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The Dynamics of Vector-Transmitted Diseases in Human Communities [and Discussion]

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The dynamics of vector-transmitted diseases in human communities

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The development of vector-transmitted disease models and their application to field studies is reviewed. The key concepts of the basic rate of reproduction and disease transmission threshold are explained, and their application to disease control briefly illustrated. The complications involved in producing appropriate models are discussed for the case of the trypanosomatid parasites *Leishmania* and *Trypanosoma* that frequently have more than one vertebrate host and are often fatal in the human host. A two-species, vector-borne disease model allows a quantification of the role of animal reservoirs in maintaining human diseases. Human prevalence may be determined more by the parasitological characteristics of wild reservoir species, about which little is generally known, than by any other single feature of the complex interaction between parasites, vectors and hosts. Domestic animals are often ideal reservoirs, maintaining large numbers of vectors and considerably enlarging the parasite pool.

When vector-transmitted diseases are fatal to the human host, human and vector dynamics interact in ways which may cause epidemic cycles, low-level endemic equilibria or disease extinction. For both leishmaniasis and trypanosomiasis it is suggested that a very small number of chronic human cases can maintain the disease in the human population over long periods of time between epidemic outbreaks. They may also be important in the maintenance of geographically distinct foci, characteristic of human trypanosomiasis in Africa.

Finally there is a plea to establish a tradition of field observation leading to, and being directed by, mathematical models which in turn are modified as the observations accumulate. All too often, one-way traffic between the two results in slow, or misguided, progress.

Introduction

Mathematical descriptions of vector-borne diseases such as malaria appeared soon after the birth of the separate discipline of medical entomology (Service 1977). Manson's almost serendipitous discovery of the role of mosquitoes in the transmission of human filariasis meant that another speciality, that of entomology (and eventually ecology), became involved in what must have been an already crowded field of clinicians, pharmacologists, parasitologists, public health workers and others. Complex parasite life cycles require an overview to establish the importance of each component part of the epidemiological puzzle, and this was provided by the mathematical models of malaria developed by Ross (1911). These models have been considerably modified over the years, but never totally replaced (Bailey 1982).

For many decades after the first malaria models, and for lack of hard data to test them, it was assumed that the models were correct. The number of parameters involved in Ross's 1909 model (five parameters and two variables were required to estimate the proportion of the human population infected with malaria), although large in comparison with others (for example, the parasitoid–host model of Nicholson & Bailey (1935), a quarter of a century later, involved just two parameters) was still inadequate to deal with such phenomena as mosquito

seasonality, immunity following infection, and super-infection, of which Ross seemed fully aware as early as 1911 (Bailey 1982). It took another 60 years for these additional features to be incorporated into newer malaria models (see, for example, Macdonald 1957; Dietz *et al.* 1974). The modification of model structure usually occurred when field data gave unexpected estimates for parameters such as the rate of recovery from infection.

Ross's work shines out now like a beacon, from a time of widespread ignorance about the biology of other vector-borne diseases. The life cycles of the vectors of trypanosomiasis and of the trypanosomes within them had only just been described (Austen 1911; Kleine 1909*a*, *b*); the vectors of leishmaniasis and onchocerciasis had still to be found. With a quantitative model for malaria transmission as a waymarker for vector-borne disease studies we are left asking the questions: 'Why was progress so slow? Why did it take 40 years to modify Ross's model significantly?' With hindsight it seems that the tacit acceptance of the Ross model, and the developments from it, limited the progress that otherwise might have occurred through purely observational studies on diseases and their vectors. One example of the application of the Ross and Macdonald malaria models (Macdonald 1957) to epidemiology is the calculation of Vectorial Capacity (C) which attempts to measure the daily rate at which future cases arise from a currently infective case, assuming totally effective transmission from the human to the mosquito population and later from the mosquitoes to the humans (Garrett-Jones 1964*a*, *b*). Vectorial Capacity is defined as

$$C = (ma)\,(P/F)\,\exp\,(-T/E)\,E, \tag{1}$$

where m is the number of vectors per person and a is the biting rate per vector (the product ma is estimated by direct observation on human bait), P is the proportion of blood meals taken on man, F is the interval between vector blood meals (thus P/F is equivalent to a), T is the duration of the disease latent period in the vector and E is the average life expectancy of each vector. Despite the sophistication of this model-based measure of vectorial challenge to the vertebrate host, the reanalysis of several field studies on different diseases reveals that Vectorial Capacity is only marginally better correlated with parasitological data from the human population than is the much simpler measure of challenge based only on the *number* of vectors, or their biting rate (i.e. ma in (1)) (Dye 1986). The additional work involved in measuring all the components of Vectorial Capacity is hardly worthwhile in that it has not obviously led to a deeper understanding of disease transmission; more brutally, 'methods based on untested assumptions are used to estimate parameters with unknown errors' (Dye 1986, p. 206). It seems that we have made less progress in understanding malaria epidemiology in the last 80 years than in understanding the epidemiology of cancer, for which no sensible mathematical models pre-existed, in the last 20 years. Has progress been slow despite having mathematical models, or because of them? Are our models so good that they have to be right, or are we so bad that we do not test them adequately? It seems that too often we use models in the same way that the drunken man uses a lamp-post, for support rather than illumination. Ross did not distinguish between the observational side and the mathematical side of his own work, the one naturally arising from the other; it is this tradition that needs to be strengthened at the present time. Predictive mathematical modelling should again be used as the original designers of models and lamp-posts intended, for illumination not for support.

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General models of vector-transmitted diseases

This look at trypanosomiasis and leishmaniasis begins with the well-established vector-borne disease model incorporating host and vector populations that pass through susceptible and infective categories at rates characterized by several crucial parameters. The general rule in all such sets of equations is that each category has at least one input and one output process (for example, birth into the susceptible category and loss from this category into the category of incubating or infective individuals). It follows that in such a dynamic system, if there is to be any stable equilibrium at all, at least one of the input or output processes must be density dependent. At equilibrium, input just balances output; away from the equilibrium, rates and the direction of change are determined by the net difference between the input and output processes. Because for a stable endemic situation to persist each category (e.g. of susceptibles or infectives) must be in equilibrium with all others, appropriate phase–plane analysis can be used to identify equilibrium prevalences. In the case of a single-vector species single-host species model for malaria a simple set of equations that describes changes in the proportion of infected vertebrates (x) and infected vectors (y) is as follows (modified from Aron & May (1982)):

$$\mathrm{d}x/\mathrm{d}t = (abM/N)\, y(1-x) - rx \tag{2}$$

for the infective humans, and

$$\mathrm{d}y/\mathrm{d}t = acx(1-y)\, \mathrm{e}^{-uT} - uy \tag{3}$$

for the infective vectors.

This basic model assumes that the population sizes of both the vectors and humans are constant and that infections are acquired by the human population from the vector at a rate dependent on the rate of man-biting by each individual vector (a bites per unit time), the proportion of vectors infected (y), the proportion of infected bites that give rise to infection (b) and the ratio of vector numbers (M) to human numbers (N). Such infections are lost at a fixed rate (r, the recovery rate per head), so that the average duration of infection in an infected host is $1/r$ days. The vector population acquires infection at a rate dependent on the prevalence of the disease in the vertebrate population (x), the proportion of bites on infective hosts that can give rise to mature infections in the vector (c) and the rate of man-biting by the vector (a); the exponential term allows for losses of infections through vector mortality during the incubation period (lasting T days); losses of mature infections also occur through the natural mortality of the mosquitoes (rate u, so that the average survival time of the vectors is $1/u$ days $= E$ of the Vectorial Capacity formula). It is important to stress that each of these equations has a considerable amount of density dependence built into it, a feature of Ross's more complete 1911 model (Ross 1911; Dietz 1988). Thus 'new' infections are only allowed into individuals that were not previously infected (the $(1-x)$ term in equation (2) and the $(1-y)$ term in equation (3)); the rate of transmission between infecteds and susceptibles is a function of the prevalence of infection in the infected population, not of the intensity of infection. Input of new infections, and consequently output, are strongly controlled. Absent, too, are any immune stages and any allowance for losses during the incubation period in the vertebrate hosts (which will be small if incubation periods are short). Realistic time delays should be included in equations (2) and (3), so that new additions to each category depend upon prevalences a latent period before the present.

The equilibrium conditions of these equations are examined by setting each in turn to zero, from which we obtain:

$$y = rx/[abm(1-x)] \tag{4}$$

for the humans, where $m = M/N$, and

$$y = acx\, e^{-uT}/(u + acx\, e^{-uT}) \tag{5}$$

for the vectors.

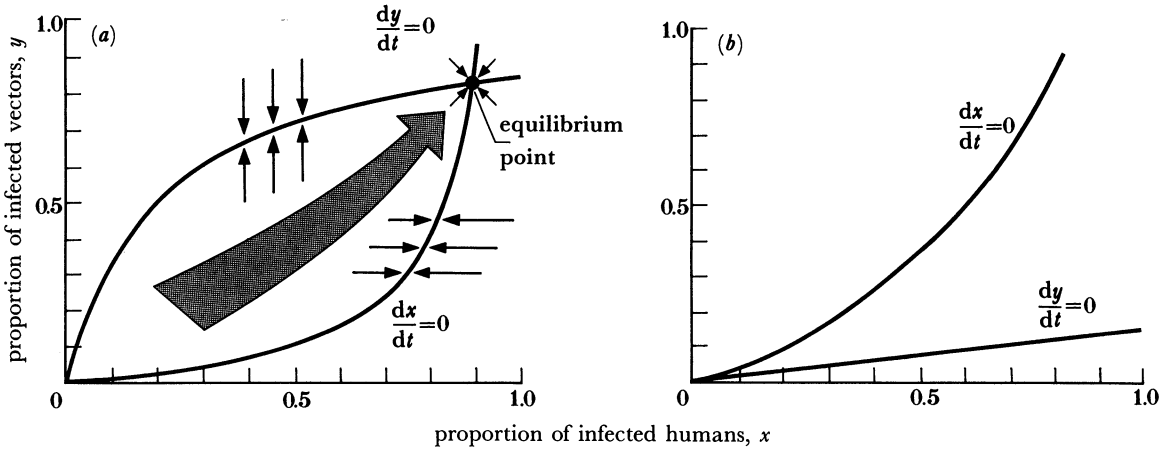

FIGURE 1. (*a*) Phase–plane relations of the equilibrium prevalence of a vector-transmitted disease from a single-host single-vector species model. Small arrows indicate changing prevalence towards equilibrium values in the vectors or humans; the larger arrow indicates movement towards the joint equilibrium. (*b*) As for (*a*), but here there is no joint equilibrium and the disease cannot persist. (Redrawn with permission from Aron & May (1982).)

These equations describe the relation between the proportion of infected vectors (y) and the proportion of infected humans (x) when either human prevalence ($dx/dt = 0$, equation (4)) or vector prevalence ($dy/dt = 0$, equation (5)) is at its equilibrium. The disease exists at equilibrium where the two curves represented by these equations cross, and this is shown for one example in figure 1*a*. Figure 1*b* shows an alternative situation in which the $dy/dt = 0$ curve for the vector lies below the $dx/dt = 0$ curve for the humans; the two curves cross at the origin which means that the disease, if introduced into the system, cannot persist and will become extinct.

