receptor binding and not of increased resistence to proteases.

The biological data obtained for analog **1** provide additional support for a receptor-bound conformation of LH-RH which contains a Tyr-Gly-Leu-Arg type II′ β-turn. Other types of β-turns known to exist in proteins (*29*) have also been examined by computer superposition with the lactam peptide. All of these accommodate the lactam ring less well. Conformations are possible that can accept the lactam and do not contain a turn. However, the enhanced potencies obtained with three different conformational constraints (D amino acids, *N*-methyl amino acids, and lactams), all of which would stabilize a turn structure, provide strong evidence for the existence of this type of structure in LH-RH when bound to the receptor in such a way as to produce a biological response. The results also indicate that the loss of activity with the L-alanine substitution in position 6 was due to destabilization of the favored conformation rather than some steric interaction with the receptor.

This successful demonstration of the application of a lactam as a new type of conformational constraint in peptides providing inference of bioactive conformation and increased biological potency suggests future applications. With the newly developed synthetic methodology, a variety of five-membered lactam-containing dipeptides can be synthesized for incorporation into specific peptides. We have previously shown the stabilization of a γ-turn structure by a six-membered lactam (*10*). These structures can complement currently used conformational constraints by adding to the information obtainable from a conformation-activity approach, thereby facilitating the design of peptide analogs of improved biological activity and duration of action.

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31 March 1980

Infectious Diseases and Population Cycles of Forest Insects

Abstract. *The regulation of natural populations of invertebrate hosts by viral, bacterial, protozoan, or helminth infections is discussed, using models that combine elements of conventional epidemiology (where the host population is assumed constant) with dynamic elements drawn from predator-prey studies; the apparent absence of acquired immunity in invertebrates simplifies the analysis. Highly pathogenic infections, with long-lived infective stages, tend to produce cyclic behavior in their host populations. The models give an explanation of the 9- to 10-year population cycles of the larch bud moth (*Zeiraphera diniana*) in the European Alps and suggest that microsporidian protozoan and baculovirus infections may be responsible for the 5- to 12-year population cycles observed in many temperate forest insects.*

It is possible that parasitic infections—broadly defined to include viruses, bacteria, protozoans, and helminths—may regulate the population density of their hosts (*1*). Recent research (*2*) combines theoretical models with field and laboratory data, seeking to fuse two well-established but separate literatures: classical epidemiology, which treats the maintenance and transmission of infections within a host population that has a constant magnitude, determined by other factors (*3, 4*), and predator-prey studies, which occupy a chapter in any current ecology text and deal with the way prey populations may be regulated by the predators that eat them (*5*).

This report deals in particular with the regulation of populations of invertebrate species by infectious diseases. Such systems are of special interest for at least two reasons. (i) They have important practical applications in pest control. (ii) The dynamics are somewhat simpler, and the relevant parameters more amenable to measurement, than is the case for most vertebrate host-parasite systems, because it appears that invertebrates do not develop acquired immunity to the agents of infectious disease (*6*).

In the simplest case, we define $X(t)$ to be the number of susceptible hosts and $Y(t)$ the number of infected hosts at time t; the total population of invertebrate hosts is thus $N(t) = X(t) + Y(t)$. We further define a to be the per capita birth rate of the hosts, b their natural death rate, α the disease-induced death rate of infected hosts, and γ the recovery rate. These are all quantities that may, in principle, be measured directly. In this simplest model for a directly transmitted infection (*7*), the transmission rate is assumed proportional to the number of

susceptible hosts and to the number of infected individuals, βXY (*8*); latency is ignored, and all infected hosts are taken to be infective. The dynamics of this system obey the pair of first order differential equations

$$dX/dt = a(X + Y) - bX - \beta XY + \gamma Y \quad (1)$$

$$dY/dt = \beta XY - (\alpha + b + \gamma)Y \quad (2)$$

Equivalently, one of these equations may be replaced with that for the total host population

$$dN/dt = (a - b)N - \alpha Y \quad (3)$$

This formulation differs from conventional epidemiological models in that the host population N is a dynamic variable. Conventional models take N to be a predetermined constant, unaffected by the presence of the disease, so that attention is focused on the single dynamical Eq. 2 [with $X(t) = N - Y(t)$]. Within such constant host populations, the infection will be maintained if its basic reproductive rate R exceeds unity (*4, 9*); R is the expected number of secondary infections (βN) produced within the infectious period $[1/(\alpha + b + \gamma)]$ of one newly introduced infected host

$$R = \beta N/(\alpha + b + \gamma) \quad (4)$$

The condition $R > 1$ for maintenance of the infection may alternatively be expressed as the requirement that the host population exceed a threshold density, $N > N_T$, with $N_T = (\alpha + b + \gamma)/\beta$ (*3, 4, 10*). This threshold population density will be relatively high for infections with relatively high pathogenicity (large α) or relatively low transmissibility (small β).

