-like ancestors, the trichostrongyloids appear to be monophyletic. They can be divided into three major branches (Fig. 13), each representing a particular morphological type, which are characterized below.

1. *Trichostrongylid type*

Body generally uncoiled. Cephalic vesicle absent (except in *Dromaeostrongylus*, and certain highly evolved forms). Didelphic (except for three

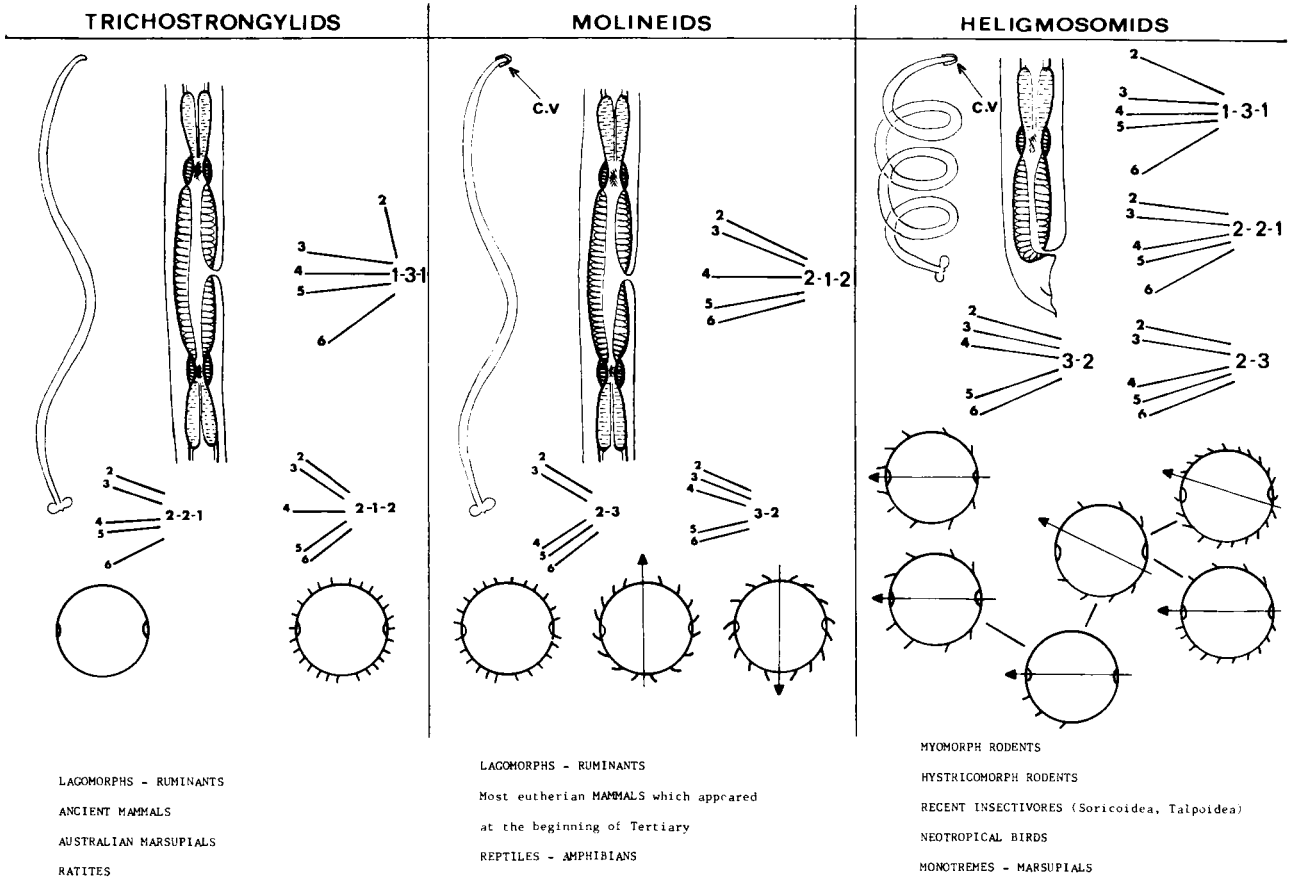


FIG. 13. Schematic representation of the different morphological types of the Trichostrongyloidea: the trichostrongylid line, the molineid line, and the heligmosomid line. Morphological characters represented are the coiling of the body, absence or presence of cephalic vesicle (c.v), didelphy or monodelphy, and the different types of bursae and synlophes.

genera). Bursa primitively of type 1-3-1 but types 2-1-2 and 2-2-1 most frequent in evolved forms. Synlophe absent or rudimentary. Axis of orientation present only in highly evolved forms (same as those listed as having cephalic vesicle). **Host and geographical distribution:** ratite and Neotropical birds, Australian marsupials, and eutherian mammals, mainly lagomorphs and ruminants.

Dromaeostrongylidae (5 genera) (Fig. 14). Cephalic vesicle absent except in *Dromaeostrongylus*. Didelphic. Bursa type 1-3-1 in three genera and 2-3 in two genera representing transitional forms with the molineid line. Synlophe absent (except in *Dromaeostrongylus*). **Host and geographical distribution:** Neotropical and ratite birds, Australian marsupials.

Trichostrongylidae (34 genera) (Figs. 15 to 17). Cephalic vesicle absent except in the Cooperiinae. Didelphic except for three genera of Cooperiinae. Bursa varied: types 1-3-1, 2-2-1, and 2-1-2 represented.

The family has been divided into three groups on the basis of the disposition of bursal rays 2 and 3. Each group consists of two subfamilies, one primitive, one more evolved. In the first (Libyostrongylinae–Cooperiinae), ray 2 is shorter than ray 3 and the extremities of these rays curve toward each other. In the second (Graphidiinae–Ostertagiinae), rays 2 and 3 are about equal in size and parallel. In the third (Trichostrongylinae–Haemonchinae), ray 2 is much smaller than ray 3 and their extremities are well separated.

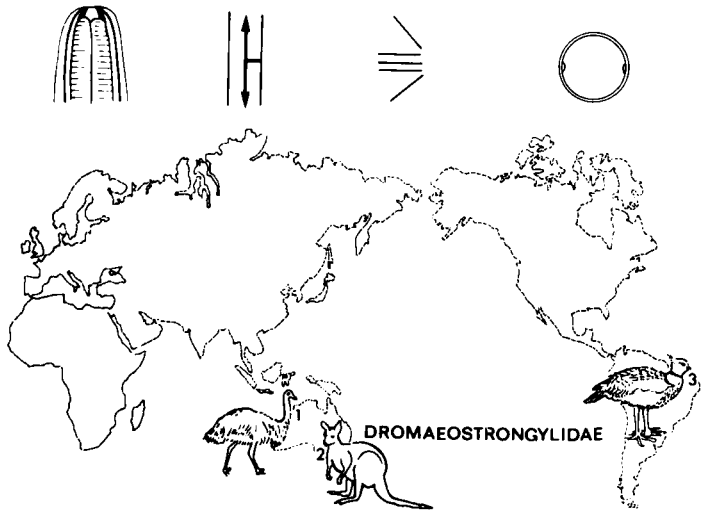


FIG. 14. Principal morphological characters, host, and geographical distribution of the Dromaeostrongylidae: 1, ratites; 2, marsupials; 3, *Chauna*.

Libyostrongylinae (6 genera) (Fig. 15). Bursa type 1-3-1. Synlophe absent or ridges oriented perpendicular to body surface. **Host and geographical distribution:** ratites, archaic rodents, and hyracoids in Africa; lemurs and rodents in Madagascar; Holarctic and Ethiopian lagomorphs; and *Antilocapra* in North America.

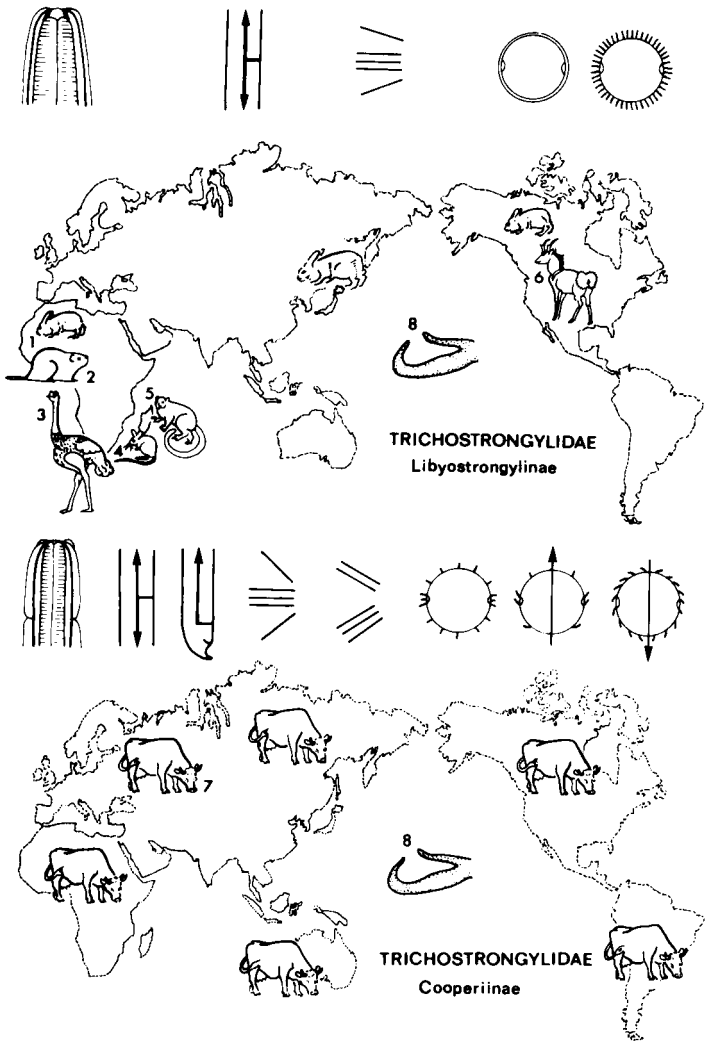


FIG. 15. Principal morphological characters, host, and geographical distribution of the Libyostrongylinae and Cooperiinae (Trichostrongylidae): 1, lagomorphs; 2, archaic rodents; 3, ratites; 4, rodents; 5, lemurs; 6, *Antilocapra*; 7, ruminants; 8, relative position of bursal rays 2 and 3.

Cooperiinae (8 genera) (Fig. 15). Bursa type 1-3-1 primitively, tending to type 2-3 in more evolved species. Synlophe primitively with ridges oriented perpendicular to body surface, and later with sagittal (ventrodorsal or dorsoventral) axis of orientation. **Host and geographical distribution:** Bathyergidae (Rodentia) and ruminants of Old World origin.

Graphidiinae (3 genera) (Fig. 16). Bursa type 2-2-1. Synlophe with ridges oriented perpendicular to body surface. **Host and geographical dis-**

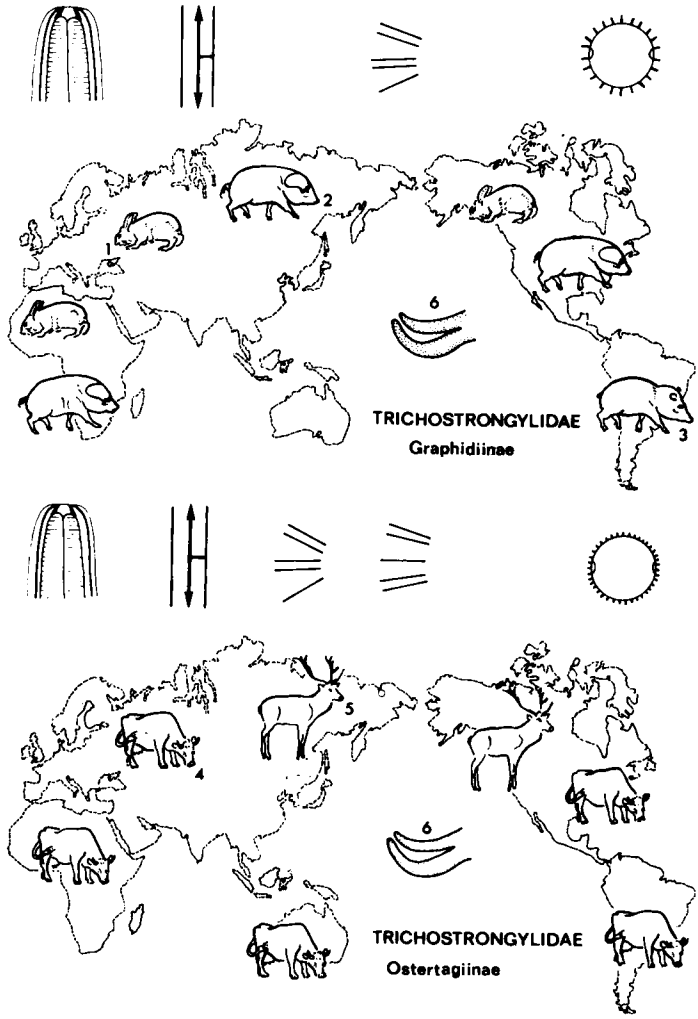


FIG. 16. Principal morphological characters, host, and geographical distribution of the Graphidiinae and Ostertagiinae (Trichostrongylidae): 1, lagomorphs; 2, Suidae; 3, Tayassuidae; 4, Bovidae; 5, Cervidae; 6, relative position of bursal rays 2 and 3.

tribution: Holarctic and Ethiopian lagomorphs, Ethiopian Tragulidae (rarely Giraffidae), Tayassuidae, and Suidae throughout the world.

Ostertagiinae (5 genera) (Fig. 16). Bursa type 2-2-1 or 2-1-2. Synlophe with ridges oriented perpendicular to body surface. **Host and geographical distribution:** ruminants, mainly in Old World.

Trichostrongylinae (3 genera) (Fig. 17). Bursa type 1-3-1. Synlophe absent or with ridges oriented perpendicular to body surface. **Host and**

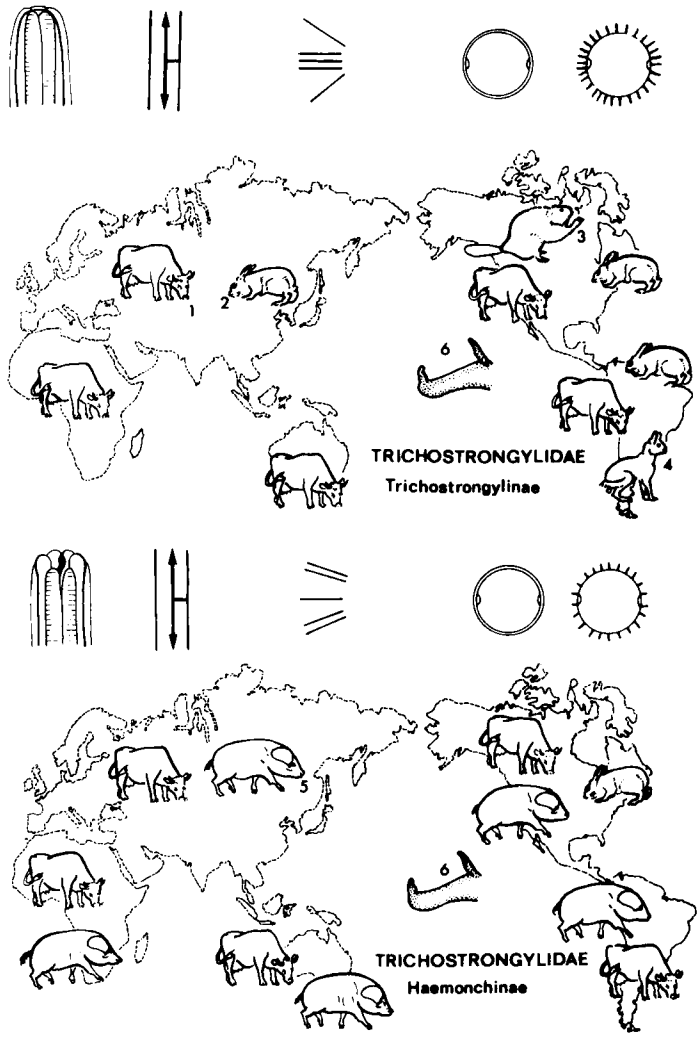


FIG. 17. Principal morphological characters, host, and geographical distribution of the Trichostrongylinae and Haemonchinae (Trichostrongylidae): 1, ruminants; 2, lagomorphs; 3, beavers; 4, *Dolichotis*; 5, Suidae; 6, relative position of bursal rays 2 and 3.

geographical distribution: cosmopolitan; caviomorphs, beavers, lagomorphs, and ruminants; occasionally in various other mammals and man.

Haemonchinae (6 genera) (Fig. 17). Neodont formation present. Bursa type generally 2-1-2 with reduced dorsal lobe. Synlophe absent or ridges oriented perpendicular to body surface. **Host and geographical distribution:** ruminants (mainly in Old World), Suidae (cosmopolitan), lagomorphs (Nearctic), *Nutria* (New World and Europe), and Soricidae (Japan).

2. *Molineid type*

Body generally uncoiled. Cephalic vesicle present except in certain Amphibiophilidae and Dictyocaulidae. Didelphic except for two genera with posterior branch of reproductive tract atrophied. Bursa type generally 2-1-2 with short ray 4. Synlophe present (except Dictyocaulidae) with or without axis of orientation but always bilaterally symmetrical. **Host and geographical distribution:** cosmopolitan; amphibians, reptiles, monotremes, marsupials, and most eutherian mammals present at beginning of Tertiary; lagomorphs and ruminants.

Amphibiophilidae (3 genera) (Fig. 18). Cephalic vesicle present or absent. Cephalic extremity primitive with buccal capsule and dorsal esophageal tooth. *Corona radiata* present or absent. Didelphic. Bursa type generally 2-1-2 but ray 4 on common trunk with rays 5 and 6 and this resulting in bursa type 2-3 in *Graphidiella*. Synlophe with ridges oriented perpendicular to body surface. **Host and geographical distribution:** cosmopolitan; Malaysian, and Ethiopian amphibians and Holarctic ochotonid lagomorphs.

Dictyocaulidae (4 genera) (Fig. 18). Cephalic vesicle present or absent. Cephalic extremity not primitive. Didelphic. Bursa type 2-1-2. Synlophe absent. **Host and geographical distribution:** digestive tract of amphibians and reptiles in Russia, Borneo, and Neotropical region; respiratory system of ungulates throughout the world.

Molineidae (45 genera) (Figs. 19 and 20). Cephalic vesicle present. Cephalic extremity not primitive. Didelphic except for a few highly evolved forms.

Ollulaninae (1 genus). Monodelphic. Bursa type 2-1-2. Synlophe absent. **Host and geographical distribution:** cosmopolitan, mainly felids.

Molineinae (18 genera) (Fig. 19). Didelphic. Bursa type 2-1-2: rays 4, 5, and 6 sharing common trunk in primitive forms parasitizing anurans; ray 3 approaching ray 2 in evolved forms and sometimes resulting in bursa of type 3-2 (for details, see Durett-Desset and Chabaud, 1981b). Synlophe with ridges oriented perpendicular to body surface. **Host and geographical distribution:** cosmopolitan; amphibians, reptiles, carnivores, insectivores

(Tenrecoidea, rarely Erinacoidea), Old World bats, Tupaiidae, primates, Pholidota, Tubulidentata, and rodents (Sciuridae).

Nematodirinae (6 genera) (Fig. 19). Neodont formation present. Didelphic or monodelphic. Bursa type 2-1-2 with dorsal ray divided at its base (except *Lamanema*). Synlophe with ridges oriented perpendicular to body surface or, with sagittal axis of orientation ventral to dorsal or vice versa, or ventrodorsal on ventral side and dorsoventral on dorsal side.

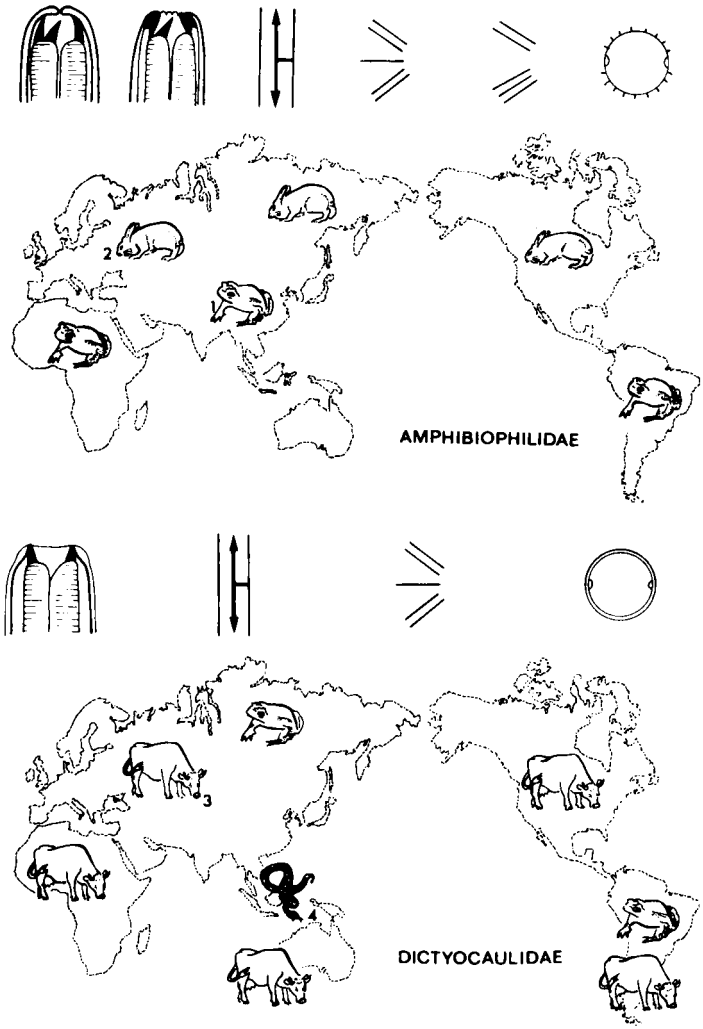


FIG. 18. Principal morphological characters, host, and geographical distribution of the Amphibiophilidae and Dictyocaulidae: 1, amphibians; 2, lagomorphs; 3, ruminants; 4, reptiles.

Host and geographical distribution: lagomorphs and ruminants; mainly Holarctic.

Anoplostrongylinae (20 genera) (Fig. 20). Didelphic (one genus with posterior branch of reproductive tract atrophied; one genus monodelphic). Bursa type 2-1-2, frequently with rays 2 and 3 strongly developed. Synlophe with ventrodorsal axis of orientation. **Host and geographical**

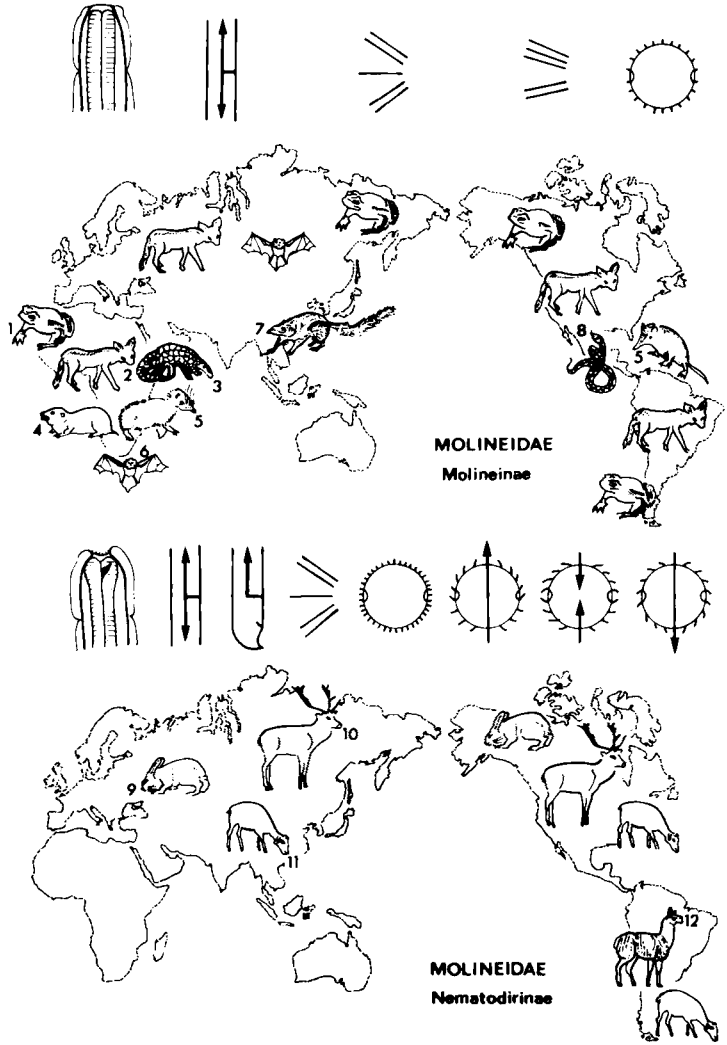


FIG. 19. Principal morphological characters, host, and geographical distribution of the Molineinae and Nematodirinae (Molineidae): 1, amphibians; 2, carnivores; 3, Pholidota; 4, phiomorph rodents; 5, tenrecoid insectivores; 6, chiropterans; 7, Tupaiidae; 8, reptiles; 9, lagomorphs; 10, Cervidae; 11, Bovidae; 12, Camelidae.

distribution: bats (mainly New World), Xenarthra, rarely Neotropical Cricetidae; Tupaiidae.