Basic rate of reproduction and threshold for transmission: single-species case

The condition for the disease to continue in the system, if once introduced, is clearly set by the simple rule that the slope of the $dy/dt = 0$ graph at the origin must be greater than the slope of the $dx/dt = 0$ graph; i.e. (referring to equations (4) and (5) for very small x) that

$$ac\, e^{-uT}/u \geqslant r/abm$$

or

$$a^2mcb\, e^{-uT}/ur \geqslant 1. \tag{6}$$

The left-hand side of (6) is usually called the basic reproductive rate of the disease (R_0) and is the number of new infections that eventually arise from a single current infection during the

period of its infectiousness in a totally susceptible population (i.e. before recovery, treatment or death). Diseases only increase at their basic reproductive rates when they are close to extinction (i.e. when all hosts are susceptible) and the higher the value of the basic reproductive rate the more difficult it will be to eradicate the disease. By setting the left-hand side of (6) equal to unity the threshold for disease transmission can be calculated. This is the point at which only one susceptible human is contacted, and eventually becomes infected, during the lifetime of all the vectors that pick up their infections from one previously infected host. In the case of vector-borne diseases the threshold is defined in terms of the ratio of vectors to hosts (m) and is found from

$$m = ur/(a^2bc\ \mathrm{e}^{-uT}). \tag{7}$$

The squared term in the denominator is a common feature of models for vector-borne diseases and arises because infections must first be picked up by susceptible vectors while biting at a rate a and later transmitted while biting at the same rate.

The basic reproductive rate is crucial in all transmission models (a conference even produced an ode to it! (Anderson & May 1982)) and is closely linked to disease prevalence at equilibrium (which is perhaps not surprising since it includes most of the parameters that determine equilibrium prevalences). It is equivalent to the Vectorial Capacity multiplied by the average duration of infection in the vertebrate hosts, hence becoming a dimensionless quantity (the transmission parameters b and c are generally not included in the Vectorial Capacity formula). Recent work points to some advantage in splitting R_0 into two components, representing transmission from the infected vertebrate to the susceptible vector population (R_1) and from the infected vector back to the susceptible vertebrate population (R_2) (figure 2). During the average infection of one vertebrate (lasting $1/r$ days) the animal will be bitten at a daily rate am (i.e. biting rate per vector multiplied by the number of vectors per vertebrate). If only the proportion c of the bites on the animal becomes established in the vectors and only the

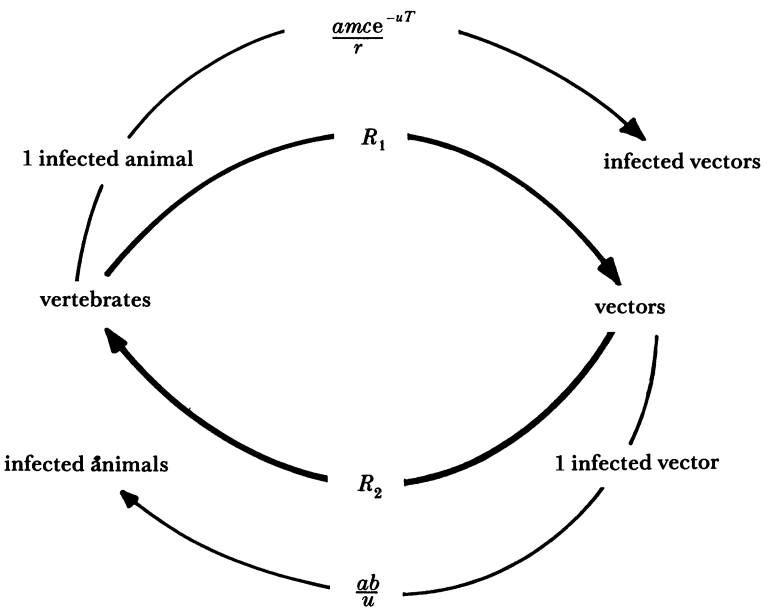

FIGURE 2. Diagrammatic representation of the transmission cycle from vertebrate to vector (R_1) and vector to vertebrate (R_2) illustrating the calculation of the basic rate of reproduction of vector-transmitted diseases. (Note that these definitions of R_1 and R_2 differ from those of Dietz (1988).)

proportion $\exp(-uT)$ vectors survive the incubation period, the total number of surviving, infective vectors produced during the course of one infection in one vertebrate will be

$$R_1 = amc\, e^{-uT}/r. \tag{8}$$

Each of these infective flies will live for a further $1/u$ days during which it will bite at the daily rate of a and therefore produce the following number of newly infected vertebrates (assuming all vertebrates are susceptible)

$$R_2 = ab/u. \tag{9}$$

The total number of newly infected vertebrates arising, through vector transmission, from one presently infected vertebrate will therefore be

$$R_0 = R_1 R_2,$$
$$= a^2 mcb\, e^{-uT}/ur \tag{10}$$

which is the left-hand side of equation (6).

Vector-transmitted diseases can be attacked by reducing either R_1 or R_2, although the consequences for prevalence in the vertebrate may not be the same because of density dependence in the transmission cycle. Generally, vertebrate prevalence is more sensitive to a reduction in R_2 than to a similar proportionate reduction in R_1. This confirms Macdonald's suggestion (Macdonald 1965) that in the case of schistosomiasis the provision of safe water supplies will be more effective than the provision of latrines (Dietz 1988). Similarly a sporozoite vaccine for malaria will be more effective than a gametocyte vaccine. The parallels with other biological systems are obvious. In the case of insect pest control strategies the greatest reduction in the pest population is achieved by placing control *after* the density dependence in the life cycle and before the damage-causing stage; if the damage-causing stage itself experiences a density-dependent mortality, the best strategy is to attack this stage directly (Rogers 1983). In the present instance any attack on R_1 may later be compensated for by density dependence in R_2; hence attack should be directed at R_2, the step immediately before the stage we seek to reduce (i.e. prevalence in the vertebrate).

Leishmaniasis and trypanosomiasis

Simplifying assumptions of the vector-borne disease models discussed so far are that only one host species is involved and that the mortality rate of the vertebrate host population is unaffected by parasitism. Neither condition applies to various forms of leishmaniasis and trypanosomiasis which are typically zoonotic diseases that can have devastating effects on human populations (Peters & Killick-Kendrick 1987; Ford 1971). *Leishmania* is an intracellular parasite of vertebrate macrophages and is transmitted by sandflies of the genera *Phlebotomus* and *Lutzomyia*. Wild reservoir-hosts show few, if any, symptoms of the disease which in humans produces visceral and cutaneous manifestations. We here concentrate on the visceral form known as Indian kala-azar, caused by *L. donovani* and transmitted by *P. argentipes* (Molyneux & Ashford 1983; Ashford & Bettini 1987). Man is certainly the most important and possibly the only host in India of this disease, which is fatal unless treated. The variability of the response of the human host to leishmaniasis is much more marked than is the response to malaria. Latent and infectious periods for visceral leishmaniasis vary in duration from days to

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years. The intensity of infection is also very variable (possibly related to variation in innate susceptibility) and those who survive the first clinical bout of leishmaniasis will normally be resistant to further clinical attacks. The mechanism for this may be premunition, in which case apparently healthy people retain lifelong, minimal infectivity to sandflies. Drug treatment of visceral leishmaniasis often induces post kala-azar dermal leishmaniasis, a chronic and infectious condition especially common in India (Rees & Kager 1987).

Trypanosoma is a blood and tissue parasite transmitted in Africa by tsetse flies, *Glossina* sp. Again the various forms of trypanosomiasis apparently affect wild animal hosts very little, whereas zebu cattle will die, if untreated, from infections of *T.* (*Duttonella*) *vivax* and *T.* (*Nannomonas*) *congolense* (Hoare 1972; Molyneux & Ashford 1983). Man is affected only by two subspecies of *T. brucei* which in West Africa produces a typically chronic form of sleeping sickness (*T. b. gambiense*) and in East Africa a more acute form (*T. b. rhodesiense*) resulting in death within weeks. A third subspecies, *T. b. brucei*, morphologically indistinguishable from the other two, does not infect man. None of the subspecies of *T. brucei* appears to be an important pathogen of domestic animals which nevertheless can support infections of them. Whereas *T. vivax* and *T. congolense* occur throughout the distributional range of the tsetse vectors, human sleeping sickness (and possibly *T. brucei* infection in animals) is much more localized, occurring in geographically restricted foci, some of very long standing (Ford 1971; WHO 1986). Humans who recover from trypanosomiasis (generally after treatment) are thought to have some immunity to homologous challenge (i.e. from the same trypanosome strain) but little, if any, to heterologous challenge (Hoare 1972). Occasional cases of infection are recorded where the individuals concerned show no apparent ill-effects ('healthy carriers').

Models for vector-transmitted diseases involving more than one vertebrate host

It is relatively straightforward to extend the vector-borne disease equations already given to the situation in which more than one host species is involved, allowing for incubation and immune periods in the vertebrate hosts. The appropriate parameter and variable definitions in the case of African trypanosomiasis are given in table 1, together with an example of the values of each (from Rogers 1988). The vertebrate and vector densities chosen are those appropriate for a West African village in the pre-forest zone of Ivory Coast, from a human sleeping sickness region (values for the various parameters in table 1 necessarily come from a variety of sources, some West and some East African; complete data do not yet exist for any single site in Africa). For the moment we will assume there is no parasite-induced host mortality. The equations relating the equilibrium prevalences of the vector and vertebrate are as follows in the cases of *T. vivax* and *T. congolense* (and for similar diseases involving two host species):

$$y = \frac{r_1 x_1}{a_1 b_1 m_1 \left[1 - x_1 \left(1 + \frac{r_1}{i_1} + \frac{r_1}{v_1}\right)\right]} \tag{11}$$

for vertebrate species 1,

$$y = \frac{r_2 x_2}{a_2 b_2 m_2 \left[1 - x_2 \left(1 + \frac{r_2}{i_2} + \frac{r_2}{v_2}\right)\right]} \tag{12}$$

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TABLE 1. VARIABLES AND PARAMETERS OF THE TWO-SPECIES VECTOR-TRANSMITTED DISEASE MODEL OUTLINED IN THE TEXT, APPLIED TO THE AFRICAN TRYPANOSOMIASES

(The values chosen are those appropriate for a West African village situation, although the transmission parameters c and b are estimated from East African field data and c' from laboratory experiments; see Rogers (1988) for more details.)

