Mathematical Studies of Parasitic Infection and Immunity

Roy M. Anderson

The techniques that underpin modern molecular biology have been rapidly adopted by those interested in the major parasitic infections of humans. The parasitological literature is full of reports of genes and their amino acid sequences, of molecules, of cell membrane receptors and channels, and of the fine details of the immunological responses mounted by the host to combat infection. Much less enthusiasm has been shown for the mathematical techniques that facilitate the analysis and interpretation of dynamical processes such as transmission, evolution, and the interplay between parasite population growth and immunological responses within the host. Molecular techniques provide enormous opportunities for description, but ultimately, understanding biological systems with the precision that physicists and engineers aspire to in their own fields will require quantitative description of the many rate processes that dictate both an observed pattern and the dynamics of its change.

The bench scientists' distrust of mathematics is easy to understand as it often centers not so much on an unfamiliarity with the language but more on the simplicity of the assumptions embedded in models in the face of known biological complexity. Simple assumptions are certainly more likely to permit analytical investigation, but of greater importance to the researcher using such models is the underlying philosophy of starting simply and slowly adding complexity in a manner akin to that adopted by experimental scientists, where one or a few factors are allowed to vary while others are held constant in the experimental design. This approach has many advantages because even simple models may exhibit very complicated patterns of dynamical behavior. It is as well to appreciate this before tackling the interplay between the many variables and parameters that characterize even the simplest of biological systems.

In the parasitological literature, the study of dynamical processes with the use of simple and complex mathematical models has progressed steadily in the past decade (*1*). This approach is finding applications in a variety of fields, ranging from the study of immunological responses (*2*, *3*) to the design of community-based programs for the control of infection and disease (*4*). Its origins go back to the early work of Ross (*5*) and Macdonald (*6*) on malaria, but a major stimulus in the expansion of the discipline has been the success of the approach in understanding the epidemiology of directly transmitted viral and bacterial infections such as measles, mumps, and rubella and the impact of mass vaccination on their transmission (*1*). Comparatively simple mathematical models of transmission and human demography can explain, for example, oscillating fluctuations in incidence (for example, the 2-year cycle of measles incidence in urban centers in industrialized countries before wide-scale immunization), the impact of mass vaccination on the average age at infection, and fluctuations in the incidence of serious disease arising from infection. Such models as a result can provide precise guidelines for the optimal design of immunization programs (*7*). Mathematical methods have thus evolved from being tools to aid interpretation of epidemiological patterns to templates for suggesting research priorities (for example, "herd immunity" profiles generated by longitudinal and cross-sectional serological surveys) to a predictive framework that facilitates the formulation of public health policy (*8*).

The author is in the Department of Zoology, University of Oxford, Oxford OX1 3PS, UK.

Host Immunological Defenses and Parasites

In the parasitological literature, mathematical studies have begun to focus on the details of the interaction between parasites and the immunological defenses of hosts. One aim of this research is to embed models of within-host dynamics in the more conventional framework that captures transmission within a community of people. The more organizationally complex parasites (such as the nematodes and flukes) possess diverse mechanisms to modulate, interfere with, or evade their hosts' defenses (*9*). Chronic or persistent infection, plus associated disease, often occurs in a small fraction of individuals living in areas of endemic infection. The parasites persist in individuals who are continually reinfected despite abundant evidence of multicomponent immunological responses to parasite antigens. It is often the case that specific T cells show defective proliferative responses in the presence of parasite antigens (*10*) (that is, tolerance or anergy).

This phenomenon is of particular interest in the context of parasite population growth within the host and the evolution of the immune response. Laboratory studies typically reveal convex relations between T cell proliferation rates and antigen concentration, with low rates of T cell proliferation at both low and high concentrations. The simplest models of the interaction [including the representation of T helper cell 1 and 2 (T_H1 and T_H2) subsets of differentiated T cells] reveal a wide array of possible outcomes, with extremes of solid immunity with no or low infection and anergy or tolerance with persistent high parasite burdens (*2*). These models suggest that the intensity of exposure to infection in early life determines the outcome of infection, with high exposure resulting in tolerance and persistent infection and low exposure resulting in the acquisition of immunity. Furthermore, as illustrated in Fig. 1, even when the rate of infection is constant across all ages, the cross-sectional age profile of infection and