For the more dynamic model represented by Eqs. 1 to 3, the disease will actually regulate the magnitude of the host population at a steady value provided that the pathogenicity exceeds the net population growth rate, $\alpha > a - b$ (*11*). As was noted above, Eq. 2 shows that the disease cannot become established (that is, $R < 1$) until the host population exceeds the threshold value N_T. If at first $N < N_T$, the population will grow exponentially until it does exceed N_T, whereupon the infection regulates the population if $\alpha > a - b$ or, at least, slows the population's rate of exponential growth if $\alpha < a - b$ (*12*). Table 1 shows the disease-induced mortality rates (α) and the natural death rates (b) for the invertebrate hosts of various parasitic infections. The effective birth rates (a) of these invertebrates are harder to determine (*13*), but Table 1 shows that α is typically an order of magnitude greater than b, which makes it plausible that some of these infections may contribute, wholly or in part, to the regulation of their host populations.

The model represented by Eqs. 1 through 3 omits many biological features that can complicate host-parasite systems. These complications—which include parasitic castration, vertical transmission, incubation or latent periods of the parasites within infected hosts, and the dependence of pathogenicity on the nutritional state of the host—are discussed in detail elsewhere (*14*). They tend, however, to preserve the basic conclusions reached from Eqs. 1 to 3. Despite their simplicity, models of this kind have been strikingly successful in explaining the outcome of laboratory experiments on the regulation of vertebrate populations by directly transmitted infections (*15*).

A major complication arises when the transmission stages of the pathogen are long-lived in the external environment. This happens for many parasitic infections of insects [see data compiled in (*14*)], and it can make the dynamical behavior of the host-parasite system qualitatively more complex. In particular, baculoviruses and microsporidia of temperate forest insects (principally of lepidopteran, hymenopteran, and dipteran species) tend to have long-lived infective stages, partly because the soil environment of temperate forests affords relative protection from the ultraviolet components of sunlight (*14, 16*). Such free-living infective stages include the spores of many bacteria, protozoans, and fungi, and the capsules, polyhedra, or free particles of viruses (*17*). These infective stages employ a variety of pathways for their passage from one host to the next (*18*). We define the population of free-living infective stages of the parasite to be $W(t)$ at time t. In Eq. 2, the transmission term is now proportional to the rate of encounters between susceptible hosts and infective stages of the parasite, νWX

$$dY/dt = \nu WX - (\alpha + b + \gamma)Y \quad (5)$$

Equation 3 for $N(t)$ remains unchanged. Infective stages are produced at a rate λ from infected hosts (*19*) and are lost by death (at a rate μ) or by absorption in hosts (at a rate νN), which gives

$$dW/dt = \lambda Y - (\mu + \nu N)W \quad (6)$$

Equations 3, 5, and 6 give a complete description of the dynamical behavior of the variables $N(t)$, $Y(t)$, and $W(t)$. If in-

Table 1. Natural and pathogen-induced mortality rates for invertebrate hosts of some viral, bacterial, protozoan, and fungal parasites (based on laboratory studies; references will be supplied on request).