(*a*) general

N_1	number of animals, species 1 (e.g. humans)	300
N_2	number of animals species 2 (e.g. domestic hosts)	50
V	number of tsetse	5000
p_1	proportion of tsetse blood meals from species 1	0.3
p_2	proportion of tsetse blood meals from species 2	0.7
u	daily mortality rate of flies	0.030
d	duration of feeding cycle in flies	4 d

$$a_1 = p_1/d,\ a_2 = p_2/d;\ m_1 = V/N_1,\ m_2 = V/N_2$$

(*b*) disease-specific

		T. vivax	*T. congolense*	*T. brucei*
$1/i_1$	incubation period in species 1	—	—	12 d
$1/i_2$	incubation period in species 2	12 d	15 d	12 d
$1/r_1$	duration of infection in species 1	—	—	70 d
$1/r_2$	duration of infection in species 2	100 d	100 d	50 d
$1/v_1$	duration of immunity in species 1	—	—	50 d
$1/v_2$	duration of immunity in species 2	100 d	100 d	50 d
T	incubation period in tsetse	10 d	20 d	25 d
b_1	probability of infected fly bite producing infection in species 1	—	—	0.62
b_2	probability of infected fly bite producing infection in species 2	0.29	0.46	0.62
c	probability of any infected blood meal eventually giving a mature infection in a fly	0.177	0.025	—
c'	probability of first feed only (taken during first day) eventually giving a mature infection in a fly	—	—	0.065

for vertebrate species 2, and

$$y = \left[\frac{c(a_1 x_1 + a_2 x_2)}{u + c(a_1 x_1 + a_2 x_2)}\right] e^{-uT} \qquad (13)$$

for the vector, where x and y refer to the prevalence in the vertebrate and vector respectively, subscripts identify the two vertebrate species, and $1/i$ and $1/v$ are the durations of the incubation and immune periods in the vertebrate hosts (other symbols as in equations (4) and (5)). These three equations can be solved simultaneously for x_1, x_2 and y. The relations between equilibrium prevalences in the two vertebrate species (assuming prevalence in the vector is also at equilibrium) are as follows:

$$x_2 = \frac{x_1}{a_2}\left[\frac{r_1 u}{c(A(1 - x_1 f_1) - r_1 x_1)} - a_1\right] \qquad (14)$$

for vertebrate species 1, and

$$x_1 = \frac{x_2}{a_1}\left[\frac{r_2 u}{c(B(1 - x_2 f_2) - r_2 x_2)} - a_2\right] \qquad (15)$$

for vertebrate species 2, where $A = a_1 b_1 m_1 e^{-uT}$, $B = a_2 b_2 m_2 e^{-uT}$, $f_1 = (1 + r_1/i_1 + r_1/v_1)$ and $f_2 = (1 + r_2/i_2 + r_2/v_2)$.

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For trypanosomiasis caused by *T. brucei* this set of equations applies only to newly emerged flies, because experimental work shows that the parameter c is relatively high for the first day or so after emergence of the adult fly, and then drops virtually to zero thereafter (Wijers 1960; Watson 1963; Gingrich *et al.* 1982*a*), except possibly in starved older flies (Gingrich *et al.* 1982*b*). Allowance can be made for this by assuming that newly emerged (i.e. teneral) flies are susceptible to infection with *T. brucei* for a period of t days only (t is less than the average duration of the feeding cycle, d days). Assuming u' is the daily emergence rate of teneral flies from puparia (related to the adult female population a puparial period ago) the unfed tenerals less than t days old (and therefore susceptible to infection) are given by

$$[u'/(a_1+a_2+u)]\,(1-\mathrm{e}^{-(a_1+a_2+u)t}), \tag{16}$$

where the first term is the total teneral population (expressed as a proportion of the total fly population), which is reduced at the rates (a_1+a_2) through feeding and u through mortality, and the second term is the proportion of these flies that are less than t days old. Allowing for this lower level of infection in the flies, the equilibrium equations (13), (14) and (15) are replaced by the following (where it is assumed that at equilibrium vector birth and death rates are equal, i.e. $u'=u$):

$$y = (a_1 x_1 + a_2 x_2)\, c' E\, \mathrm{e}^{-uT} \tag{17}$$

for the vector species, where

$$E = (1-\mathrm{e}^{-(a_1+a_2+u)t})/(a_1+a_2+u)$$

and c' is the proportion of first, infected blood meals that gives rise to infection in newly emerged flies when they feed within t days of emergence,

$$x_2 = \frac{x_1}{a_2}\left[\frac{r_1}{c'AE(1-x_1 f_1)} - a_1\right] \tag{18}$$

for vertebrate species 1, and

$$x_1 = \frac{x_2}{a_1}\left[\frac{r_2}{c'BE(1-x_2 f_2)} - a_2\right] \tag{19}$$

for vertebrate species 2.

The phase–plane relations for equations (11)–(15) are shown in figure 3. The sides and base of the block shown in figure 3 illustrate the predictions of pairs of equations for equilibrium prevalences in the two vertebrate species and in the vectors (view A equations (11) and (13), assuming $x_2 = 0$; view B equations (12) and (13), assuming $x_1 = 0$; and view C equations (14) and (15), which assume that prevalence in the vector is at equilibrium). The inclined plane within the block (the $\mathrm{d}y/\mathrm{d}t = 0$ surface drawn with dashed lines in figure 3) shows the range of equilibrium disease prevalence in the vector for any combination of prevalences in the two host species (vector prevalence is rather less variable than vertebrate prevalence). A projection of view C on to this plane (shown by the thick lines on the plane itself) fixes the equilibrium point for the disease system (Rogers 1988).

Basic rate of reproduction and threshold for transmission: two-species case

The basic rate of reproduction of diseases involving two (or more) vertebrate hosts and thresholds for transmission can be calculated by using an argument similar to that already given for malaria. By considering the number of newly infected vectors arising from one infected

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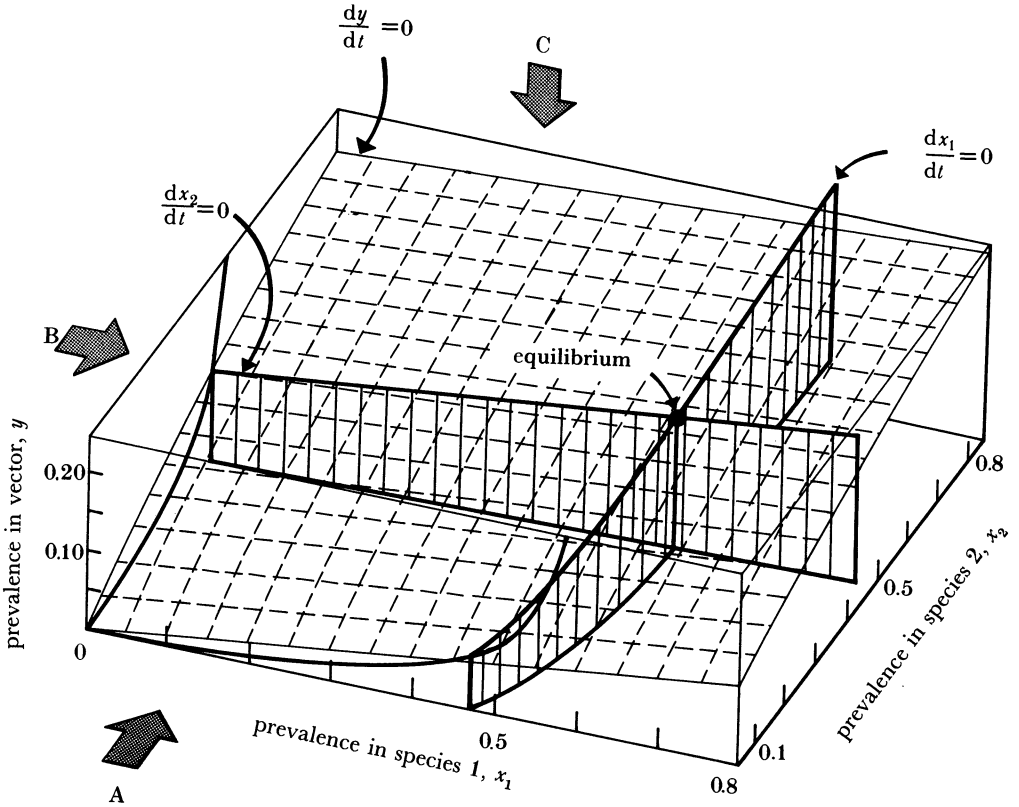

FIGURE 3. Phase-plane relations for the two-host, single-vector species model described in the text. Faces A, B and C of the block are the relations for pairs of equations (11)–(15) in the text. The equilibrium prevalence in the vector is shown by the dashed, inclined plane (equation (13)). The system equilibrium is indicated by an arrow (from Rogers 1988). Values for the variables and parameters were: $N_1 = N_2 = 300$, $V = 5000$, $p_1 = 0.3$, $p_2 = 0.7$, $u = 0.025$, $d = 4$, $1/i_1 = 1/i_2 = 0$, $1/r_1 = 35$ days, $1/r_2 = 20$ days, $1/v_1 = 1/v_2 = 20$ days, $T = 25$ days, $b_1 = 0.62$, $b_2 = 0.3$, $c = 0.1$.

vertebrate of each species, and the number of newly infected vertebrates from each of the infected flies, the basic rate of reproduction in the case of infections of *T. vivax* and *T. congolense* becomes

$$R_0 = R_{0_1} + R_{0_2}, \tag{20}$$

where

$$R_{0_1} = \frac{1}{r_1} a_1 m_1 c \, \mathrm{e}^{-uT} \left(\frac{a_1 b_1}{u} \right)$$

and

$$R_{0_2} = \frac{1}{r_2} a_2 m_2 c \, \mathrm{e}^{-uT} \left(\frac{a_2 b_2}{u} \right). \tag{21}$$

The condition for disease persistence is therefore

$$\frac{c \, \mathrm{e}^{-uT}}{u} \left(\frac{a_1^2 b_1 m_1}{r_1} + \frac{a_2^2 b_2 m_2}{r_2} \right) \geqslant 1. \tag{22}$$

The threshold for transmission is obtained by setting the left-hand side of (22) equal to unity and rearranging as shown in table 2, where the formulae for *T. brucei* are also listed. The additive nature of equation (20) indicates that the disease will continue to affect species 1, even

when this species alone is incapable of maintaining the disease, because of the presence of species 2 which acts as a reservoir of infection; the disease persists at vector densities at and above those corresponding to the lowest threshold value of any of the vertebrate species involved. One example is shown here in figure 4, from which it can be seen that equilibrium prevalences in the vector species may be rather insensitive to changes in prevalence of one of the vertebrate species. This is more likely to be the case when the vertebrate in question is not the major provider of blood meals for the vectors. The reservoir species introduces considerable density dependence in the example shown in figure 4 so that prevalence in the species represented on the x-axis of figure 4 is almost entirely determined by its own susceptibility to infection and not (as in the case of malaria) by its interaction with the vector species. It follows from this that a species, such as man, that is relatively susceptible to diseases that mainly involve other host species may be relatively disease-free in the presence of a large (and prevalence-stabilizing) population of alternative hosts, but that as these hosts are reduced (often through interference from man) humans provide a larger proportion of the blood meals of the vectors, so that human and vector prevalences increase considerably, and epidemics occur.

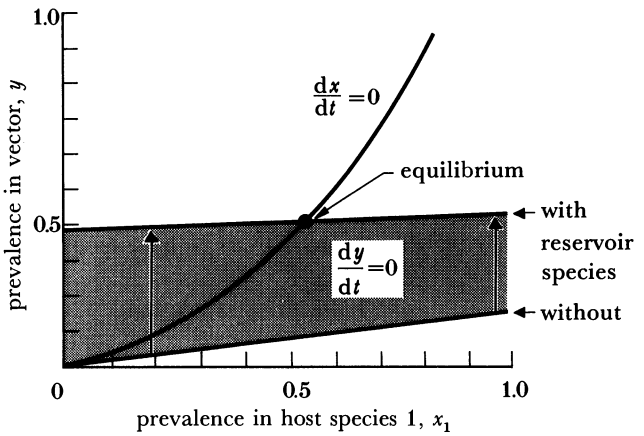

FIGURE 4. The effect of a reservoir species (species 2 in the example in the text) is to elevate the equilibrium prevalence line of the vector so that the disease persists in the first species where otherwise it could not do so. Without the reservoir species the equilibrium point for the first species is at zero, as in figure 1*b*.