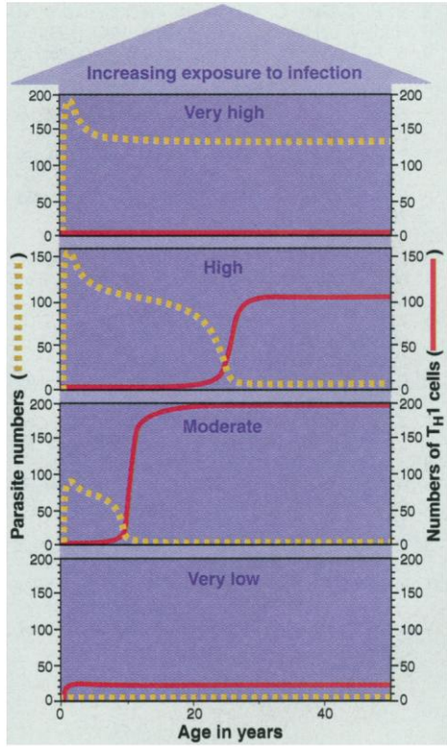

Fig. 1. Model of the relation between exposure to helminth infection, parasite burden, and acquired immunity. This model is an illustration of how the degree of exposure to helminth infection (rate of infection per unit of time) influences the cross-sectional profile of parasite burden and acquired immunity (abundance of T_H1-type CD4 cells), as predicted by a simple model of T cell proliferation to parasite antigens. For methodology, see (*2*).

immunity may be very nonlinear in form, with the precise shape depending on the intensity of exposure (*11, 12*). Field studies of the immunoepidemiology of helminth infection are beginning to provide information with which to test the validity of these predictions (*13*).

Models of Antigenic Variation

Microparasites, such as the parasitic protozoa, often exhibit antigenic variation. This is another method by which the parasite may evade the host's immunological defenses. Antigenic variation within the host (such as that used by trypanosomes and malarial parasites) prolongs the typical duration of infection, increasing the likelihood of transmission (*14*). Genetic variability in the total parasite population helps to evade herd immunity (*15*) and therefore promotes the long-term persistence of the infectious agent. Models of the dynamics of antigenic variation, driven by the selective pressure imposed by the specificity of the immune system, contain many equations as a result of the need to track changes in the abundances of many variants.

However, progress has been made in their formulation and analysis, and simple models can generate complex patterns of behavior. One illustration is presented in Fig. 2, which shows predictions of changes over time in the abundances of different antigenic variants within an individual host exposed to repeated infection (*16*). The biological model here is that of *Plasmodium falciparum* (the cause of malaria infection in humans), where an individual is repeatedly exposed to infection by different variants (a stochastic process) or serotypes and builds up immunity by means of specific responses to antigens that are unique to a given variant and cross-reactive responses to antigens common to all variants. This model may or may not have an equilibrium state, although the host can eventually suppress the parasite to low abundance or even eliminate it because of the build-up of cross-reactive responses. Theory suggests that for any given interaction, no new strains will be established once a critical number of strains or variants have been experienced (which ensures that cross-reactive immunity inhibits further infection). One testable prediction of this model is that the abundance of any one variant will fluctuate widely, driven by Lotka-Volterra type neutral stability, with total parasite abundance summed across variants and showing irregular changes in the course of malarial infection in children. Another prediction is that cross-reactive immunity will dominate in those who clear infection or who suppress parasite abundance to small amounts.