Mackerrastrongylidae (*7 genera*) (*Fig. 20*). Buccal capsule or *corona radiata* present (Tasmanematinae), or cephalic extremity lacking primitive characters (Mackerrastrongylinae). Didelphic (except *Sprattellus*). Bursa type 2-1-2. Synlophe with ridges oriented perpendicular to body

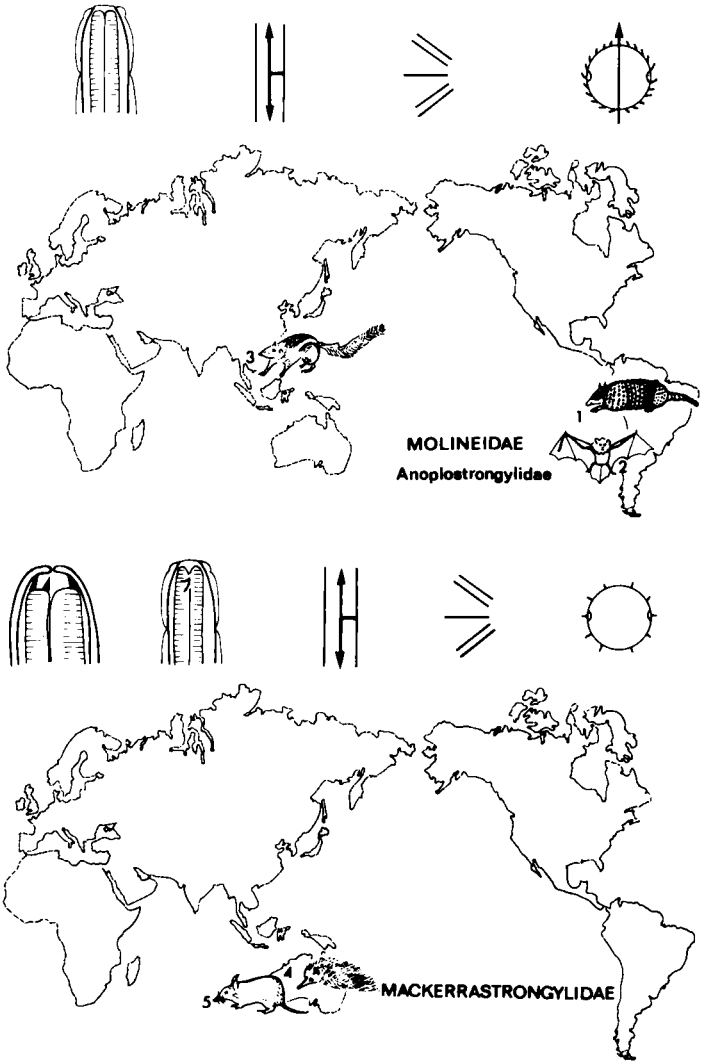


FIG. 20. Principal morphological characters, host, and geographical distribution of the Anoplostrongylinae (Molineidae) and the Mackerrastrongylidae: 1, Xenarthra; 2, chiropterans; 3, Tupaiidae; 4, monotremes; 5, perameloid marsupials.

surface (except *Sprattellus*). **Host and geographical distribution:** monotremes (Australia, New Guinea) and Australian dasyuroid and perameloid marsupials.

3. *Heligmosomid type*

Body generally highly coiled. Cephalic vesicle present. Monodelphic except for a few primitive forms. Bursal types varied but very rarely of type 2-1-2. Synlophe never bilaterally symmetrical. Axis of orientation oblique or frontal; if frontal, synlophe may be dorsoventrally symmetrical. **Host and geographical distribution:** cosmopolitan; amphibians, reptiles, monotremes, marsupials, Neotropical birds, recent insectivores, histricognath, caviomorph and myomorph rodents, and lagomorphs.

Nicollinidae (*3 genera*) (*Fig. 21*). Cephalic extremity with buccal capsule, six lips, and dorsal oesophageal tooth. Didelphic (except for *Copemania*). Bursa type 1-3-1; axis of orientation 45° from sagittal primitively and frontal in evolved forms. **Host and geographical distribution:** Neotropical and Malaysian amphibians and monotremes; one species (*Copemania obendorfi*) in an Australian dasyuroid marsupial.

Herpetostrongylidae (*11 genera*) (*Fig. 21*). Cephalic extremity with buccal capsule, six lips, and dorsal oesophageal tooth. Didelphic or monodelphic. Bursa type 1-3-1, tending toward type 2-3 as a result of development of rays 2 and 3. In certain forms, ray 3 separating from rest of rays, giving bursa of type 1-4. Synlophe primitively with three ventral left ridges; axis of orientation becoming subfrontal in most evolved forms. **Host and geographical distribution:** Oriental reptiles and Australian reptiles and marsupials.

Viannaiidae (*5 genera*) (*Fig. 22*). Cephalic extremity without primitive characters. Monodelphic. Bursa type 2-1-2, with elongated lateroventral lobes or with rays 2 and 3 more developed than rays 5 and 6 (bursa of *Viannella* not conforming to any classic type but with dorsal ray deeply divided into two divergent branches). Synlophe primitively with three ventral left ridges; axis of orientation frontal in evolved forms. **Host and geographical distribution:** New World marsupials and Neotropical caviomorph rodents and primates.

Ornithostrongylidae (*8 genera*) (*Fig. 22*). Cephalic extremity with buccal capsule, dorsal oesophageal tooth, and four lips (Inglamidinae) or without primitive characters (Ornithostrongylinae). Didelphic or monodelphic. Bursa type 2-2-1. Synlophe with frontal axis of orientation. **Host and geographical distribution:** Neotropical, Oriental, and Ethiopian birds; bats, (mainly in New World); *Tupaia* in Borneo; geomyoid rodents in North America and cricetid rodents in North America and Chile.

Heligmosomidae (*9 genera*) (*Fig. 23*). Cephalic extremity without primitive characters. Didelphic (three genera) or monodelphic. Bursa gen-

erally with robust ray 3 and primitively of type 1-3-1; bursa type 2-3 with reduced dorsal rays in evolved forms. Synlophe primitively with three ventral left ridges; axis of orientation subfrontal in evolved forms. **Host and geographical distribution:** Holarctic, Ethiopian, and Oriental soricoid insectivores; Palearctic and Oriental lagomorphs, and Holarctic sciurids and myomorph rodents.

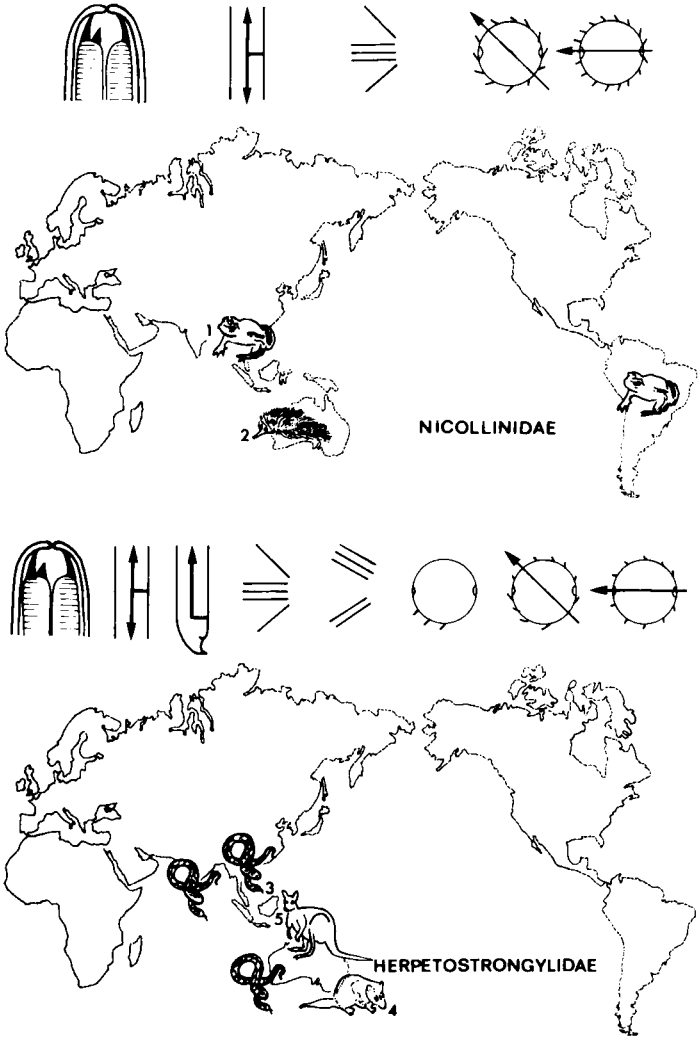


FIG. 21. Principal morphological characters, host, and geographical distribution of the Nicollinidae and Herpetostrongylidae: 1, amphibians; 2, monotremes; 3, reptiles; 4, dasyuroid marsupials; 5, phalangeroid marsupials.

Heligmonellidae (*32 genera*) (*Figs.* 23 and 24). Cephalic extremity without primitive characters. Monodelphic.

Heligmonellinae (6 genera) (Fig. 23). Bursa type most commonly 2-2-1. Axis of orientation 45° at most from sagittal. **Host and geographical distribution:** Holarctic in talpoid insectivores; Neotropical and Old World lagomorphs; phiomorph and caviomorph rodents.

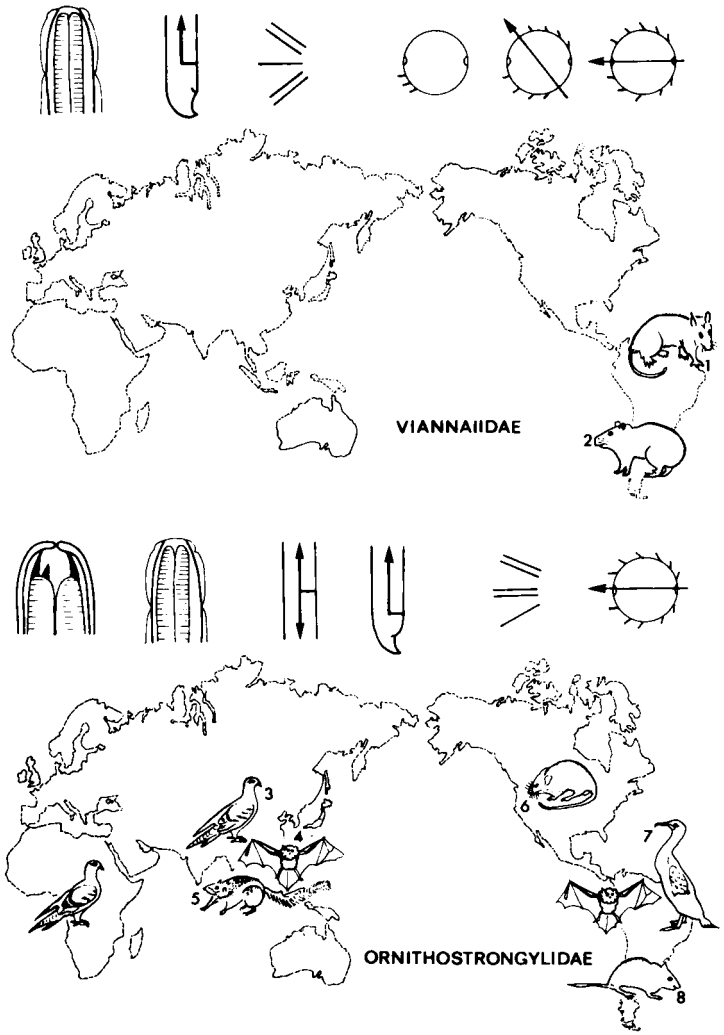


FIG. 22. Principal morphological characters, host, and geographical distribution of the Viannaiidae and Ornithostrongylidae: 1, didelphioid marsupials; 2, caviomorph rodents; 3, Old World birds; 4, chiropterans; 5, Tupaiidae; 6, geomyoid rodents; 7, Neotropical birds; 8, Cricetidae.

Pudicinae (5 genera) and Brevistriatinae (9 genera) (Fig. 24). Bursa type 2-2-1; in Pucidinae, ray 6 often very long and in Brevistriatinae, dorsal lobe often hypertrophied. Axis of orientation 67–90° from sagittal. **Host and geographical distribution:** Pudicinae: New World distribution; caviomorph and sciurid rodents, rarely lagomorphs and cricetid rodents.

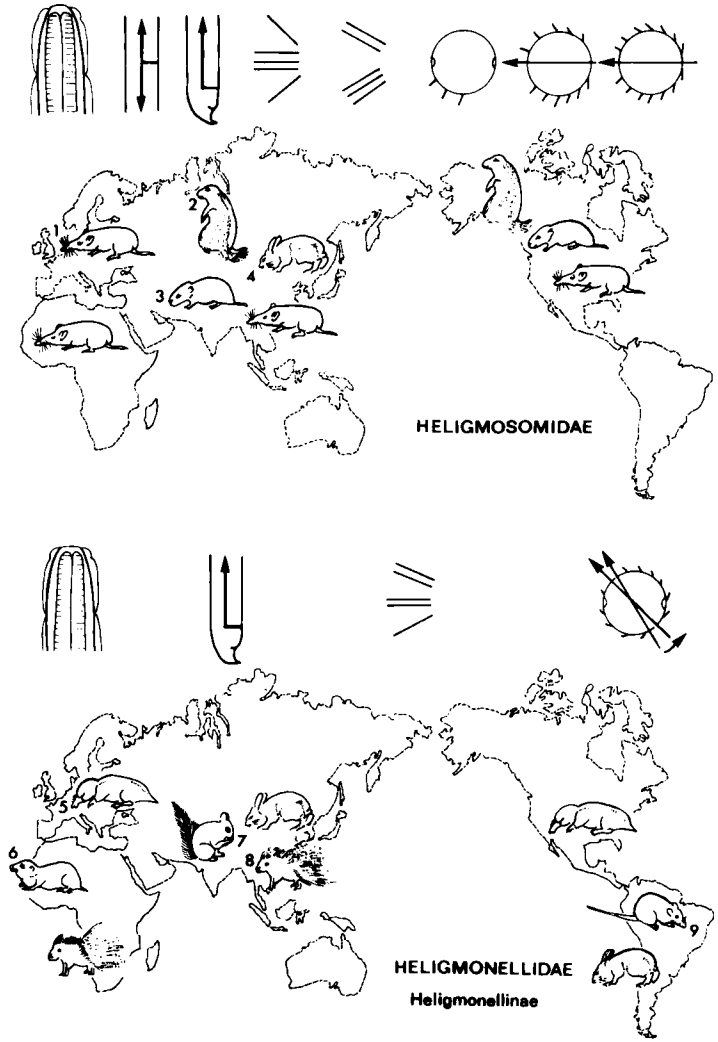


FIG. 23. Principal morphological characters, host, and geographical distribution of the Heligmosomidae and the Heligmonellinae (Heligmonellidae): 1, soricoid insectivores; 2, ground squirrels; 3, Arvicolidae; 4, lagomorphs; 5, talpoid insectivores; 6, phiomorph rodents; 7, Sciuridae; 8, Hystricidae; 9, caviomorph rodents.

Brevistriatinae: Old World distribution; Hystricidae, Sciuridae, and Gliridae, rarely Tragulidae and Muridae.

Nippostrongylinae (12 genera) (Fig. 24). Bursa type generally 2-2-1 but 1-3-1 in some genera. Bursa often highly asymmetrical. Axis of orientation 45–67° from sagittal. **Host and geographical distribution:** myomorph rodents throughout the world and New World cricetid rodents.

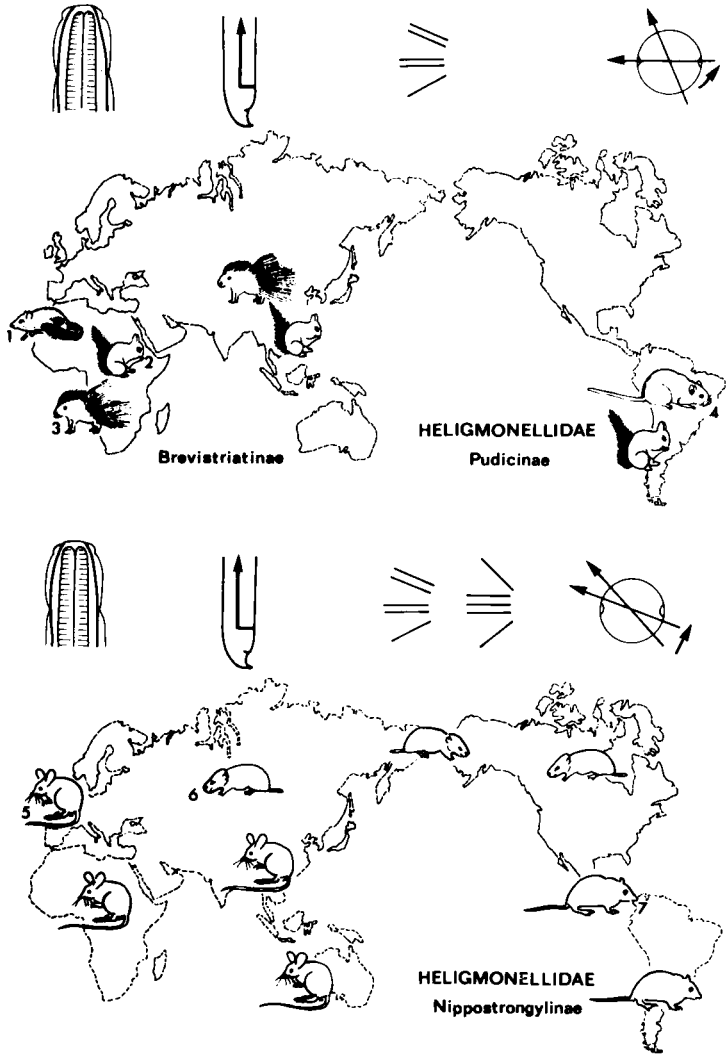


FIG. 24. Principal morphological characters, host, and geographical distribution of the Pudicinae, Brevistriatinae, and Nippostrongylinae (Heligmonellidae): 1, Gliridae; 2, Sciuridae; 3, Hystricidae; 4, caviomorph rodents; 5, Muridae; 6, Arvicolidae; 7, Cricetidae.

III. Data Concerning the Hosts

In the preceding section, we attempted to reconstruct the phylogeny of the Trichostrongyloidea based entirely on morphological characters. In this section we will collate these results with information on host evolution and, more particularly, palaeobiogeography. This information has been taken largely from Lavocat (1967), Thenius (1972), and Hoffstetter (1982).

A. Host and Geographical Distribution

Details concerning host and geographical distribution of each family or subfamily were given in Section II and are summarized schematically in Figs. 13–24. In Figs. 25–27 I have summarized phylogenetic histories of the families and subfamilies comprising the three main branches of the

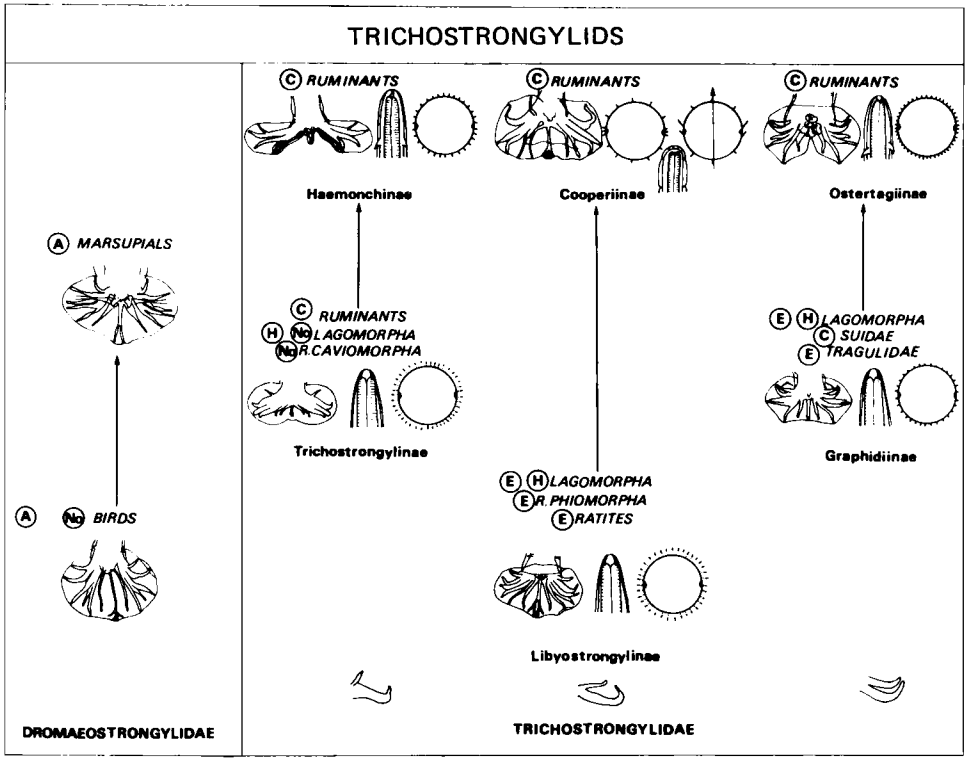


FIG. 25. Phylogenetic histories of families and subfamilies comprising the trichostrongylid line. Host groups are indicated and encircled letters indicate biogeographical regions: A, Australian; E, Ethiopian; H, Holarctic; No, Neotropical; C, cosmopolitan.

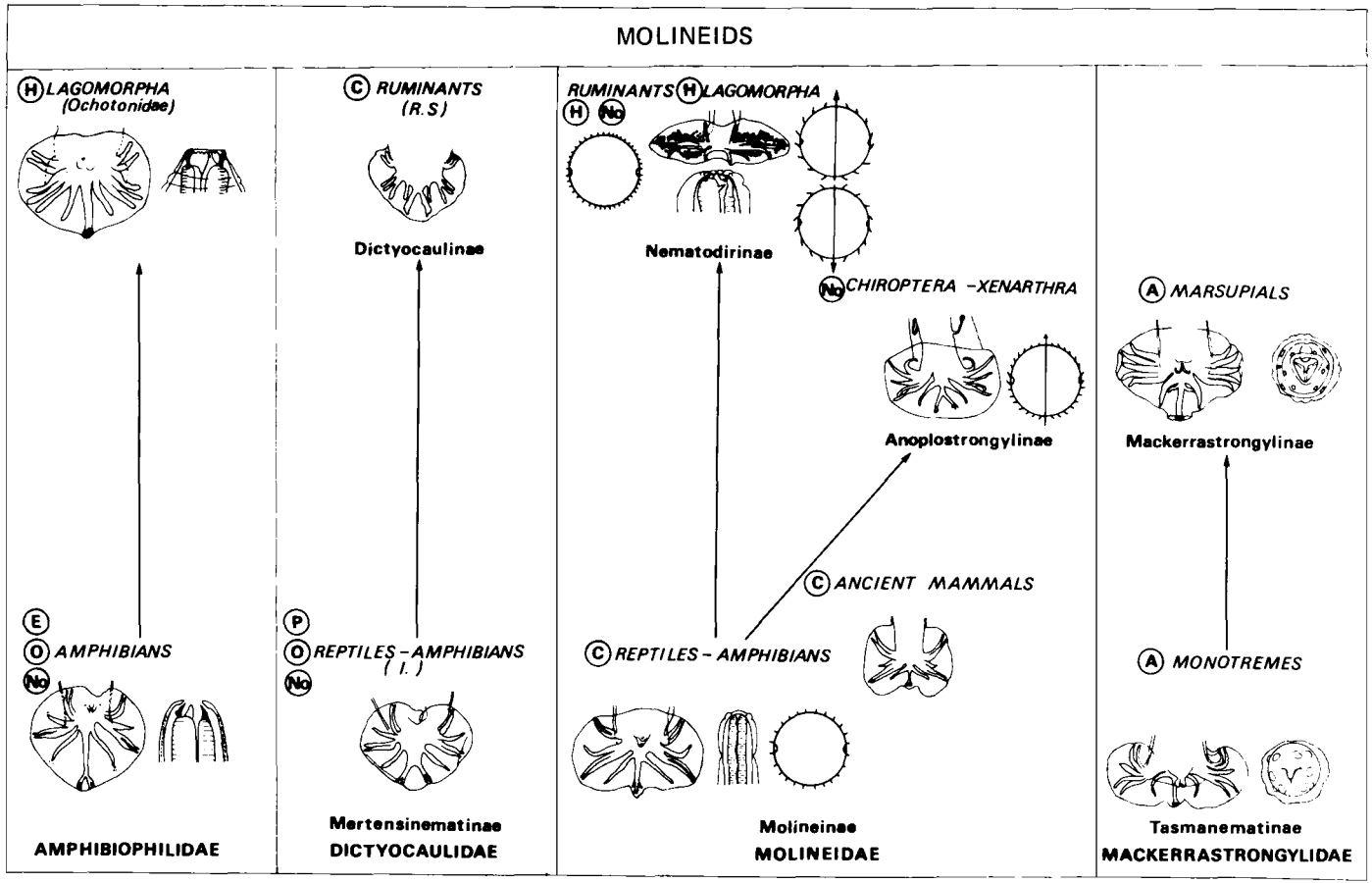


FIG. 26. Phylogenetic histories of families and subfamilies comprising the molineid line. Host groups are indicated and encircled letters indicate biogeographical regions: A, Australian; O, Oriental; E, Ethiopian; P, Palearctic; H, Holarctic; No, Neotropical; C, cosmopolitan. Dictyocaulids occur in the respiratory system (RS) of ruminants and in the intestine (I) of reptiles and amphibians.

Trichostrongyloidea. It is noticeable that for all practical purposes, each parasitic group is characteristic of a particular host group and/or geographical region. In addition, it will be seen that (1) hosts of a given parasitic group are not necessarily closely related phylogenetically (see for example, the host distribution of the Molineidae); (2) certain hosts may be parasitized by more than one evolutionary line (e.g., caviomorph rodents by the Viannaiidae and Pudicinae, and lagomorphs by the Trichostrongylidae, Molineidae, and Heligmonellidae); (3) a given parasitic line may occur in the same host group in geographical regions quite distant from one another (e.g., the Nicollinidae in amphibians).

B. ANALYSIS OF SOME PARASITIC LINES WITH RESPECT TO HOST PALAEOBIOGEOGRAPHY

Many of the host and geographical distributions are impossible to explain if we do not make use of host palaeobiogeography. Analysis of some representative parasitic lines will illustrate how it is possible, even in the absence of fossil evidence, to specify the geological period in which a given family or subfamily arose and those factors which determined its evolutionary history in successive hosts.

1. *Parallel evolution between host and parasite: Herpetostrongylidae*

It is a classical notion in parasitology that parasites of a given host are derived from those of the host's ancestors. This notion seems to apply best to relatively ancient parasitic groups such as the cestodes and protozoans (Baer, 1955; Eichler, 1982). However, the Herpetostrongylidae among trichostrongyloids present us with just such an example (Fig. 28).

Except for two genera parasitic in reptiles (one in varanids in Malaysia and the other in varanids and pythons in Australia), the evolution of the group has occurred in Australian marsupials. The most primitive parasites occur in the most primitive marsupials, the Dasyuroidea; the most evolved parasites occur in the most evolved marsupials, the Phalangeroidea, and, in particular, the Macropodidae. The Perameloidea, which from an evolutionary point of view are situated between the Dasyuroidea and the Phalangeroidea, do not harbour herpetostrongylids but are parasitized by another family, the Mackerrastrongylidae.

When host and parasite evolution parallel one another as they do in this example, we can assume that the parasitic line arose at the same time as its hosts. Thus, the evolution of the Herpetostrongylidae occurred in all probability during the first half of the Tertiary when marsupials were radiating.