TABLE 2. BASIC REPRODUCTIVE RATES OF THE AFRICAN TRYPANOSOMIASES (R_0) AND THRESHOLDS FOR TRANSMISSION PREDICTED BY THE TRYPANOSOMIASIS MODEL DESCRIBED IN THE TEXT

(See text and table 1 for parameter and variable definitions (from Rogers 1988).)

R_0	threshold
$\frac{c\,e^{-uT}D}{u}\left(\frac{a_1^2 b_1 m_1}{r_1}+\frac{a_2^2 b_2 m_2}{r_2}\right)$	$m_1=\frac{u}{[(a_1^2 b_1/r_1)+(a_2^2 b_2 h/r_2)]\,c\,e^{-uT}D}$, where $h=N_1/N_2$, $m_2=m_1 N_1/N_2$

For *T. vivax* and *T. congolense*, $D=1$.

For *T. brucei*, c' replaces c and $D=\frac{u[1-e^{-(a_1+a_2+u)}]}{(a_1+a_2+u)}$.

Application to the African trypanosomiases

The equilibrium disease prevalences, basic rates of reproduction and thresholds for transmission for the values of the three trypanosome species listed in table 1 are given in table 3. The calculated equilibrium prevalences coincide with field experience. *T. vivax* is often the most abundant trypanosome in susceptible domestic animal populations, such as cattle, and fly infection rates with the different trypanosome species, when they co-occur, are much more variable than the corresponding animal infection rates. Of particular interest is the calculation of the basic reproductive rate, which is considerably lower for *T. brucei* (2.65) than for *T. congolense* (64.4) and *T. vivax* (388.2). Threshold vector numbers are correspondingly higher, being approximately 40, 1.6 or 0.3 flies per host respectively. This may well explain the very much more restricted geographical distribution of *T. brucei* infections than of the other trypanosome species in Africa. Only within certain parts of the overall range of the tsetse vectors will their numbers reach sufficiently high levels to exceed the transmission threshold (Rogers & Randolph 1986). Table 3 also shows that the basic rate of reproduction of trypanosomiasis in the human host is very much less than 1.0, and therefore that the disease cannot be maintained by the human host alone. Although this has been accepted for a long time for the case of East African sleeping sickness, it has always been thought that the West African disease could be supported by the human population alone.

Table 3. Predictions from the trypanosomiasis model, using the parameters and variables of table 1 (from Rogers 1988)

(Basic reproductive rates and thresholds for transmission are calculated by using the formulae in table 2. For *T. vivax* and *T. congolense* infections $b_1 = 0$. The last column shows what would happen if the alternative species were incapable of supporting the disease (i.e. $b_2 = 0$ for species 1 or $b_1 = 0$ for species 2).)

	T. vivax	*T. congolense*	*T. brucei* (species 1+2)	*T. brucei* (species 1 or 2)
equilibrium trypanosomiasis prevalence in species 1 (man)	—	—	7.0%	
equilibrium trypanosomiasis prevalence in species 2 (animals)	47.0%	45.8%	28.7%	
equilibrium trypanosomiasis prevalence in tsetse	24.2%	3.4%	0.61%	
basic reproductive rate	388.2	64.4	2.65	species 1 = 0.11, species 2 = 2.54
threshold for transmission (flies/host), species 1	—	—	6.29	species 1 = 153.0
threshold for transmission (flies/host), species 2	0.26	1.55	37.7	species 2 = 39.3

The animal reservoir is particularly significant when it is closely associated with man. In many parts of West Africa domestic pigs are kept within or near to villages, and local populations of the vector *G. palpalis* increase. One example is shown in figure 5. Studies in these situations show that 7% of fly blood meals come from man and 75% from domestic pigs. In coffee and cocoa plantations away from the villages (where there are few alternative hosts) 68% of fly blood meals are taken from man and only 14% from pigs (A. Seketeli, personal communication). Figure 6 shows how the equilibrium disease prevalence in man for each of these situations is quite low, approximately 2%. This is because when only a few feeds are

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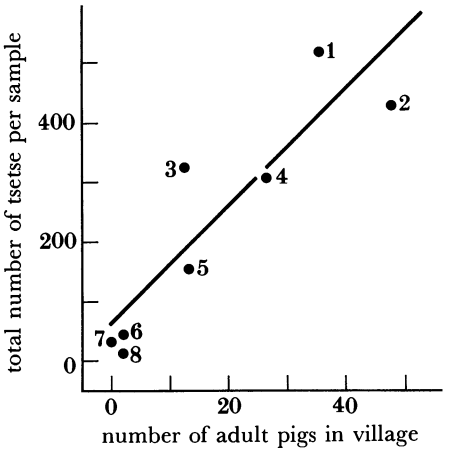

FIGURE 5. The relation between the regular trap samples of the tsetse fly *Glossinia palpalis palpalis* in various villages in Ivory Coast and the number of domestic pigs (censused in March–July 1981). Sites were: 1, Tuyankro; 2, Degbézéré; 3, Klebo I; 4, Kouassi Perita; 5, Congo Aboisso II; 6, Yaokro; 7, Koffikro; 8, Koudougou (from Rogers *et al.* 1984).

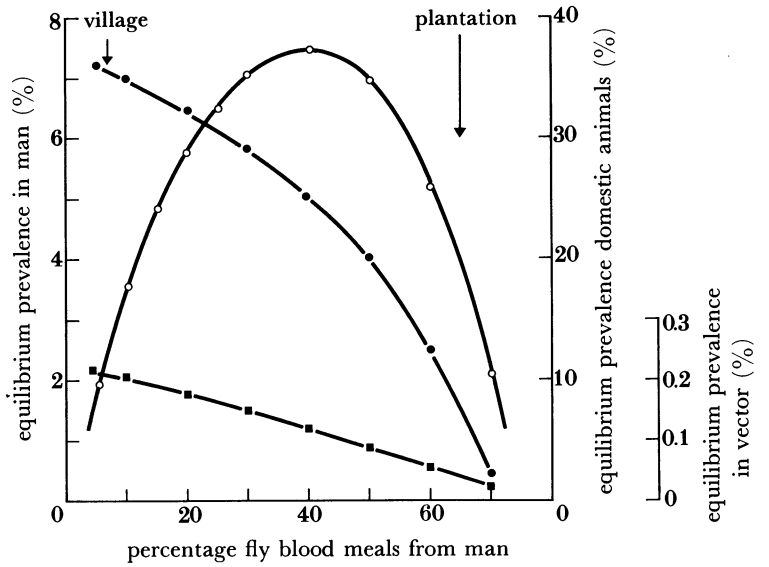

FIGURE 6. Relation between the equilibrium prevalences of *T. brucei* infections in man, domestic animals and the tsetse vectors predicted by the two-species model described in the text (parameters and variables as in table 1). Arrows above the curve indicate typical values for village and plantation sites in Ivory Coast, West Africa. ○, Man; ●, domestic animals; ■, tsetse.

taken on man a higher proportion of them are infected, because most flies obtain most of their food from the heavily infected pigs. When man becomes the major source of food, the much lower ratio of flies to humans (because men are more numerous than pigs) results in much lower fly and thus human infection rates. Usually, however, there is movement of flies from the village to the plantation (Randolph & Rogers 1984), so that the plantation workers are at a considerable risk of infection. Although the pigs, the preferred hosts of tsetse, therefore 'protect' the humans from being bitten in the villages they also provide the major source of infection for the flies biting humans in the plantations.

The equilibrium prevalences in table 3 refer to a particular tsetse population size. The

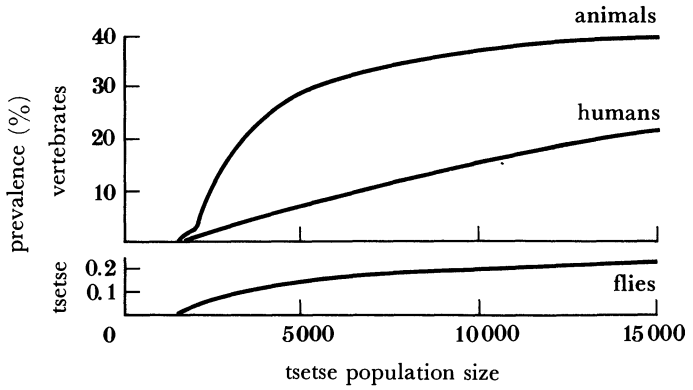

FIGURE 7. Relation between the equilibrium prevalences of *T. brucei* infections and tsetse population size predicted from the two-species model outlined in the text (from Rogers 1988).

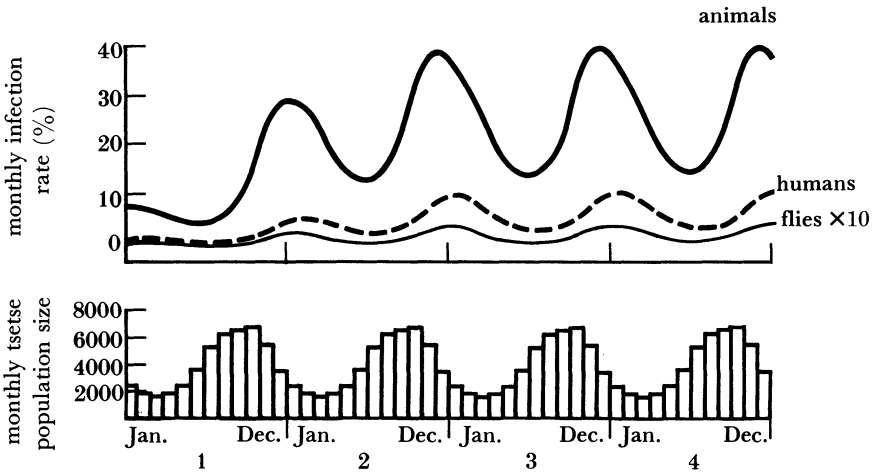

FIGURE 8. Changes in seasonal infection rates in man, an alternative host species and the tsetse vectors (upper graph) predicted by the two-species model described in the text when tsetse numbers fluctuate as shown by the lower graph.

relation between equilibrium prevalences of *T. brucei* and tsetse population size is shown in figure 7. Once the disease is present in any single one of the species involved (i.e. above the threshold) it is present in all species, and prevalence increases with vector density up to levels set by the durations of the incubation, infectious and immune periods of the affected animals. Ross & Hudson (1931) looked at the effects of vector seasonality on malaria infection rates in humans, pointing out that human prevalence will always tend to reach a peak after the peak seasonal abundance of the vectors. Results for the present two species model are shown in figure 8. The infection rate in the favoured host species (the animals in figure 8) reaches a peak relatively soon after the fly numbers reach their annual maximum. Peak human infection rates occur approximately three months after the fly peak. Field evidence supporting this prediction of the model is shown in figure 9 which records the seasonal change in tsetse numbers in the large *G. morsitans* fly-block in Western Tanzania, together with the number of cases of human sleeping sickness from the same area (data from Jackson (1944) and Fairbairn (1948)

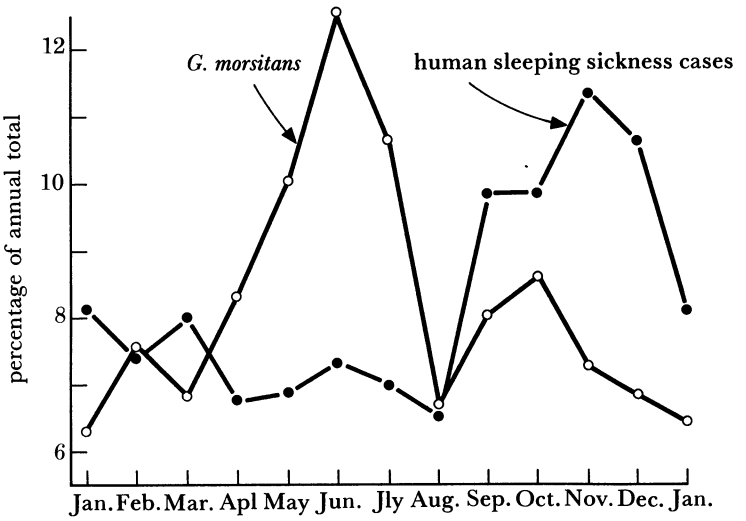

FIGURE 9. Relation between the monthly density of the tsetse fly *G. morsitans* and the number of sleeping sickness cases recorded in the western fly block of Tanzania (data from Jackson (1944) and Fairbairn (1948) respectively). Case numbers peak five months after vector density.

respectively). The case numbers peak five months after the seasonal maximum of fly numbers (rather longer than predicted by the model, but this delay includes the time from the moment of infection to the time at which infected people present themselves for treatment).