Pathogen	Host	Natural mortality rate b (per week)	Pathogen-induced mortality rate α (per week)
Viruses			
Sack brood	*Apis mellifera*	0.17	1.2
Nuclear polyhedrosis	*Cadra cautella*	0.061	0.54
Nuclear polyhedrosis	*Hyphantria cunea*	0.003	0.80
Noninclusion	*Panonychus citri*	0.34	0.91
A.B.P.	*Apis mellifera*	0.25	1.9
R.O.	*Oryctes rhinoceros*	0.10	0.19
Nuclear polyhedrosis	*Porthetria dispar*	0.060	0.63
Nuclear polyhedrosis	*Malacosoma americanum*	0.070	0.37
Bacteria			
Bacillus thuringiensis	*Simulium vittatum*	0.035	2.4
Bacillus thuringiensis	*Choristoneura fumiferana*	0.001	4.0
Aeromonas punctata	*Anopheles annulipes*	0.36	2.9
Erwinia spp.	*Colladonus montanus*	0.031	0.17
Protozoa			
Nosema stegomyiae	*Anopheles albimanus*	0.23	0.41
Pleistophora schubergi	*Hyphantria cunea*	0.003	0.036
Herpetomonas muscarum	*Hippelates pusio*	0.17	0.43
Tetrahymena pyriformis	*Culex tarsalis*	0.26	0.66
Mattesia dispora	*Laemophloeus minutas*	0.022	0.11
Fungi			
Beauveria tenella	*Aedes siemensis*	0.026	0.50
Beauveria tenella	*Culex tarsalis*	0.11	0.84
Beauveria bassiana	*Musca domestica*	0.27	0.74
Beauveria bassiana	*Hylemya antiqua*	0.30	0.55
Beauveria bassiana	*Phormia regina*	0.24	0.56
Metarrhizium anisopliae	*Musca domestica*	0.27	0.38
Metarrhizium anisopliae	*Hylemya antiqua*	0.30	0.48
Metarrhizium anisopliae	*Phormia regina*	0.24	0.42
Aspergillus flavus	*Culex peus*	0.020	0.17
Aspergillus flavus	*Culex tarsalis*	0.061	0.22
Fusarium oxysporum	*Culex pipiens*	0.027	0.62

Table 2. Cyclic variations in the abundance of forest insect species.

Host insect species	Locality	Period of cycles in population abundance (years)	Pathogen	Reference
Orgyia pseudotsugata (Douglas-fir tussock moth)	North America	7 to 10	Nuclear polyhedrosis virus	(*28*)
Acleris variana (black-headed budworm)	Eastern Canada	10 to 15	Nuclear polyhedrosis virus	(*29*)
Bupalus piniarius (pine looper)	Europe	5 to 8	Nuclear polyhedrosis virus	(*30*)
Zeiraphera diniana (larch bud moth)	Europe	9 to 10	Granulosis virus	(*22-24*)
Diprion hercyniae (spruce sawfly)	North America	8	Nuclear polyhedrosis virus	(*31*)
Malacosoma disstria (tent caterpillar)	North America	8 to 12	Nuclear polyhedrosis virus; microsporidian protozoan	(*32*)

fected hosts produce transmission stages of the parasite at a sufficiently fast rate (*20*), then the disease will again regulate its host population so long as $\alpha > a - b$. However, the regulated state may be a stable point, or it may be a stable cycle (*21*); the cyclic solutions tend to arise for infections of high pathogenicity that produce large numbers of long-lived infective stages. Figure 1 illustrates the relation between the period T of the host's population cycles and the parameters μ and $a - b$, for large α.

Many microsporidian, protozoan, and baculovirus infections of insects appear to possess the combination of relatively large α and small μ that produce cyclic changes in host abundance. Insertion of a plausible range of values for μ and $a - b$ in Fig. 1, moreover, suggests that the cycles have periods in the general range of 3 to 30 years (*14*); these are to be compared with the observed periods of 5 to 12 years for cycles in populations of forest insect pests (Table 2). We suggest that the population cycles in Table 2 may be driven by the interactions between the host insect and a pathogen.

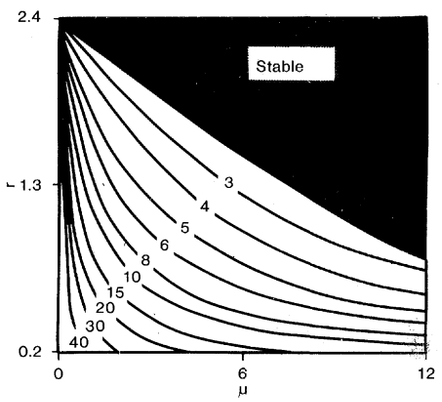

Fig. 1 The solutions to Eqs. 3, 5, and 6 are indicated for various values of μ and r ($r = a - b$), with the other relevant rate parameters fixed at $\alpha = 9.0$, $b = 3.3$, $\gamma = 0$ (units of year^{-1}). For combinations of μ and r in the shaded region, the solution is a stable equilibrium point. The contour lines correspond to stable limit cycle solutions, with periods (in years) as labeled.

In support of this broad suggestion, Fig. 2 shows a comparison between theory and observation for the population dynamics of the larch bud moth, *Zeiraphera diniana*, in the Engadine Valley in Switzerland. Figure 2A shows the data for the abundance of the insect and for the prevalence of infection with a granulosis virus over a 20-year period (*22, 23*). Figure 2B shows the same quantities calculated from Eqs. 3, 5, and 6 with approximate values of the parameters a, b, α, γ, λ, and μ estimated independent of this population data (*24*). Estimation of the transmission parameter v is impossible, but it only enters into determinations of the relative magnitude or "scaling" of $N(t)$ (*21*) and not at all into determinations of the prevalence of the infection. The agreement between A and B of Fig. 2, with respect both to the period and to the shape and magnitude of the oscillations in bud moth population and prevalence of virus infection, is encouraging, particularly as there are no adjustable parameters involved in the fit, except for the absolute scale—but not the logarithmic amplitude of the cycle—of $\log N(t)$. Unfortunately, we have no knowledge of other examples where all the important parameters in our host-parasite model can be estimated independent of the data on the population cycle itself.

Several general features of population cycles driven by host-parasite associations are illustrated by Fig. 2. First, the peak in prevalence of the infection within the host population occurs shortly after the peak in host abundance. Second, the host population falls below the threshold value N_T during part of the cycle; the infection survives primarily by virtue of its relatively long-lived transmission stages. Third, when N is below N_T, the prevalence declines effectively to zero, so that the disease seems to have disappeared from its host population even though the population of free-living infective stages remains abundant; it is a mistake to think that disappearance of the disease, or "epidemic" reappearance, is inconsistent with the pathogen driving the host population cycle. Fourth, the cyclic patterns of host abundance tend to be characterized by a slow rise and a rapid fall, whereas the cycles in pathogen prevalence tend to be more symmetrical.

Other mechanisms are capable of producing cycles in host-parasite associations. It has been argued that the bud moth cycles are produced by the interaction between the insect and the vegetation it eats (*23*). Seasonal changes in the transmission rate in the simple Eqs. 1 and 2 can produce annual cycles in the host population or, under some circumstances, even cycles with periods of 2 years or other higher harmonics (*25*). Predation or other factors extrinsic to the host-parasite association can produce cycles in the host population (*26*). Furthermore, these different cycle-producing mechanisms can interact to produce very complex oscillatory behavior in the host abundance (*14*). We suggest, however, that the simple host-parasite mecha-

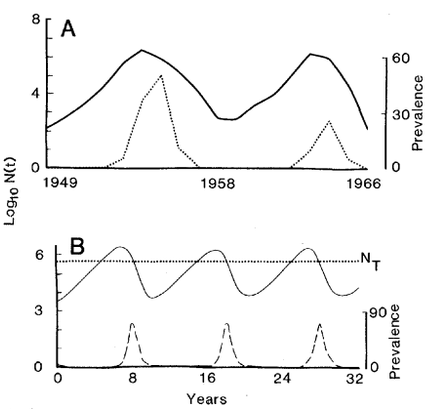

Fig. 2 (A) Observed changes in the abundance, $N(t)$ (plotted logarithmically, solid line) of the larch bud moth, *Zeiraphera diniana*, in the European Alps, and in the prevalence (expressed as a percentage and plotted linearly, dashed line) of infection with a granulosis virus (*22*). (B) The asymptotic solutions of Eqs. 3, 5, and 6 for host abundance, $N(t)$, and for the prevalence of infection, $Y(t)/N(t)$, are plotted as functions of time; the parameters in Eqs. 3, 5, and 6 are assigned values appropriate to the larch bud moth and the granulosis virus that infects it (*24*).

nisms discussed in this report are sufficient to account for many long-term population cycles of forest insects.

Systematic acquisition of more data will allow these ideas to be subjected to additional tests similar to that of Fig. 2. The model represented by Eqs. 3, 5, and 6 is of more than academic interest as it enables us to calculate the rate at which a virus or other pathogen must be artificially introduced if it is to be effective in the control, or extinction, of a population of insect pests (*14*). Beyond this, evolutionary aspects of the association between invertebrate hosts and their pathogens (*1*, *27*) must be examined; we have focused only on the dynamics of existing associations.

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7. In many cases, the parasite's life cycle involves one or more intermediate host species (for example, the mosquitoes that malarial *Plasmodium* species use as a developmental stage on the way from one human host to the next, or the snail vectors involved in the transmission of schistosomiasis). A brief review of the complications thus introduced by indirect transmission from one primary host to the next is in (*2*).
8. The proportionality coefficient β in this transmission term is the hardest parameter to measure in practical applications. If the age-specific prevalence of the infection in the host population is known, and is in equilibrium, β can sometimes be estimated indirectly from the typical age at which the infection is acquired (*4*).
9. This notion of the infection's "basic reproductive rate" is discussed more fully by J. A. Yorke, N. Nathanson, G. Pianigiani, and J. Martin [*Am. J. Epidemiol.* **109**, 103 (1978)] and R. M. Anderson [in *The Mathematical Theory of the Dynamics of Populations*, R. W. Hiorns, Ed. (Blackwell, Oxford, in press)].
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11. In this case, the equilibrium value of the host population is $N^* = N_T/(1 - r/\alpha)$, with $r = a - b$ and $N_T = (\alpha + b + \gamma)/\beta$ as discussed in the text. Of this population, a fraction r/α is infected.
12. If $\alpha < r$ (with $r = a - b$), the host population grows at the diminished rate $r - \alpha$ for $N >> N_T$. We have elsewhere (*2*) argued that trends in human population growth over the past 10,000 years or so exemplify this general pattern.
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19. An infected host that releases Λ infective particles into the environment when it dies is essentially equivalent to a host that produces infective stages at a steady rate $\lambda = \Lambda\ (\alpha + b + \gamma)$ throughout the expected lifetime, $1/(\alpha + b + \gamma)$, of its infection.
20. Specifically, we require $\lambda > A$, where $A = \alpha(\alpha + b + \gamma)/(\alpha - r)$. As documented in (*14*), actual values of λ are typically very large.
21. For $\lambda > A$ [A defined as in (*20*)] and $\alpha > r$ ($r = a - b$), Eqs. 3, 5, and 6 give a nontrivial solution corresponding to a locally stable point if
$$[\mu + (A - r)(1 - A/\lambda)][A - \alpha] - [1 - A/\lambda]^2\alpha(\alpha + b + \gamma) > 0$$
Conversely, if this expression is negative, there is a stable limit cycle. In the limit $\lambda >> A$, which is true in most real situations (*14*), this criterion reduces to
$$(\mu + A - r)(A - \alpha) - \alpha(\alpha + b + \gamma) > 0$$
It is clear that cycles are most likely to arise when α is large and μ is small. Notice that these dynamical criteria do not involve the transmission coefficient ν, which enters only in the scaling of the variables N, Y, and W.
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33. We thank M. P. Hassell, T. R. E. Southwood, and two anonymous reviewers for helpful comments. This work was supported in part by NSF grant DEB79-03290.

2 February 1980; revised 16 July 1980

Reorganization of the Axon Membrane in Demyelinated Peripheral Nerve Fibers: Morphological Evidence

Abstract. *Cytochemical staining of demyelinated peripheral axons revealed two types of axon membrane organization, one of which suggests that the demyelinated axolemma acquires a high density of sodium channels. Ferric ion–ferrocyanide stain was confined to a restricted region of axon membrane at the beginning of a demyelinated segment or was distributed throughout the demyelinated segment of axon. The latter pattern represents one possible morphological correlate of continuous conduction through a demyelinated segment and suggests a reorganization of the axolemma after demyelination.*

At least three responses have been demonstrated when an action potential arrives at a demyelinated segment of an axon. Conduction block may occur if the demyelinated axolemma is inexcitable (*1*, *2*) or as a result of impedance mismatch (*3*, *4*). Slowed saltation of action potentials between nodes of Ranvier results when passive internodal properties are altered due to loss of myelin (*5*). Finally, continuous conduction can occur across demyelinated internodal membranes that possess electrical excitability (*6*, *7*).

In normal myelinated fibers, Na^+ channels are concentrated at the nodes of Ranvier; in the internodal axolemma their density is lower than that necessary to sustain conduction (*2*). It has been suggested that demyelinated axonal regions develop electrical excitability, much as denervated muscle develops hypersensitivity (*2*). Electrophysiological observations of continuous conduction in demyelinated axons (*6*, *7*) indicate that internodal membranes undergo reorganization resulting in the development of electrical excitability. The physiological observations (*6*, *7*) suggest that (i) Na^+ channels and associated structures remain aggregated in clusters that become distributed along the length of the axon, (ii) reorganization of the axon membrane occurs such that individual Na^+ channels are dispersed through the demyelinated internodal membrane, and/or (iii) new channels are added to the demyelinated axon membrane.

Although the structural heterogeneity (*8*) of the axolemma of normally myeli-

0036-8075/80/1107-0661$00.50/0