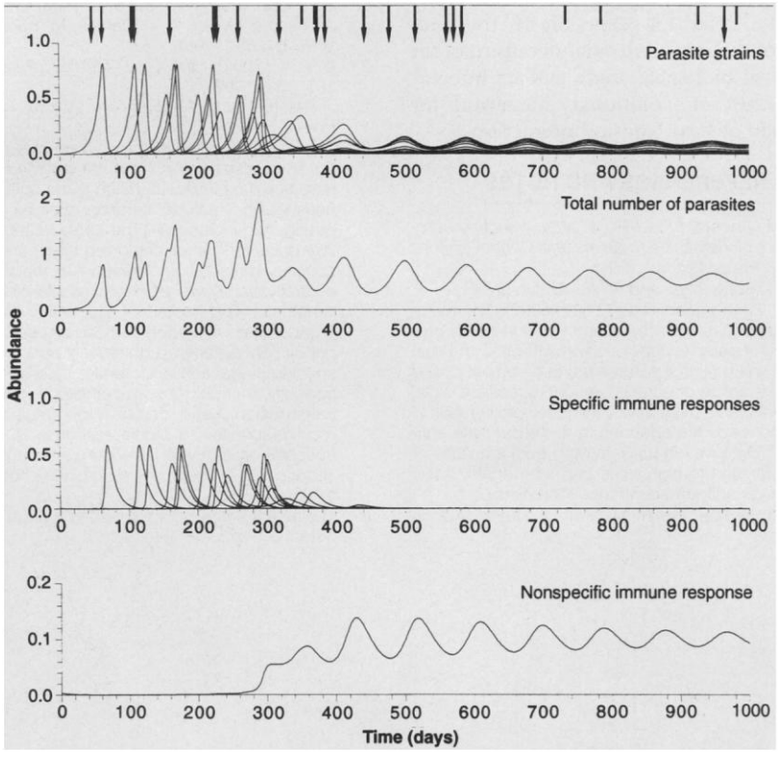

Fig. 2. Model of repeated infection of a host by a microparasite (for example, *P. falciparum*). The parasite population consists of many distinct strains or serotypes against which specific and cross-reactive immunological responses are mounted by the host, as predicted by a simple mathematical model of multistrain transmission and selection by the immune system (*25*). Some of the new infecting parasite strains have (bars) or have not (arrows) been already "experienced" by the immune system of the host. Eventually, nonspecific immunological responses build up and suppress total parasite abundance (either to a low level or to extinction). Before this suppression, the periods of the oscillations in the abundances of each strain are set by the replication rate of each parasite strain and the magnitude of the parasite death rate induced by the specific immunological responses. This type of model is applicable to many fields (*26*). Units of abundance are all relative, scaled to a maximum of 1.

Models of multistrain transmission can be used to examine other issues, such as the factors that facilitate the maintenance of genetic variation in the parasite population, the evolution of virulence, and the interaction between antigenic variation and immunodominance in simultaneous immune responses against several variable parasite antigen epitopes (*17*). The conventional wisdom that successful parasites evolve to become benign to their host has been overturned by theoretical work that shows that rather than minimizing virulence, selection will act to maximize a parasite's reproductive success. If the rate of transmission is linked with pathogenicity, then selection may lead to intermediate or high levels of virulence (*18–20*).

Recent multistrain transmission models, based on the assumption that the more pathogenic strain is always able to outcompete the less virulent one within the host (superinfection), reveal very complicated dynamics, with sudden and dramatic changes in the average level of virulence. These models also show that superinfection leads to an increase in average virulence, to a polymorphism of parasite strains, to the persistence of very virulent strains that could not persist alone in an otherwise uninfected host population, and to the most abundant strains not having the highest reproductive rates (measured in the absence of other strains) (*17*).

Extensions of this type of approach to specific problems, such as the circulation of multiple strains or serotypes of malaria, suggest that the degree of cross-reactive immunity is central to the maintenance of genetic diversity (*21*). If cross-reactive responses are important in the acquisition of immunity, then to avoid severe fluctuations in strain abundance (with the associated risks of extinction in the troughs), the models suggest that the various strains should not have very dissimilar reproductive or transmission success rates (*8, 21*). Preliminary observations seem to support this prediction (*15*).

Applications of Models

Macroparasitic infections, such as the major helminths that induce disease in tropical regions, have also been the subject of math-

ematical studies of transmission (*1*), the development of acquired immunity (*12*), and the design of community-based control programs (*4*). The last area is one in which much progress has been made recently. Early models revealed how simple characteristics of a parasite's life history and population biology—for example, life expectancy of the various developmental stages, reproductive success, the probability distribution of worm burdens in a human community, and predisposition to heavy or light infection—influenced the way in which the parasite population responded to perturbations induced by various control options (*1*).

Such predictions have been largely supported by field studies (*22*); this has given researchers confidence to begin promoting the use of such mathematical models in the design of cost-effective control programs based on the community-wide use of chemotherapeutic agents. Published models range from complex simulation programs (*23*) to simple sets of differential equations (*1*), but a common feature of all this work is the degree to which simple models capture the major features of observed epidemiological patterns in both treated and untreated communities (*24*). In this applied context, these models have been particularly successful in showing in quantitative terms how the prevalence of infection (an easily measured epidemiological statistic) is related to the burden of disease (more difficult to measure) in defined communities. Such relations provide the template for more elaborate calculations on how best to use limited resources to control infection and, more importantly, disease by targeting chemotherapy to selected groups in the population.

Conclusion

Underlying all such work is a mathematical framework that captures the major features of a particular parasite's population dynamics. These methods are slowly gaining acceptance in national and international agencies responsible for public health policy formulation, but much suspicion remains. The coming decade may see their application not just in drug treatment programs for filariasis, schistosomiasis, and intestinal nematodes, but also in examining how to slow the evolution of drug resistance and in assessing the relative merits of immunotherapeutic treatments (and perhaps even of vaccines).

Transmission and control are the conventional areas for the application of mathematical techniques. The real challenge for this approach lies in the fields of molecular epidemiology (the study of parasite evolution and the impact of genetic diversity) and parasite immunology. In both areas, information is accumulating rapidly, but much of it is descriptive in character. To unravel how this detail fits into a broader landscape that encompasses population-level phenomena and evolutionary processes (whether within the host or in a population of hosts) will require mathematical methods. It is to be hoped that in the acquisition of the technical skills required of a competent practitioner in the molecular fields, time is allotted for reflection on the relevance of the new molecular details to other aspects of biological study and its integration within an evolutionary framework for the study of host-parasite interactions.

REFERENCES AND NOTES

1. R. M. Anderson and R. M. May, *Infectious Diseases of Humans: Dynamics and Control* (Oxford Univ. Press, Oxford, 1991).
2. A. N. Schweitzer and R. M. Anderson, *Proc. R. Soc. London Ser. B.* **247**, 107 (1992). The major assumptions are a basic immigration-death process for parasite population growth within the host plus an additional parasite mortality term imposed by the action of parasite antigen-specific T cells, where the function determining cell proliferation in response to the abundance of the parasite antigens is convex in form, moving from low rates of proliferation to high rates and then again to low rates as antigen abundance increases.
3. M. A. Nowak and R. M. May, *J. Theor. Biol.*, in press.
4. G. F. Medley, H. L. Guyatt, D. A. P. Bundy, *Parasitology*, in press.
5. R. Ross, *The Prevention of Malaria* (Murray, London, 1911).
6. G. Macdonald, *The Epidemiology and Control of Malaria* (Oxford Univ. Press, Oxford, 1957).
7. H. R. Babad *et al.*, *Epidemiol. Infect.*, in press.
8. R. M. Anderson, *Philos. Trans. R. Soc. London Ser. B.*, in press.
9. R. M. Maizels, D. A. P. Bundy, M. E. Selkirk, D. F. Smith, R. M. Anderson, *Nature* **365**, 797 (1993).
10. A. F. Sher and R. L. Coffman, *Rev. Immunol.* **10**, 385 (1992).
11. A. N. Schweitzer, J. Swinton, R. M. Anderson, *Parasite Immunol.* **15**, 85 (1993).
12. R. M. Anderson and R. M. May, *Nature* **315**, 493 (1985).
13. A. E. Butterworth *et al.*, *Parasitology* **103**, 399 (1991).
14. Z. Agur, D. Abiri, L. H. T. Van der Ploeg, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 9626 (1989).
15. S. Gupta, K. Trenholme, R. M. Anderson, K. P. Day, *Science* **263**, 961 (1994).
16. R. M. Anderson, R. M. May, J. Swinton, unpublished data.
17. M. A. Nowak and R. M. May, *Proc. R. Soc. London Ser. B* **255**, 81 (1994).
18. R. M. Anderson in *Population and Biology*, N. Keyfitz, Ed. (Ordina, Liege, 1981), pp. 249–268.
19. S. Levin and D. Pimentel, *Am. Nat.* **117**, 309 (1981).
20. R. M. Anderson and R. M. May, *Parasitology* **85**, 411 (1982).
21. S. Gupta, J. Swinton, R. M. Anderson, *Proc. R. Soc. London Ser. B.*, in press.
22. H. L. Guyatt, D. A. P. Bundy, D. Evans, *Trans. R. Soc. Trop. Med. Hyg.* **87**, 568 (1993).
23. J. Remme, O. Ba, K. Y. Dadzie, M. Karam, *Bull. WHO* **64**, 667 (1986).
24. D. A. P. Bundy and G. F. Medley, *Parasitology* **105**, 151 (1992).
25. J. Swinton, R. M. Anderson, R. M. May, in preparation.
26. The model is essentially a multispecies predator (immune system)-prey (parasite strain) Lotka-Volterra structure, with saturation in the specific and nonspecific T cell proliferation rates as parasite abundance increases. (The Lotka-Volterra structure ensures that for any given strain and strain-specific immunological response, the model is neutrally stable with perpetual oscillations in both variables.) This model is a specific case of a broader class of models that can be used to study population dynamic problems in ecology (multispecies interaction and spatial heterogeneity in population structure), epidemiology (multistrain transmission), and immunology [multicompartment responses, a single response to multiple epitopes on a single pathogen, and multiple responses to antigenically variable pathogens (*3, 17*)].

27. The author acknowledges research grant support from the Wellcome Trust.