EFFECT OF VECTOR-TRANSMITTED DISEASES ON HOST POPULATIONS: LEISHMANIASIS

When vector-borne diseases kill their hosts, the dynamics of the host population cannot be omitted from the transmission equations given so far. Recently this has been allowed for in a model for Indian kala-azar which killed many tens of thousands of people in Assam in the period 1875–1950 (Ashford & Bettini 1987). Although previous authors accepted a fairly regular interval between epidemic peaks they nevertheless generally subscribed to the view that epidemics followed other natural catastrophes such as earthquakes or influenza outbreaks. Drug treatment, commencing around 1920, reduced the case mortality rate from 90 % to 10 % while at the same time causing an increase in the number of people with post-kala-azar dermal leishmaniasis, a condition chronically infectious to sandflies. A recent reanalysis of the kala-azar data suggests there were three major epidemics in Assam in this 75-year span, with inter-epidemic intervals of about 30 and 20 years (Dye & Wolpert 1988) and these can be described by a deterministic mathematical model which predicts the changes over time in the numbers of susceptible (S), infected (I) and resistant (R) humans as follows (from Dye & Wolpert 1988):

$$S_{t+1} = S_t + aN_t - (cN_t^{x-1})\, I_t(S_t/N_t) - bS_t, \tag{23}$$

$$I_{t+1} = I_t + (cN_t^{x-1})\, I_t(S_t/N_t) - (b+d)\, I_t, \tag{24}$$

$$R_{t+1} = R_t + \mathrm{e}\, N_t - bR_t, \tag{25}$$

where $N_t = S_t + I_t + R_t$ is the total human population size at time t. The vital category of resistant humans includes some individuals who quickly and spontaneously cure after infection (these are regarded as an unimportant component of the infectious pool) (Heyneman 1971; Rees & Kager 1987) and some who are never bitten by the sandfly vector. Susceptible and resistant individuals are born at the rates of a and e respectively, and the natural death rate b is much smaller than the disease-induced mortality rate d. The transmission term of equations (23)–(25) depends sensitively on the value of parameter x. If N is constant and the fly population takes a fixed number of bites per unit time then $x = 0$ and c is a measure of the infective biting rate of the entire sandfly population (thus c/N is the annual infective biting rate per host). When N is allowed to vary it becomes necessary to make an assumption about how the vector population also varies. If vector numbers are closely related to host numbers, then vector population size will be some function of them, for example kN, where k is the number of vectors 'produced' by each host. The number of vectors per host is therefore $kN/N = k$, and parameter x of equations (23) and (24) takes the value of 1.0, at which point the model resembles that of directly transmitted infections in which cyclic phenomena are quite common and well understood (Anderson 1982). A yearly time-step is used in the model as this adequately reflects the seasonality of the vector that generates during one part of the year new cases which, after a 2–6-month incubation period, are infective mainly to sandflies emerging the following year.

The best fit of this model to the data for the whole of Assam is shown in figure 10. The main conclusion of the original authors was that the second epidemic was provoked by intrinsic rather than extrinsic processes, although to achieve the fit shown in figure 10 the model also included the effect of the gradual spatial spread of the disease after its first introduction into Assam, the occurrence of 1% of chronic infectives from 1918 onwards (i.e. associated with the

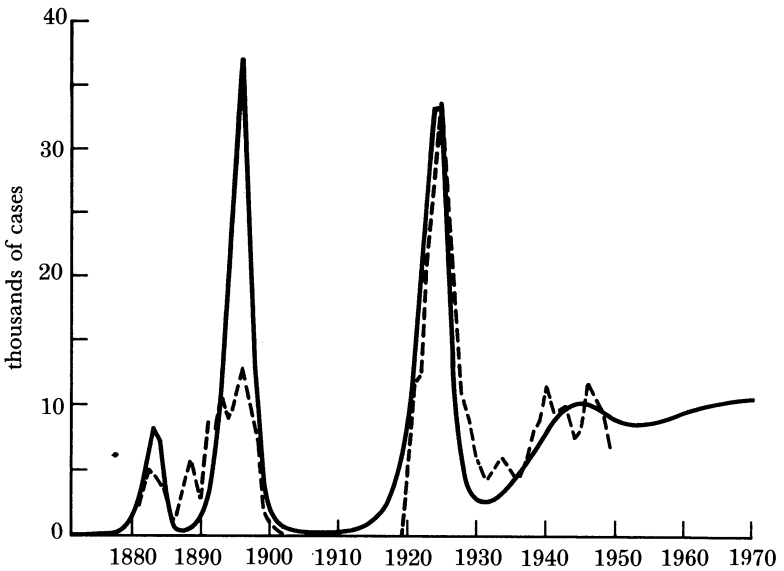

FIGURE 10. The number of kala-azar cases recorded from the districts of Goalpara, Kamrup, Nowgong and Darrang in Assam for the period 1880–1950 (dashed lines) and the output of the model for kala-azar described in the text (from Dye & Wolpert 1988). Parameters for the model were as follows: $a = 0.19$, $b = 0.037$, $c = 7.5$, $d = 0.95$, $e = 0.04$, $x = 1$.

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introduction of drug treatment), and the effect of an influenza outbreak that rendered 1% of the resistants susceptible during 1921–25 and so exacerbated the second epidemic (Dye & Wolpert 1988). The introduction of even a small percentage of chronic infectives has two effects on the model; it tends to shorten the inter-epidemic period and it dampens the epidemic cycles, converting an epidemic disease into an endemic one.

Effect of vector-transmitted diseases on host populations: trypanosomiasis

Epidemics of human sleeping sickness in Africa are, like the kala-azar epidemics in Assam, associated with the opening up of the continent by the colonial authorities. Increased population movement resulted in the transfer of humans and their parasites into regions in which susceptible resident populations, living at relatively high population densities and in association with appropriate vector species, provided ideal conditions for the spread of vector-borne diseases. In the case of West Africa, it appears that new strains of *T. b. gambiense* spread from what is now Zaire in a wave that took 27 years to reach its westernmost extension into Sierra Leone (Scott 1965). In 1896 strains from the same general area were carried by Sudanese followers of Emin Pasha into the Lake Victoria region of Uganda, which does not appear to have experienced any form of sleeping sickness before this time. The ensuing outbreak of human sleeping sickness resulted in the death of approximately two thirds of the human population in the affected areas (Duggan 1970). In another region in Africa, in what is now Zambia, a new and virulent strain of human sleeping sickness was first recorded from a European traveller in 1908. This new disease, caused by *T. b. rhodesiense*, gradually spread up through Africa, reaching Tanzania around 1920 and the shores of Lake Victoria around 1940. From the first introduction into Tanzania it appears that most sleeping sickness cases from this country were due to the more virulent *T. b. rhodesiense*, an organism derived from a wild animal reservoir. The numbers of cases recorded each year for the whole of Tanzania during the period 1922–1980 is shown in figure 11, which bears certain similarities to the kala-azar data (i.e. a first, pronounced epidemic peak followed by apparently damped epidemic cycles). The result of autocorrelation analysis of these data is shown in figure 12. The autocorrelation coefficient takes significant negative values at lags of around 9 years, and

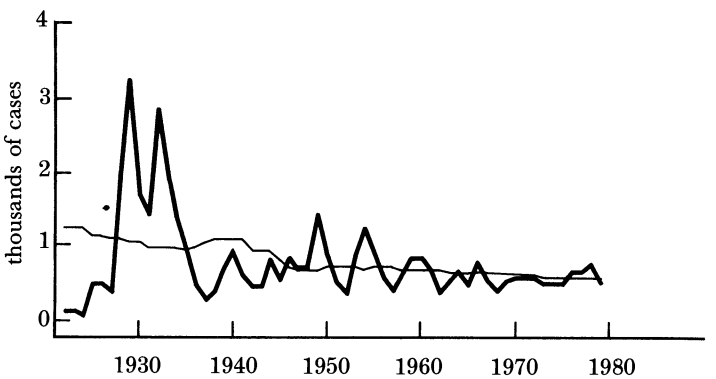

Figure 11. The number of cases of human sleeping sickness recorded from the whole of Tanzania for the period 1922–1980. (Data from Kilama *et al.* (1981).) The thin line is the 24-point moving average.

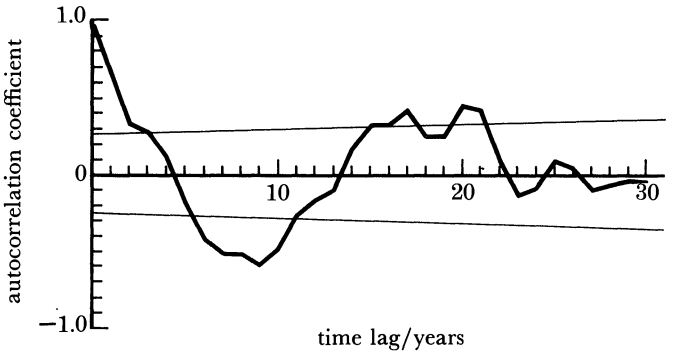

FIGURE 12. Deviations from the 24-point moving average line of figure 12 are autocorrelated at increasing lags to detect periodicity in the data. Fluctuations in the autocorrelation indicate a periodicity of 17–21 years.

positive values at lags of 17–21 years, indicating that this is the duration of each epidemic cycle.