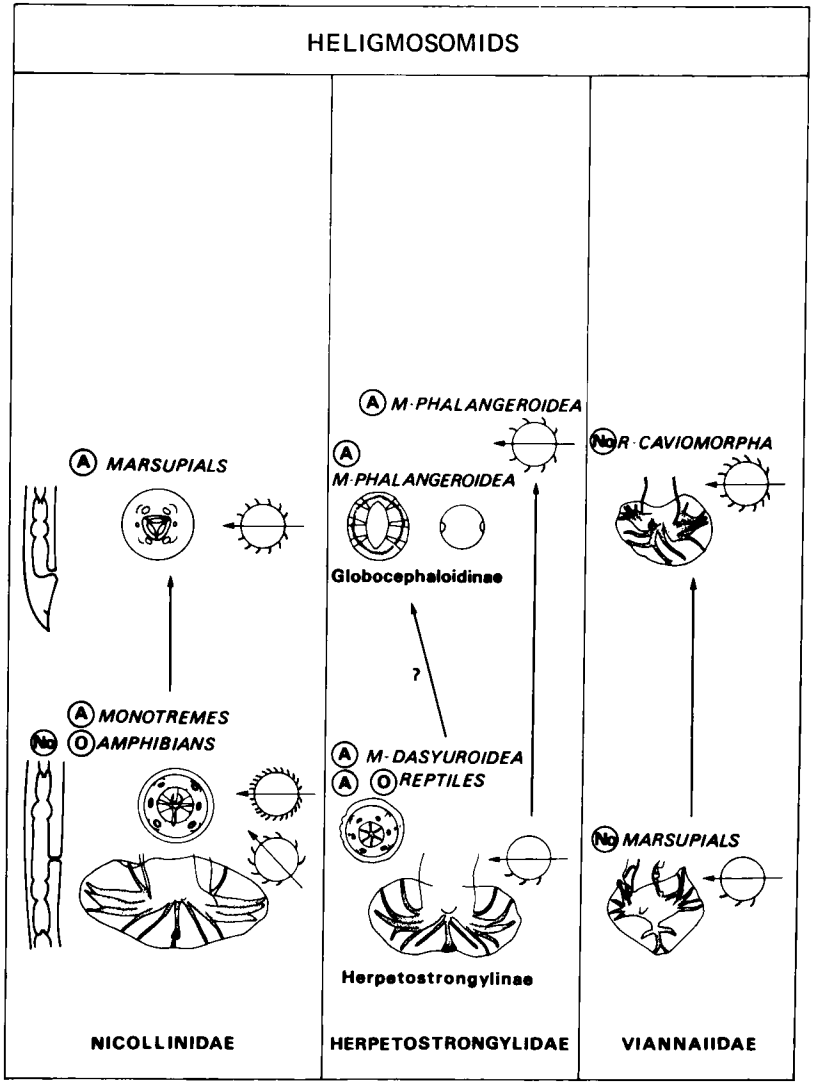


FIG. 27. Phylogenetic histories of families and subfamilies comprising the heligmosomid line. Host groups are indicated and encircled letters indicate biogeographical regions: A, Australian; O, Oriental; E, Ethiopian; P, Palearctic; Ne, Nearctic; H, Holarctic; No, Neotropical; C, cosmopolitan.

2. *Nonparallel evolution between host and parasite*

Analysis of the various families and subfamilies of trichostrongyloids reveals that phylogenetic parallelism between host and parasite as exemplified by the Herpetostrongylidae is a rather isolated phenomenon. In

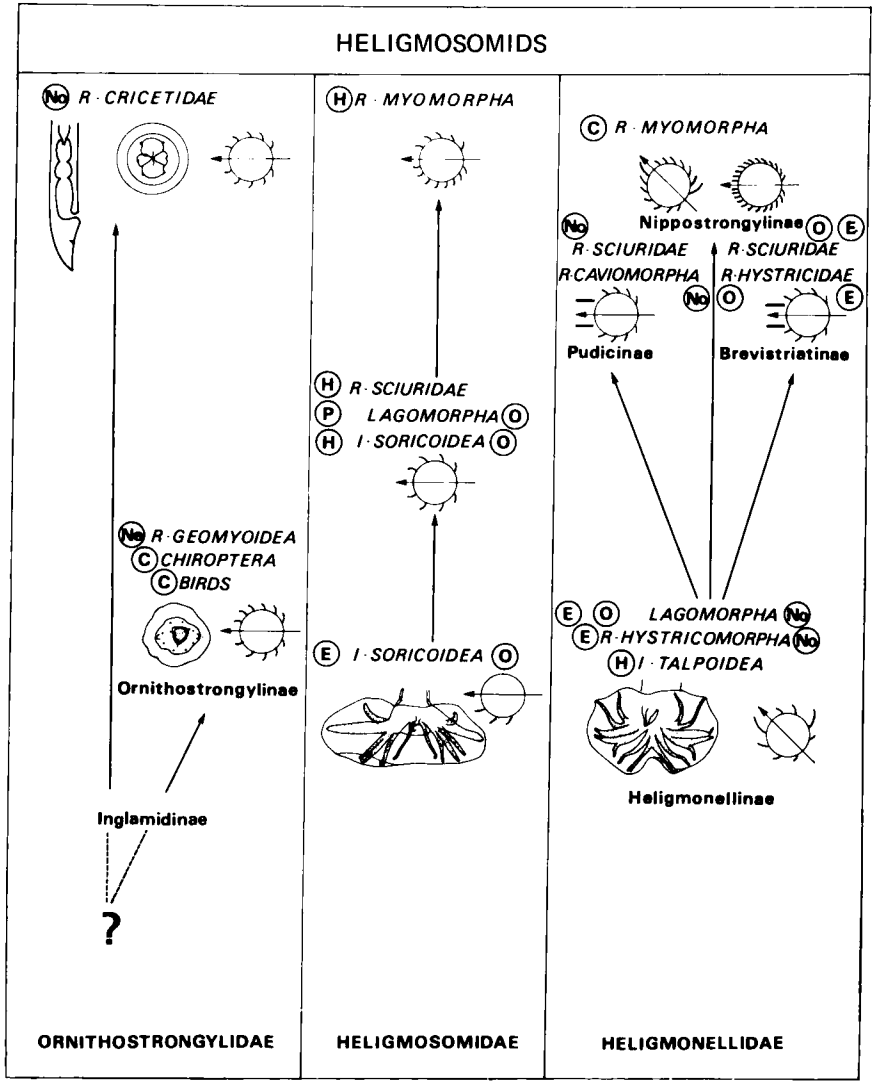


FIG. 27 (*continued*)

cases of nonparallel evolution between parasites and their hosts, dating a parasitic line may be complicated by the passage of parasites from one host group to another and/or by host migration.

(*a*) *Dating a parasitic line*

(i) *Molineinae* (*Fig. 29*). This subfamily occurs in anurans, reptiles, and mammals, and morphological analysis suggests that the Molineinae of

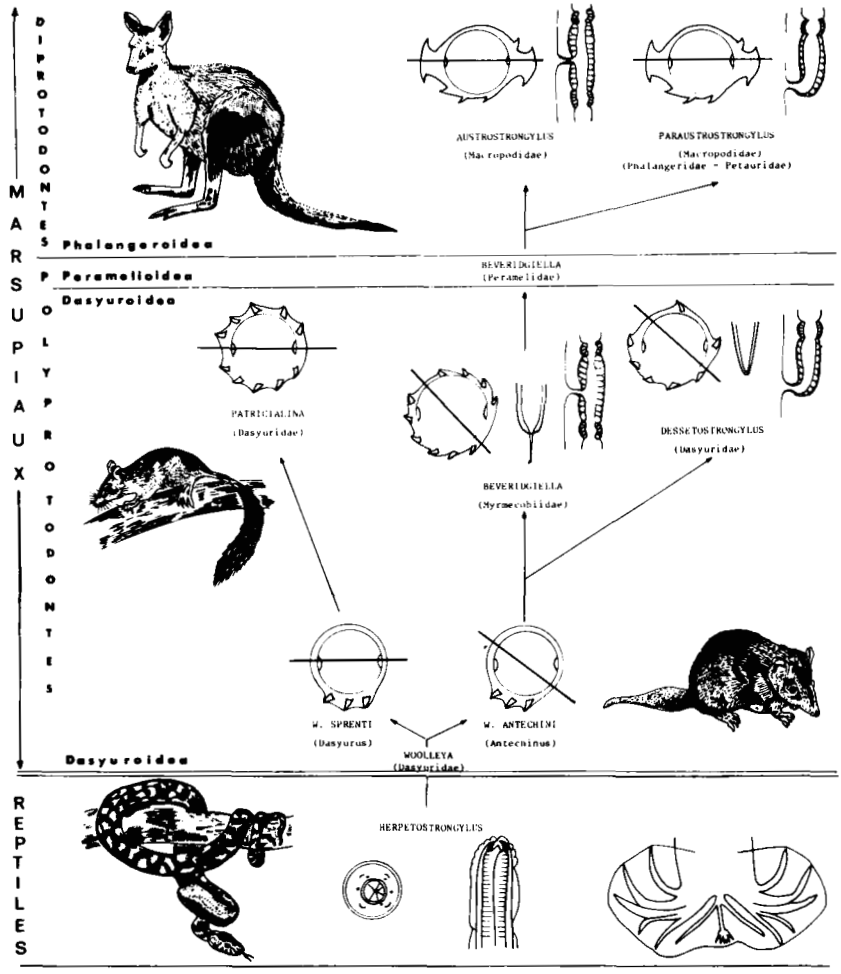


FIG. 28. An example of parallel evolution between host and parasite—the Herpetostrongylinae. The subfamily spread to marsupials from forms parasitizing reptiles; thereafter, the most primitive forms occur in primitive marsupials (Dasyuroidea) and the most evolved forms in evolved marsupials (Phalangeroidea). (After Durette-Desset, 1982.)

mammals are derived from forms similar to those in anurans and reptiles (Chabaud *et al.*, 1967; Durette-Desset and Chabaud, 1981b). The mammalian hosts are extremely diverse: carnivores, tubulidentates, tenrecoid insectivores, Pholidota, Old World bats, tupaiids, primates, and certain Old World sciurids. In fact, this host spectrum represents the major part of eutherian mammals which appeared and had their period of expansion at the beginning of the Tertiary. These hosts can be considered "ancient"

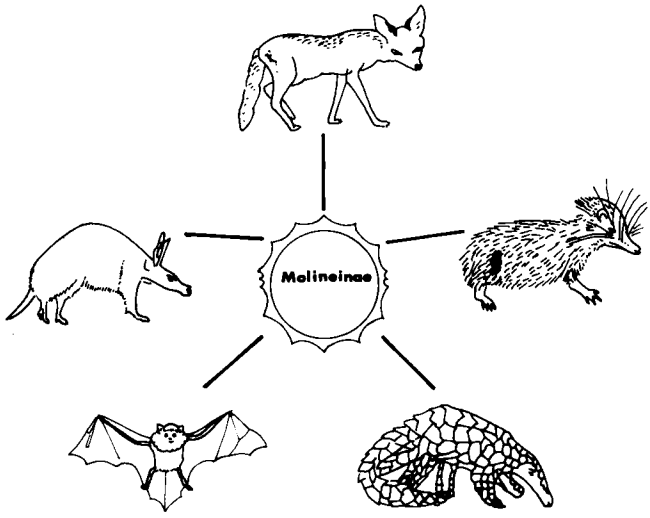


FIG. 29. The Molineinae. A parasitic line undergoes radiation when new host groups appear and radiate offering new ecological niches. The common element in the host distribution is not the phylogenetic relationships but the fact that they all appeared and radiated at the same time, in this case, the beginning of the Tertiary. (After Durette-Desset, 1982.)

in the sense of Chabaud (1982), since they have remained morphologically similar to their Eocene ancestors. Although they were not present at the beginning of the Tertiary, carnivores were derived with relatively little morphological change from their creodont ancestors of the Eocene and can thus be considered "ancient."

Because these mammals have changed little since the Tertiary we can suppose that their parasites have also changed little. The Molineinae can therefore be considered a relict fauna and we suggest that the forms in mammals arose in the early Tertiary. It can be seen from this example that a parasitic line can infect hosts which are not necessarily phylogenetically close. The common element of mammalian hosts of the Molineinae is that they appeared and radiated in the same geological period.

(ii) *Trichostrongylidae*. Morphologically this family is divided into three groups each consisting of two subfamilies, one primitive and one evolved. The three most evolved subfamilies are parasites of ruminants (Bovidae, Cervidae); they are not, however, derived from forms in primitive ruminants but from forms (represented by the three primitive subfamilies) which arose in ratite birds or ancient mammals and which also occur in lagomorphs.

As in the previous example, the hosts are not necessarily phylogenetically close. Rather, the most evolved subfamilies have diversified in hosts which have the same diet; all are strict herbivores. Modern ruminants do

not resemble their Eocene ancestors and do not harbour primitive trichostrongylids. We feel, therefore, that trichostrongylids of existing ruminants appeared relatively recently, in the Miocene, when forms resembling modern ruminants first appeared. Durette-Desset and Chabaud (1977) suggested that in each of the three branches of this family, the transfer to ruminants has occurred by way of a lagomorph intermediary.

(iii) *Ornithostrongylidae*. This family is composed of two subfamilies. The most primitive, the Inglamidinae, is represented by a single genus, *Inglamidum*, which occurs in a Chilean cricetid and has conserved very primitive cephalic characters. The second subfamily, the Ornithostrongylinae, occurs in Neotropical birds and bats, and archaic rodents, the Geomyoidea, in North America.

Cricetids did not arrive in South America before the upper Pliocene and the presence of the primitive genus *Inglamidum* in these hosts can be understood only if it represents a "capture" (Chabaud, 1965) from a more ancient host group. The genus, in fact, belongs to an ancient line and further investigations will probably turn up more primitive members of the same line in Neotropical amphibians, reptiles, or endemic mammals.

The similarity between cephalic structures of *Inglamidum* and those of the Herpetostrongylidae of Australian marsupials suggests that the Ornithostrongylidae had its origin near the end of the Secondary when marsupials radiated in South America and Australia (Durette-Desset *et al.*, 1976).

(iv) *Nicollinidae*. Essentially parasites of monotremes, this family also includes a genus, *Batrachonema*, in Malaysian and South American amphibians and therefore probably existed as early as the Secondary (Durette-Desset *et al.*, 1984).

(*b*) *Problems posed by host dispersal*. Most of the host groups have at one time or another undergone relatively important displacements. The history of these movements is particularly well known in mammals, the host group in which trichostrongyloids have had their greater success. Below we give some of the most significant examples illustrating how host dispersal has been an important factor in parasitic evolution.

(i) *Caviomorph fauna* (*Fig. 30*). Caviomorph rodents harbour a very rich trichostrongyloid fauna. The parasites belong to two quite distinct families, the Viannaiidae and the Heligmonellidae.

The most primitive Viannaiidae occur in Neotropical marsupials. The family thus probably arose during the Eocene and, in the upper Eocene, spread to certain caviomorph families: Caviidae, Hydrochoeridae, Chinchillidae, and Cuniculidae.

The most primitive of the Heligmonellidae, the Heligmonellinae, occur in Old World insectivores (Talpoidea) and the family thus probably arose in the middle Eocene. The subfamily spread to phiomorph rodents in

FIG. 30. Caviomorph fauna. Caviomorph trichostrongyloids belong to two evolutionary lines, the Heligmonellinae (Heligmonellidae) and the Viannaiidae. Certain mammologists believe that African phiomorphs passed into South America during the upper Eocene and lower Oligocene giving rise to caviomorph line; thus, a *Heligmonella*-like ancestor in African phiomorphs (1) would have given rise to *Paraheligmonella* which we presently find in South American Echimyidae (2). At the same time the Viannaiidae, whose most primitive forms occur in marsupials (3), spread to caviomorph families such as the Caviidae (4).

Africa with the genus *Heligmonella*. A remarkably similar genus, *Paraheligmonella*, occurs in South American caviomorphs of the family Echimyidae (Fig. 30). We have thus been led, following Hoffstetter and Lavocat's (1970) hypotheses, to conclude that certain phiomorph rodents passed from Africa to South America during the Tertiary (upper Eocene or lower Oligocene) giving rise to caviomorphs.

Evolution of the Heligmonellinae in South America gave rise to the Pudicinae. The most primitive pudicines occur in caviomorph families other than those parasitized by Viannaiidae: Erethizontidae, Echimyidae, Capromyidae, Myocastoridae, and Dasyproctidae. The more evolved forms parasitize the Sciuridae.

(ii) *Sciurid fauna*. Trichostrongyloids of the Sciuridae belong to two subfamilies: Pudicinae in South America and Brevistriatinae in Africa and Asia. These subfamilies are morphologically very similar and are derived from heligmonelline-like ancestors. However, it is likely that they parasitized the Sciuridae at very different times.

The Sciuridae originated in Asia. While the Pudicinae, beginning with a

Paraheligmonella-like ancestor, were radiating in South American caviomorphs, the Brevistriatinae, starting with a *Heligmonella*-like ancestor, diversified in Old World Histricidae and Sciuridae (Fig. 31A). Sciurids subsequently moved into North America and, in the upper Pliocene, crossed into South America by way of the isthmus of Panama (Fig. 31B).

Trichostrongyloids of Neotropical Sciuridae belong to a single genus, *Sciurodendrium*, a Pudicinae derived from forms in Caviomorph rodents. We believe that sciurids were devoid of trichostrongyloids when they moved into South America. Trichostrongyloids are rare in holarctic Sciuridae and those that exist belong to a recent family, the Heligmosomidae. Ancient evolutionary lines such as the Heligmonellidae, to which the Pudicinae and Brevistriatinae belong, are restricted to tropical and subtropical regions. It is therefore likely that the Sciuridae lost their brevistriatine parasites during their migration into North America and were reinfected after contacting South American pudicines.

This example illustrates that, at least until relatively recently, the Pudicinae had sufficient evolutionary potential to parasitize a new host group. In addition, the close parallel evolution of the Brevistriatinae and Pudicinae would seem to indicate that the direction of evolution was already predetermined in their common ancestor.

(iii) *Cricetid fauna*. Like the Sciuridae, the Cricetidae originated in the Old World and subsequently passed into North America before arriving in South America in the upper Pliocene. The history of the trichostrongyloid parasites of cricetids and sciurids, however is quite different.

The Cricetidae are among the most ancient existing myomorph rodents; their cricetodont ancestors diversified in the Oligocene. Present-day cricetids resemble cricetodonts and according to our earlier hypotheses, we would not expect their parasites to have changed much since the Oligocene. Trichostrongyloids of present-day cricetids are rare, except in South America, and curiously enough they seem to date from the Miocene since they belong to genera parasitizing more recent rodents such as the Muridae and Arvicolidae. The only way we can explain this is that, during the Oligocene when the Cricetidae appeared and diversified, trichostrongyloids were in a period of evolutionary stasis. Cricetids were infected much later by the Nippostrongylinae (Heligmonellidae) of Nearctic Arvicolidae and they and their parasites later underwent a radiation in South America.

This example shows that a parasitic line can come out of a rather long period of evolutionary stasis and spread to new hosts. What is important is that new niches become available, through either host radiation or host migration.

(iv) *Microchiropteran fauna*. Thirteen trichostrongyloid genera occur

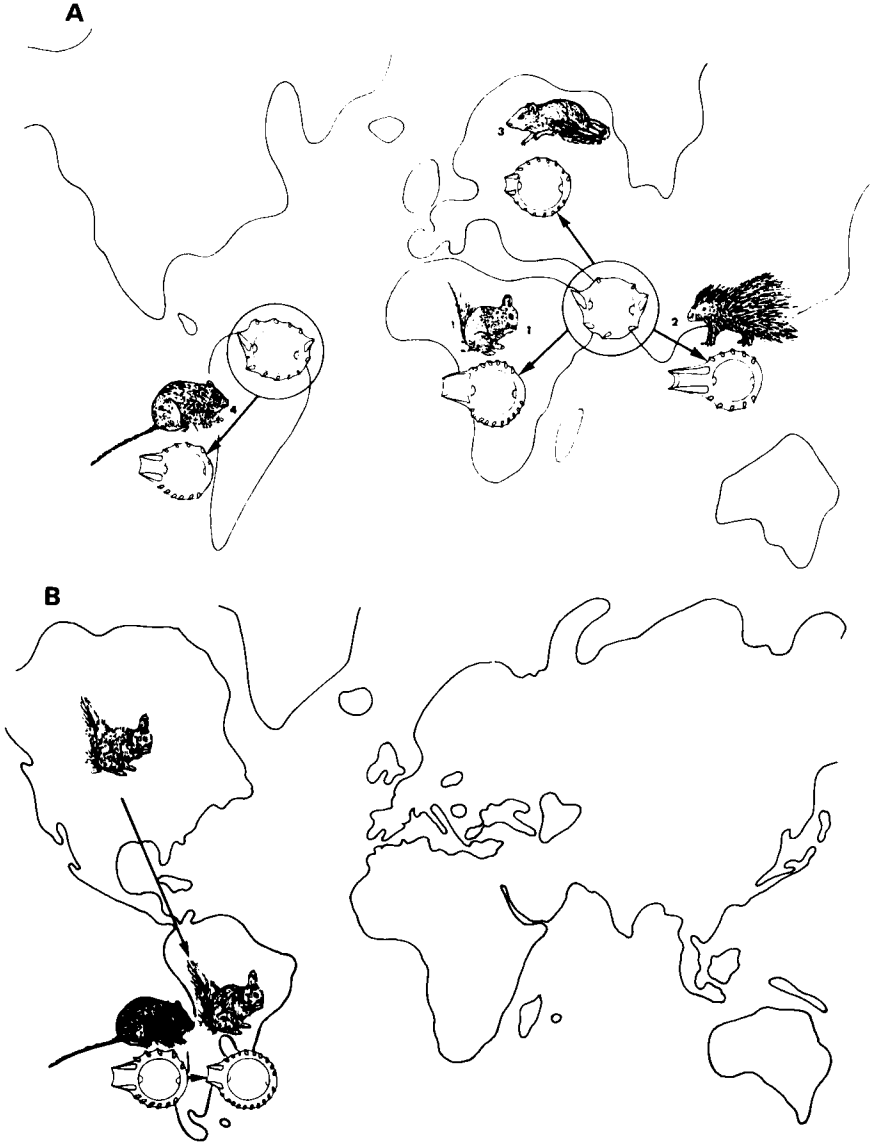


FIG. 31. Sciurid fauna. The Sciuridae (1) were parasitized by the Heligmonellidae at two different times. (A) The first time occurred in the upper Eocene and lower Oligocene when the Brevistriatinae (originating from the heligmonelline line) spread throughout Old World Sciuridae, Hystricidae (2), and Gliridae (3). At the same time, the Pudicinae (genus *Heligmostrongylus*) diversified in caviomorph rodents (4) in South America. (B) In the upper Pliocene, sciurids, free of trichostrongyloids, entered South America and became parasitized by *Heligmostrongylus* of caviomorphs, giving rise to the genus *Sciurodendrium*. (Modified after Durette-Desset, 1971.)

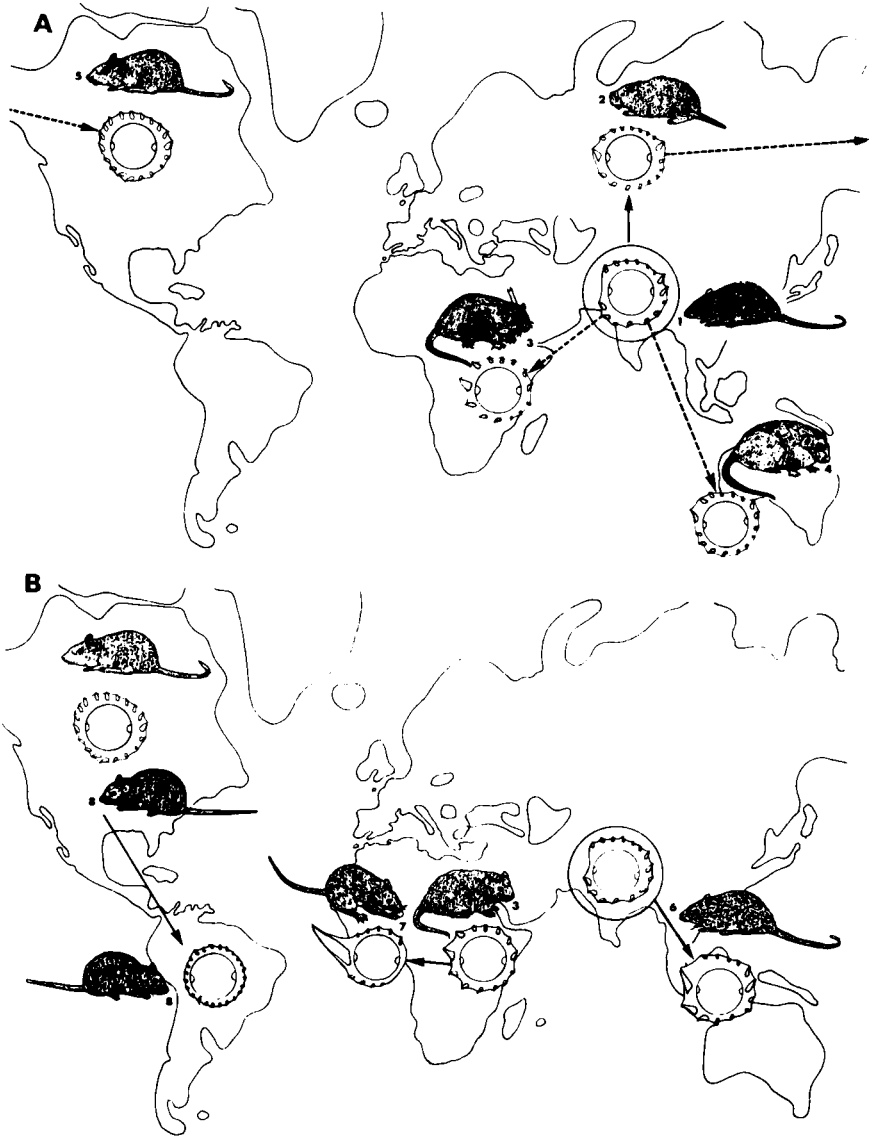


FIG. 32. Myomorph fauna; Nippostrongylinae. (A) During the upper Miocene, the Muridae (1) arose in Southeast Asia and spread to the Palearctic region; the Nippostrongylinae arose with the Muridae from an *Orientostrongylus*-like ancestor and spread (solid arrow) to the Arvicolidae (2) giving rise to the genus *Carolinensis*. In the lower and middle Pliocene, the Muridae spread to Africa (3) where the Nippostrongylinae gave rise to *Neoheligmonella*, and to Australia (4) (with the *Melomys*-group) where the nippostrongyline genus *Odilia* appeared. At the same time, arvicolids spread throughout the Holarctic region (5) and *Carolinensis* gave rise to *Hassalstrongylus*. (B) In the upper Pliocene, the Muridae radiated

in the Microchiroptera. One of these, *Strongylacantha* (Strongylacanthidae) from the Rhinolophoidea, is quite independent of the rest, but the remaining 12 form a coherent ensemble. They are probably derived from the Molineinae, whose most primitive forms occur in tenrecoid insectivores and carnivores.

The most primitive genera parasitizing bats occur in Old and New World forms. However, the most evolved genera are very different in the two regions; those of Nearctic bats seem to be derived from Neotropical forms. Nearctic bats are derived from Palearctic bats and not from the endemic Neotropical forms. We must assume therefore that Palearctic bats lost their parasites during their migration into North America. Elimination of this primitive trichostrongyloid fauna left ecological niches available for the parasites of Neotropical bats. This example resembles that illustrated by the Sciuridae in that the host has lost its parasites during its migrations; in general, however, the parasite fauna remains with the hosts throughout their migrations.

(v) *Myomorph fauna*. Myomorphs are the most recent rodents and are parasitized by two trichostrongyloid families, the Heligmonellidae (represented by the Nippostrongylinae) and the Heligmosomidae.

The Nippostrongylinae (Fig. 32) illustrate most remarkably the radiation of a parasitic group in response to the migrations of its hosts. Although they are the most recent of the Heligmonellid subfamilies, they are morphologically less evolved than the Pudicinae and Brevistriatinae. The most primitive forms occur in Southeast-Asian Muridae and resemble evolved Heligmonellinae. We suggest that the Nippostrongylinae arose from a heligmonelline-like ancestor and that this occurred in Southeast Asia, when murids appeared and diversified in the upper Miocene.

Nippostrongylines first spread throughout the world following migrations of the Muridae, and later in most other groups of myomorphs whether more ancient (i.e., Cricetidae, Gerbillidae) or more recent (Arvicolidae) than murids. During the Pliocene, Australia, Africa, and South America each received a branch of this parasitic line. The passage of the subfamily into South America occurred by the Holarctic route and involved the evolutionary line *Carolinensis–Hassalstrongylus–Stilestrongylus*. *Carolinensis* passed from the Muridae to Palearctic and then Nearctic Arvicolidae. The Cricetidae, infected by Nearctic Arvicolidae,

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in the Oriental and Australian zones (6) giving rise to *Nippostrongylus*. *Neoheligmonella* of murids in south and east Africa (3) gave rise to *Heligmonina* of murids in the forests of west Africa (7). Finally, Nearctic Cricetidae (8) parasitized by *Hassalstrongylus* moved into South America and radiated. Concomitantly, *Hassalstrongylus* underwent a radiation and gave rise to *Stilestrongylus* in Neotropical cricetids (8). (Modified after Durette-Desset, 1971.)

introduced the parasites (*Hassalstrongylus*) into South America in the upper Pliocene; there, *Stilestrongylus* appeared and radiated in South American cricetids (Fig. 32B).

The Heligmosomidae (Fig. 33) probably arose in soricoid insectivores since the most primitive forms occur in these hosts. Thus the family would have its origin around the Eocene. Its evolution continued in ground squirrels and lagomorphs and later, the family passed to the Arvicolidae (with the genera *Heligmosomoides* and *Heligmosomum*) during their period of expansion in the late Pliocene.

Thaler (1962) and Kowalski (1961) agree that the Arvicolidae arose from the cricetid line near the end of the Pliocene but they are uncertain as to the region of origin: North America, Mongolia, or Central Europe. A Central European origin would fit our data best since the most primitive trichostrongyloids of the Arvicolidae occur in this region. This is easily followed in parasite morphology: the further away the species in question is from Central Europe, the longer are the spicules and the more numerous are the cuticular ridges. Thus, *Heligmosomoides* would have gradually evolved with its host group as the latter spread across the Bering Strait and into North America. Unlike the Nippostrongylinae, the Heligmosomidae never penetrated as far as South America. The few nonarvicolid rodents that they were able to infect occur in the central Palaearctic region.

(vi) *Ruminant fauna.* As mentioned above, ruminants throughout the world are parasitized by the Trichostrongylidae. They are also parasitized by the Nematodirinae, one of the most evolved of the molineid subfamilies, but practically uniquely in the Holarctic region. The Nematodirinae are present in lagomorphs but unlike trichostrongylids, nematodirines of ruminants are not derived from those in lagomorphs. We proposed (Durette-Desset and Chabaud, 1981a) that the Nematodirinae became divided near the end of Oligocene into two evolutionary lines: one which radiated in ruminants with little change in the synlophe and another which radiated in lagomorphs with great diversification of this organ.

Rossi (1983) proposed the following hypothesis on the origin and diversification of the Nematodirinae of ruminants. The genus *Nematodirus* arose in North American Camelidae from an ancestor similar to *Lamanema,* a genus which still occurs in Neotropical Camelidae. From camelids, *Nematodirus* spread to Nearctic Odocoileinae and Caprinae and entered the Palearctic region with these hosts. *Nematodirella* of Holarctic ruminants is derived from *Nematodirus*.

This hypothesis conforms with information coming from parasite morphology since the most primitive species of *Nematodirus* occur in North America. It also conforms with our knowledge of host paleobiogeography. Camelids did, in fact, originate in North America near the end of

FIG. 33. Myomorph fauna; Heligmosomidae. The Heligmosomidae arose in soricoid insectivores in the middle Eocene. In the Pleistocene starting with *Citellinema* in ground squirrels (1) the family diversified in Arvicolidae in central Europe (2) and from there spread throughout the Holarctic region mainly with arvicolids (2). (Modified after Durette-Desset, 1971.)

the Oligocene. In the late Pliocene they spread to Eurasia and to South America where certain species remain to this day. During the Pleistocene, the Camelidae become extinct in North America. The Odocoileinae and Caprinae arose in the Palearctic region but later passed into North America, the former during the Miocene and the latter during the Pleistocene, and could therefore have been infected by the *Nematodirus* of camelids before the latter went extinct in North America. The fact that Palearctic *Nematodirus* are morphologically more evolved than those in North America suggest that some Caprinae and Odocoileinae passed from North America into Eurasia by the Bering Strait.

C. TEMPO IN EVOLUTION

1. *Slow evolution: the Molineinae*

The molineine parasites of the most primitive insectivores, the Tenrecoidea, offer an excellent example of slow evolution. The parasites belong to three morphologically similar genera: *Shattukius* in the Antilles, *Hugotnema* in Africa, and *Brygoonema* in Madagascar. What is remarkable is that every host species harbours one or two parasite species which are restricted to it. The homogeneity of this group as well as the fact that every host species has its own molineine parasites seem to indicate that there has been little evolutionary change since the Tertiary and that parasites may persist for very long periods if there are no drastic changes in host ecology.

2. *Rapid evolution: Heligmosomidae*

The trichostrongyloid parasites of the Nearctic Arvicolidae are probably still evolving. As stated above, Nearctic arvicolids are parasitized by Heligmosomidae of Palearctic origin belonging to the genus *Heligmosomoides* (Fig. 34). This genus has evolved from east to west and the most evolved species presently occur in the Nearctic zone.

Curiously, certain subspecies of *Heligmosomoides polygyrus* (= *Nematospiroides dubius*), normally a parasite of European domestic and field mice, occur in the Nearctic zone (Durette-Desset *et al.*, 1972). Morphological studies suggest that a first subspeciation occurred in *Mus musculus* and *Reithrodontomys* (Cricetidae) in North America, and a second subspeciation occurred in this newly evolved form in the arvicolid, *Phenacomys*.

The presence of two subspecies of *H. polygyrus* in North America cannot be explained unless we admit that the species was introduced from Europe with the domestic mouse by boat. In other words, during the space of three centuries the species has given rise to two new subspecies.

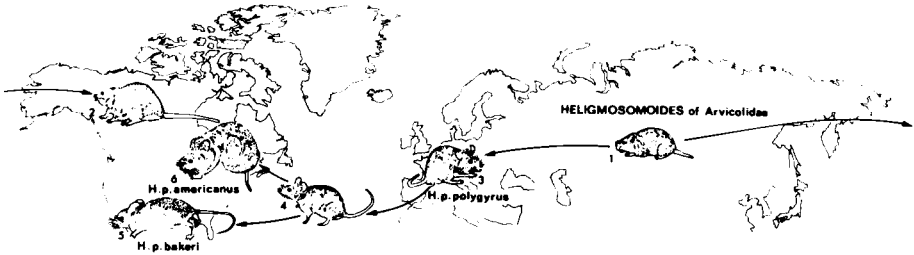

FIG. 34. The Heligmosomidae: an example of rapid evolution. The Arvicolidae (1) arrived in North America (2) during the Pleistocene and are parasitized by Heligmosomidae of Palearctic origin belonging to the genus *Heligmosomoides*. The presence of two subspecies of *H. polygyrus*, normally parasites of European domestic and field mice (3) in North America, is explained by the hypothesis that the species was introduced to North America with the domestic mouse some 300 years ago and has since undergone two successive subspeciations: the first in *Mus* (4) and *Reithrodontomys* (5) giving rise to *H. p. bakeri*, and the second in *Phenacomys* (6) giving rise to *H. p. americanus*.

This would seem to attest to the rapidity of evolutionary change in the group.

3. *Evolutionary stasis*

In the section on cricetid fauna, we discussed the concept of evolutionary stasis in a parasitic line, and gave the example of cricetodont rodents which are known to have radiated during the Oligocene and yet were not infected by trichostrongyloids.

In fact, if we examine the host spectrum of the Trichostrongyloidea we see that it includes almost all terrestrial mammals except ancient ungulates; thus, trichostrongyloids do not occur in proboscideans and perissodactyles and only one species is known from hyracoids. Instead, ancient ungulates are parasitized by primitive Strongyloidea, the Oesophagostominae.

To explain these findings the hypothesis is proposed that trichostrongyloid evolution has occurred in three major stages. During the first stage (the Eocene), trichostrongyloids with a primitive biology (i.e., skin-penetrating larvae) evolved in virtually all the mammals which were present. In the second stage (lower Oligocene), trichostrongyloids were in evolutionary "stasis." Primitive ungulates and cricetodonts, which appeared and radiated during this period, were parasitized by primitive strongyloids but not by trichostrongyloids. Finally, during the third stage (upper Oligocene), trichostrongyloids with an evolved biology (larvae infective by oral route) appeared. This biology allowed them to spread to herbivorous mammals which appeared and radiated at this time, i.e., lagomorphs, ruminants, and myomorph rodents (in particular, the Arvicolidae).

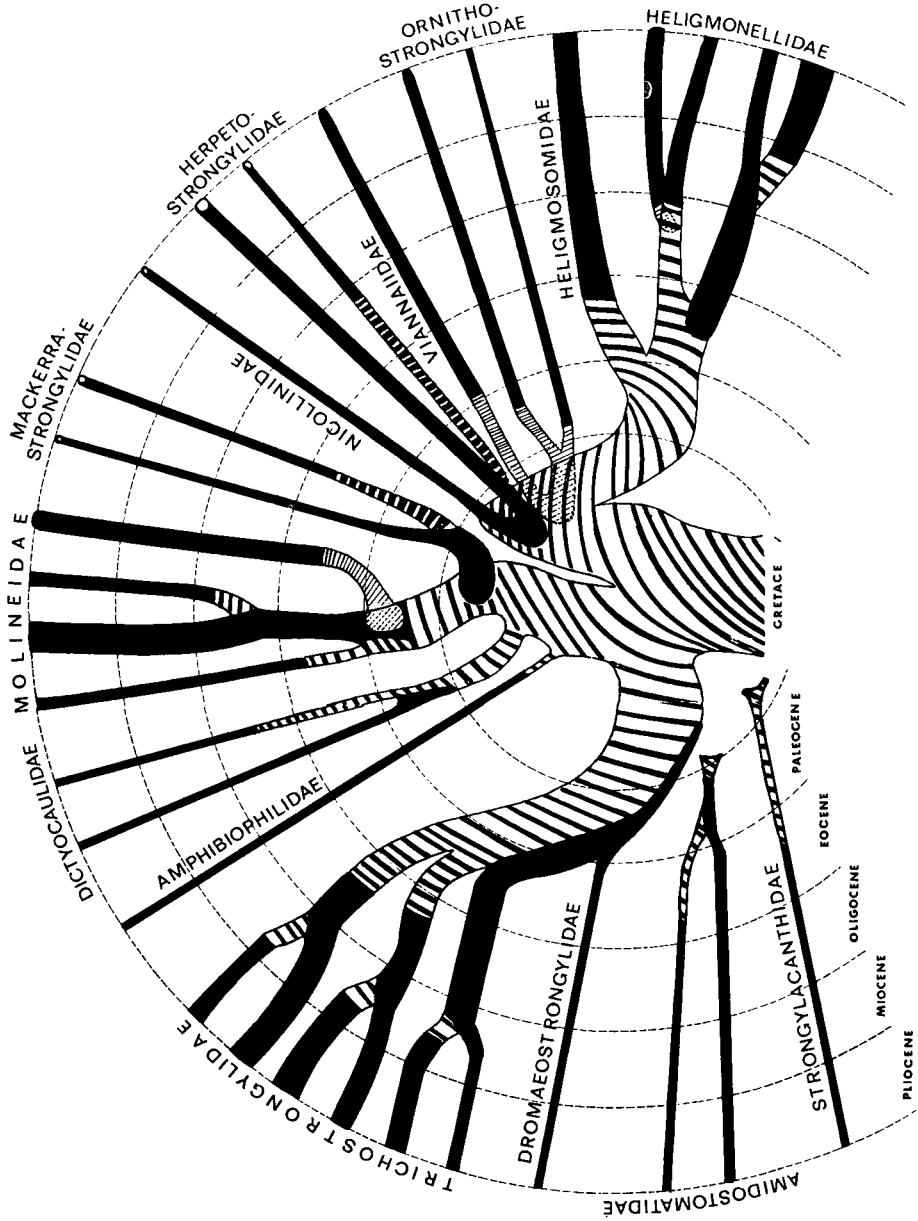

FIG. 35. Hypothetical phylogenetic tree to the Trichostrongyloidea illustrating the date of origin of each family and subfamily. With the exception of the Strongylacanthidae and Amidostomatidae, the group is considered monophyletic and to be composed of three principal branches: the trichostrongylid line, the molineid line, and the heligmosomid line. The branch of each family or subfamily is shaded in solid black starting at the geological period in which the group originated. Typically Australian groups are depicted as arising from the underside whereas typically Neotropical groups are depicted as arising from the upper side of the principal branches. (After Durette-Desset and Chabaud, 1981a.)

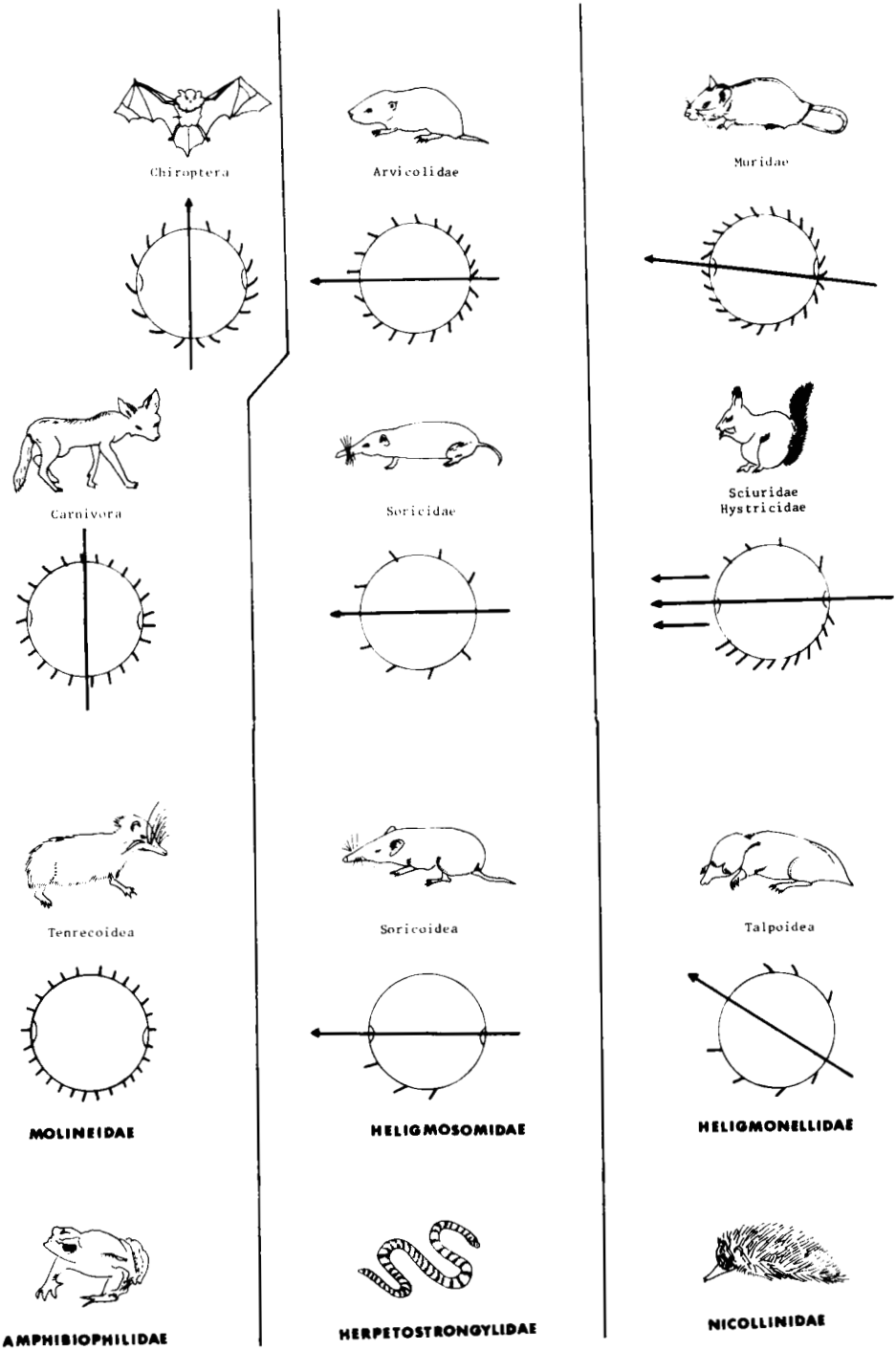

FIG. 36. The Trichostrongylidae spread throughout the world with lagomorphs and ruminants. However, the conquest of eutherian mammals and Laurasia in the Molineidae, Heligmosomidae, and Heligmonellidae occurred via a proto-insectivore intermediary. The most primitive forms of the three families are found in insectivores.

IV. The Phylogenetic Tree of the Trichostrongyloidea

Host and parasite data are summarized schematically in Fig. 35, which presents a phylogenetic tree to the superfamily (after that given in Durette-Desset and Chabaud 1977, 1981a). The various families and subfamilies are shaded in solid black beginning at the geological period in which they appeared. Typically Australian groups are depicted as arising from the upper side and typically Neotropical groups are depicted as arising from the underside of the principal branches.

The Amidostomatidae and Strongylacanthidae are cosmopolitan in birds and bats and are thus of no particular biogeographical interest. The distribution of the other families is however quite remarkable. All of the ancestral forms and most families and subfamilies are typically Gondwanian. Only four families are represented in the Holarctic region: the Trichostrongylidae, Molineidae, Heligmosomidae, and the Heligmonellidae. The Trichostrongylidae have spread throughout the world with lagomorphs and, later, with ruminants. The conquest of eutherian mammals and of Laurasia by the remaining three families has apparently taken place by way of insectivore hosts. Thus, the most primitive molineids of eutherian mammals occur in tenrecoids. The most primitive heligmosomids and heligmonellids occur in soricoids and talpoids, respectively (Fig. 36).

Most trichostrongyloid families were probably present as early as the beginning of the Tertiary. They are either parasites of amphibians or reptiles or their most primitive members occur in monotremes, marsupials, or insectivores, mammals which were represented at the end of the Secondary by forms similar to those which exist today. The superfamily continued its radiation throughout the Tertiary and in some groups this radiation is apparently still taking place.

V. Conclusions

Using trichostrongyloid nematodes as a model, I have tried to show how it is possible to reconstruct the phylogenetic history of a parasitic group in spite of the absence of fossil evidence.

Morphological and biological characters are studied and assessed for their relative phylogenetic importance. The evolutionary trends of each character are analyzed and used to construct a classification which recognizes different phylogenetic lines. In the Trichostrongyloidea, the most important characters from a phylogenetic point of view are those of the caudal bursa and synlophe. Using these characters, a number of different

evolutionary lines become evident and the degree of evolution of the different genera composing each of those lines can be assessed.

This classification is then collated with information on host palaeobiogeography, i.e., the date of origin of the hosts and their history of migration. The analysis of the different evolutionary lines brings to the fore a number of fundamental ideas.

1. A parasitic line may become isolated from its ancestral forms by passing from one host group to another; the isolation may be followed by evolutionary radiations of variable importance. This phenomenon, which Chabaud (1965) designated as capture, is absolutely essential for comprehending parasitic phylogenies. Captures may be of minor importance as is the case in *Heligmosomoides:* essentially parasites of Holarctic Arvicolidae, isolated species are also known in cricetid, sciurid, and murid rodents. Similarly, *Moennigia* spp. are mainly parasites of Xenarthra but one species occurs in Neotropical marsupials. Alternatively, captures may be followed by rather important radiations. Thus, species of *Viannaia* are parasites of marsupials; some became adapted to caviomorph rodents and gave rise to the genus *Viannella.* The evolutionary history of the Holarctic Nippostrongylinae, parasites of myomorph rodents, involves two successive captures: the first, with *Carolinensis,* from murid to arvicolid rodents, and the second, with *Hassalstrongylus* from arvicolid to cricetid rodents.

Captures may occur between phylogenetically distant host groups and thus, parallelism between host and parasite evolution is often not respected.

2. Radiation of a parasitic line occurs only when a large number of ecological niches are available.

a. These niches may arise from the appearance and radiation of new host groups. Thus, the Molineinae spread to most groups of eutherian mammals which appeared and radiated at the beginning of the Tertiary. The essential common factor in the hosts is not their phylogenetic relationship but the fact that they appeared and radiated at the same time.

b. Niches may be provided by uninfected hosts moving into the area occupied by the parasite. These hosts may be uninfected due to prior loss of their parasites. For example, sciurids lost their brevistriatine parasites during their migration into North America and were subsequently reinfected in South America by the Pudicinae of caviomorph rodents. Alternatively, the hosts may never have been parasitized previously. Thus, cricetids were not parasitized by trichostrongyloids when they appeared in Asia during the Oligocene, but rather much later, in North America during the Pliocene, and developed their own endemic trichostrongyloid fauna during their passage into and radiation in South America.

3. Availability of niches, although a necessary condition, is not a sufficient condition for parasite radiation. For example, host radiation may occur when the parasitic line is in evolutionary stasis. Thus, between the radiation of the Heligmonellidae in ancient rodents (Hystricidae and Sciuridae) during the Oligocene and that in the Muridae during the upper Miocene and Pliocene, the Cricetidae appeared and spread throughout the world without being parasitized by trichostrongyloids.

4. When a parasite is adapted to a host which is evolving very slowly, the parasite changes little. Random speciations may occur as a result of isolation of populations but morphological changes are slight. It is this phenomenon which allows us to date parasitic lines. Thus, the Molineinae are considered as having arisen at the beginning of the Tertiary because the most primitive forms in the subfamily occur in mammals which differ little from their Eocene ancestors. Similarly, the Nippostrongylinae can be dated as having appeared during the Miocene; the most primitive forms occur in Asian Muridae which arose in the Miocene and have changed little since.

5. The degree of evolution of a parasite is not necessarily a good indication of its date of origin. Thus the Nippostrongylinae appeared relatively recently, in the Miocene, but are morphologically more primitive than the Pudicinae and Brevistriatinae, which appeared in the upper Eocene and lower Oligocene. We interpret this as indicating that evolution of the Heligmonellidae has occurred in two "bursts" and that the most recent (giving rise to the Nippostrongylinae) did not attain the same evolutionary level as the first.

The reconstruction of the phylogenetic history of the Trichostrongyloidea has led us far away from the classical notions of gradual evolutionary change and parallelism between host and parasite evolution. I agree with Chabaud (1970) and Quentin (1971) that evolutionary "bursts" occur at particular geological periods when evolutionarily active parasitic lines come into contact with new niches offered by the expansion of migration of various host groups.

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REFERENCES

Alicata, J. E. (1932). Life history of the rabbit stomach worm, *Obeliscoides cuniculi*. *Journal of Agricultural Research* **44,** 401–419.

Alicata, J. E. (1935). Early developmental stages of nematodes occurring in swine. United States Department of Agriculture, Washington, Technical Bulletin No. 489, pp. 1–96.

Andrews, J. S. (1939). Life history of the nematode *Cooperia curticei*, and the development of resistance in sheep. *Journal of Agricultural Research* **58,** 771–785.

Baer, J. C. (1955). Incidence de la spécificité parasitaire sur la taxonomie. Problèmes d'évolution chez les Cestodes Cyclophyllidiens. *Bulletin de la Société zoologique de France* **80,** 275–287.

Baker, M. R. (1978). Development and transmission of *Oswaldocruzia pipiens* Walton, 1929 (Nematoda; Trichostrongylidae) in amphibians. *Canadian Journal of Zoology* **56,** 1026–1031.

Boulenger, C. L. (1915). The life history of *Nematodirus filicollis* Rud., a nematode parasite of the sheep's intestine. *Parasitology* **8,** 133–155.

Bryant, V. (1973). The life cycle of *Nematospiroides dubius* Baylis, 1926 (Nematoda: Heligmosomidae). *Journal of Helminthology* **47,** 263–268.

Chabaud, A. G. (1955). Essai d'interprétation phylétique des cycles évolutifs chez les Nématodes parasites de Vertébrés. *Annales de Parasitologie Humaine et Comparée* **30,** 83–126.

Chabaud, A.G. (1956). Remarques sur les Nématodes parasites du caecum des Eléphants, milieu très préservé des phénomènes de sélection. *Compte Rendus Hebdomadaire des Séances de l' Académie des Sciences* **243,** 436–439.

Chabaud, A. G. (1959). Remarques sur la systématique des Nématodes Trichostrongyloidea. *Bulletin de la Société zoologique de France* **84,** 473–483.

Chabaud, A. G. (1965). Spécificité parasitaire. I. Chez les Nématodes parasites de Vertébrés. *In* "Traité de Zoologie" (P. P. Grassé, ed.), Vol. 4, pp. 548–557. Masson et Cie

Chabaud, A. G. (1970). Adaptation hôte-parasite chez les Nématodes de Vertébrés. Evolution du phènomène. *Journal of Parasitology* **56,** 50–51.

Chabaud, A. G. (1982). Spectre d'hôtes et évolution des Nématodes parasites de Vertébrés. *Mémoires du Muséum National d'Histoire Naturelle (Sér. A, Zoologie)* **123,** 73–76.

Chabaud, A. G., and Durette-Desset M.-C. (1978). Parasitisme par plusieurs espèces congénériques. *Bulletin de la Société Zoologique de France* **103,** 459–464.

Chabaud, A. G., Bain, O., and Puylaert, F. (1967). Description de trois nouveaux Nématodes Molineinae et considérations sur la systématique et le caractère archaïque de cette sous-famille. *Bulletin du Muséum National d'Histoire Naturelle* **38,** 904–920.

Chabaud, A. G., Puylaert, F., Bain, O., Petter, A. J., and Durette-Desset, M.-C. (1970). Remarques sur l'homologie entre les papilles cloacales des Rhabditides et les côtes dorsales des Strongylida *Comptes Rendus Hebdiomadaire des Séances de l'Academie des Sciences* **271,** 1771–1774.

Chandler, A. C. (1932). Experiments on resistance of rats to superinfection with the nematode *Nippostrongylus muris*. *American Journal of Hygiene* **16,** 750–782.

Chitwood, B. G., and Chitwood M. B. (1950). The reproductive system. *In* "An Introduction to Nematology," (B. G. Chitwood, ed.), pp. 136–159. Monumental Printing, Baltimore.

Cowan, A. B. (1955). Some preliminary observations on the life history of *Amidostomum anseris* Zeder, 1800. *Journal of Parasitology* **41,** 43–44.

Cuvillier, E. (1937). The nematode, *Ornithostrongylus quadriradiatus*, a parasite of the domesticated pigeon. United States Department of Agriculture, Washington, D.C., Technical Bulletin No. 569, pp. 1–36.

Diaw, O. (1976). Contribution à l'étude de Trichostrongyloidea parasites de Xenarthre, Marsupiaux et Rongeurs néotropicaux. *Bulletin du Muséum National d'Histoire Naturelle* **51,** 335–363.

Dikmans, G., and Andrews, J. S. (1933). A comparative morphological study of the infective larvae of common nematodes parasitic in the alimentary tract of sheep. *Transactions of the American Microscopical Society* **52,** 1–25.

Dougherty, E. C. (1951). Evolution of zooparasitic groups in the phylum Nematoda with special reference to host distribution. *Journal of Parasitology* **37,** 353–378.

Douvres, F. W. (1956). Morphogenesis of the parasitic stages of *Ostertagia ostertagi*, a nematode parasite in cattle. *Journal of Parasitology* **42,** 626–635.

Douvres, F. W. (1957). The morphogenesis of the parasitic stages of *Trichostrongylus axei* and *Trichostrongylus colubriformis*, nematode parasites of cattle. *Proceedings of the Helminthological Society of Washington, D.C.* **24,** 4–11.

Durette-Desset, M.-C. (1964). Les systèmes d'arêtes cuticulaires chez les Nématodes Héligmosomes. Etude de cinq espèces parasites de Rongeurs de la Maboké. *Cahiers dè La Maboké* **2,** 40–77.

Durette-Desset, M.-C. (1968). Helminthes de Marsupiaux américains. Trichostrongyloidea. *Bulletin de La Société Zoologique de France* **93,** 581–594.

Durette-Desset, M.-C. (1969a). Les systèmes d'arêtes cuticulaires chez les Nématodes Héligmosomes parasites de Muridés australiens. *Annales de Parasitologie Humaine et Comparée* **44,** 733–747.

Durette-Desset, M.-C. (1969b). Sept nouvelles espèces de Nématodes héligmosomes, parasites d'un *Atherurus africanus* Gray, et remarques sur leur répartition dans l'intestin. *Cahiers de La Maboké* **7,** 109–130.

Durette-Desset, M.-C. (1970). Les systèmes d'arêtes cuticulaires chez les Nématodes Héligmosomes. IV. Description de six espèces nouvelles, parasites de Sciuridés africains; redescription d'*Heligmonina magna* Baylis, 1928 et d'*Heligmonella streptocerca* Baylis, 1928. *Cahiers de La Maboké* **8,** 41–62.

Durette-Desset, M.-C. (1971). Essai de classification des Nématodes Héligmosomes. Corrèlation avec la paléobiogéographie des hôtes. *Mémoires du Muséum National d'Histoire Naturelle (Sér. A,* Zoologie), **49,** 1–126.

Durette-Desset, M.-C. (1974). Nématodes (Trichostrongyloidea) parasites d'un Marsupial de Guyane. *Annales de Parasitologie Humaine et Comparée* **49,** 555–556.

Durette-Desset, M.-C. (1982). Relations hôtes-parasites chez les Trichostrongyloides. *Memoires du Muséum National d'Histoire Naturelle (Sér. A, Zoologie)* **123,** 93–100.

Durette-Desset, M.-C., and Chabaud, A. G. (1977). Essai de classification des Nématodes Trichostrongyloidea. *Annales de Parasitologie Humaine et Comparée* **52,** 539–558.

Durette-Desset, M.-C., and Chabaud, A. G. (1981a). Nouvel essai de classification des Nématodes Trichostrongyloidea. *Annales de Parasitologie Humaine et Comparée* **56,** 297–312.

Durette-Desset, M.-C., and Chabaud, A. G. (1981b). Sur les Molineinae parasites de Mammifères. *Annales de Parasitologie Humaine et Comparée* **56,** 489–502.

Durette-Desset, M. C., Chabaud A. G., and J. Cassone (1977). Nématodes Trichostrongyloides (dont sept nouveaux) coparasites d'un Fourmilier brésilien. *Bulletin du Muséum National d'Histoire Naturelle (Sér. A, Zoologie)* **298,** 133–158.

Durette-Desset, M. C., Denke, M. A., and Murua, R. (1976). Présence chez un Rongeur du Chili d'un Nématode Inglamidinae (sub. fam. nov.) appartenant aux Amidostomatidae, famille connue des Mammifères d'Australie. *Annales de Parasitologie Humaine et Comparée* **51,** 453–460.

Durette-Desset, M. C., Kinsella, J. M., and Forrester, D. J. (1972). Arguments en faveur de la double origine des Nématodes néarctiques du genre *Heligmosomoides* Hall, 1916. *Annales de Parasitologie Humaine et Comparée* **47,** 365–382.

Durette-Desset, M.-C., Baker, M.R., and Vaucher, C. (1984). Présence chez un Amphibien du Pérou d'une nouvelle espèce du genre *Batrachonema* (Yuen, 1965) (Nématode: Trichostrogyloidea) chez des Amphibiens orientaux. *Revue Suisse de Zoologie* **91,** 459–466.

Eichler, W. (1982). Les règles parasitophylétiques comme phénomène de la théorie de l'evolution. *Mémoires du Muséum National d'Histoire Naturelle (Sér. A, Zoologie)* **123,** 69–71.

Gibbons, L. M. (1981). Revision of the African Species of the genus *Cooperia* Ransom, 1907 (Nematoda, Trichostrongylidae). *Systematic Parasitology* **2,** 219–252.

Gupta, S. P. (1961). The life history of *Molineus barbatus* Chandler, 1942. *Canadian Journal of Zoology* **39,** 579–587.

Gupta, S. P. (1963). Mode of infection and biology of infective larvae of *Molineus barbatus* Chandler, 1942. *Experimental Parasitology* **13,** 252–255.

Hendrikx, W. M. L. (1983). *Oswaldocruzia filiformis* (Nematoda; Trichostrongylidae). The epidemiology of the infection in the common toad *Bufo bufo* (Amphibia; Anura). Morphology, routes of infection and some pathological aspects." Doctoral thesis, University of Utrecht.

Herlich, H. (1954). The life history of *Nematodirus helvetianus* May, 1920, a nematode parasitic in cattle. *Journal of Parasitology* **40,** 60–70.

Herlich, H. (1965a). The development of *Cooperia pectinata* a nematode parasite of cattle. *American Journal of Veterinary Research* **26,** 1026–1031.

Herlich, H. (1965b). The effects of the intestinal worms *Cooperia pectinata* and *Cooperia oncophora* on experimentally infected calves. *American Journal of Veterinary Research* **26,** 1032–1036.

Hoffstetter, R. (1982). Introduction sur les hôtes. I-phylogénie des Mammifères: Méthodes d'étude, résultats, problèmes. *Mémoires du Muséum Nationale d'Histoire Naturelle (Sér. A, Zoologie)* **123,** 13–20.

Hoffstetter, R., and Lavocat, R. (1970). Découverte dans le Déséadien de Bolivie du genre *Pentalophodontes* appuyant les affinités africaines des Rongeurs Caviomorphes. *Comptes Rendus Hebdomadaires des Séances de l'Academie des Sciences* **271,** 172–175.

Kobulei, T. (1956). [The phenomenon of specificity of *Amidostomum anseris* (Zeder, 1800) against its host]. *Helminthologia* **8,** 241–246 (in Russian).

Kouyaté, B. (1981). Nématodes Trichostrongyloïdes parasites de Sciuridés en Afrique Centrale. *Bulletin du Muséum Nationale d'Histoire Naturelle, Sér. A, Zoologie* No. 2, 467–494.

Kowalski (1961). Les micromammifères du Pliocène et du Pleistocène inférieur de la Pologne. *Colloque International du CNRS* No. 104, 409–416.

Lavocat, R. (1967). "Histoire des Mammifères." Edition du Seuil, Paris.

Looss, A. (1901). The Sclerostomidae of horses and donkeys in Egypt. *Records of the Egyptian Government School of Medicine* pp. 25–139.

Michel, J. F. (1974). Arrested development of nematodes and some related phenomena. *Advances in Parasitology* **12,** 279–366.

Osche, G. (1958). Die Bursa- und Schwanzstrukturen und ihre Aberrationen bei den Strongylina (Nematoda); morphologische Studien zur Problem der Pluri und Paripotenzerscheinungen. *Zeitschrift für Morphologie und Ökologie der Tiere* **46,** 571–635.

Ow-Yang, C. K. (1974). On the life history of *Hepatojarakus malayae* (Nematoda: Trichostrongylidae), a parasite of the feral rat in Malaysia. *Journal of Helminthology* **48,** 293–310.

Petter, A. J. (1966). Equilibre des espèces dans les populations de Nématodes parasites du côlon des Tortues terrestres. *Mémoires du Muséum National d'Histoire Naturelle (Sér. A, Zoologie)* **34,** 1–252.

Quentin, J.-C. (1971). Sur les modalités d'évolution chez quelques lignées d'Helminthes de Rongeurs Muroidea. *Cahiers de ORSTOM, Series Entomologie Médicale et Parasitologie* **9,** 103–176.

Ransom, B. H. (1906). The life history of the twisted wire worm (*Haemonchus contortus*) of sheep and other ruminants. *United States Bureau of Animal Industries Circular,* **93,** 1–7.

Rossi, P. (1983). Sur le genre *Nematodirus* Ransom, 1907 (Nematoda: Trichostrongyloidea). *Annales de Parasitologie Humaine et Comparée.* **58,** 557–581.

Schad, G. (1963). Niche diversification in a parasitic species flock. *Nature (London)* **198,** 404–406.

Schad, G. (1977). The role of arrested development in the regulation of nematode populations. *In* "Regulation of Parasite Populations" (G. W. Esch, ed.) pp. 111–167. Academic Press, New York.

Schwartz, B., and Alicata, J. E. (1934). The development of the trichostrongyle, *Nippostrongylus muris,* in rats following ingestion of larvae. *Journal of the Washington Academy of Sciences* **24,** 334–338.

Schwartz, B., and Alicata, J. E. (1935). Life history of *Longistriata musculi,* a nematode parasitic in mice. *Journal of the Washington Academy of Sciences* **25,** 128–146.

Schwartz, B., Alicata, J. E., and Lucker, J. T. (1931). Resistance of rats to superinfection with a nematode *Nippostrongylus muris* and an apparently similar resistance of horses to superinfection with nematodes. *Journal of the Washington Academy of Sciences* **21,** 259–261.

Seurat, L. G. (1920). Histoire naturelle des Nématodes de la Berbérie. Première partie: Morphologie, développement, ethologie et affinités des Nématodes. Université d'Alger, Faculté des Sciences, Fondation J. Azoubib.

Sukhdeo, M. V. K., and D. F. Mettrick (1983). Site selection by *Heligmosomoides polygyrus* (Nematoda): Effects of surgical alteration of the gastrointestinal tract. *International Journal of Parasitology* **13,** 355–358.

Thaler, L. (1962). Campagnols primitifs de l'Ancien et du Nouveau Monde. *Collections internationaux de CNRS* No. 104, 387–398.

Thenius, E. (1972). "Grundzüge der Verbreitungsgeschichte der Säugetiere. Eine historische Tiergeographie." Fischer, Stuttgart.

Thomas, R. J. (1959). A comparative study of the life histories of *Nematodirus battus* and *N. filicollis,* nematode parasites of sheep. *Parasitology* **49,** 374–386.

Threlkeld, W. L. (1946). The life history of *Ostertagia ostertagi. Virginia Agricultural Experimental Station Bulletin* No. 100, pp. 1–14.

Veglia, F. (1915). The anatomy and life-history of *Haemonchus contortus* (Rud.). *Third and Fourth Report of the Director of Veterinary Research* pp. 347–500.

Wetzel, R., and Enigk, K. (1937). Zur Biologie von *Graphidium strigosum,* dem Magenwurm der Hasen und Kaninchen. *Deufsche tierärztliche Wochenschrift* **45,** 401–405.

Wright, K. A. (1975). Cephalic sense organs of the rat hookworm, *Nippostrongylus brasiliensis*—form and functions. *Canadian Journal of Zoology* **53,** 1131–1146.

Nematodes as Biological Control Agents: Part I. Mermithidae

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I. Introduction

Nematodes are usually considered pests because of the diseases they cause in humans and animals and the economic impact they have on many agricultural products. There are, however, a small but significant number of beneficial entomogenous nematodes, i.e., nematodes associated, often parasitically, with insects. Some of these nematodes are of considerable interest because of their potential as biological control agents of pest insects.

Poinar (1979) listed 19 families of nematodes containing members that are facultative or obligate parasites of insects. Nine families (Allantone-

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matidae, Diplogasteridae, Heterorhabditidae, Mermithidae, Neotylenchidae, Rhabditidae, Sphaerulariidae, Steinernematidae, and Tetradonematidae) include species that attack insects and kill, sterilize, or alter host development. This two-part work will concentrate on the more promising of these entomogenous nematodes. Part I covers the mermithids and Part II in a subsequent volume will cover the tylenchids, steinernematids, and heterorhabditids.

The mermithids are a large and important group of nematodes. They are obligate parasites of arthropods, principally insects, but have also been recorded from spiders, crustaceans, earthworms, leeches, and mollusks (Poinar, 1979). They are usually specific to a single species or to one or two families of insects and are almost always lethal to their hosts. One of the earliest records of mermithids is found in the writings of Aldrovandi in 1623; he observed dead grasshoppers associated with long worms and considered the worms responsible for the death of the insects. Lister in 1671 described worms (most likely mermithids) from beetles found in his garden (Poinar, 1975).

Mermithids have since been reported from a variety of arthropods, in a variety of environments, and often infecting large percentages of host populations. The study of these nematodes, however, has been slow to develop because most mermithid observations were made by entomologists with little interest or training in nematology. Thus, much of the early work was limited to parasite–host associations or observations on incidence of parasitism.

Most of our knowledge of this group has been developed in the last 20 years and has been stimulated by increased interest in biological control. Mermithids are particularly attractive because (1) they offer little or no environmental hazard; (2) they offer no threat from competitive displacement of other desirable organisms because of their life cycle; and (3) the potential exists for inundative release to give high initial host reduction, or inoculative releases to establish the nematode and give partial control for an indefinite period.

II. Morphology and Taxonomy

Mermithids are filiform in shape with a smooth cuticle often possessing two distinct crossed layers of spiral fibers. The head usually has six flat cephalic papillae and well-developed amphids. The body has six or eight longitudinal cords, and the digestive tract is similar to free-living nematodes only in the young preparasitic larvae. In parasitic and postparasitic larvae and adults, the esophagus does not connect with the midintestine (trophosome) which is filled with food reserves. The esophagus extends

one-fourth to nine-tenths of the body length and is almost devoid of musculature. The anus is absent in females. Gonads are paired in both sexes; in the female the genital aperture occurs at midbody, and in the male at the posterior end of the body in the form of one or two spicules. Eggs are round or oval, and in some terrestrial species have processes for adherence. The preparasite, postparasite, and adult worms are free living (Rubzov, 1972).

Mermithid taxonomy is in a state of confusion for several reasons. First, entomologists untrained in the biology and preservation of nematodes have historically been the persons encountering mermithids either by dissection of hosts or by observations of natural emergence. As a result, the nematodes were frequently destroyed during preservation or were improperly preserved as postparasitic juveniles. Second, mermithids present, at best, a difficult taxonomic group with few measurable morphological characteristics. Most of the early descriptions were incomplete and have become inadequate as more species are described and a more refined knowledge of this group is required. Third, many species have been described without knowledge of host associations and from only a few specimens. In some instances descriptions have been made from single specimens without knowledge of the opposite sex. Curran (1981) reported that many quantitative characteristics are affected by the environment, and suggested that many ratios commonly used in mermithid taxonomy should be rejected. Curran concluded that descriptions based on a single or a few specimens do not provide a sound foundation for mermithid taxonomy. The use of large samples, all developmental stages, and both quantitative and qualitative characters may overcome this problem. Fourth, improper mounting techniques distort morphological characteristics. Curran and Hominick (1980) found that qualitative characters, particularly head shape and cuticle thickness, and quantitative characters were differentially altered.

As a result of these classification problems, even the taxonomy of the most extensively studied mermithid, *Romanomermis culicivorax*, remains in doubt. This mermithid was first determined to be an undescribed species of *Romanomermis* (W. R. Nickle, personal communication). Nickle (1972) subsequently determined the Louisiana isolate to be the same as *Reesimermis nielseni* from Wyoming. In a detailed study of this group, Ross and Smith (1976) resurrected the genus *Romanomermis* and described the Louisiana isolate as *R. culicivorax*. Recently, Curran and Hominick (1980) reported that the characteristics used to separate *R. culicivorax* from a morphologically similar species *R. iyengari* (Galloway and Brust, 1979) were fixation artifacts and that *R. culicivorax* is *species inquirenda* until interbreeding studies can be done.

Poinar (1979) lists 32 genera of mermithids and suggests that there are

over 200 species that have been described with many more still awaiting characterization.

III. Biology

A. Life Cycle

1. *Aquatic mermithids*

Mermithids that attack the aquatic stage of their hosts are similar, varying mostly in the length of time required to complete their life cycle. The infective stage (preparasite) hatches from the egg as a second-stage larva and in most species is free swimming in still-water environments, but species that develop in moving water environments may attach themselves to surface substrate (Molloy and Jamnback, 1975). The preparasite appears to be nondirectional in its swimming activity, leading several authors to suggest that host contact is accidental. Kurihara (1976) reported that the preparasites of *R. culicivorax* (*Reesimermis nielseni*) did not aggregate in the vicinity of restrained hosts over time. In contrast, Poinar (1979) suggested that the large amphidial openings in the preparasitic stage of *R. culicivorax* were associated with host attraction. Behavioral characteristics unique to the parasite–host association may increase the chance of contact. *Romanomermis culicivorax* is positively thigmotactic and negatively geotactic, which greatly increases their chance of contact with a suitable mosquito host (Petersen, 1973a). The preparasite is generally short lived: *Gastromermis viridis*, a parasite of blackflies, at all temperatures becomes sluggish when 2 days old (Phelps and De Foliart, 1964); and 50% of the preparasites of *R. culicivorax* survived for 2.0 days at 12°C and 0.9 days at 30°C (Brown and Platzer, 1977). However, Johnson (1955) reported that the infective stage of *Hydromermis contorta*, a parasite of chironomids, survived 12 days at 2°C and 6 days at 17°C.

Upon successful contact, the preparasite attaches to the host by means of a stylet and enters the hemocoel through a hole made in the host's cuticle. The preparasites of *Mesomermis flumenalis* attach themselves to the thoracic region of blackfly larvae, pierce the integument, and enter the host within a few minutes. During this period and for several minutes thereafter, the hosts appear to be paralyzed. Gradually normal movement and feeding resume (Molloy and Jamnback, 1975). Though cuticular penetration is the usual mode of entry for mermithids, ingestion of the eggs and penetration of the gut wall have been suggested for several blackfly mermithids and have been reported for *Pheromermis pachysoma*, a parasite of wasps (Poinar *et al.*, 1976).

Mermithids species that develop in larval hosts usually begin maturing soon after entering the host. The parasitic juvenile derives its nourish-

ment directly from the host's hemolymph by transcuticular uptake. Generally, there is a single molt inside the host. The two final molts occur simultaneously after the mermithid leaves the host and enters the environment (Poinar and Otieno, 1974). The parasitic stage of *R. culicivorax* grows slowly for the first 3–4 days and then rapidly increases in size, requiring a total of 7–8 days at 26°C (Gordon *et al.*, 1974). Similar growth patterns have been reported for other mermithid species. The developmental period varies greatly with the temperature of the aquatic environment and many mermithid species overwinter in parasitized hosts.

Some mermithid species develop only in larval hosts under normal environmental conditions, while others may complete development in any host stage usually depending on the age of the host at the time of penetration. Still others mature only in the adult host. In the parasitic stage, mermithids stop feeding just prior to emergence and form a second cuticle (retaining the previous larval cuticle), permitting them to become tolerant to the external environment. The postparasitic stage emerges by rupturing a hole in the host's cuticle by simple mechanical pressure, usually through the intersegmental membranes. Death usually occurs in larval hosts at the time of emergence. Adult hosts occasionally survive parasite emergence and can occasionally develop a reduced batch of eggs (Petersen *et al.*, 1967).

After emergence, the free-living, nonfeeding postparasites burrow in the habitat substrate where they molt to the adult stage, mate, and lay eggs. This period may be as short as 7–10 days in some species but may require up to a year in mermithids that parasitize univoltine hosts.

The eggs of aquatic mermithids are usually spherical and transparent and contain small amounts of gelatinous material on the surface. The eggs of most aquatic mermithids have little tolerance for desiccation. However, eggs of mermithids that parasitize floodwater mosquitoes are known to tolerate long periods in dry habitats. Egg maturation begins immediately following oviposition and maturation is temperature dependent (Thornton and Brust, 1979). The eggs hatch if temperatures are optimal and adequate moisture is available. Where free water is absent, eggs mature but generally do not hatch until the habitat is flooded. Thus, when habitats remain flooded for extended periods, there is a continuous production of mermithids at low levels, but when habitats dry out and are reflooded, synchronized hatching of the mermithid and host eggs occur, often resulting in high levels of parasitism (Petersen and Willis, 1971).

A number of other unknown factors may also influence egg hatch. Recently, Platzer (1982a) reported that the eggs of *Octomyomermis muspratti* hatched more readily if they were ingested and passed through the alimentary canal of a larval mosquito, an apparent survival mechanism that assures the presence of hosts at the time of egg hatch.

2. *Terrestrial mermithids*

The life cycle of this group of mermithids follows that of aquatic mermithids but is usually more protracted with modifications to overcome desiccation. Females of *Mermis nigrescens* migrate from the soil to vegetation and lay eggs during periods of high moisture. The eggs are later eaten by grasshoppers and hatch in the gut, and the preparasites penetrate through the gut wall into the hemocoel. However, the preparasites of most terrestrial mermithids hatch from eggs in the soil and migrate to the surface in search of a suitable host. This migration usually occurs at night or during periods of rain or heavy dew. The preparasites of *Filipjevimermis leipsandra* in soil remain infective for up to 50 days (Cuthbert, 1968).

The length of the parasitic phase varies with species. *Filipjevimermis leipsandra* required less than 7 days (Cuthbert, 1968); *Hexamermis arvalis*, 7–12 days (Poinar and Gyrisco, 1962); *Agamermis decaudata*, 1–3 months (Christie, 1936); and *M. nigrescens* males 4–6 weeks and females 10–12 weeks (Christie, 1937). The postparasites emerge, killing the host, and enter the soil to a depth of 1–15 cm determined by soil moisture. Maturation and the beginning of egg laying may take as little as 2 weeks for *F. leipsandra* or a year for *A. decaudata*. Mating is usually necessary but at least two species, *F. leipsandra* and *M. nigrescens*, can reproduce parthenogenetically. The eggs of most species are laid in the soil where they mature and remain until adequate temperature and moisture stimulate hatching. Females of *A. decaudata* are reported to lay up to 10,000 eggs over a 2-year period (Christie, 1936).

The most complex and unusual life cycle reported to date for a mermithid is that of *Pheromermis pachysoma*, a parasite of yellowjackets, *Vespula pensylvanica*. *Pheromermis pachysoma* utilizes a paratenic host in its life cycle, a behavior unique for the Mermithidae. The eggs are deposited in wet seepage adjacent to springs and hatch only when ingested by caddisflies or other aquatic insects. After hatching, the nematodes penetrate various host tissues and enter a quiescent phase. They are carried into the adult stage of the insect but develop no further unless ingested by *V. pensylvanica*. Wasp larvae are probably infected when they are fed paratenic hosts captured by worker yellowjackets. Postparasitic juveniles emerge from the adult host when the wasp visits wet sites (Poinar, 1976; Poinar *et al.*, 1976).

B. ENVIRONMENTAL LIMITATIONS

With few exceptions, knowledge of environmental limitations is restricted to that developed for *R. culicivorax*, first, because this parasite is easily manipulated and can be field tested, and second, because no other

mermithid species have been investigated to the point that this type of information is important for their use as biological control agents.

1. *Physical factors*

The effects of temperature on development and parasitism are fairly well documented for a number of mermithid species. However, specific temperature limitations become critical when a nematode is to be used to control host populations. *Romanomermis culicivorax,* naturally found only in the southern United States, is active only when temperatures are above 15°C (Petersen, 1973b). Brown and Platzer (1977) reported parasitism in the laboratory at 12°C; and Galloway and Brust (1977) reported only limited parasitism in field releases at 10°C and concluded that the use of *R. culicivorax* for mosquito control in colder temperature zones is precluded. Mermithids vary greatly in their tolerance to low temperatures as certain species parasitize snowmelt mosquitoes and have been isolated from mosquitoes as far north as the Arctic Circle (Frohne, 1955).

The effect of photoperiod on parasitism by *R. culicivorax* remains controversial. Brown and Platzer (1974) reported that mosquito larvae were more susceptible to preparasites when kept in continuous darkness. However, Galloway and Brust (1977) reported that photoperiod had no significant effect on infectivity. They also observed that there was no interaction between the temperature and the photoperiod. In a more recent study, Sharma and Gupta (1982a) determined that there was a definite interaction between the photoperiod and temperature, and in contrast to Brown and Platzer (1974), reported that the highest rate of larval infection occurred in continuous light at ambient temperature.

For aquatic mermithids, water movement can be an important factor. *Romanomermis culicivorax* was ineffective in releases against pasture mosquitoes in California because irrigation water was continually flowing through the field and the preparasites were apparently washed away before they could make contact with the host (Hoy and Petersen, 1973). Also, attempts to parasitize simuliid larvae with the mosquito parasite *R. culicivorax* in running water environments were ineffective. Limitations associated with water movement were further substantiated in field releases of *R. culicivorax* at a lake in El Salvador. Releases made prior to heavy wave action on the lake resulted in levels of parasitism of about half those when releases were made following heavy wave activity (Petersen *et al.*, 1978b).

Desiccation is not a serious limiting factor for aquatic mermithids. Although the nematodes and eggs cannot tolerate desiccation even for a few minutes, there is sufficient moisture even when the habitat dries out to maintain the parasite populations until the habitat again becomes flooded. In contrast, moisture is a major factor for terrestrial mermithids. The

highest levels of parasitism by *A. decaudata* and *M. nigrescens* are always associated with persistently moist environments (Mongkolkiti and Hosford, 1971; Christie, 1936).

2. *Chemical factors*

Petersen and Willis (1970) found that *R. culicivorax* was inhibited by mild salinity (0.04 *M* NaCl). This was confirmed by Brown and Platzer (1978a) who also ranked ion toxicity for *R. culicivorax* for the following ions: cations, sodium < potassium < calcium; and anions, chloride < carbonate = sulfate < nitrate < nitrite < phosphate. Therefore, *R. culicivorax* is ineffective for mosquito control in habitats under conditions of increased water salinity. A similar tolerance was shown for *R. iyengari* (Bheema Rao *et al.*, 1979). In contrast, the mosquito mermithid *O. muspratti* has been shown to be tolerant of diluted seawater (3000–4000 μmhos cm^{-1}) and water from tree holes (10,000 μmhos cm^{-1}) (Petersen, 1981). The mermithid *Perutilimermis culicis* develops in *Aedes sollicitans*, a salt marsh mosquito, and therefore has adapted to tolerate very high salinity.

Chen (1976) reported that the optimum pH for infection by *R. culicivorax* was 6.7–7.2. In contrast, recent studies showed that aquatic mermithids tolerate a broad pH range. Brown and Platzer (1978a) reported that parasitism occurred over a pH range of 3.6–8.6. Similarly, Petersen (1979a) showed that host mosquitoes were readily infected at all pH concentrations tested (5.4–7.9) and that infection increased at the lower pH ranges. More recently, Sharma and Gupta (1982b) reported a limited tolerance for higher pH levels and concluded that *R. culicivorax* did not appear suitable for biological control of *Culex quinquefasciatus* because of the high pH characteristic of habitats of this mosquito.

Mermithids have a high tolerance for many agricultural chemicals. Mitchell *et al.* (1974) reported that levels of Abate, Dieldrin, and Gamma-HCH, normally used then for mosquito control, did not adversely affect host parasitism by *R. culicivorax*. Levy and Miller (1977a) reported similar tolerance by *R. culicivorax* to four pesticides and a growth regulator. Finney *et al.* (1977) found that Altosid 5E, an insect growth regulator, did not interfere with parasite development, and that host mortality increased when a combination of Altosid and *R. culicivorax* was used in laboratory experiments. Also, copper-based organic algacides and copper sulfate did not compromise the infectivity of *R. culicivorax* at concentrations used for algae and weed control (Platzer and Brown, 1976).

Brown and Platzer (1978b) showed that transient exposure to low oxygen tension increased the survival and infectivity of preparasites of *R. culicivorax*. However, Platzer (1981) found that preparasites of this mer-

mithid stopped moving within 8 hours in water rich in organic content and low in oxygen content. This explained, at least in part, why *R. culicivorax* has proved ineffective against mosquitoes in polluted environments. Mermithid species also vary in their tolerance to pollution. *Octomyomermis muspratti* has been shown to tolerate much higher levels of organically rich tree-hole water than *R. culicivorax* (Petersen, 1981), again demonstrating the diversity in tolerance of aquatic mermithid species.

3. *Biological limitations*

Mermithids, with few exceptions, parasitize the immature stages of their hosts. The age of the immature host influences the susceptibility of that host to attack by some mermithid species. Petersen and Willis (1970) showed that second-instar larvae of *Cx. quinquefasciatus* were most readily invaded by *R. culicivorax*, third instars were slightly less susceptible than first instars and limited parasitism occurred in fourth-instar larvae. Host age can greatly influence the outcome of attempts to control fast growing floodwater mosquitoes with mermithids because some floodwater mosquito species can develop to a stage where control with mermithids is ineffective within 48 hours during midsummer temperatures.

Research suggests that predators and parasites of mermithids can reduce their effectiveness especially in aquatic environments. Mitchell *et al.* (1974) were the first to report the predation of preparasites of *R. culicivorax* by ostracods. Platzer and MacKenzie-Graham (1978) have since shown that the preparasitic stage is also preyed upon by copepods, young gammarids, diving beetles, dragonfly and damselfly naiads, and small crayfish. In the laboratory, mermithid parasite populations were reduced significantly by copepod densities of 20–100 liter $^{-1}$ (Platzer and MacKenzie-Graham, 1980). The authors concluded that copepods may play a significant role in the success or failure of field applications of mermithids.

Pathogens may also limit populations of both aquatic and terrestrial mermithids. Nolan (1977) reported the presence of a phycomycete and hyphomycete in *M. flumenalis* and suggested that the occurrence of fungi might affect the success of this mermithid for the control of simuliids. A highly virulent chytridiomycetous fungus, *Cantenaria anguillulae*, reached epizootic proportions in laboratory cultures of *R. culicivorax*, but was eliminated by rearing the mosquito hosts in acidified water (Sterling and Platzer, 1978). Recently a soil hyphomycete was reported attacking eggs of *O. muspratti* in the laboratory (Platzer, 1982b). The impact of pathogens and parasites of mermithid nematodes in nature remains unknown.

C. HOST SPECIFICITY

Mermithids of terrestrial insects have a broader host range than those that parasitize aquatic insects. Because of the difficulty in manipulating mermithids in the laboratory, much of what we know about host specificity is derived from observations of naturally infected insects. *Mermis nigrescens* is a parasite of grasshoppers but has also been reported from Dermaptera, Coleoptera, and Lepidoptera and is known to parasitize 61 species of insects (Poinar, 1979). *Agamermis decaudata* is principally a parasite of grasshoppers of the Acrididae and Tettigoniidae families but has also been collected from at least one coleopteran; and *F. leipsandra* has been reported from seven species in five genera of coleopterans and lepidopterans (Poinar, 1979).

Host range is more restricted in aquatic mermithids, often to a single or a few species of closely related hosts. Specificity of blackfly mermithids is difficult to assess because of systematics problems within the parasite and host groups. Host lists give the impression that blackfly mermithids have a broad host range. However, it is likely that several species of parasites are involved (Molloy, 1981). On several occasions one species of blackfly has been reported infected in a stream while others remain uninfected or parasitized at substantially reduced levels (Colbo and Porter, 1980; Molloy and Jamnback, 1975). Blackfly mermithids have not been reported from other insects inhabiting the same stream. Willis (1971) reported an *Amphimermis* sp. in naiads of two species of damselflies while at least one species of damselfly and several species of dragonflies were not parasitized. Similarly, Poinar and Petersen (1978) reported *Drilomermis leioderma* in larvae of the beetle *Cybister fimbriolatus* while all other insects in the habitat were free of this parasite; a mosquito mermithid also present in the same pool was not found in other insect species.

The most extensive host specificity studies have been made with mosquito mermithids. With the exception of two species of Chaoboridae (closely related to mosquitoes) mermithids parasitic in mosquitoes have not been found parasitizing other organisms in nature (Galloway and Brust, 1979).

In the laboratory, *R. culicivorax* develops in most species of Culicidae. In tests against 87 species of mosquitoes in 13 genera, susceptibility was generally highest in *Anopheles*, but at least one anopheline species was highly refractory and another moderately so; both exhibited the ability to encapsulate and melanize the nematode. Similar patterns of individual species showing some form of refractiveness were seen for the *Aedes*, *Culex*, and *Psorophora* species. *Anopheles sinensis* was found to be highly susceptible to *Romanomermis jingdeensis*, a mosquito species that is completely refractory to *R. culicivorax;* further, *R. jingdeensis* failed to

produce significant levels of parasitism in *Cx. quinquefasciatus*, a highly susceptible host of *R. culicivorax* (Xinshi *et al.*, 1983). These data are sufficient to demonstrate the complexity of mermithid–host interactions and the need to know these interactions if effective use of a mermithid species is to be accomplished.

In tests against nontarget organisms, *R. culicivorax* was able to penetrate early instars of some Chaoboridae, Chironomidae, and Simuliidae but failed to complete development. No other organisms were found to be susceptible to attack even under very heavy challenges (Ignoffo *et al.*, 1973). Considerable research has been done with *R. culicivorax* as a possible biological control agent for blackflies (Finney, 1975; Poinar *et al.*, 1979a). Though early-instar simuliids could be infected under laboratory conditions, successful parasite development could not be demonstrated. *Romanomermis culicivorax* has little invasiveness in moving water, and thus, it becomes impractical to attempt the control of an insect that inhabits a running water environment with a parasite adapted to the nonmoving water habitat of mosquitoes (Finney and Mokry, 1980). Though *R. culicivorax* has a wide range of mosquito hosts, other species parasitic in mosquitoes vary widely in range of suitable hosts. One species, *Strelkovimermis peterseni*, was found to be generically specific for *Anopheles* mosquitoes and failed to develop in culicine hosts (Petersen and Chapman, 1970). Further, mermithids that complete their parasitic development only in adult hosts are usually specific for a single host species (*P. culicus* for *Aedes sollicitans*, *Culicimermis culcivora* for *Aedes communis*, *Empidomermis cozii* for *Anopheles funestus*, and *Empidomermis riouxi* for *Aedes detritus*). However, at least one species, *Culicimermis schakovii*, readily develops in several *Aedes* species.

D. PATHOLOGY

Bailey and Gordon (1973) reported that *R. culicivorax* depleted host metabolites, reduced fat body and other host storage tissues while accumulating stored materials in their trophosomes, and thus inhibited the development of imaginal disks in the host mosquito. Hemolymph proteins were depleted sixfold in mosquitoes (Schmidt and Platzer, 1978).

Mermithid parasites of larval diptera probably resemble *M. nigrescens* in obtaining dietary amino acids by stimulating the catabolism of proteins within the host fat body (Gordon, 1981). In addition to the reduction of most protein fractions, significant decreases also occurred in hemolymph glucose in parasitized blackflies; however, blood trehalose concentrations were not affected (Gordon *et al.*, 1978). Glycogen reserves were shown to be similarly reduced in the fat body of mermithid-parasitized simuliids (Condon and Gordon, 1977). Gordon *et al.* (1979) found that parasitism

did not significantly affect either the overall concentration of lipids or relative proportions of the lipid fraction in the hemolymph of mosquitoes. Mermithid parasitism of mosquitoes and simuliids caused almost complete degeneration of host fat body tissue. All storage metabolites, including glycogen, within the fat body may directly or indirectly be utilized by the developing nematode.

Responses are somewhat different in larger hosts with longer periods of parasitism. Protein in the fat body of grasshoppers parasitized by *M. nigrescens* was depleted after 2 weeks; corresponding reductions in proteins were not recorded from the hemolymph until 1 week later. The third week of infection represented a period of maintenance and reconstruction of fat body soluble proteins, but corresponding effects were not found for hemolymph proteins until the fourth week of infection (Gordon *et al.*, 1978).

Gordon and Webster (1971) found that the overall level of amino acids in the hemolymph of adult female grasshoppers was not affected by mermithid parasitism, but the content of amino acids within the fat body was significantly reduced. Parasitism by *M. nigrescens* resulted in glucose levels remaining low for the first 4 weeks of parasitism relative to trehalose, but no significant difference for glucose levels when compared to unparasitized controls. Trehalose levels dropped and remained low for much of the parasitic period. These data suggested that the nematode modifies its host's metabolism to favor production of small molecules such as glucose and amino acids from carbohydrate and protein reserves and that the host cell's ability to sequester nutrients is impaired during parasitism (Rutherford and Webster, 1978).

Craig and Webster (1974) found that ecdysone levels in locusts were unaffected by *M. nigrescens* and attributed the inhibition of molting in parasitized insects to depletion by the nematode of precursors required by the host for protein and cuticle synthesis. However, ovaries of parasitized locusts were unable to sequester vitellogenic proteins available within the hemolymph, suggesting endocrine dysfunction in the host (Gordon, 1981).

Major modifications of the host's metabolism by mermithid parasitism are manifested in host tissue degeneration and retarded development including resorption or suppression of oocyte development. As a result, hosts are usually prevented from maturing to the adult stage or when they do they are generally unable to reproduce.

Hosts are occasionally able to prevent parasite development by either cellular or humoral responses. The most common cellular response is encapsulation. Poinar *et al.* (1979b) reported that *Culex territans* responded to the development of parasitic juveniles of *R. culicivorax* by covering the 2- to 3-day-old parasites with blood cells. These nematodes failed to complete development. A more frequent condition, melanotic

encapsulation, was reported in *Diabrotica* beetle larvae attacked by *F. leipsandra*. Host hemocytes lysed on the cuticle of the nematode soon after it entered the host, and within 6–8 hours an inner layer of melanin had formed around the nematode (Poinar, 1979).

Similar responses were observed for larvae of *Psorophora ferox, Aedes triseriatus,* and *Anopheles quadrimaculatus* to the *R. culicivorax*. However, some 70 species of mosquitoes have not elicited this type of defense response to *R. culicivorax* (Petersen and Chapman, 1979). Recently, Gaugler *et al.* (1984) reported an encapsulation response when *Empidomermis* sp. entered larvae of *Aedes stimulans* if the nematodes were unable to migrate to the host's head and enter central nervous tissue. After pupation, the nematodes dropped back into the hemocoel where they no longer elicited a host defense reaction. This response may be common in mermithids that enter the larval stage but fail to mature until the host reaches the adult stage. Also, Harlos *et al.* (1980) noted that *Culicimermis* sp. entered the nerve tissue of *Aedes vexans* larvae and later developed in adult hosts; Petersen (unpublished data) observed a similar response in *Ae. sollicitans* when parasitized by *P. culicis*.

Humoral responses, noncellular components of the insect's hemolymph which have an adverse effect on nematode development (Poinar, 1979), may account for the host resistance observed in *Aedes intrudens* and *Aedes provocans* to an *Empidomermis* sp. when no discernible host response was observed, which was unlike the encapsulation response this nematode elicited in *Ae. stimulans* (Gaugler *et al.*, 1984).

Another type of humoral response may be that observed when blackflies were subjected to the mosquito mermithid *R. culicivorax*. The mermithid initiated development in early-instar blackflies, and direct host reaction to this unnatural parasite was not observed; eventually, however, both nematode and host died (Poinar, 1979).

Physical and behavioral responses also influence parasitism by mermithids. Host age, especially in aquatic insect hosts, has been shown to have a considerable effect on host susceptibility. Refractiveness because of age appears to be caused by the thicker cuticle in older larvae (Petersen and Willis, 1970). In the laboratory, as a result of mass-rearing practices for *R. culicivorax,* where exposed but uninfected hosts were retained to supply the next generation, the host mosquitoes were found to have become measurably less susceptible to the nematode after some 100 generations. No evidence of humoral defense mechanisms were found and the mode of defense was not determined (Petersen, 1978a). In a similar buildup of refractiveness in *An. quadrimaculatus* to *S. peterseni,* it was reported that less susceptible hosts were more active and aggressive in attempting to remove attacking preparasites (Woodard and Fukuda, 1977).

E. NATURAL POPULATION REGULATION

Mermithids generally have localized, discontiguous distribution. This is especially true for mermithids that develop in larval hosts. *Romanomermis culicivorax* was found in only seven pools out of several thousand examined in southwestern Louisiana. This is understandable because the hosts are killed prior to emergence from the habitat, thus greatly reducing the nematodes ability to disperse.

Generally, observations of mermithid parasitism are based on isolated collections and often give the impression of higher parasite activity than actually exists. In extended studies, levels of parasitism are usually found to vary greatly. In a 27-month survey of five habitats containing populations of *R. culicivorax,* mean parasitism of *Anopheles crucians* for individual habitats ranged from 8 to 42%, with parasitism of individual populations as high as 80%. Similar but lower levels of parasitism were observed for several other mosquito species (Petersen and Willis, 1971). Similarly, Phelps and De Foliart (1964) observed parasitism of blackflies, *Simulium vittatum,* in four Wisconsin streams over a 1-year period. Parasitism typically ranged from 10 to 90% and the authors suggested that localized parasite populations probably attained levels of parasitism sufficient to virtually eliminate some host populations. Similar population reductions of blackflies were reported by Welch and Rubtsov (1965).

Parasitism of adult aquatic insects usually occurs over a wider geographical area and often reaches very high levels but fluctuates greatly over time. Steiner (1924) observed 80% parasitism of adult *Ae. vexans* in British Columbia in 1920, but only 20% the following year. Trpis *et al.* (1968) reported 100% parasitism of the same host in the same locality in 1967. Similar observations were made on parasitism of *Ae. sollicitans* adults by *P. culicis* in southwestern Lousiana. During an entire year only collections made in January failed to produce infected hosts; mean monthly parasitism ranged from 0 to 48% with individual populations reaching 96%. During a period of high parasitism, a survey was made along 80 km of coastline and revealed parasitism ranging from 48 to 94% for seven populations (Petersen *et al.*, 1967).

Similar isolated high levels of parasitism are frequently observed in terrestrial insects. Christie (1936) reported a heavy outbreak of grasshoppers in Wisconsin in 1923–1925 with a correspondingly heavy infestation of *M. nigrescens*. The author concluded that the parasites were an important factor in terminating the grasshopper problem. Similarly, Mongkolkiti and Hosford (1971) reported that a population of the grasshopper *Hesperotettix viridis pratensis* was totally destroyed prior to egg laying by *M. nigrescens*. Other species of grasshoppers in this population were only partially affected or not affected by the mermithid.

Though reports of natural insect control are impressive and suggest the potential of mermithids as biological control agents, these parasites generally do not influence significant control over host populations. In a review of blackfly–mermithid literature, Molloy (1981) reported that parasitism in most blackfly populations is moderate, ranging from 3 to 15%, and is perennial with only rare and highly localized epizootics. This pattern probably holds true for most mermithid–host associations.

F. SAFETY

As previously mentioned, mermithids are generally specific to one or a few species of insects and are rarely found in other insects. As a result, little concern has been shown for potential danger of these parasites to mammals. To date, only limited mammalian safety studies have been made. Ignoffo *et al.* (1974) reported that when suckling and adult mice and adult rats were subjected to either *per os*, intranasal, intraperitoneal, or dermal challenge of *R. culicivorax*, their body weight gain and histologies were identical to those of untreated animals. Immunodepressed rats also were not susceptible. Similar findings were reported for *R. iyengari* in India (Anonymous, 1978). Similarly, studies in the People's Republic of China showed that no pathology was apparent in dermally challenged suckling mice, in orally exposed adult rats, or in three species of fish when exposed to *R. jingdeensis* (Anonymous, 1982).

Mermithids have occasionally been reported as accidental parasites of man. Poinar (1979) reviewed all such cases in the literature and concluded that in most cases the data were insufficient to ascertain if human parasitism actually occurred. He further concluded that the question of accidental human infection by mermithids cannot be definitely answered at this time and should only be accepted as fact when proven experimentally or when parasites are found developing *in situ* in the human organism. Further, the Environmental Protection Agency (United States) has exempted mermithids from safety regulations.

IV. MASS PROPAGATION

Mass production systems at economical costs are essential if a given biological control agent is to be effectively used. Mermithids take in their nutritional needs directly through the cuticle, making them especially difficult to propagate by *in vitro* methods. Therefore, pest control attempts have been limited to those mermithid–host systems that are conducive to *in vivo* rearing.

A. *In Vivo* PROPAGATION

The *in vivo* rearing of mermithids of terrestrial insects is especially difficult because of the protracted life cycles of many of the hosts. Though numerous mermithid species have been encountered, laboratory culture has been limited to *M. nigrescens* and *F. leipsandra*. Laboratory infections are relatively easy with *M. nigrescens*. Gordon and Webster (1971) collected adult females of *M. nigrescens* from the field, allowed the females to oviposit, concentrated the eggs on moist filter paper, and stored the eggs at 5°C until needed. To infect hosts, eggs were transferred onto small pieces of grass previously coated with an adhesive material. The grass was readily eaten by host grasshoppers. This method permitted extensive research on the physiological effects of mermithid parasitism on a host system (Gordon, 1981). The long developmental period of the nematodes during both the parasitic and free-living stages (1 year) has prevented meaningful use of this nematode in field trials.

Creighton and Fassuliotis (1981) were the first to give a detailed report of the laboratory culture of a mermithid of terrestrial insects. Preparasitic juveniles of *F. leipsandra* and the larvae of the cucumber beetle, *Diabrotica blateata,* were placed in holes in soil in clay pots. The pots were sealed and held for parasite emergence. Ratios of 1000 nematodes per 100 host larvae were sufficient for maximum recovery of postparasitic nematodes. The method has the potential of producing between 80,000 and 240,000 nematode eggs per experimental unit. From this basic procedure, Creighton and Fassuliotis (1982) developed an *in vivo* mass rearing system for *F. leipsandra*. As eggs were laid, they were concentrated, sterilized by immersion for 10 minutes in 0.28% sodium hypochlorite, and rinsed. The eggs were transferred to a Baermann funnel and allowed to mature and hatch. First instar larvae of the banded cucumber beetle were exposed to the preparasites in clay pots as previously described. Twenty-four pots were placed in a plastic box and held 4–5 days at 24–27°C. The contents of the clay pots were then transferred to porous baskets. The baskets were placed at one end of a larger container with sand at the other end. As the host larvae matured, they migrated to the sand and pupated. After about 10 days the nematodes began to emerge from their hosts. The postparasites were then transferred to a container of aerated water until the nematodes molted to the adult stage and began to deposit eggs (7–10 days). Each larger container (37 × 27 × 10 cm) produced an average yield of 1.9×10^6 nematode eggs. The system can produce about 5×10^6 eggs $week^{-1}$ at a cost of $0.40 (US$) per 1000 eggs including supplies and labor for producing the host insects (1981).

Although mermithids are relatively common in aquatic insects, especially in the Simuliidae, Chironomidae, Ceratopogonidae, and Culicidae,

many of these host species cannot be successfully maintained in laboratory colonies or cannot be maintained in large numbers. Also many mermithid species undergo egg diapause or have an asynchronous hatch which prevents their mass production. As a result, few aquatic mermithid species have been studied extensively. The midge parasite, *Hydromermis conopophaga,* has been readily maintained in colony because the host, *Tanytarsus* midges, can be easily maintained. However, *H. conopophaga* has never been mass produced or released in the field (Poinar, 1979). Similarly, the mermithid *Limnomermis rosea,* a parasite of chironomid larvae, has been reared through several generations but has not been released in the field.

Muspratt (1947) was the first person to develop, maintain, and report a laboratory culture of a mermithid nematode. He collected *O. muspratti* (*Agamomermis*) from naturally infected host mosquito larvae and placed the nematodes in containers filled with moist sandy soil. The soil was allowed to dry out over a period of several months. After 11–12 months some of the soil was placed in a container of water and first instar mosquitoes added. Seventy to 80% of the host larvae contained nematodes. The original work by Muspratt though very basic provided the direction for future work with mosquito mermithids. Subsequent studies with *O. muspratti* have refined the rearing technique and defined biological limitations (Petersen, 1977). A mass production system for *O. muspratti* has failed to develop, even though a suitable laboratory host system is available, because the eggs of this species failed to hatch at the same time although they appeared to mature. Because of the nonsynchronous hatch, cultures were observed to produce infective stage nematodes after periodic floodings for over 5 years (Petersen, 1981).

The mermithid, *S. peterseni,* a parasite of *Anopheles* mosquitoes, has been maintained in colony for over 10 years (Woodard and Fukuda, 1977). Though this nematode appears to be an infective parasite, and is easily maintained in laboratory colony, economical mass production systems have been difficult to achieve because the only hosts are *Anopheles* mosquitoes, which are less suitable for mass rearing systems than are certain *Aedes* and *Culex* species.

The most efficient and effective *in vivo* rearing system for mermithids is that developed for *R. culicivorax*. The primary techniques were developed in 1971 (Petersen and Willis, 1972a). This initial system called for the exposure of 20,000 first-instar *Cx. quinquefasciatus* larvae in 136 × 52 × 5 cm galvanized trays to preparasites at a parasite–host ratio of 12 : 1. The hosts were then fed a regimented diet for 7 days. After this period the culture trays were drained and the mosquitoes concentrated. Pupae of uninfected mosquitoes were separated using a chilled water procedure, and the infected mosquitoes were placed in 36 × 25 × 10 cm trays and

held for nematode emergence. Postparasitic nematodes were then washed and 10–15 g placed in paraffin-coated aluminum pans (22 × 33 × 5 cm) which contained clean, coarse, sterile sand and water. After 3 weeks the free water was removed and the cultures stored an additional 4–15 weeks before use. When preparasitic nematodes were needed the cultures were flooded with chlorine-free water to stimulate nematode hatch. Nematode cultures averaged 1.91 million preparasites (45–60% of total yield) if they were flooded for the first time when they were 11–19 weeks old. Total yields were highest (5.32 million preparasites) when cultures were flooded for the first time when 8–10 weeks old and then at 3–4 week intervals thereafter (Petersen, 1978b).

It has since been determined that yields can be increased by having a density of 24 postparasites cm^{-2} in the culture trays. Yields of preparasites were tripled by simply setting up three cultures (22 × 33 × 5 cm), each containing 5 g of nematodes, instead of the usual method of one culture containing 15 g of postparasites (Petersen, 1980). The longevity of cultures could be extended for up to 9 weeks if the cultures were allowed to mature at ambient temperature and then held at 5–10°C. Also, immature cultures survived best at 15–20°C (Petersen, 1979b). Further, Sterling and Platzer (1978) reported that by adjusting the pH of water to 4.5 in *R. culicivorax* cultures, the nematophagous fungus *C. anguillulae* could be effectively controlled. Chapman and Finney (1982) reported that mature eggs of *R. culicivorax* can be stored for 12 weeks at 10°C and 21 weeks if stored during early development at 15°C and later transferred to 10°C. They also reported that eggs of *R. culicivorax* placed in a damp fluoroform product could be shipped with only a 10% loss. The technique has the advantages over the standard shipment of sand cultures of being about eight times lighter, and costing less to ship in addition to reducing shipping losses.

In an actual test of the mass propagation system, sufficient *R. culicivorax* were reared to treat 144,000 m^2 of breeding area in El Salvador. The necessary inoculum required the exposure of 1.6 million first-instar *Cx. quinquefasciatus* to 137 million preparasites (1 : 14 ratio) each week for 6 weeks. The system produced an average of 13.7 g (about 2000 g^{-1}) of postparasitic nematodes per rearing tray (20,000 mosquitoes), a total of 6392 g for the 6-week period and 435 cultures (Petersen *et al.*, 1978a).

B. *In Vitro* PROPAGATION

The main attribute of successful *in vitro* rearing systems is that they will permit the production of species not currently available by *in vivo* methods. Also, *in vitro* systems offer the potential for reduction of costs over *in vivo* systems, and better product standardization and formulation.

The development of a successful *in vitro* rearing system for mermithids has been slow because of a lack of readily available material. Consequently, most basic *in vitro* research has been done with *R. culicivorax*. Another major problem involves the nature of food ingestion in mermithids. Unlike most nematodes, mermithids lack a functional gut and must rely on transcuticular uptake of nutrients. Since these nematodes feed only during their parasitic phase while in the hemocoel of the host, nutritional products must be in a form that can be readily absorbed through a selective and delicate cuticle (Poinar and Hess, 1977; Rutherford and Webster, 1974). Thus, they are very sensitive to mechanical damage and to hypo- and hypertonic changes.

In initial studies with *R. culicivorax*, Sanders *et al.* (1973) reported growth of 1–4 mm in length after 15 days and 5–7 mm after 25 days and some stichosome and trophosome development when preparasites were placed in Schneider's *Drosophila* medium with 10% fetal calf serum at pH of 6.5–7.0 and 25°C. Growth rates were about one-third that of nematodes grown *in vivo*.

More recently, Castillo *et al.* (1982) tested more than 50 combinations of vertebrate and invertebrate tissue culture media and microbiological media. Slow growth and limited development of internal structures were obtained with various supplemented Grace's tissue culture media and Schneider's *Drosophila* media. Nematodes attained a stage of development after 3–4 weeks comparable to that attained in the host after 4–5 days.

The most successful attempts to rear *R. culicivorax in vitro* were reported by Finney (1981). She reported that the best results were obtained using Grace's medium containing 10% fetal calf serum at 26°C with osmotic pressure adjusted to 240 mOsm and pH 6.4–6.5. Slow growth of the nematodes occurred over a 6-week period during which only juvenile females developed, but storage material in the trophosome was lacking. Finney has since reduced the time to reach parasitic maturity to 3 weeks with the trophosome filled with material. However, she was still unable to produce male nematodes (Chapman and Finney, 1982).

In an important breakthrough, Fassuliotis and Creighton (1982) were successful in rearing *F. leipsandra*, a parasite of agricultural pests, *in vitro*. After unsuccessful attempts with several media, the researchers found that juveniles of *F. leipsandra* would develop to the postparasitic stage on Schneider's *Drosophila* medium containing fetal bovine serum. To complete the life cycle the nematodes had to be transferred to a solid substrate which preconditioned them and triggered the mechanism necessary for the final molt to the adult stage. *In vitro* development took about 1 week longer than the time it takes *F. leipsandra* to be reared *in vivo*. This accomplishment may aid greatly in determining if economical *in vitro* rearing methods for other mermithids are practical.

V. Field Studies

Mermithids have attracted considerable attention as potential biological control agents because they are readily apparent, often occur in high numbers in host populations, and almost always kill their host. However, because of the difficulty in mass culture, the manipulation of these nematodes for the control of host insect populations has developed slowly. The first recorded attempt to infect insects in nature occurred when a mermithid, later described as *O. muspratti*, was released in tree holes on Nauru Island in 1967 (Reynolds, 1972). Eight days after the release of an undetermined number of parasites, infected larvae of two species of mosquitoes were recovered. No further observations were recorded. About this time the initial releases with *R. culicivorax* were made in semipermanent freshwater habitats producing *Anopheles* mosquitoes as suggested by background research to be the most likely conditions for success. Preparasitic nematodes were applied 20 times by compressed-air sprayer to 10 sites at various dosage rates. Parasitism ranged from 14 to 100% with dosage rates of 1000 m^{-2} and resulted in 94% parasitism of second-instar *Anopheles* larvae and 64% parasitism of all *Anopheles* sampled (Petersen and Willis, 1972b). *Romanomermis culicivorax* recycled in at least 7 of the 10 treated habitats during the breeding season.

Although this initial release left many questions unanswered, it established several important principles in the use of mermithids for control of native host populations. The study established that (1) the preparasitic stage of *R. culicivorax* could be easily applied by using a compressed-air sprayer commonly used for pesticidal application; (2) *R. culicivorax* readily parasitized larval stages of *Anopheles* mosquitoes, and high levels of parasitism could be achieved; and (3) the nematode readily establishes itself and recycles for indefinite periods in certain habitats.

In a follow-up to the initial release study, 23 semipermanent to permanent *Anopheles* habitats were treated 15 times at 836 m^{-2} and 15 at 1673 m^{-2} (Petersen and Willis, 1974a). Seven of the 15 habitats treated at 836 preparasites m^{-2} resulted in >80% parasitism, and 10 of 13 sites treated at 1673 preparasites m^{-2} resulted in >90% parasitism of all hosts collected. One habitat, although possessing the apparent suitable environmental characteristics, consistently produced lower than expected parasitism (three treatments) for unknown reasons. Later, it was shown that some microcrustaceans are predacious on preparasitic *R. culicivorax* (Platzer and MacKenzie-Graham, 1978). The habitat was permanent and heavily shaded, and probably had a comparatively high microcrustacean population.

Limited releases were made in rice fields in California against *Culex tarsalis* and *Anopheles freeborni*. Again preparasitic nematodes were re-

leased by means of a compressed-air hand sprayer. *Culex tarsalis* was not parasitized but results were inconclusive because of low and clumped host populations. However, 50 and 80–85% of the *An. freeborni* were parasitized at application rates of 418 and 836 preparasites m^{-2}, respectively, despite heavy masses of floating vegetation (Petersen *et al.*, 1972).

Releases of *R. culicivorax* in rice field plots in Louisiana resulted in 38% parasitism of *Psorophora columbiae* at rates of 1213 preparasites m^{-2}. It was estimated that 3262 preparasites m^{-2} would be required to produce >95% in early instars of this species. Similarly, 61% of *An. quadrimaculatus* were parasitized at 606 preparasites m^{-2} and an estimated 1087 preparasites m^{-2} would be required to produce >95% parasitism of this species (Petersen *et al.*, 1973).

Additional relatively successful releases of *R. culicivorax* were made in Florida. Levy and Miller (1977b) achieved 37 and 54% parasitism of *Cx. quinquefasciatus* in two abandoned sewage settling tanks at parasite–host ratios of 3.5 : 1 (6400 preparasites m^{-2}) and 4.6 : 1 (11,000 preparasites m^{-2}), respectively. Releases of *R. culicivorax* in grass fields containing potholes, ditches, and low areas periodically flooded by rainfall resulted in 97% parasitism of first- to fourth-instar larvae of four mosquito species at a dosage rate of 360 preparasites m^{-2}. This is perhaps the most effective field trial reported when considering the host species and parasite dosage rate (Levy and Miller, 1977c).

Levy *et al.* (1979) also studied the feasibility of aerial application of *R. culicivorax* to control mosquitoes. They applied preparasites of *R. culicivorax* via helicopter using standard insecticide spray equipment at a rate of 4692 m^{-2} of water surface to three ponds. A mean of 52, 67, and 44% of the *Anopheles* spp. and 39, 40, and 53% of *Culex erraticus* were parasitized from the three ponds, respectively. This study, though limited in scope, demonstrated that preparasites could survive aerial application and that mosquito habitats could be quickly and effectively treated in this manner.

Otieno (1977) achieved 70–97% control of *An. freeborni* in a California lake by treating areas ranging from 15 to 149 m^2 at a dosage rate of 1200 preparasites m^{-2}. Brown *et al.* (1977) conducted field tests against four species of mosquito larvae in three natural and two artificial sites in California. All species of mosquitoes were infected and the percentage infection was dependent on the mosquito subfamily, application rate, and test site. In mixed populations anophelines were more susceptible to parasitism than culicines. Limited field trials have been made in the People's Republic of China with the recently described species *R. jingdeensis*. Preparasites introduced into three ponds at rates of 1000, 2000, and 3000 m^{-2} of surface area produced levels of parasitism of 40, 59, and 50%, respectively, in *An. sinensis* (Anonymous, 1982).

In the largest field trial to date, Petersen *et al.* (1978b) treated a band of floating surface vegetation (total area 10,700 m^2) around the margins of a lake in El Salvador to control *Anopheles albimanus* and *Anopheles pseudopunctipennis*. Parasitism averaged 58% for 11 treatments and varied greatly from treatment to treatment and from site to site. However, three applications made during evening hours to avoid wind and wave action on the lake produced an average 86% parasitism. No significant differences in susceptibility to *R. culicivorax* were found between instars or between species. Though the parasitism averaged about 60% of the desired level, *Anopheles* populations dropped from more than 10 per dip at the beginning of the 6-week release program to 0.6 per dip at the end of the release period (a 94% reduction). This study was the first successful attempt to control mosquitoes on a large scale by using a parasite or pathogen. In a follow-up study, Willis *et al.* (1980) again treated the lake on two occasions in the evening at a dosage rate of 3600 preparasites m^{-2} and obtained levels of parasitism exceeding 95%.

During the releases in El Salvador, wind was determined to be an important factor and was not initially considered to be a potential problem. The five releases made in the evening to avoid the wave action on the lake averaged >90% parasitism of the *Anopheles* spp. This was much higher than the 46% parasitism achieved during the eight midday treatments. About 2 hours elapsed between the time of the midday treatments and the start of the wind and wave action which lasted about 4 hours daily. In contrast, there was about 20 hours between the early evening treatments and the beginning of turbulence the next day.

During their studies Willis *et al.* (1980) also treated coastal freshwater pastures, roadside ditches, ponds, and swamps containing larval populations of *An. albimanus*. The sites ranged in size from 21 to 450 m^2 and dosage rates ranged from 2400 to 4800 preparasites m^{-2}. Parasitism averaged >95% for 22 treatments. The authors mentioned that the determined levels of parasitism were undoubtedly lower than those actually obtained because multiple parasitism is often lethal to first-instar mosquitoes and because the small day-old preparasites are easily overlooked during dissections of host larvae, particularly in fourth-instar hosts.

Most field tests with *R. culicivorax* have been made using the preparasitic stage because of the ease of handling and dispersal. However, the successful use of preparasites of *R. culicivorax* required careful timing when used to control floodwater mosquitoes, because of the rapid growth of the potential hosts and decreased susceptibility with age. Thus, studies have been made to measure the effectiveness of releases of the postparasitic stage of *R. culicivorax* and allowing them to mature in the environment to provide a synchronized hatching of nematode and mosquito eggs in temporary habitats, or to produce a continuous hatch of maturing nematode eggs in semipermanent water habitats.

Petersen and Willis (1972b) first introduced the postparasitic stage of *R. culicivorax* into three *Anopheles* habitats in Louisiana and produced long-term levels of parasitism with monthly averages of 20–24% and monthly highs up to 100%. In a second study, Petersen and Willis (1976) released 15 g of postparasites into each of six pastures or open grassy areas and 11 woodland mosquito breeding sites when the sites were free of water but still damp. Significant levels of parasitism were achieved when cultures were placed in damp habitats possessing adequate vegetation or organic debris and were subject to minimum flushing action when flooded. Fifty-two percent of *Aedes atlanticus*, 59% of *Aedes tormentor*, 38% of *Ps. columbiae*, and 15% of *Psorophora howardii* were parasitized in 39 larval collections from 13 habitats. Some sites produced substantial levels of parasitism 14–18 weeks after release. The study demonstrated that introduction of postparasites permitted the synchronous hatching of the eggs of the parasite and hosts and more effective control of floodwater mosquitoes.

The most effective release of postparasites of *R. culicivorax* was reported by Brown-Westerdahl *et al.* (1982). They introduced postparasites into early season rice fields in California and demonstrated that the nematodes could mature to adults, mate, and lay eggs in the rice field environment. This method provided continuous partial control of larvae of *An. freeborni* and *Cx. tarsalis* throughout the rice growing season. The mean weekly infection level for both species exceeded 60%. Surprisingly the nematodes survived chemical application, drying, harvest, winter, and cultivation and successfully parasitized mosquitoes the following summer.

Established populations of *R. culicivorax* were observed in many of the sites treated in the early 1970s in Louisiana. Three of five sites treated in 1971 and five of six sites treated in both 1971 and 1973 produced levels of parasitism from 2 to 52% in *An. crucians* in 1974. Also, five of 12 sites treated in 1973 produced *An. crucians* with levels of infection ranging from 11 to 85% throughout 1974. One site treated in 1973 produced 100% parasitism for 14 weeks and 94% parasitism for the year in third and fourth instar hosts (Petersen and Willis, 1975). Though these studies have shown *R. culicivorax* to have potential as a biological control agent when used properly, other studies have shown it to be ineffective when applied to incompatible environments or against unsuitable hosts.

As early as 1973, Mitchell *et al.* (1974) demonstrated that *R. culicivorax* was ineffective against *Cx. quinquefasciatus* (*fatigans*), *Culex t. summorosus*, and *Anopheles sinensis* under the conditions imposed. The authors concluded that reduced water temperatures and possibly a predacious ostracod reduced the effectiveness of the nematode against the *Culex* species and that *An. sinensis* was physiologically resistant to *R. culicivorax*. Chapman *et al.* (1972) treated polluted drains and ditches in

Bangkok, Thailand, with preparasites of *R. culicivorax* for the control of *Cx. quinquefasciatus* (*fatigans*). Dosage rates up to 252,000 m^{-2} resulted in parasitism of only 0–21% and no evidence of reduction of the host population or recycling of the parasite. It has since been established that organically polluted environments are inhibitory to the preparasitic stage.

Galloway (1975) attempted to control early spring *Aedes* mosquitoes in Canada with *R. culicivorax*. Dosage rates of 20,000 preparasites m^{-2} resulted in no parasitism of *Aedes dorsalis* and *Aedes spencerii* and >20% in *Aedes sticticus*. The author attributed this failure to the low habitat temperatures. During the same study Galloway attempted to control *Ae. vexans* during warmer weather. Dosage rates of 50,000 preparasites m^{-2} resulted in only 48% parasitism. Again, a problem of using an incompatible host resulted in lower than expected levels of parasitism.

In additional studies in Canada, Galloway and Brust (1976) reported that temperature was the primary factor limiting infection by *R. culicivorax* in mosquito larvae developing in snowmelt pools. Less than 20% parasitism was obtained in *Aedes* mosquitoes at dosage rates of 50,000 preparasites m^{-2}.

In tests in California against the pasture mosquito *Aedes nigromaculis*, different problems were encountered (Hoy and Petersen, 1973). Application of the preparasites directly to the flooded pastures gave poor results and only pooled water at the end of fields produced significant levels of parasitism. The practice of continually running water through the pastures during the irrigation period effectively removed the nondirectional free-swimming preparasites but did not effect the mosquito populations.

In a recent study, Dhillon *et al.* (1980) applied *R. culicivorax* to cemetery vases in California to control mosquito breeding. At a parasite–host ratio of 20 : 1, only 30% of the *Cx. quinquefasciatus* and 11% of *Culiseta incidens* larvae were infected. The low levels of parasitism were probably due to the low oxygen tension and high conductivity of the water in the vases. Table 1 lists and summarizes chronologically the attempts to control field populations of mosquitoes with *R. culicivorax*.

Limited field studies have been conducted with other species of mermithids because of the difficultly in obtaining sufficient material. Petersen and Willis (1974b) collected populations of *Anopheles* mosquitoes parasitized with *S. peterseni* (*Diximermis peterseni*), and introduced them into a natural pond. The release of 2300 *Anopheles* (85–90% infected) during January through March produced 12–100% parasitism during the 8-month breeding season the following September through March. During the same period the next year parasitism averaged 88% in *Anopheles* spp. Parasitism remained high during the winter months (Louisiana) for the next 8 years (unpublished data). *Strelkovimermis peterseni* usually produces high levels of parasitism in *Anopheles* mosquitoes where it is estab-

TABLE 1

Chronological list of experimental releases of R. culicivorax *to control field populations of mosquitoes*

Location	Year	Area treated	Dosage (m^2)	Host species	(%) Parasitism	Reference
Louisiana	1970	11 ponds	180–14,700	*Anopheles* spp.	14–100	Petersen and Willis (1972a)
California	1971	Rice fields	418	*Cx. tarsalis*	0	Petersen *et al.* (1972)
			418	*An. freeborni*	50	
			836		80–85	
Taiwan	1971	Four small ponds	35,000	*Cx. quinquefasciatus*	0–5	Mitchell *et al.* (1974)
		Two small pools	90,000	*Cx. t. summorosus*	0–1	
		Edge of rice paddy	4,000	*Culex* spp.	0	
California	1972	Pastures		*Ae. nigromaculis*	0–57	Hoy and Petersen (1973)
Louisiana	1972	Experimental rice plots	150–1213	*Ps. columbiae*	6–38	Petersen *et al.* (1973)
			150–606	*An. quadrimaculatus*	16–61	
Thailand	1972	Ditches and drains	18,000	*Cx. quinquefasciatus*	0–3	Chapman *et al.* (1972)
			90,000–180,000		0–27	
Louisiana	1973	Edges of 23 ponds	836	*An. crucians*	76 (52–100)	Petersen and Willis (1974a)
			1673		85 (36–100)	

TABLE 1 (*continued*)

Location	Year	Area treated	Dosage (m^2)	Host species	(%) Parasitism	Reference
Manitoba	1974	Three pools	20,000	*Ae. dorsalis*	0	Galloway (1975)
				Ae. spencerii	0	
		Two artificial pools	10,000	*Ae. sticticus*	<20	
			20,000		<20	
		Three artificial pools	10,000	*Ae. vexans*	0–36	
			20,000		4–46	
			50,000		0–48	
Taiwan	1974	Pool	2,000	*Cx. quinquefasciatus*	68	Chen (1976)
			1,000 postparasites		0	
Louisiana	1975	Open pastures	15 g postparasites	*Ae. atlanticus*	33 (0–67)	Petersen and Willis (1976)
				An. crucians	68 (0–100)	
				Ps. ciliata	20 (0–100)	
				Ps. columbiae	38 (12–72)	
		Woodland pools	15 g postparasites	*Aedes* spp.	49 (0–100)	
				An. crucians	83 (50–100)	
				Ps. howardii	51 (0–100)	

Maryland	1975	Ditches	560	*Anopheles, Culex* spp.	92	Nickle (1979)
Manitoba	1975–1976	Woodland pools	50,000	*Ae. communis, Ae. pionips*	0–32	Galloway and Brust (1976)
California	1975–1976	Artificial ponds	1,000	*An. franciscanus*	67, 88	Brown *et al.* (1977)
			10,000		83	
			25,000		100	
			1,000	*Cx. tarsalis*	10–20	
			5,000		24	
			10,000		57	
			25,000		62	
			1,000	*Cs. inornata*	22	
			10,000		56	
			25,000		58	
		Natural ponds	1,070	*An. franciscanus*	29	
		Rice fields	706	*An. freeborni*	85	
			1,280		36–49	
California	1976	Ponds and lake edge	1,200	*An. freeborni*	70–97	Otieno (1977)
Florida	1976	Sewage settling	6,400	*Cx. quinquefasciatus*	37	Levy and Miller (1977b)
		Tanks			54	
Florida	1976	Grassy field	360	*Ps. columbiae, Ps. ciliata, Cx. nigripalpus,* and *Ae. taeniorhynchus*	97 (88–100)	Levy and Miller (1977c)

TABLE 1 (*continued*)

Location	Year	Area treated	Dosage (m^2)	Host species	(%) Parasitism	Reference
El Salvador	1977	Edges of large lake	2,400 3,000 3,600 4,200 4,800	*An. albimanus* and *An. pseudopunctipennis*	63 (13–88) 63 (9–100) 50 (17–95) 87 (80–94) 53 (7–92)	Petersen *et al.* (1978b)
El Salvador	1977–1978	Miscellaneous breeding sites and edge of large lake	2400–4800	*An. albimanus* and *An. pseudopunctipennis*	96 (74–100)	Willis *et al.* (1980)
California	1977–1978	Rice field	15,000 postparasites	*An. freeborni* *Cx. tarsalis*	69 (0–100) 65 (0–100)	Brown-Westerdahl *et al.* (1982)
Florida	1978	Artificial ponds	4,629	*An. quadrimaculatus* and *An. crucians* *Cx. erraticus*	54 (44–67) 44 (39–53)	Levy *et al.* (1979)
Tokelau Islands	1978	Tree holes Water drums	10–15 : 1 parasite–host ratio	*Ae. polynesiensis* *Ae. aegypti*	3 32	Laird *et al.* (1982)
California	1979	Cemetery vases	20 : 1 parasite–host ratio	*Cx. quinquefasciatus* *Cs. incidens*	30 11	Dhillon *et al.* (1980)

lished. This nematode apparently has a strong potential for recycling but has not been extensively tested because of problems associated with its mass production.

Limited releases of *R. iyengari,* a mermithid similar in morphology and biology to *R. culicivorax,* was released in cesspools and soak pits in Pondicherry, India. Dosage rates of 1172–312,000 preparasites m^{-2} resulted in only one parasitized *Cx. quinquefasciatus* from habitats examined during the 3 weeks following treatments (Gajanana *et al.,* 1978). This failure was subsequently attributed to the environmentally adverse physicochemical conditions prevailing in the breeding sites (Bheema Rao *et al.,* 1979).

In the only field trial with mermithids to control a host population other than mosquitoes, Molloy and Jamnback (1977) released preparasites of *M. flumenalis* against backfly larvae in a small stream in New York. The preparasites for the study were obtained by collecting naturally infected hosts, collecting the postparasites as they emerged, and allowing them to mature, mate, and lay eggs. Approximately 1.5 million preparasites of *M. flumenalis* were released into the stream over a 4-day period and resulted in infection rates up to 71%. The preparasite density and blackfly infection rate decreased progressively below the point of introduction. A substrate density of 0.7 preparasites cm^{-2} was required to achieve a 50% parasitism rate for *Simulium venustum.* Since blackfly mermithids could not be mass reared in the laboratory, the author concluded that the cost for production of preparasites is at present too great even for intermediate stage field trials.

VI. Potential and Future

A. Status

Extensive nematode research has been conducted in the past 15 years with a small number of mermithid species resulting in greatly expanded knowledge of this group of potential biological control agents. The potential of most of these parasites remains in question because of the difficulty in obtaining sufficient numbers of nematodes for field testing. This is especially true for the terrestrial mermithids.

At present, essentially all of the available information relating to use of mermithids for the control of insects has been generated from studies with *R. culicivorax.* Thus, *R. culicivorax* serves as a model system for other aquatic mermithid species as their mass production systems are developed. Studies with this species have shown the potential for either inundative control systems, that is, the release of infective stages in sufficient

numbers to give immediate control of mosquito populations, or inoculative control, that is, the introduction of the postparasitic stage or reduced numbers in the preparasitic stage to establish the nematode population in the environment to give partial control for an indefinite period. Studies with *R. culicivorax* have also demonstrated the limitations associated with the use of agents of this type. As living organisms, a knowledge of limiting physical and chemical factors is essential if the parasite is to be effectively used. Without this knowledge potentially effective agents may be discarded because they were used in environments outside their limits of tolerance.

One attractive characteristic of mermithids is their safety for nontarget organisms, but, because of this, it is important to know the host specificity of the parasite and to be sure that the intended host system is compatible with the parasite. Mermithids may be species specific (i.e., *P. culicis*), generically specific (i.e., S. peterseni), generally family specific (i.e., *O. muspratti, R. culicivorax*) or may have a broad host range over several orders (i.e., *M. nigrescens*). However, as with *R. culicivorax* which parasitizes many mosquito species, the host species still vary greatly in their susceptibility. Studies with *R. culicivorax* have also demonstrated the importance of timing of application, and that it is essential that the parasite–host systems be synchronized for effective control.

Hominick and Tingley (1984) discussed the theoretical problems associated with (1) density–dependent parasite reproduction (i.e, sex ratios, fecundity, nutritional stress, and postparasite densities), (2) distribution of parasite numbers per host, (3) density of host populations, (4) pathogenicity of the parasites, (5) reproduction of the parasites and their hosts, and (6) predation. They concluded that mermithid populations are controlled by such tight density-dependent constraints that they can cause at most only moderate depressions of their host populations, and that mermithids are unlikely to be useful in biological control programs aimed at providing effective long-term control of hosts with single introduction of the parasite. These works clearly point out the complexity of these biological control systems and the need for extensive background data for each parasite species in order to develop effective control strategies.

The key to success with any biological control agent lies first with sufficient material for study and field testing, and second with availability of quantities of the agent to permit host control beyond the research stage.

B. COMMERCIAL DEVELOPMENT

Mermithids (especially *R. culicivorax*) have drawn attention because they possess the following characteristics of an ideal biological control

agent: (1) they are host specific to one or a few species of hosts; (2) parasitism is usually lethal to host; (3) they are generally easy to manipulate in the laboratory; (4) some can be mass produced; (5) they are easily disseminated in the environment with standard pesticide application techniques; (6) they have the potential for establishment and recycling and give control for extended periods; and (7) they present no environmental threat.

Conversely, many of the desired characteristics of these agents make them unattractive for commercial development. For example, host specificity, a characteristic that gives mermithids a unique advantage over chemical pesticides, also limts their usefulness, to at most, only a few target insects. This means that the total product volume sold per year will be considerably less than would be sold if the product were applicable to a range of pests. Also, other characteristics such as the potential for establishment and recycling further threaten to reduce the potential market for a mermithid product in the eyes of prospective producers. In addition, the problems of environmental limitations on the mermithid further reduce the potential effective use of a given mermithid species.

Additional factors make production of mermithids a risky commercial enterprise. First, mermithids are living organisms. To keep them alive, one must maintain favorable environmental conditions. Shipping and storage of biological agents are major problems for any producer. Second, the people who will use mermithids must be trained and develop some degree of skill in application. Biologicals cannot be frozen, cooked, ground to pieces, or stored on a shelf for years (Petersen and Cupello, 1981).

These problems are academic if economical methods of production cannot be developed for desired mermithid species. At present only *R. culicivorax* can be produced economically. In the past, commercial production of *R. culicivorax* was undertaken by two companies. The first company entered the market place before serious problems with handling and shipping had been adequately studied and they were forced to stop production for economic reasons. A second and larger company became interested in *R. culicivorax* because of its control potential and ease of production, and because it was exempt from costly regulatory registration. The company allocated 2 years of effort (6 person years) for development of this nematode into a commercial product. They developed efficient and less costly *in vivo* rearing techniques and developed a shipping container that would keep the nematode eggs viable during transportation and storage (Cuppello *et al.*, 1982). Just prior to test marketing of the new product the company changed direction and discontinued all marketing studies on this and other biological agents. Although this work established that a marketable product could be developed and that *R. culicivorax* had

market potential, the limited market evidently puts production economics outside the interests of large manufacturers. Thus, the future for these types of biological control agents probably lies with small corporations or partnerships or with government-subsidized production systems.

C. PROSPECTS FOR THE FUTURE

Mermithid species appear attractive as biological control agents but most remain untested. Because most can be reared only by *in vivo* methods, and the hosts have long life cycles or cannot be maintained under laboratory conditions, these mermithids will remain unstudied and untested until satisfying *in vitro* rearing methods can be developed. The recent development of an *in vitro* system for the terrestrial mermithid *F. leipsandra* (Fassuliotis and Creighton, 1982) may serve as a model system for at least a few of the terrestrial mermithid species.

If and when these mermithids are successfully brought to the state of the art presently held by *R. culicivorax*, they will undoubtedly confront the same road blocks to commercialization encountered with *R. culicivorax*. The characteristics of the true biologicals make them unattractive to commercial producers; coupled with the previously mentioned environmental limitations, special training needed by users and the lack of patent protections associated with these agents will continue to discourage the research and development needed to put these agents on the market.

As things now stand, we still await the success of the first truly effective commercially available product that will demonstrate the feasibility of mermithids as biological control agents for insect control. It appears, that as mermithids are developed to the stage presently held by *R. culicivorax*, they will be placed "on the shelf" until such time as the need for such biological control provides small business with the incentive to make them available for general use.

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REFERENCES

Anonymous. (1978). Pathogens and parasites. *Vector Control Research Center, Pondicherry. Indian Council of Medical Research, Annual Report*, pp. 68–83.

Anonymous. (1982). Annual report July 1981–June 1982. *Institute of Parasitic Diseases, Chinese Academy of Medical Science, Shanghai*, pp, 38–39.

Bailey, C. H, and Gordon, R. (1973). Histopathology of *Aedes aegypti* (Diptera: Culcidae) larvae parasitized by *Reesimermis nielseni* (Nematoda: Mermithidae). *Journal of Invertebrate Pathology* **22,** 435–441.

Bheema Rao, U. W., Gajanana, A., and Rajagopalan, P. K. (1979). A note on the tolerance of the mermithid nematode, *Romanomermis* sp., to different pH and salinity. *Indian Journal of Medical Research* **69,** 423–427.

Brown, B. J., and Platzer, E. G. (1974). The effect of temperature, light, larval age and exposure time on the infectivity of preparasitic larvae of *Reesimermis nielseni*. *Journal of Nematology* **6,** 137.

Brown, B. J., and Platzer, E. G. (1977). The effects of temperature on the infectivity of *Romanomermis culicivorax*. *Journal of Nematology* **9,** 166–72.

Brown, B. J., and Platzer, E. G. (1978a). Salts and the infectivity of *Romanomermis culicivorax*. *Journal of Nematology* **10,** 53–64.

Brown, B. J., and Plazter, E. G. (1978b). Oxygen and the infectivity of *Romanomermis culicivorax*. *Journal of Nematology* **10,** 110–113.

Brown, B. J., and Platzer, E. G., and Hughes, D. S. (1977). Field trials with the mermithid nematode *Romanomermis culicivorax*, in California. *Mosquito News* **37,** 603–608.

Brown-Westerdahl, B., Washino, R. K., and Platzer, E. G. (1982). Successful establishment and subsequent recycling of *Romanomermis culicivorax* (Mermithidae: Nematoda) in a California rice field following postparasite application. *Journal of Medical Entomology* **19,** 34–41.

Castillo, J. M., Chin, P., and Robert, D. W. (1982). Growth and development of *Romanomermis culicivorax* Ross and Smith *in vitro*. *Journal of Nematology* **14,** 476–485.

Chapman, H. C., and Finney, J. R. (1982). Mass production of mermithid and steinernematid nematodes with vector control potential. *Proceedings International Colloquium on Invertebrate Pathology, Brighton* **3,** 358–362.

Chapman, H. C., Pant, C. P., Mathis, H. L., Nelson, M. J., and Phantomochinda, B. (1972). Field releases of the nematode *Reesimermis nielseni* for the control of *Culex p. fatigans* in Bangkok, Thailand. *World Health Organization, VBC* **412,** 1–7.

Chen, P. S. (1976). A study of *Reesimermis nielseni* for control of *Culex pipiens fatigans* in Taiwan. *Bulletin of the Institute of Zoology Academia Sinica* **15,** 21–28.

Christie, J. R. (1936). Life history of *Agamermis decaudata*, a nematode parasite of grasshoppers and other insects. *Journal of Agricultural Research* **52,** 161–198.

Christie, J. R. (1937). *Mermis nigrescens*, a nematode parasite of grasshoppers. *Journal of Agricultural Research* **55,** 353–364.

Colbo, M. H., and Porter, G. N. (1980). Distribution and specificity of Mermithidae (Nematoda) infecting Simuliidae (Diptera) in Newfoundland. *Canadian Journal of Zoology* **44,** 911–921.

Condon, W. J., and Gordon, R. (1977). Effects of the mermithid nematode *Mermis nigrescens* on the levels of hemolymph and fecal uric acid in its host, the migratory locust *Locusta migratoria*. *Canadian Journal of Zoology* **55,** 690–692.

Craig, S. M., and Webster, J. M. (1974). Inhibition of molting of the desert locust, *Schistocerca gregaria*, by the nematode *Mermis nigrescens*. *Canadian Journal of Zoology* **52,** 1535–1539.

Creighton, C. S., and Fassuliotis, G. (1981). A laboratory technique for culturing *Filipjevimermis leipsandra*, a nematode parasite of *Diabrotica balteata* larvae. *Journal of Nematology* **13,** 226–227.

Creighton, C. S., and Fassuliotis, G. (1982). Mass rearing a mermithid nematode, *Filipjevimermis leipsandra* (Mermithida: Mermithidae) on the banded cucumber beetle (Coleoptera: Chrysomelidae) *Journal of Economic Entomology* **75,** 701–703.

Cupello, J. M., Petersen, J. J., and Chauthani, A. R. (1982). An improved method for long-distance shipping the mosquito parasite *Romanomermis culicivorax*. *Journal of Nematology* **14,** 121–125.

Curran, J. (1981). Morphological variations in aquatic mermithids. *Journal of Nematology* **13,** 434.

Curran, J., and Hominick, W. M. (1980). Effect of mounting methods on taxonomic characters of adult male mermithids (Nematoda: Mermithidae). *Nematologica* **26,** 455–466.

Cuthbert, F. P., Jr. (1968). Bionomics of a mermithid (Nematode) parasite of soil-inhabiting larvae of certain chrysomelids (Coleptera). *Journal of Invertebrate Pathology* **12,** 283–287.

Dhillon, M. S., Mulla, M. S., and Platzer, E. G. (1980). Evaluation of the nematode *Romanomermis culicivorax* against cemetery mosquitoes. *Mosquito News* **40,** 531–535.

Fassuliotis, G., and Creighton, C. S. (1982). *In vitro* cultivation of *Filipjevimermis leipsandra. Journal of Nematology* **14,** 126–131.

Finney, J. R. (1975). The penetration of three simuliid species by the nematode *Reesimermis nielseni. Bulletin of the World Health Organization* **52,** 235.

Finney, J. R. (1981). Mermithid nematodes: *In vitro* culture attempts. *Journal of Nematology* **13,** 275–280.

Finney, J. R., and Mokry, J. E. (1980). *Romanomermis culicivorax* and simuliids. *Journal of Invertebrate Pathology* **35,** 211–213.

Finney, J. R., Gordon, R., Condon, W. J., and Rusted, T. N. (1977). Laboratory studies on the feasibility of integrated mosquito control using an insect growth regulator and a mermithid nematode. *Mosquito News* **37,** 6–11.

Frohne, W. C. (1955). News and notes. *Mosquito News* **15,** 125.

Gajanana, A., Kazini, S. J., Bheema Rao, U. S., Suguna, S. G., and Chandrahas, R. K. (1978). Studies on a nematode parasite (*Romanomermis* sp.: Mermithidae) of mosquito larvae isolated in Pondicherry. *Indian Journal of Medical Research* **68,** 242–247.

Galloway, T. D. (1975). Application of a mermithid nematode (*Reesimermis nielseni* Tsai and Grundmann) from Louisiana for mosquito control in Manitoba. *Proceedings of the Alberta Mosquito Abatement Symposium, University Alberta* pp. 191–205.

Galloway, T. D., and Brust, R. A. (1976). Field application of the mermithid nematode, *Romanomermis culicivorax* Ross and Smith, for the control of mosquitoes, *Aedes* spp., in spring in Manitoba. *Manitoba Entomologist* **10,** 18–25.

Galloway, T. D., and Brust, R. A. (1977). Effects of temperature and photoperiod on the infection of two mosquito species by the mermithid, *Romanomermis culicivorax. Journal of Nematology* **9,** 218–21.

Galloway, T. D., and Brust, R. A. (1979). Review of the genus *Romanomermis* (Nematoda: Mermithidae) with a description of *R. communensis* sp. n. from Canada. *Canadian Journal of Zoology* **57,** 281–289.

Gaugler, R., Wraigth, S., and Molloy, D. (1984). Bionomics of a mermithid parasitizing snowpool *Aedes* spp. mosquitoes. *Canadian Journal of Zoology* **62,** 670–674.

Gordon R. (1981). Mermithid nematodes: Physiological relationships with their insect hosts. *Journal of Nematology* **13,** 266–273.

Gordon, R., and Webster, J. M. (1971). *Mermis nigrescens*: Physiological relationship with its host, the adult desert locust *Schistocerca gregaria. Experimental Parasitology* **29,** 66–79.

Gordon, R., Bailey, C. H., and Barber, J. M. (1974). Parasitic development of the mermithid nematode *Reesimermis nielseni* in the larval mosquito *Aedes aegypti. Canadian Journal of Zoology* **52,** 1293–1302.

Gordon, R., Condon, W. J., Edgar, W. J., and Babie, S. J. (1978). Effects of mermithid parasitism on the hemolymph composition of the larval blackflies *Prosimulium mixtum/fuscum* and *Simulium venustum. Parasitology* **77,** 367–374.

Gordon, R., Finney, J. R., Condon, W. J., and Rusted, T. N. (1979). Lipids in the storage organs of three mermithid nematodes and in the hemolymph of their hosts. *Comparative Biochemical Physiology* **64B,** 369–374.

Harlos, J., Brust, R. A., and Galloway, T. D. (1980). Observations on a nematode parasite of *Aedes vexans* (Diptera: Culicidae) in Manitoba. *Canadian Journal of Zoology* **58,** 215–220.

Hominick, W. M., and Tingley, G. A. (1984). Mermithid nematodes and the control of insect vectors of human disease. *Biocontrol News and Information* **5,** 7–20.

Hoy, J. B., and Petersen, J. J. (1973). Fish and nematodes—current status of mosquito control techniques. *Proceedings of the California Mosquito Control Association* **41,** 49–50.

Ignoffo, C. M., Biever, K. D., Johnson, W. W., Sanders, H. O., Chapman, H. C., Petersen, J. J., and Woodard, D. B. (1973). Susceptibility of aquatic vertebrates and invertebrates to the infective stage of the mosquito nematode *Reesimermis nielseni*. *Mosquito News* **33,** 599–602.

Ignoffo, C. M., Petersen, J. J., Chapman, H. C., and Novoty, J. F. (1974). Lack of susceptibility of mice and rats to the mosquito nematode *Reesimermis nielseni* Tsai and Grundmann. *Mosquito News* **34,** 425–428.

Johnson, A. A. (1955). "Life History Studies on *Hydromermis contorta*, a Nematode Parasite of *Chironomus plumosus* (L.)." Ph.D. thesis, University of Illinois, Urbana.

Kurihara, T. (1976). Population behavior of *Reesimermis nielseni*, a nematode parasite of mosquitoes, with notes on the attraction of infective stage nematodes by mosquito larvae. *Culex pipiens molestus*. *Japanese Journal of Parasitology* **25,** 8–16.

Laird, M., Urdang, J., and Tinielu, I. (1982). Establishment and long-term survival of *Romanomermis culicivorax* in mosquito habitats, Tokelau Islands. *Mosquito News* **42,** 86–92.

Levy, R., and Miller, T. W., Jr. (1977a). Susceptibility of the mosquito nematode *Romanomermis culicivorax* (Mermithidae) to pesticides and growth regulators. *Environmental Entomology* **6,** 447–448.

Levy, R., and Miller, T. W., Jr. (1977b). Experimental release of a mermithid to control mosquitoes breeding in sewage settling tanks. *Mosquito News* **37,** 410–414.

Levy, R., and Miller, T. W., Jr. (1977c). Experimental release of *Romanomermis culicivorax* (Mermithidae: Nematoda) to control mosquitoes breeding in southwest Florida. *Mosquito News* **37,** 483–486.

Levy, R., Hertlein, B. C., Petersen, J. J., Doggett, D. A., and Miller, T. W., Jr. (1979). Aerial application of *Romanomermis culicivorax* (Mermithidae: Nematoda) to control *Anopheles* and *Culex* mosquitoes in southwest Florida. *Mosquito News* **39,** 20–25.

Mitchell, C. J., Chen, P., and Chapman, H. C. (1974). Exploratory trials utilizing a mermithid nematode as a control agent for *Culex* mosquitoes in Taiwan. *Journal of the Formosan Medical Association* **73,** 241–254.

Molloy, D. P. (1981). Mermithid parasitism of black flies (Diptera: Simuliidae). *Journal of Nematology* **10,** 250–256.

Molloy, D. and Jamnback, H. (1975). Laboratory transmission of mermithids parasitic in blackflies. *Mosquito News* **35,** 337–342.

Molloy, D., and Jamnback, H. (1977). A larval black fly control field trial using mermithid parasites and its cost implication. *Mosquito News* **37,** 104–108.

Mongkolkiti, S., and Hosford, R. M. (1971). Biological control of the grasshopper *Hesperotettix viridis pratensis* by the nematode *Mermis nigrescens*. *Journal of Nematology* **3,** 356–363.

Muspratt, J. (1947). The laboratory culture of a nematode parasite of mosquito larvae. *Journal of the Entomological Society of South Africa* **10,** 131–132.

Nickle, W. R. (1972). A contribution to our knowledge of the Mermithidae (Nematoda). *Journal of Nematology* **4,** 113–146.

Nickle, W. R. (1979). Probable establishment and overwintering of a mermithid nematode parasite of mosquitoes in Maryland. *Proceedings of the Helminthological Society of Washington* **46,** 21–27.

Nolan, R. A. (1977). Physiological studies with the aquatic hyphomycetes *Pleuropedium tricladioides* isolated from the fresh water nematode *Neomesomermis flumenalis*. *Mycologia* **69,** 914–926.

Otieno, W. A. (1977). "The Pathology and Host-Parasite Relationship of the Entomogenous Nematode *Romanomermis culicivorax* Ross and Smith (Mermithidae) in a Mosquito Host *Culex pipiens* Say (Culicidae): Its Application in Integrated Control." Ph.D. thesis, University of California, Berkeley.

Petersen, J. J. (1973a). Relationship of density, location of hosts, and water volume to parasitism of larvae of the southern house mosquito by a mermithid nematode. *Mosquito News* **33,** 516–520.

Petersen, J. J. (1973b). Role of mermithid nematodes in biological control of mosquitoes. *Experimental Parasitology* **33,** 239–247.

Petersen, J. J. (1977). Biology of *Octomyomermis muspratti*, a parasite of mosquitoes, as it relates to mass production. *Journal of Invertebrate Pathology* **30,** 155–159.

Petersen, J. J. (1978a). Development of resistance by the southern house mosquito to the parasitic nematode *Romanomermis culicivorax*. *Economic Entomology* **7,** 518–520.

Petersen, J. J. (1978b). Observations on the mass production of *Romanomermis culicivorax*, a nematode parasite of mosquitoes. *Mosquito News*.**38,** 83–86.

Petersen, J. J. (1979a). pH as a factor in parasitism of mosquito larvae by the mermithid *Romanomermis culicivorax*. *Journal of Nematology* **11,** 105–106.

Petersen, J. J. (1979b). Effects of temperature on longevity of laboratory cultures of *Romanomermis culicivorax*, a mermithid parasite of mosquitoes. *Southwestern Entomologist* **4,** 65–69.

Petersen, J. J. (1980). Mass production of the mosquito parasite *Romanomermis culicivorax*: Effect of density. *Journal of Nematology* **12,** 45–48.

Petersen, J. J. (1981). Observations on the biology of *Octomyomermis muspratti*, a nematode parasite of mosquitoes. *Journal of Invertebrate Pathology* **37,** 290–294.

Petersen, J. J., and Chapman, H. C. (1970). Parasitism of *Anopheles* mosquitoes by a *Gastromermis* sp. (Nematoda: Mermithidae) in southwestern Louisiana. *Mosquito News* **30,** 420–424.

Petersen, J. J., and Chapman, H. C. (1979). Checklist of mosquito species tested against the nematode parasite *Romanomermis culicivorax*. *Journal of Medical Entomology* **15,** 468–471.

Petersen, J. J., and Cupello, J. M. (1981). Commercial development and future prospects for entomogenous nematodes. *Journal of Nematology* **13,** 280–284.

Petersen, J. J., and Willis, O. R. (1970). Some factors affecting parasitism by mermithid nematodes in southern house mosquito larvae. *Journal Economic Entomology* **63,** 175–178.

Petersen, J. J., and Willis, O. R. (1971). A two year survey to determine the incidence of a mermithid nematode in mosquitoes in Louisiana. *Mosquito News* **31,** 558–566.

Petersen, J. J., and Willis, O. R. (1972a). Procedures for the mass rearing of a mermithid parasite of mosquitoes. *Mosquito News* **32,** 226–230.

Petersen, J. J., and Willis, O. R. (1972b). Results of preliminary field applications of *Reesimermis nielseni* (Mermithidae: Nematoda) to control mosquito larvae. *Mosquito News* **32,** 312–316.

Petersen, J. J., and Willis, O. R. (1974a). Experimental release of a mermithid nematode to control *Anopheles* mosquitoes in Louisiana. *Mosquito News* **34,** 316–319.

Petersen, J. J., and Willis, O. R. (1974b). *Diximermis peterseni* (Nematoda: Mermithidae): A potential biocontrol agent of *Anopheles* mosquito larvae. *Journal of Invertebrate Pathology* **24,** 20–23.

Petersen, J. J., and Willis, O. R. (1975). Establishment and recycling of a mermithid nematode for the control of mosquito larvae. *Mosquito News* **35,** 526–532.

Petersen, J. J., and Willis, O. R. (1976). Experimental release of a mermithid nematode to control floodwater mosquitoes in Louisiana. *Mosquito News* **36,** 339–342.

Petersen, J. J., Chapman, H. C., and Woodard, D. B. (1967). Preliminary observations on the incidence and biology of a mermithid nematode of *Aedes sollicitans* (Walker) in Louisiana. *Mosquito News* **27,** 493–498.

Petersen, J. J., Hoy, J. B., and O'Berg, A. G. (1972). Preliminary field tests with *Reesimermis nielseni* (Mermithidae: Nematoda) against mosquito larvae in California rice fields. *California Vector Views* **19,** 47–50.

Petersen, J. J., Steelman, C. D., and Willis, O. R. (1973). Field parasitism of two species of Louisiana rice field mosquitoes by a mermithid nematode. *Mosquito News* **33,** 573–575.

Petersen, J. J., Willis, O. R., and Chapman, H. C. (1978a). Release of *Romanomermis culicivorax* for the control of *Anopheles albimanus* in El Salvador. I. Mass production of the nematode. *American Journal of Tropical Medicine and Hygiene* **27,** 1265–1267.

Petersen, J. J., Chapman, H. C., Willis, O. R., and Fukuda, T. (1978b). Release of *Romanomermis culicivorax* for the control of *Anopheles albimanus* in El Salvador. II. Application of the nematode. *American Journal of Tropical Medicine and Hygiene* **27,** 1268–1273.

Phelps, R. J., and De Foliart, G. R. (1964). Nematode parasitism of Simuliidae. *University of Wisconsin Agricultural Experiment Station Research Bulletin* 245.

Platzer, E. G. (1981). Biological control of mosquitoes with mermithids. *Journal of Nematology* **13,** 257–262.

Platzer, E. G. (1982a). Hatching in the mermithid nematode *Octomyomermis muspratti*. *Proceedings of the California Mosquito and Vector Control Association* **49,** 30–32.

Platzer, E. G. (1982b). Biology of mermithids and steinernematids with vector control potential. *Proceedings International Colloquium on Invertebrate Pathology* **3,** 374–379.

Platzer, E. G., and Brown, B. J. (1976). Physiological ecology of *Reesimermis nielseni*. *Proceedings of the International Colloquium on Invertebrate Pathology, Kingston, Canada* **1,** 263–267.

Platzer, E. G., and MacKenzie-Graham, L. L. (1978). Predators of *Romanomermis culicivorax*. *Proceedings of the California Mosquito and Vector Control Association* **46,** 93.

Platzer, E. G., and MacKenzie-Graham, L. L. (1980). *Cyclops vernalis* as a predator of the preparasitic stages of *Romanomermis culicivorax*. *Mosquito News* **40,** 252–257.

Poinar, G. O., Jr. (1975). "Entomogenous Nematodes." Brill, Leiden.

Poinar, G. O., Jr. (1976). Presence of mermithidae (Nematoda) in invertebrate paratenic hosts. *Journal of Parasitology* **62,** 843–844.

Poinar, G. O., Jr. (1979). "Nematodes for Biological Control of Insects." CRC Press, Boca Raton, Florida.

Poinar, G. O., Jr., and Gyrisco, G. G. (1962). Studies on the bionomics of *Hexamermis arvalis* Poinar and Gyrisco, a mermithid parasite of the alfalfa weevil, *Hypera postica* (Gyllenhal). *Journal of Insect Pathology* **4,** 469–483.

Poinar, G. O., Jr., and Hess, R. (1977). *Romanomermis culicivorax* morphological evidence of transcuticular uptake. *Experimental Parasitology* **42,** 27–33.

Poinar, G. O., Jr., and Otieno, W. A. (1974). Evidence of four molts in the Mermithidae. *Nematologica* **20,** 370–371.

Poinar, G. O., Jr., and Petersen, J. J. (1978). *Drilomermis leioderma* n. gen., n. sp. (Mermithidae: Nematoda) parasitizing *Cybister fimbriolatus* (Say) (Dytiscidae: Coleoptera). *Journal of Nematology* **10,** 20–23.

Poinar, G. O., Jr., Lane, R. S., and Thomas, G. M. (1976). Biology and redescription of *Pheromermis pachysoma* (V. Linstow) n. gen. n. comb. (Nematoda: Mermithidae) a parasite of yellowjackets (Hymenoptera: Vespidae). *Nematologica* **22,** 360–370.

Poinar, G. O., Jr., Hess, R., Hansen, E., and Hansen, J. (1979a). Laboratory infection of

blackflies (Simuliidae) and midges (Chironomidae) by the mosquito mermithid *Romanomermis culicivorax Journal of Parasitology* **65,** 613–615.

Poinar, G. O., Jr., Hess, R. T., and Petersen, J. J. (1979b). Responses of mosquitoes against *Romanomermis culicivorax* (Mermithidae: Nematoda). *Journal of Nematology* **11,** 110–116.

Reynolds, D. G. (1972). Experimental introduction of a microsporidian into a wild population of *Culex pipiens fatigans* Wied. *Bulletin of the World Health Organization* **46,** 807–812.

Ross, J. F., and Smith, S. M. (1976). A review of the mermithid parasites (Nematoda: Mermithidae) described from North American mosquitoes (Diptera: Culicidae) with descriptions of three new species. *Canadian Journal of Zoology* **54,** 1084–1102.

Rubzov, I. A. (1972). "Aquatic Mermithidae of the Fauna of the USSR," Vol. 1. Zoological Institute, Academy of Science USSR.

Rutherford, T. A., and Webster, J. M. (1974). Transcuticular uptake of glucose by the entomophilic nematode *Mermis nigrescens. Journal of Parasitology* **60,** 804–808.

Rutherford, T. A., and Webster, J. M. (1978). Some effects of *Mermis nigrescens* on the hemolymph of *Schistocerca gregaria. Canadian Journal of Zoology* **56,** 339–347.

Sanders, R. D., Stockstad, E. L. R., and Malatesta, C. (1973). Axenic growth of *Reesimermis nielseni* (Nematoda: Mermithidae) in insect tissue culture media. *Nematologica* **19,** 567–568.

Schmidt, S. P., and Platzer, E. G. (1978). Hemolymph composition of mosquito larvae infected with a mermithid nematode. *Journal of Nematology* **10,** 299.

Sharma, R. K., and Gupta, L. N. (1982a). Role of photoperiod and temperature on biological control of *Culex fatigans* larvae by the mermithid nematode *Romanomermis culicivorax* Ross and Smith. *Zeitschrift fur Angewandte Entomologie* **93,** 187–190.

Sharma, G. K., and Gupta, L. N. (1982b). Role of pH factor in biological control of *Culex fatigans* by a mermithid nematode *Romanomermis culicivorax* Ross and Smith, 1976. *Zeitschrift fur Angewandte Entomologie* **93,** 326–328.

Steiner, G. (1924). Remarks on a mermithid found parasitic in the adult mosquito *Aedes vexans* (Meigen) in B. C. *Canadian Entomologist* **56,** 161–164.

Sterling, A. M., and Platzer, E. G. (1978). *Cantenaria anguillulae* in the mermithid nematode *Romanomermis culicivorax. Journal of Invertebrate Pathology* **32,** 348–354.

Thornton, D. P., and Brust, R. A. (1979). Embryonic development of *Romanomermis communensis* (Nematoda: Mermithidae) at different temperatures. *Canadian Journal of Zoology* **57,** 1710–1712.

Trpis, M., Haufe, W. O., and Shemanchuk, J. A. (1968). Mermithid parasites of the mosquito *Aedes vexans* Meigen in British Columbia. *Canadian Journal of Zoology* **46,** 1077–1079.

Welch, H. E., and Rubtsov, I. A. (1965). Mermithids (Nematoda: Mermithidae) parasitic in blackflies (Insecta: Simuliidae). I. Taxonomy and bionomics of *Gastromermis boophthorae* sp. n. *Canadian Entomologist* **97,** 581–596.

Willis, O. R. (1971). A mermithid nematode in naiads of damselflies (Odonata: Coenagrionidae). *Florida Entomologist* **54,** 321–324.

Willis, O. R., Chapman, H. C., and Petersen, J. J. (1980). Additional field testing of the mermithid parasite *Romanomermis culicivorax* against *Anopheles albimanus* in El Salvador. *Mosquito News* **40,** 71–73.

Woodard, D. B., and Fukuda, T. (1977). Laboratory resistance of the mosquito *Anopheles quadrimaculatus* to the mermithid nematode *Diximermis peterseni. Mosquito News* **37,** 192–195.

Xinshi, Y., Tianzhi, F., Denghong, C., Guoying, C., and Mingsheng, L. (1983). Studies on the life cycle of *Romanomermis jingdeensis* (Nematoda: Mermithidae) and host-parasite relationship. *Zoological Research* **4,** 139–146.

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