A simple descriptive model of the situation in Tanzania would be as follows:

$$S_{t+1} = S_t + aN_t - KS_t - (b + \lambda N_t)\, S_t, \tag{26}$$

$$I_{t+1} = I_t + KS_t - (b + d + \lambda N_t)\, I_t, \tag{27}$$

where S, I, a and b have the same meaning as in equations (23)–(25) and λ is a density-dependent component of human survival found from

$$N_0 = (a - b)/\lambda. \tag{28}$$

In the absence of any disease-induced mortality the introduction of λ allows the human population to grow logistically up to its carrying capacity, N_0. The parameter K now subsumes all those variables that affect the rate at which susceptibles become infected. Once again we assume that vector numbers are related to host abundance, but in this case the hosts are both wild animals and humans. The abundance of wild animals is assumed to be constant, W, and they are assumed to have a fixed infection rate i. There is some evidence that the local abundance of tsetse populations is related to the abundance of hosts (figure 5, for example), but it is also well known that not all host species are equally suitable for the flies. We allow for this by calculating tsetse abundance on the basis of the weighted abundance of the humans and wild animals; the animals have a weighting of 1.0 and the humans a weighting of w, which is always less than 1.0. Finally the infection rate of the fly population is assumed to be related to the total number of infected hosts (i.e. both human and animal) divided by the total population of all hosts. These assumptions lead to the following calculation for K in equations (26) and (27):

$$K = \frac{c(I_t + Wi)\,(wN_t + W)}{(N_t + W)\,(wN_0 + W)}. \tag{29}$$

Unlike other epidemic models, equations (26) and (27) do not include an immune category of humans. This reflects the belief that human immunity, if it exists at all, is of a rather transient nature (Hoare 1972). Two examples of the predictions of this model are shown in figure 13 for the situation in which five infected individuals are introduced into a population of 100000 people. In the first example (figure 13*a*) there are assumed to be only 50 wild hosts. A first

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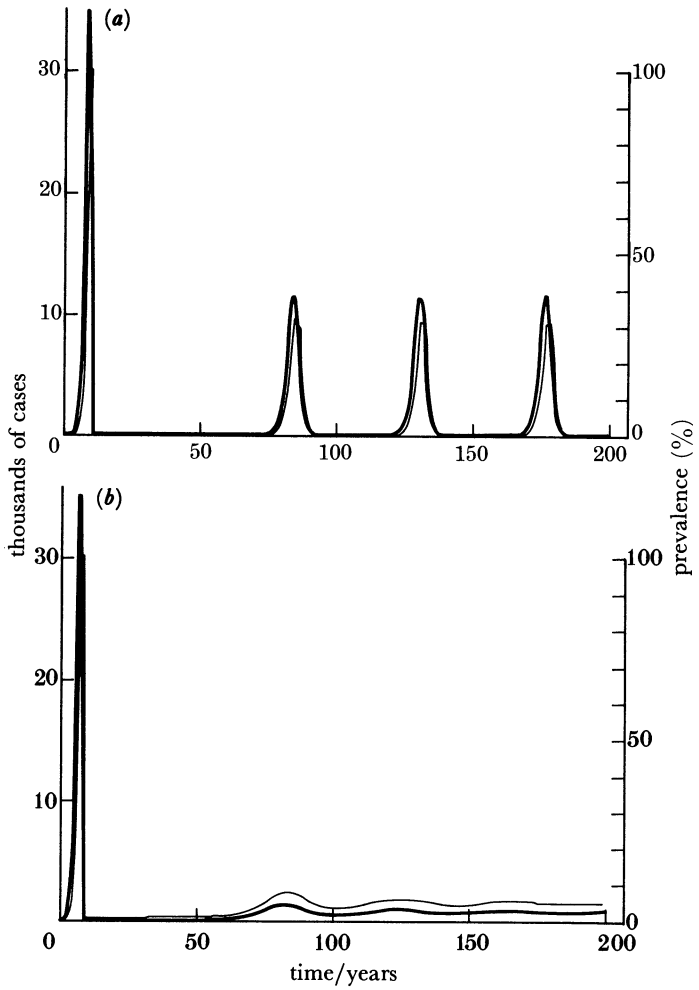

FIGURE 13. Predictions of the model for human sleeping sickness described in the text. Parameters and variables were as follows: $a = 0.1$, $b = 0.037$, $d = 0.97$, $c = 4$, $i = 0.01$, $w = 0.1$, $\lambda = 6.3 \times 10^{-7}$, $S_0 = 100000$, $I_0 = 50$. For (*a*) $W = 50$, for (*b*) $W = 5000$. Thick line, cases; thin line, prevalence.

epidemic, with a prevalence reaching nearly 100%, is followed by a period of about 80 years during which the human population shows a negligible infection rate, after which epidemic cycles are repeated every 40–50 years. Disease prevalence reaches about 30% during these epidemics. In the second example (figure 13*b*) a larger wild animal reservoir of 5000 has been assumed (with the same infection rate as in figure 13*a*). The larger reservoir considerably dampens the epidemic cycles following the first catastrophic outbreak, but does not obviously affect the timing of these cycles.

A number of models, in essence the same as that illustrated in figure 13, point to the importance of a residuum of infection between epidemic peaks. Without this reservoir an epidemic tends to result in disease extinction following the death of virtually all susceptible individuals. The severity of the epidemics is generally linked to the size of this reservoir. When it is small, epidemic peaks are pronounced; when it is large, the disease cycles are rapidly dampened and the disease becomes endemic. These patterns accord with the human sleeping

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sickness situation in Africa where epidemics are always associated with rapid person-to-person transmission that occurs either in the dry savannah zones of West Africa, or in particular localized situations in East Africa (where strains introduced from an essentially sylvatic cycle are transmitted from person-to-person in a village situation by tsetse that adopt peri-domestic habits). Human sleeping sickness in the forest zones of West Africa is invariably endemic and occurs at very low prevalences; in such a situation the alternative hosts of tsetse are relatively more abundant and there is little direct person-to-person transmission (Duggan 1970; Ford 1971).

Models based on equations (26)–(29), and using demographic parameters appropriate for humans, rarely give epidemic cycles of the relatively short period detected in the Tanzanian data (figure 11). An alternative explanation is that epidemic cycles seen in the human population are reflections of cycles taking place in the wild animal reservoir that 'spill over' into the human population through tsetse transmission. This can quite easily be modelled. Figure 14 shows the predictions of a model for a wild ungulate population exposed to

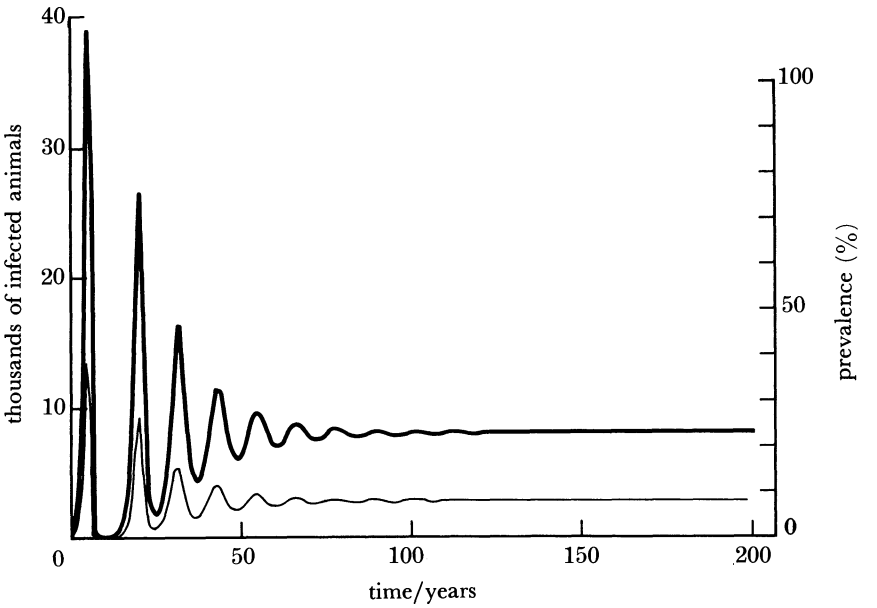

FIGURE 14. Predictions of a susceptible–infected–immune model of trypanosomiasis applied to an ungulate population (e.g. bushbuck). The model assumes that after infection the animals become lifelong immune. Parameters and variables (similar to those of equations (23)–(25), but with R now representing a category of immune animals and disease-induced losses of equation (24) representing animals that lose their infections and become immune) were as follows: $a = 0.15$, $b = 0.15$, $d = 1.0$, $c = 3$, $S_0 = 100\,000$, $I_0 = 400$, $R_0 = 0$. Thick line, cases; thin line, prevalence.

trypanosomiasis. The wild animals are assumed to develop a lifelong immunity following natural recovery from infection. The model is exactly the same as the kala-azar model of equations (23)–(25) but with the middle term of equation (25) being replaced by dI_t. This third equation now refers to the immune category of wild hosts. Figure 14 shows that such a model produces epidemic cycles with a period of 10–20 years.

Analysis of age-prevalence curves

When a cohort of susceptible individuals (usually new-born young) enters an endemic disease situation the individuals gradually acquire infection at a rate, and to a level, determined by the rate of transmission in the area and the duration of infection in each individual. If i_a is the proportion of this cohort that is infected by the time it reaches age a (i.e. $i_0 = 0$), an appropriate model for changes in i is

$$\mathrm{d}i/\mathrm{d}a = abmy^*(1-i) - ri, \tag{30}$$

where y^* is the equilibrium disease prevalence in the vector, and other terms are as in equations (1)–(4). Assuming no other time-dependent changes (for example in the ratio of vectors to hosts) this equation can be simplified to

$$\mathrm{d}i/\mathrm{d}a = h(1-i) - ri, \tag{31}$$

where $h = abmy$, from which

$$i_a = h\{1 - \exp[-(r+h)\,a]\}/(r+h) \tag{32}$$

(from Bailey 1982).

Translating these parameters into measurable quantities, $1/r$ is the average duration of infection before the infected individual is removed from the age-class (through recovery, treatment or death) and h is the 'force' of infection (Bailey 1982); $1/h$ is the average age to the first infection of a new-born susceptible.

The application of this model to the malaria situation raises problems (as discussed by Bailey (1982)). Because of the high chance of superinfection, and because of the uncertainty of the immunological response of the human host, the parameter r (and hence h) cannot be easily interpreted. Superinfection in the case of human trypanosomiasis would appear to be very unlikely, because the force of infection is very much lower. Table 4 shows the result of fitting this model to the human trypanosomiasis data from the Yimbo location of Central Nyanza, Kenya (Bailey *et al.* 1967). This survey covered more or less the complete population in the area, and hospitalized cases were also traced and included in the figures (P. de Raadt, personal communication). Omitting the somewhat anomalous data for individuals more than 60 years of age the estimates of r and h indicate a duration of infection of approximately 38 years and an average age to first infection of 315 years (the latter figure simply means that most people die without ever having contracted trypanosomiasis). Although both estimates would appear to be rather large, any higher value of h would cause the infections to accumulate more rapidly with age, and any higher value of r would cause the age–prevalence curve to reach a plateau at an earlier age. Immunological evidence from two other sites in Africa tend to confirm the very low estimates of r.

A few additional data collected at the time of the survey in Yimbo allow us to estimate $a = 0.118$ (i.e. 9/19 identified fly blood meals were from hominids and we assume a 4-day tsetse feeding cycle) and $y^* = 0.003$ (1 in 292 flies dissected had a *T. brucei* infection, assumed here to be infective to man) (Persoons 1967). Taking a value of $b = 0.62$ (table 1) gives an estimate for m of 0.040 flies per human, which will result in each human being bitten on average only 0.013 times per day, or once every 76 days. This seems a vanishingly small force of infection.

Although there may be a number of reasons for obtaining such long estimates for the duration of infection of a disease which in most cases is regarded as acute and rapidly fatal, it is also possible that surveys such as the one recorded in table 4 reveal the extent of 'hidden', chronic infections within the human community. A small number of chronic cases (which are undetected because the people concerned do not become clinically sick) will serve to maintain the disease at a low endemic level for many years, after which a change of conditions, or the gradual accumulation of susceptible individuals, will result in fly transmission accelerating to produce a mini-epidemic. These recrudescences in long-established foci are characteristic of the history of sleeping sickness outbreaks in Africa (Duggan 1970). The only possible reservoir of the disease over several decades of time is man himself, a host to which, increasingly, parasites have to adapt if they are to survive.

TABLE 4. AGE–PREVALENCE CURVE FOR HUMAN SLEEPING SICKNESS CASES (HOSPITALIZED OR DIAGNOSED PARASITOLOGICALLY) FROM THE YIMBO AREA OF CENTRAL NYANZA, KENYA, TOGETHER WITH THE BEST FIT OF AN AGE–PREVALENCE MODEL

(See text for more details; data from Bailey *et al.* (1967).)

age range (years)	median age	percentage infected	model to age 60
0–10	5	0.96	1.48
11–20	15	5.63	3.86
21–30	25	5.88	5.63
31–40	35	5.71	6.96
41–50	45	9.50	7.94
51–60	55	7.30	8.68
61–70	65	17.14	
71–80	75	16.67	

Model parameters: $r = 7.166 \times 10^{-5}$, $h = 8.709 \times 10^{-6}$.
Average duration of infection = 38.2 years; average age to first infection = 315 years.

CONCLUSIONS

Confrontation of models with field data reveals gaps in our understanding both of the models and of the field situation. Vector-borne diseases are able to survive in human communities at well below the human population density necessary for many directly transmitted diseases. Nevertheless we have shown that in many respects the dynamics of transmission of the trypanosomatid protozoans in the genera *Leishmania* and *Trypanosoma* are rather more similar to those of directly transmitted infections than might appear at first sight. Although it is unlikely that the population density of adult vectors such as mosquitoes should in any way be determined by the abundance of the human host (because the uncertainty of larval survival will more than override any dependence of adult fertility on human abundance), the smaller the number of eggs produced by each vector, or the greater the reliance on the human host (or domestic animals), the more likely it will become that vector numbers per host will be a constant. For the larviparous tsetse flies, vector numbers are tightly linked to host abundance (figure 5) and, but for the complication of several alternative hosts, the dynamics of transmission would appear to be relatively straightforward.

The relatively small basic rates of reproduction of both leishmaniasis and trypanosomiasis

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make epidemic cycles of infection more likely. Without either a long-term animal reservoir (in which constant levels of infection will dampen epidemic outbreaks), or a few chronic human infections of these usually fatal parasites, the disease is unlikely to persist within the human community. Clinicians repeatedly come to the conclusion that the extent of leishmaniasis and trypanosomiasis is underestimated during routine survey work; increasingly sensitive tests detect increasing numbers of infections. More attention should be paid, and a greater significance attached, to chronic cases that may well form the 'Trojan horse' of the next epidemic outbreak.

Finally, heterogeneity of vector attack on the human population may affect many of the conclusions about rates of increase and thresholds. Recent modelling work has shown how, in a situation in which vectors and hosts are distributed in patches, with the vectors moving between patches, the basic rate of reproduction of the disease can exceed its value in a single, homogenously mixed population of vectors and hosts (Dye & Hasibeder 1986; Hasibeder & Dye 1988), while equilibrium disease prevalence may be lowered or raised. This is because at least one of the host patches experiences a higher vector-to-host ratio than in the homogenous situation with the same total numbers of vectors and hosts. Such patches become 'hot spots' in which infection can persist and from which infections can spread, via vector transmission, to all other patches. This realistic and necessary complication will mean that such vector-borne diseases will be more difficult to eradicate than a simple calculation of the basic reproductive rate (i.e. assuming homogenous mixing) will suggest. To some extent alternative host species will play a similar role in concentrating infections in a small sub-sample of the total host range (generally, though not always, in those hosts which are preferred by the vectors), because the disease only has to survive in one host species for all host species to be affected, again via vector transmission (see text and figure 6 for an example). The higher the vector:host ratio on any one vertebrate species, the greater this host's susceptibility to infection; and the more rapidly the vectors move during their lifetime from one host species to another, the more difficult it will be to eradicate the disease. Domestic animals must in many cases be prime candidates for such an 'ideal' reservoir. They tend to be more susceptible to infection than the sylvatic hosts, and their proximity to man means that vector transmission is particularly likely. The identification in West Africa of domestic animals as hosts of human-infective trypanosomes (Mehlitz 1986), and the calculation that such trypanosomes could not survive within the human host alone (see text and table 3) leads to the suggestion that domestic animals should be treated in order to free the human community of sleeping sickness more effectively. It is a suggestion that does not obviously arise either from the field-work alone (which could not quantify the significance of the observation) or from the model alone, but from a combination of the two.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

References

Anderson, R. M. (ed.) 1982 *Population dynamics of infectious diseases: theory and applications*. London: Chapman & Hall.

Anderson, R. M. & May, R. M. (eds) 1982 *Population biology of infectious diseases* (Dahlem Konferenzen 1982). Berlin, Heidelberg, New York: Springer-Verlag.

Aron, J. L. & May, R. M. 1982 The population dynamics of malaria. In *Population dynamics of infectious diseases: theory and applications* (ed. R. M. Anderson), pp. 139–179. London: Chapman & Hall.

Ashford, R. W. & Bettini, S. 1987 Ecology and epidemiology: Old World. In *The leishmaniases in biology and medicine. Volume I. Biology and epidemiology* (ed. W. Peters & R. Killick-Hendrick), pp. 365–424. London: Academic Press.

Austen, E. E. 1911 *A handbook of the tsetse flies* (*Genus Glossina*). London: British Museum.

Bailey, N. M., de Raadt, P. & Krampitz 1967 The investigation of an epidemic of human trypanosomiasis in Yimbo, Central Nyanza, Kenya. In *East African Trypanosomiasis Research Organization report 1966*, pp. 65–66. Entebbe: Government Printer.

Bailey, N. T. J. 1982 *The biomathematics of malaria*. London & High Wycombe: Griffin.

Dietz, K. 1988 Density dependence in parasite transmission dynamics. *Parasitol. Today* **4**, 91–97.

Dietz, K., Molineaux, L. & Thomas, A. 1974 A malaria model tested in the African Savannah. *Bull. Wld Hlth Org.* **50**, 347–357.

Duggan, A. J. 1970 An historical perspective. In *The African trypanosomiases* (ed. H. W. Mulligan), pp. xli–lxxxviii. London: George Allen & Unwin Ltd.

Dye, C. M. 1986 Vectorial capacity: must we measure all its components? *Parasitol. Today* **2**, 203–209.

Dye, C. M. & Hasibeder, G. 1986 Population dynamics of mosquito-borne disease: effects of flies which bite some people more frequently than others. *Trans. R. Soc. trop. Med. Hyg.* **80**, 69–77.

Dye, C. & Wolpert, D. M. 1988 Earthquakes, influenza and cycles of Indian kala-azar. *Trans. R. Soc. trop. Med. Hyg.* (In the press.)

Fairbairn, H. 1948 Sleeping sickness in Tanganyika Territory. *Trop. Dis. Bull.* **45**, 1–17.

Ford, J. 1971 *The role of the trypanosomiases in African ecology: a study of the tsetse-fly problem*. Oxford: Clarendon Press.

Garrett-Jones, C. 1964*a* The human blood index of malaria vectors in relation to epidemiological assessment. *Bull. Wld Hlth Org.* **30**, 241–261.

Garrett-Jones, C. 1964*b* Prognosis for interruption of malaria transmission through assessment of the mosquito's vectorial capacity. *Nature, Lond.* **204**, 1173–1175.

Gingrich, J. B., Ward, R. A., Macken, L. M. & Schoenbechler, M. J. 1982*a* *Trypanosoma brucei rhodesiense* (Trypanosomatidae): factors influencing infection rates of a recent human isolate in the tsetse *Glossina morsitans* (Diptera, Glossinidae). *J. med. Ent.* **19**, 268–274.

Gingrich, J. B., Ward, R. A., Macken, L. M. & Esser, K. M. 1982*b* African sleeping sickness: new evidence that mature tsetse flies (*Glossina morsitans*) can become potent vectors. *Trans. R. Soc. trop. Med. Hyg.* **76**, 479–481.

Hasibeder, G. & Dye, C. M. 1988 Population dynamics of mosquito-borne disease: persistence in a completely heterogeneous environment. *Theor. Popul. Biol.* **33**, 31–53.

Heyneman, D. 1971 Immunology of leishmaniasis. *Bull. Wld Hlth Org.* **44**, 499–514.

Hoare, C. 1972 *The trypanosomes of mammals*. Oxford: Blackwell Scientific Publications.

Jackson, C. H. N. 1944 The analysis of a tsetse fly population II. *Ann. Eugen.* **12**, 176–205.

Kilama, W. L., Mtera, K. N. M. & Paul, R. K. 1981 Epidemiology of human trypanosomiasis in Tanzania. In *International Scientific Council for Trypanosomiasis Research and Control. 17th Meeting, Arusha 1981*, pp. 187–193. Nairobi: OAU/STRC.

Kleine, F. K. 1909*a* Positive infektionsversuche mit *Trypanosoma brucei* durch *Glossina palpalis*. *Dt. med. Wschr.* **35**, 469–470.

Kleine, F. K. 1909*b* Weitere wissenschaftliche Beobachtungen über die Entwicklung von Trypanosomen in Glossinen. *Dt. med. Wschr.* **35**, 924–925.

Macdonald, G. 1957 *The epidemiology and control of malaria*. London: Oxford University Press.

Macdonald, G. 1965 The dynamics of helminth infections with special reference to schistosomes. *Trans. R. Soc. trop. Med. Hyg.* **59**, 489–506.

Mehlitz, D. 1986 Le reservoir animal de la maladie du sommeil à *Trypanosoma brucei gambiense*. *Études et Syntheses de l'I.E.M.V.T.* 18. Maisons Alfort: Institut d'Élevage et de Médicine Vétérinaire des Pays Tropicaux.

Molyneux, D. H. & Ashford, R. W. 1983 *The biology of Trypanosoma and Leishmania, parasites of man and domestic animals*. London: Taylor & Francis.

Nicholson, A. J. & Bailey, V. A. 1935 The balance of animal populations. Part I. *Proc. zool. Soc. Lond.* 1935 (2), 551–598.

Persoons, C. J. 1967 Entomological studies during an outbreak of human sleeping sickness in Yimbo location, Central Nyanza, Kenya. *East African Trypanosomiasis Research Organization report 1966*, pp. 66–69. Entebbe: Government Printer.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Peters, W. & Killick-Kendrick, R. (eds) 1987 *The leishmaniases in biology and medicine. Volume I. Biology and epidemiology*. London: Academic Press.
Randolph, S. E. & Rogers, D. J. 1984 Movement patterns of the tsetse fly *Glossina palpalis palpalis* (Robineau-Desvoidy) around villages in the pre-forest zone of Ivory Coast. *Bull. ent. Res.* **74**, 689–705.
Rees, P. H. & Kager, P. A. 1987 Visceral leishmaniasis and post-kala-azar dermal leishmaniasis. In *The leishmaniases in biology and medicine. Volume II. Clinical aspects and control* (ed. W. Peters & R. Killick-Kendrick), pp. 583–615. London: Academic Press.
Rogers, D. J. 1983 Interpretation of sample data. In *Pest and vector management in the tropics* (ed. A. Youdeowei & M. W. Service), pp. 139–160. London & New York: Longman.
Rogers, D. J. 1988 A general model for the African trypanosomiases. *Parasitology* **97**, 195–212.
Rogers, D. J. & Randolph, S. E. 1986 Distribution and abundance of tsetse flies (*Glossina* spp.). *J. Anim. Ecol.* **55**, 1007–1025.
Rogers, D. J., Randolph, S. E. & Kuzoe, F. A. S. 1984 Local variation in the population dynamics of *Glossina palpalis palpalis* (Robineau–Desvoidy) (Diptera: Glossinidae). I. Natural population regulation. *Bull. ent. Res.* **74**, 403–423.
Ross, R. 1909 *Report on the prevention of malaria in Mauritius*. London: Churchill.
Ross, R. 1911 *The prevention of malaria*. London: Murray.
Ross, R. & Hudson, H. P. 1931 *A priori pathometry*. London: Harrison & Sons.
Scott, D. 1965 *Epidemic disease in Ghana 1901–1960*. London, New York, Toronto: Oxford University Press.
Service, M. W. 1977 Patrick Manson and the story of bancroftian filariasis. In *Medical Entomology Centenary Symposium Proceedings* (ed. S. Wilmott), pp. 11–14. London: Royal Society of Tropical Medicine & Hygiene.
Watson, H. J. C. 1963 The domestic pig as a reservoir of *T. gambiense*. In *International Scientific Committee for Trypanosomiasis Research 9th Meeting, Conakry, 1962*, p. 327. Lagos: Commission for Technical Co-operation in Africa.
WHO 1986 *Epidemiology and control of African trypanosomiasis. Report of a WHO Expert Committee* (WHO Technical Report Series no. 739). Geneva: World Health Organisation.
Wijers, D. J. B. 1960 The importance of the age of *G. palpalis* at the time of the infective feed with *T. gambiense*. In *International Scientific Committee for Trypanosomiasis Research 7th Meeting, Bruxelles, 1958*, pp. 319–320. London: Commission for Technical Co-operation in Africa South of the Sahara.

Discussion

D. W. Onstad (*Department of Agricultural Entomology, University of Illinois, U.S.A.*). In his analysis, Dr Rogers assumed that the system was in equilibrium. But he also stated that the interaction between villages and plantations and the vector's spatial dynamics are important. I cannot imagine that these factors were at an equilibrium over the past 80 years. Did he include these processes in his model, and do they influence his equilibrium analysis?

D. J. Rogers. As stated in the paper, most of the analysis assumed equilibrium conditions, without migration of vectors in or out of the study area. The results shown in figure 6 are the predicted equilibrium prevalences when flies take the proportions of blood meals from humans shown on the abscissa. Thus the 'village' and 'plantation' values are those that would obtain in closed systems, without migration between the two. When this constraint is relaxed, and flies are allowed to move between the village and plantation, the appropriate equilibrium model becomes much more complex (in fact an m/n model of the sort described by Hasibeder & Dye (1988), where $m = n = 2$) and apparently has no analytical solution (G. Hasibeder, personal communication). Non-equilibrium models could be devised but, as pointed out above, we need to know much more about the degree of movement of vectors and hosts, and how this changes over time, before these can be at all realistic.

R. Killick-Kendrick (*MRC External Scientific Staff, Imperial College at Silwood Park, U.K.*). One important factor in the transmission of sleeping sickness is the variation in contact between man and tsetse fly at different seasons. As Vale (1974) has so elegantly shown, at least some species

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of tsetse flies normally find man repellent. But in the hot, dry season the fly has two problems. First, movement of game to water may pose a difficulty for the fly to find a blood meal. Secondly, the accelerated use of energy at high temperatures may force the fly to feed in villages on man, in spite of his repellent effect. Thus at such times of year contact between man and fly is closer than at other times, enhancing the chances of transmission of the trypanosome.

On a second point, can the differences in the epidemiologies on the two sides of the continent really be explained by an abundance of various species of reservoir-hosts in the east and a dearth in the west? Very few animals in East Africa have been shown to harbour trypanosomes likely to infect man. In the west, *T. gambiense* can fortunately be identified by isoenzymes and the proportion of pigs or dogs shown to be carriers in some countries is not inconsiderable. If abundance of reservoir-hosts is an explanation of the differences in the epidemiologies, the meagre data available suggest the opposite to that which Dr Rogers suggests.

Reference

Vale, G. A. 1974 The responses of tsetse flies (Diptera, Glossinidae) to mobile and stationary baits. *Bull. ent. Res.* **64**, 545–588.

D. J. Rogers. Certainly contact rate will vary from place to place and season to season, as Dr Killick-Kendrick suggests. Other factors will also change seasonally; for example, flies are more easily infected with *T. brucei* if they are kept during puparial development at higher temperatures, thus tending to increase prevalence in the vectors. In the hot season, however, fly mortality rates may well be higher, thus tending to reduce prevalence. What we measure will be the seasonally changing balance between such factors. The approach to modelling adopted here was to investigate the simplest situation first, assuming everything to be at equilibrium. Seasonality, of various sorts (see, for example, figure 8), can be incorporated later when its effects on the various parameters are known.

The second point is more complex. The classical story (i.e. until around 1970) was that West African human sleeping sickness had no animal reservoir, whereas the East African form was a typical zoonosis (see, for example, Scott 1970; Hoare 1972; Molyneux & Ashford 1983; Gibson 1986). Hoare's table 4 (p. 523) is quite categorical. This opinion was reinforced by research and control workers on each side of the continent. Thus game animals were never surveyed in West Africa (where they are scarcer than in East Africa because of higher human population densities) and human sleeping sickness control tended to involve treatment and prophylaxis of the humans alone (presumably denying a reservoir role for any other vertebrate species). In East Africa, however, game animals were periodically surveyed for *T. brucei* infections, and game destruction suggested as a means of reducing or eliminating trypanosomiasis in both domestic animals and humans. The logic of this approach was confirmed by the demonstration that trypanosomes isolated from bushbuck in East Africa were infective to man (Heisch *et al.* 1958).

The potential role of domestic animals as reservoir-hosts of human sleeping sickness was raised by van Hoof's (1947) demonstration (in what is now Zaire) that *T. gambiense* could infect domestic pigs and be transmitted cyclically to them and to humans. Interest in domestic animal hosts increased when a naturally occurring *T. brucei* infection in a cow in East Africa was found to infect a human volunteer (Onyango *et al.* 1966; van Hoeve *et al.* 1967), and when high levels of *T. brucei* infections were found in domestic stock in the Lambwe Valley area of Kenya

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(Robson & Ashkar 1972) and in the Musoma District of Tanzania (Mwambu & Mayende 1971). These East African studies continue up to the present time, with domestic animal reservoirs being identified as likely sources of human infective trypanosomes in the same area of Kenya (Gibson & Wellde (1985), who also looked at game animals) and in Uganda (Okuna *et al.* 1986). As I explained in the paper the greater susceptibility of domestic animals to trypanosome infection and their proximity to man makes them a most important potential reservoir of human infection. This applies equally to West and to East Africa. The West African studies referred to by Dr Killick-Kendrick were widely quoted because in this region the existence of *any* reservoir host was long disputed.

Until recently it was difficult to identify to sub-specific level *T. brucei* isolates from non-human hosts in West Africa. Using the modern techniques of isoenzyme analysis and DNA probes *T. b. gambiense* can now be distinguished from *T. b. brucei* (Tait *et al.* (1984), disputed by Gibson (1986)). The percentage of West African *T. brucei* isolates from non-human (usually domestic animal) hosts that would appear to be human-infective varies considerably from place to place and is often very low (despite high overall prevalences of *T. brucei*); in parts of Ivory Coast it is *ca.* 1% (Mehlitz 1986; D. Mehlitz, personal communication); in central Africa it is zero (Noireau *et al.* 1986).

My conclusion about the greater reservoir in East Africa is therefore based on the assumption that although highly susceptible domestic animals are equally important in West and East Africa, wild animals are more numerous in East Africa.

References

Gibson, W. C. 1986 Will the real *Trypanosoma b. gambiense* please stand up. *Parasitol. Today* **9**, 255–257.

Gibson, W. C. & Wellde, B. T. 1985 Characterisation of *Trypanozoon* stocks from the South Nyanza sleeping sickness focus in Western Kenya. *Trans. Roy. Soc. trop. Med. Hyg.* **79**, 671–676.

Heisch, R. B., McMahon, J. P. & Manson-Bahr, P. E. C. 1958 The isolation of *Trypanosoma rhodesiense* from a bushbuck. *Br. med. J.* **2**, 1203–1204.

Hoeve, K. van, Onyango, R. J., Harley, J. M. B. & Raadt, P. de 1967 The epidemiology of *Trypanosoma rhodesiense* sleeping sickness in Alego location, Central Nyanza, Kenya. II. The cyclical transmission of *Trypanosoma rhodesiense* isolated from cattle to a man, a cow and to sheep. *Trans. R. Soc. trop. Med. Hyg.* **61**, 684–687.

Hoof, L. van 1947 Observation on trypanosomiasis in the Belgian Congo. *Trans. R. Soc. trop. Med. Hyg.* **40**, 728–761.

Mwambu, P. M. & Mayende, J. S. P. 1971 Sleeping sickness survey in Musoma District, Tanzania. III. Survey of cattle for evidence of *T. rhodesiense* infections. *Acta tropica* **28**, 206–210.

Noireau, F., Gouteux, J. P. & Frezil, J. L. 1986 Les nouvelles perspectives de l'épidémiologie de la trypanosomiase à *Trypanosoma brucei gambiense*. *Bull. Soc. Path. exot.* **79**, 372–379.

Okuna, N. M., Mayende, J. S. P. & Guloba, A. 1986 *Trypanosoma brucei* infection in domestic pigs in a sleeping sickness epidemic area of Uganda. *Acta tropica* **43**, 183–184.

Onyango, R. J., Hoeve, K. van & Raadt, P. de 1966 The epidemiology of *Trypanosoma rhodesiense* sleeping sickness in Alego Location, Central Nyanza, Kenya. I. Evidence that cattle may act as reservoir hosts of trypanosomes infective to man. *Trans. R. Soc. trop. Med. Hyg.* **60**, 175–182.

Robson, J. & Ashkar, T. S. 1972 Trypanosomiasis in domestic livestock in the Lambwe Valley area and a field evaluation of various diagnostic techniques. *Bull. Wld Hlth Org.* **47**, 727–734.

Scott, D. 1970 The epidemiology of Gambian sleeping sickness. In *The African trypanosomiases* (ed. M. W. Mulligan), pp. 614–644. London: George Allen & Unwin.

Tait, A., Babiker, E. A. & Le Ray, D. 1984 Enzyme variation in *Trypanosoma brucei* spp. I. Evidence for the subspeciation of *Trypanosoma brucei gambiense*. *Parasitology* **89**, 311–326.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES