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ANTHROPOGENIC DISTURBANCES ENHANCE OCCURRENCE OF CUTANEOUS LEISHMANIASIS IN ISRAEL DESERTS: PATTERNS AND MECHANISMS

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Abstract. A continuous and gradual increase in the incidence of cutaneous leishmaniasis (CL) has been reported in southern Israel over the last 20 years. The goal of our research was to determine if and how anthropogenic disturbances enhance the occurrence of the disease. To assess the effect of anthropogenic disturbances, we selected twelve 60 × 60 m plots, six in disturbed and six in undisturbed habitats at each of five study sites in southern Israel. We trapped rodents and sand flies, determined *Leishmania major* infection prevalence in rodents, and measured various environmental parameters. Infection prevalence in the reservoir host, the rodent *Psammomys obesus*, was significantly higher in disturbed habitats than in undisturbed ones. Infection prevalence was positively correlated with vector (*Phlebotomus papatasi*) density but not with host density. *P. papatasi* density was positively correlated with soil moisture. Soil in disturbed habitats had significantly more moisture, and plants were significantly more lush than in undisturbed habitats. *P. obesus* density was positively correlated with plant lushness. These results suggest that an important impact of anthropogenic disturbance, the addition of water, improves the conditions for vector breeding and promotes larger host populations by improving the quality of their food. These effects, in turn, should enhance disease transmission risk to humans.

Key words: *anthropogenic disturbance; cutaneous leishmaniasis; disease ecology; Israel;* Leishmania major; *Negev and Arava deserts;* Phlebotomus papatasi; Psammomys obesus; *reservoir host; zoonosis.*

INTRODUCTION

The past decade has seen the emergence and resurgence of many infectious diseases around the world (reviewed in: Epstein 1995, Schrag and Wiener 1995, Childs et al. 1998, Mills and Childs 1998, Murphy 1998, Daszak et al. 2000). The majority of these are zoonoses, i.e., disease transmitted to humans from a nonhuman animal reservoir (Childs et al. 1998, Murphy 1998, Thompson 2000). This increase in infectious diseases was attributed partly to the effect of humans on the evolution of parasites (e.g., drug resistance), but mostly to human-induced changes in the ecology of host–pathogen interaction (Schrag and Wiener 1995). The latter may occur through processes that may affect the abundance of the host or vector, and thus enhance the probability of exposure to known or novel pathogens (Daszak et al. 2000). These processes may include habitat and ecosystem alteration through agricultural practices, urbanization, and other regional developmental practices (Epstein 1995, Schrag and Wiener 1995, Birley and Lock 1999), encroachment into pristine habitats (Daszak et al. 2000), translocation of the pathogen by humans or livestock (Schrag and Wiener 1995, Daszak et al. 2000), or human-induced climatic change (Dobson and Carper 1992, Engelthaler et al. 1999, Epstein 2000, Harvell et al. 2002).

Since zoonotic diseases are so complex, the prevention and control strategies for these systems require unique strategies, based more on fundamental research than on traditional medical approaches (Murphy 1998). Such a study usually requires an interdisciplinary approach combining expertise from the molecular level, through the organismal levels, to the community and ecosystem levels of organization, and their integration from an ecological perspective (Ashford 1996, Murphy 1998, Schmidt and Ostfeld 2001). The holistic ecological approach, which concentrates on the interactions among the various links of the disease transmission chain and their environment, provides a powerful conceptual tool for understanding the structure and func-

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tion of such systems (Sousa and Grosholtz 1991). Despite the call by leading experts (Pavlovsky 1966, Muul 1970, Carey et al. 1980, Ashford 1996, Murphy 1998, Thompson 2000), few ecologically based epidemiological field studies have been conducted. In the cases where such an approach has been applied, a substantial advance in understanding and the ability to reduce the risk of infection has been achieved (e.g., Muul et al. 1977, Carey et al. 1980, Mills and Childs 1988, Ostfeld 1997).

Leishmaniases, in their various forms, appear to be emerging globally (Ashford 2000, Desjeux 2001) and locally in the Middle East (Oumeish 1999), with human activity incriminated as the main cause. However, this contention has never been empirically addressed. In this study we apply an ecologically based approach in order to study the role of anthropogenic disturbances in the enhancement of the incidence and distribution of cutaneous leishmaniasis (CL) in the Negev and Arava Deserts of Israel. CL provides a model for the study of complex, vector-borne zoonoses, including Lyme disease, West Nile encephalitis, Rift Valley Fever, and many others, because the incidence of human disease appears linked to complex interactions among pathogens, arthropod vectors, vertebrate reservoirs and nonreservoirs, and both the biotic and abiotic components of the ecosystems in which these interactions occur.

CL is a vector-transmitted skin disease, which in southern Israel is caused by the kinetoplastid zooflagellate *Leishmania major* (Trypanosomatidae) (Schlein et al. 1984). The disease is manifested as a 3–4 cm papular self-healing lesion, which renders the patient immune but often leaves a disfiguring scar (Oumeish 1999). The life cycle of *Leishmania* parasites comprises two stages: the intracellular amastigote (2–6 μm) within the reticulo–histiocytic system of the mammalian host, and the flagellated promastigote (15–30 μm length), which occurs within the intestinal tract of the vector. The principal reservoir host of *L. major* in Israel is the fat sand rat *Psammomys obesus* (Cricetidae: Gerbillinae), and the vector is the sand fly *Phlebotomus papatasi* (Diptera: Psychodidae) (Schlein et al. 1982, 1984). *P. obesus* (180 g) is a diurnal, herbivorous rodent that mostly consumes halophytic Chenopodiaceae plants (Daly and Daly 1973). It is gregarious and usually inhabits complex burrow systems where organic matter, in the form of plant debris and feces, accumulates. This, together with the relatively warm and moist ambient conditions, provides excellent breeding conditions for the sand fly larvae, diurnal refuge for its adults, and an easy blood-meal source for the females (Ashford 1996).

CL, due to *L. major*, is prevalent in arid and semiarid regions in Northern Africa, the Middle East, and central Asia (Ashford 1996, 1999, 2000). The disease used to be highly endemic in the Jordan Valley and Jericho area and more sporadic along the Dead Sea, Arava and the Negev Deserts of Israel and the West-Bank (Schlein et al. 1984, Greenblatt et al. 1985, Klaus et al. 1994) (Fig. 1). A substantial increase in the occurrence of CL, coinciding with the expansion of its geographic range, was reported from Israel in the last 20 years, particularly during the last decade. From 1990 to 1998 the annual incidence of CL has doubled, from 95 to 199 cases, with the proportion of cases from the Negev and the Arava rising from 10% to 80% (Klaus et al. 1994, Anonymous 1999, 2000). Three new foci have emerged and another three reestablished within the last 20 years (Giladi et al. 1985, Biton et al. 1997, Anonymous 2000) (Fig. 1). The increase in the incidence and distribution of the disease appears to be highly associated with the growth of human populations and urban and agricultural development in the endemic regions (Giladi et al. 1985, Greenblatt et al. 1985, Biton et al. 1997).

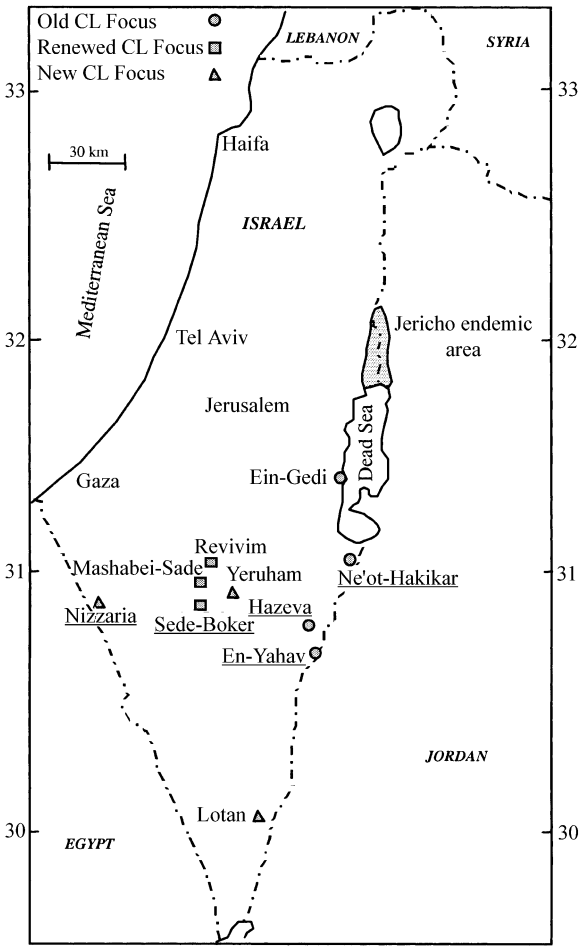

FIG. 1. Map of the distribution of cutaneous leishmaniasis (CL) due to *Leishmania major* in Israel and the location of the study sites (bold and underlined).

The goal of this study was to determine if and how anthropogenic disturbance enhances the occurrence of the disease within the natural zoonotic system, thereby increasing transmission risk to humans. Our hypothesis

TABLE 1. Topographic, climatic, geologic, and anthropogenic characterization of the study sites.

Site	SB	NIZ	EY	HAZ	NHK
Altitude (m)	500	286	−68	−105	−352
Mean yearly temperature (°C)	18°	20°	23°	23°	25°
Daily maximum (°C)	32°	33.5°	36°	36°	38°
Daily minimum (°C)	6°	6°	10°	10°	11°
Precipitation (mm/yr)	92	87	40	42	30
Soil type	L	L, SM, SS	SS	SS	SS
Land use	agriculture	military, agriculture, ruins	agriculture	agriculture	agriculture

Notes: Climatic data were supplied by the Israel Meteorological Service (Bet-Dagan). Topographical and geological data are based on Israel Atlas (Anonymous 1985). Land use data is based on personal observations. Abbreviations: L = loess, SM = semistabilized sand, SS = stabilized sand, military = military camps and training fields, ruins = ancient (AD 500) and recent (1950s) ruins, NIZ = Nizzana, SB = Sede-Boker, HAZ = Hazeva, EY = En-Yahav, NHK = Ne'ot-Hakikar.

was that anthropogenic disturbance should enhance disease transmission by enhancing the environmental factors that are favorable to the host, the vector, or both. Two, not mutually exclusive, environmental factors often associated with anthropogenic disturbances, which may benefit host, vector, or both, are water and organic matter addition. Both should improve the breeding and sheltering conditions for the vector, and food quality and abundance for the host. These effects should result in increased population size and altered distribution of the vector, host, or both, and should consequently increase the risk of CL infection in disturbed habitats.

We therefore predicted: (1) higher disease prevalence within the host populations in disturbed habitats compared with undisturbed ones; (2) higher vector abundance in disturbed habitats; (3) a positive correlation between vector abundance and soil moisture, soil organic matter content, or both; (4) higher soil moisture or soil organic matter content in the disturbed habitat; (5) a positive relationship between sand rat and sand fly abundance; (6) higher quality, abundance, or both, of Chenopodiaceae plants in the disturbed habitat; and (7) a positive correlation between sand rat density and Chenopodiaceae plant abundance, quality, or both. Finally, assuming anthropogenic disturbance enhances the environmental conditions in a manner favorable to *P. obesus*, and assuming the degree of disturbance declines monotonically with distance from the human settlement, we predicted that, (8) *P. obesus* abundance (as indicated by the number of active burrows) would decline with distance from the settlement.

METHODS

Study sites

The study was conducted at five previously reported CL foci, three in the hyper-arid Arava Valley: Hazeva, En-Yahav, and Ne'ot-Hakikar salt marsh, and two in the arid Negev Desert: Sede-Boker and Nizzana (Table 1, Fig. 1). These sites lie along four major environmental gradients: topography, climate, soil type, and soil moisture, but differ with respect to land use (Table 1). At each site we delimited twelve 60 × 60 m homogeneous plots: six in natural habitat and six in an anthropogenically disturbed habitat. The definition of ''disturbance'' used here was broad and included major human-induced perturbation of the land such as old fields, ruins, dump sites, roadsides, dams, etc. A random selection of study plots was not appropriate because sand rats have a highly patchy distribution (see *Results*), resulting in many of these plots being unoccupied. Therefore we selected our study plots in a nonrandom, stratified manner with respect to the reservoir host population density. Following a two-day survey at each site, we selected six plots in areas with a high density of apparently active (Fichet-Calvet 1999*b*, and see *Methods* and *Results*) sand rat burrows, and six in areas with low burrow density. Three plots in each sand rat density category were selected in disturbed habitat and three in natural habitat. This design allowed us to use a multiple regression statistical approach in order to identify the important environmental variables that influence the abundance of *P. obesus*. It further allowed us to study the quantitative relations between disease prevalence within the host population vs. vector and host abundance. In each plot, we trapped rodents and sand flies and measured a variety of environmental variables.

Rodent trapping

P. obesus are known for low capture success in grid-trapping designs, and therefore directed trapping is commonly used (Schlein et al. 1984, Ilan and Yom-Tov 1990, Fichet-Calvet et al. 1999*a*, *b*). We placed a pair of live traps in front of each potential host burrow system (characterized by an elaborate network of large-sized burrow openings [Fichet-Calvet et al. 1999*a*, *b*]). We used collapsible mesh cage live traps (41 × 13 × 13 cm, Tomahawk M-201, Tomahawk, Wisconsin) baited with fresh saltbush (*Atriplex halimus*) leaves for trapping *P. obesus* and standard folding live traps (8 × 9 × 23 cm, H. B. Sherman Traps, L-Fatdg, Tallahassee, Florida) baited with millet seeds to trap other rodents, suspected to be potential hosts. Each trapping session was 5–7 days long, until achieving at least a

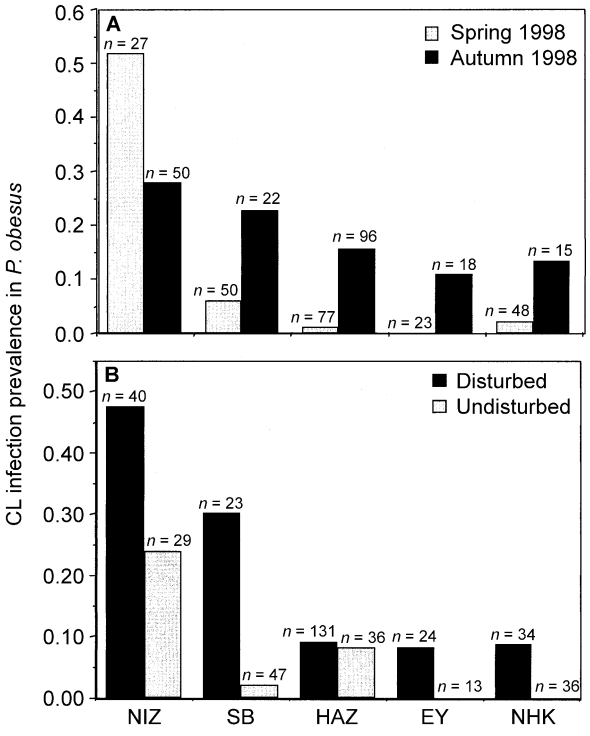

FIG. 2. Comparison of CL infection prevalence in the reservoir host (*P. obesus*) population (A) between the beginning (spring) and the end (autumn) of the vector (*P. papatasi*) activity period, and (B) between disturbed and undisturbed habitats, in the five study sites (NIZ = Nizzana, SB = Sede-Boker, HAZ = Hazeva, EY = En-Yahav, NHK = Ne'ot-Hakikar). Numbers above the bars indicate sample size.

75% recapture rate. Trapped rodents were individually marked by toe-clipping, and their mass, sex, reproductive state, and existence of external infection marks (usually eroded ear pinnae) were recorded. A small skin sample was taken from the ear pinnae (the common site of the infection [Schlein et al. 1984, Ashford 1996]) for microscopic detection of infection using a Giemsa-stained smear preparation. From each of these samples an additional smear was made on a sterilized filter paper for polymerase chain reaction (PCR)-based screening and parasite species identification. Rodent trapping was conducted twice in order to measure initial and final infection rates: once at the beginning of the activity period of the sand flies (May–June 1998) and the second about 1–2 months after the end of the sand fly season (December 1998–January 1999). This schedule provided information regarding the dynamics of the disease within the host population. Due to the low sand rat densities, we added, in January 1999, two trapping plots in two densely populated sites in Hazeva (one in disturbed and one in undisturbed habitats). These were used only for the analysis of infection prevalence (Fig. 2) but not for the other analyses.

Sand fly trapping

Adult sand flies were trapped using sticky traps composed of A4 paper sheets soaked in castor oil, which were attached to a wooden peg and placed about 5 cm aboveground (Schlein et al. 1984). Each trapping unit contained three sticky traps, arranged in a triangle, and spaced 1.5 m apart. Four such trapping units were arbitrarily located along the four edges of a plot, at least 15 m away from the burrow (hereafter, random stations), and five additional stations were selected each next to a reservoir-host burrow (hereafter burrow stations), totaling nine trapping units per plot. Two-day-long sand fly trapping sessions, at each site, were conducted between 8 and 19 September 1998. This period was selected because it represents the peak of sand fly activity (Yuval 1991, Janini et al. 1995). Trapping was conducted only during warm, low-wind nights, which constitute optimal activity conditions for the sand flies (Killick-Kendrick 1999).

Vegetation characteristics

We measured a variety of vegetation characteristics thought to affect either the host or the vector. These included: total and relative (by plant species) percent plant coverage, plant size, as well as foliage characteristics, which included foliage transparency and lushness. To estimate plant percent cover we used the standard line intercept procedure (Krebs 1999). In each study plot we measured percent plant coverage at 16 points, 15 m apart, arranged in a 4×4 grid. From each point we measured percent plant coverage along 10-m line transects radiating in random directions. At each point we randomly selected a chenopod bush and measured its height, width, and length, to estimate its quadratic volume. Transparency relates to the percent coverage of a measuring stick, visible through the canopy, at a standard distance, while lushness pertains to the percent coverage of that stick by green matter. We used a 3 m long measuring stick divided into 0.5-m segments and placed it vertically in the middle of the bush. Four, height-specific (for every 0.5-m segment) transparency and lushness estimates were taken for each bush from four perpendicular points located at a distance of 3 m away from the measuring stick. We used the following index to estimate transparency and lushness: 0–5% was scored as 0; 6–25% as 1; 26–50% as 2; 51–75% as 3; 76–95% as 4; and 95–100% as 5. The overall transparency and lushness score was the mean of all height-specific estimates per bush.

Soil characteristics

Soil characteristics measured included: soil moisture content, organic matter content, electrical conductivity (an indicator of soil salinity), and pH. Nine soil samples per plot were taken, using a soil corer, from a depth of ~30 cm, which is the average depth of 75% of the *P. obesus* burrow area (Orr 1974). Five soil samples were taken from sand rat burrows and four from the margins of the plots, all next to sand fly trapping units, in late September 1998 (the end of the dry season). For measuring soil moisture content we desiccated soil samples

in an oven at 105°C for 48 hours. Soil moisture content was calculated as the ratio of the difference between pre- and postdesiccation soil mass divided by the predesiccation soil mass (Brower and Zar 1977). Analysis of soil organic matter content, electrical conductivity, and pH was conducted at the field service laboratory of the Israel Ministry of Agriculture, Beer-Sheva. Soil organic matter content analysis included 100 samples: 60 from the Negev (Nizzana and Sede-Boker) and 40 from the Arava, all from active *P. obesus* burrows.

Due to the high cost of organic matter analysis, and in order to maintain large enough sample size, we had to exclude samples from En-Yahav, which is ecologically similar to Hazeva. One composite sample (a sample containing equal shares of the four ''nonburrow'' samples) per plot was assessed for electrical conductivity and pH analysis.

Parasite detection

Leishmanial infections in rodents were exposed by microscopic examination of Giemsa-stained ear tissue smears. This was corroborated by a *Leishmania*-specific PCR, conducted on a subgroup of these samples, using kDNA-specific primers (Wasserberg et al. 2002).

Radial transect survey

This survey was conducted in Hazeva, in April 1998. The survey was composed of 12 transects, 2 km long by 20 m wide each, which radiated outward from the edges of the settlement in 30° intervals (0°, 30°, 60°, etc.). Each transect was divided into 100-m sampling units. Two people walked along each transect at an average speed of 1.5 km/h. Each person recorded any sand rat burrow encountered at a distance of up to 5 m to either side, forming a rectangular 100 × 20 m sampling unit. We recorded the habitat type of each sampling unit and whether it was disturbed or undisturbed. In disturbed units we recorded the type of land use. Sand rat burrows were easily identified by their large openings, surrounded by a dirt mound containing soil, feces, plant debris, and by distinctive angular cutting marks on the adjacent chenopod bush (Daly and Daly 1973, Orr 1974, Fitchet-Calvet et al. 1999*b*; G. Wasserberg et al., *personal observations*). Sand rat burrows are elaborate and composed of many openings. Therefore, based on Orr (1974), who found that the average burrow system radius is 4.5 m, we defined a burrow system according to a 10-m nearest neighbor distance criterion: any burrow entrance that was <10 m away from its nearest neighbor was considered a part of that particular burrow system. A burrow system was considered active if it contained at least one of the following activity marks: loose soil surrounding burrow entrance, clear sand rat tracks, fresh food debris, or fresh feces (in partial concordance with Fichet-Calvet et al. 1999*b*). To determine the reliability of these activity marks in predicting burrow activity, we performed the following test in our survey plots in Hazeva and En-Yahav (similar sites in terms of habitat composition and land use) in April 1998. At each of the survey plots we mapped the burrows and noted whether they appeared active or not according to the presence of these activity marks. We then placed an M-201 Tomahawk trap in front of each burrow and trapped for six days.

Data reduction and statistical analysis

Spatial and temporal infection patterns in the reservoir host population were analyzed using log-linear models. Data from the two plots from Hazeva that were added in the winter trapping session (see *Radial transect survey*) were used only for this analysis.

P. papatasi sand fly abundance was measured in terms of the mean number of sand flies caught per station per plot (i.e., the mean of all nine trapping stations within a plot). A parametric test was not feasible due to normality problem (Lilliefors' test: $P < 0.001$). We therefore used the Mann-Whitney U test to assess the effect of habitat type and the Kruskal-Wallis test to assess the effect of site on *P. papatasi* abundance.

For comparing the relative effect of vector vs. host density on host infection prevalence, and for comparing the effect of the proportion of chenopod plants vs. mean chenopod plant lushness on sand rat abundance, we used multiple linear regression analyses. Mean sand rat density per plot was calculated as the mean of the two trapping sessions. Infection prevalence was arcsine transformed. The analysis of the infection rate was restricted to plots that had three or more host individuals per plot.

Since no statistical difference was found between soil moisture samples from burrows compared with nonburrow samples within a plot (see *Results*) we lumped all nine together to estimate the mean soil moisture content per plot. We tested the effect of soil moisture, site, and their interaction on sand fly density using ANCOVA with site as a main effect and soil moisture as a covariate. Due to data scarcity we lumped the three Arava sites together. Two data points were removed from the analysis, one as an outlier (Studentized residual = 3.877, $P < 0.01$) and one due to high leverage (= 0.666) (Wilkinson et al. 1992).

Sand fly density per burrow was transformed, due to a severe normality problem (Lilliefors' test: $P < 0.0001$), to presence/absence of sand flies in a burrow. We compared the relative effect of soil moisture content (percent) and soil organic matter content (percent) on sand fly occurrence using logistic regression (Hosmer and Lemeshow 1989). This analysis is statistically legitimate despite collinearity of these two variables ($r = 0.405$, $n = 100$, $P = 0.0001$) due to the low value of the variance inflation factor (VIF = 1.196) (Philippi 1993). To test for the existence of moisture by site or organic matter by site interactions we used likelihood-ratio tests in order to compare the interactive model (with independent variable × site interaction) to the

additive model (without the above interaction). When a statistical interaction was found, logistic regression was conducted for each site separately. Here too, due to data scarcity, we lumped the three Arava Valley sites together.

We used two-way ANOVAs to assess the effect of site and habitat type on the proportion of soil moisture content and soil organic matter content (both, arcsine transformed). We also used two-way ANOVAs to test the effect of habitat type, site, and their interaction on: chenopod plants percent cover, the proportion of chenopod plants (from total percent cover) (all proportions arcsine transformed), bush volume, bush transparency, and bush lushness. We then conducted multiple linear regression for the variables found to differ significantly with respect to habitat against sand rat density.

Vector–host relations were analyzed using linear regression with density of active host burrows per plot as the independent variable and mean sand fly density per trapping station per plot as the dependent variable. We used a paired *t* test to compare per plot mean sand fly densities between burrow stations and random stations (see *Methods*), and between active and nonactive burrows. We also used a paired *t* test to compare per plot means of soil moisture and organic matter content (arcsine transformed) between active and nonactive host burrows.

The relations between distance from the settlement and burrow density were analyzed using linear regression, with number of burrows per 100-m transect segment as the dependent variable. The proportion of active burrows per transect segment (arcsine transformed) was calculated as the ratio between the number of burrows with activity marks and the total number of burrows in that segment. The spatial dispersion of *P. obesus* burrows in the disturbed and undisturbed habitats was estimated by two methods: the index of dispersion (I), and the negative-binomial exponent, k. The index of dispersion is, simply, the variance-to-mean ratio, and its departure from random (Poisson) dispersion was determined by the Index of dispersion test. The negative-binomial exponent, k, was estimated by the maximum likelihood method. The fit of the observed distribution to the negative-binomial distribution was tested using χ^2 goodness-of-fit test (Krebs 1999). We excluded from this analysis all sampling units ($n = 13$) that had a minor level of disturbance and therefore could not be categorized as either disturbed or undisturbed.

Results

The parasites in all sites were confirmed as *L. major* (Wasserberg et al. 2002). Microscope detectability for infection in the sand rat was 71.4% (20 leishmania-positive by microscopy out of 28 leishmania-positive detected by PCR, $n = 36$). All phlebotomine sand flies captured were *P. papatasi* ($n = 208$) except for three specimens of *P. alexandri* (one in Nizzana, one in Sede-Boker, one in Hazeva). The main reservoir host was confirmed to be the fat sand rat with a total of 57 ($n = 413$) (13.8%) infected specimens from all study sites (see also Wasserberg et al. 2002).

Our basic approach was to assess the degree to which spatial and temporal variation in reservoir hosts, parasitism rate, and vectors was associated with variation in habitat quality, as affected by human disturbance. In what follows, we discuss each of these biotic components of the CL system in turn in a manner corresponding with the predictions list (see *Introduction*).

Temporal and spatial infection patterns in the fat sand rat

Infection prevalence differed significantly among sites ($G = 31.99$, df = 4, $P < 0.001$), with Nizzana being the most heavily infected site (34%), followed by Sede-Boker (11%), Hazeva (9%), En-Yahav (4.9%), and Ne'ot-Hakikar (4.2%) (Fig. 2A). A significant interaction was found between site and trapping session ($G = 22.28$, df = 4, $P < 0.0001$) in influencing infection prevalence. In all sites, except for Nizzana, prevalence rate increased, as expected, from spring to autumn (Fig. 2A). In Nizzana, however, infection prevalence decreased, which appeared to result from a substantial increase in the abundance of the fat sand rat (from one individual in spring to 18 individuals in the late autumn) in two adjacent plots located in a stabilized sand habitat, which are characterized by CL prevalence of 0% (Wasserberg et al. 2002). This increase in host abundance diluted the overall infection prevalence in Nizzana.

We found a highly significant effect of disturbance on infection prevalence ($G = 42.04$, df = 4, $P < 0.0001$). In all sites, infection prevalence was higher in the disturbed habitat than in the undisturbed habitat (Fig. 2B).

The effect of habitat type and site on sand fly abundance

P. papatasi abundance was significantly higher in disturbed habitats than in the undisturbed habitats (Mann-Whitney $U = 625.5$, $\chi^2 = 7.615$, df = 1, $P = 0.0058$). Sites also differed significantly (Kruskal-Wallis statistic = 20.156, df = 4, $P = 0.0005$), with Nizzana being the most heavily infested site (Fig. 3). The pattern of *P. papatasi* abundance and *P. obesus* infection prevalence (Fig. 2B) was similar across sites and habitat types.

Comparison of the relative effect of vector vs. host density on host infection prevalence

Only the effect of vector abundance was statistically significant in influencing host infection prevalence. Sand fly density was positively correlated with host infection prevalence (CL prevalence = 0.461 × sand fly density + 0.179, $R^2 = 0.532$, $n = 19$, $P = 0.0006$).

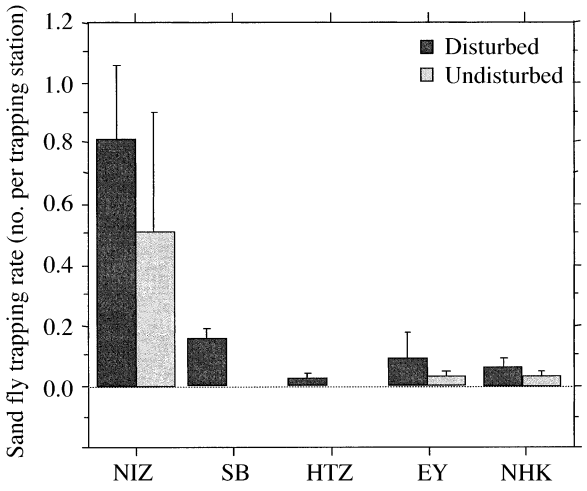

FIG. 3. Comparison of sand fly trapping rates in disturbed vs. undisturbed habitats in the five study sites. Values are means + 1 SE.

Spatial variation in soil characteristics and their relation to vector occurrence

Since a significant statistical interaction between site and soil moisture was found ($F_{4,47} = 22.669$, $P < 0.0001$) we conducted linear regressions between soil moisture content and sand fly density for each of the sites (the three Arava Valley sites were lumped). Significant positive correlation between soil moisture and sand fly density occurred for Nizzana, Sede-Boker, and the Arava Valley. However, the slopes of these regression lines differed by an order of magnitude, with Nizzana having the largest slope (slope ± confidence intervals ($P < 0.05$) = 1.413 ± 0.335), followed by Sede-Boker (0.133 ± 0.034), and the Arava Valley sites (0.017 ± 0.011) (Fig. 4).

As at the plot level, we found at the burrow level a significant statistical interaction between soil moisture and site with respect to sand fly occurrence per active host burrow ($AIC_{(interactive\ model)} = 91.338$, $AIC_{(additive\ model)} = 102.96$, likelihood ratio test: deviance = 15.6, df = 2, $P = 0.0004$). Significant relations occurred in Nizzana (β ± 1 SE = 3.80 ± 1.56, $n = 30$, $P = 0.006$) but not the other sites (Sede-Boker: β ± 1 SE = 0.66 ± 0.73, $n = 30$, $P = 0.36$, Arava: β ± 1 SE = −0.03 ± 0.27, $n = 40$, $P = 0.92$). With respect to organic matter content, there was no significant difference between the interactive (Akaike's Information Criterion [AIC] = 100.26) and the additive model (AIC = 100.22) (likelihood ratio test: deviance = 3.698, df = 2, $P = 0.138$); hence analysis was conducted over all sites combined. Organic matter content had a significant effect overall on sand fly occurrence (β ± 1 SE = 2.05 ± 0.99, $n = 100$, $P = 0.038$), but this effect was not significant within individual sites.

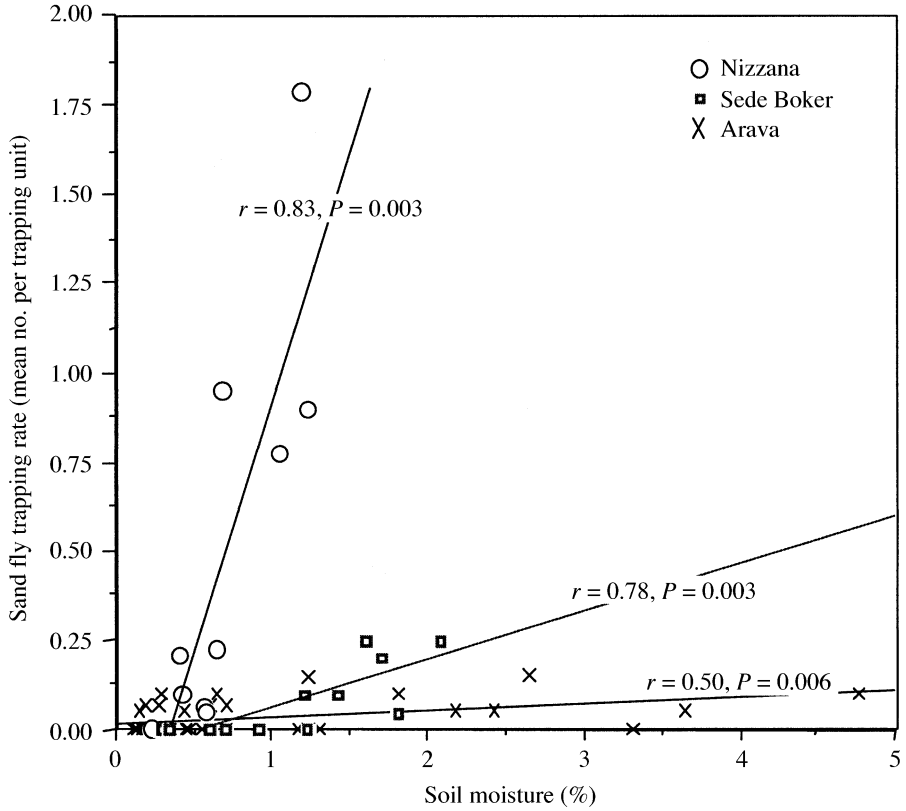

FIG. 4. The relationships between sand fly trapping rate and soil moisture in Nizzana, Sede-Boker, and the Arava.

TABLE 2. Two-way ANOVA table testing the effect of human activity and site on proportion of soil moisture content.

Source	df	Sum of squares	Mean square	F	P
Site	4	0.046	0.012	11.521	0.0001
Habitat	1	0.007	0.007	7.452	0.0087
Habitat × site	4	0.004	0.001	1.086	0.3735
Residual	50	0.050	0.001		

We hypothesized that soil moisture or organic matter addition are the mechanisms by which anthropogenic disturbance enhances infection risk. We therefore compared these two variables between disturbed and nondisturbed habitats within the different sites. Both site and habitat had a significant effect on soil moisture content, while the interaction term did not (Table 2). A general pattern of higher soil moisture level in the disturbed habitat was common to all sites. The difference, however, was significant only in Sede-Boker and Nizzana (Fig. 5). Among sites, Ne'ot-Hakikar salt marsh had the highest soil moisture level (mean ± 1 SE = 2.010 ± 0.414%), followed by Sede-Boker (1.151 ± 0.171%), Nizzana (0.800 ± 0.150%), En-Yahav (0.505 ± 0.128%) and Hazeva (0.315 ± 0.044%). Habitats did not differ with respect to soil organic matter content ($F_{1,40} = 1.824$, $P = 0.18$), but sites did. Soil organic content was highest at Sede-Boker and Nizzana, followed by Ne'ot-Hakikar and Hazeva ($F_{3,40} = 14.76$, $P = 0.0001$). We also found a statistically significant interaction between site and habitat type, indicating higher soil organic matter at the undisturbed habitat in Nizzana and the opposite in Ne'ot-Hakikar ($F_{3,40} = 3.428$, $P = 0.0201$) (Fig. 6). Therefore, despite the positive effect of soil organic matter content on sand fly occurrence, this effect was not consistent with the effect of anthropogenic disturbance.

Neither soil electrical conductivity nor pH differed between habitat types ($F_{1,50} = 0.712$, $P = 0.403$; $F_{1,50} = 2.39 \times 10^{-34}$, $P = 1$; two-way ANOVA). Soil electrical conductivity differed between sites ($F_{4,50} = 11.53$, $P < 0.0001$) with Ne'ot-Hakikar being significantly higher than the other sites (Bonferroni means comparison: $P < 0.002$). Soil pH did not differ between sites ($F_{4,50} = 0.714$, $P = 0.586$).

The vector–host relations

No statistically significant relations between sand rat and sand fly abundance were found ($r^2 = 0.017$, $n = 60$, $P = 0.831$). When comparing sand fly densities between the random stations and burrow stations of each plot we found that the number of sand flies caught at the burrow stations was about four times higher than that in the random stations (0.275 ± 0.092, 0.071 ± 0.024 sand flies per trapping station, respectively, $n = 60$, paired $t = 2.629$, $P = 0.01$). When comparing sand fly densities, within a plot, between active (burrows with activity marks) and nonactive burrows, we found

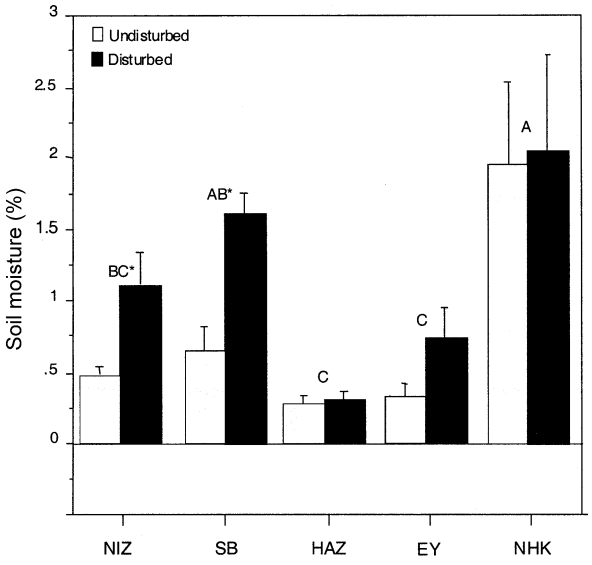

FIG. 5. Comparison of soil moisture (%) between disturbed and undisturbed habitats in the five study sites. Values are means + 1 SE. Asterisks (*) indicate significant differences between habitats (planned comparisons, $P < 0.05$). Significant differences between sites are indicated by different letters above the bars (Bonferroni/Dunn means comparisons, $P < 0.0005$).

that density of sand flies caught adjacent to active burrows was 3.6 times higher than those adjacent to nonactive burrows (0.551 ± 0.196, 0.153 ± 0.069 sand flies per trapping station, respectively, $n = 37$, paired $t = 2.684$, $P = 0.01$). Active and nonactive burrows did not differ with respect to either soil moisture (0.82

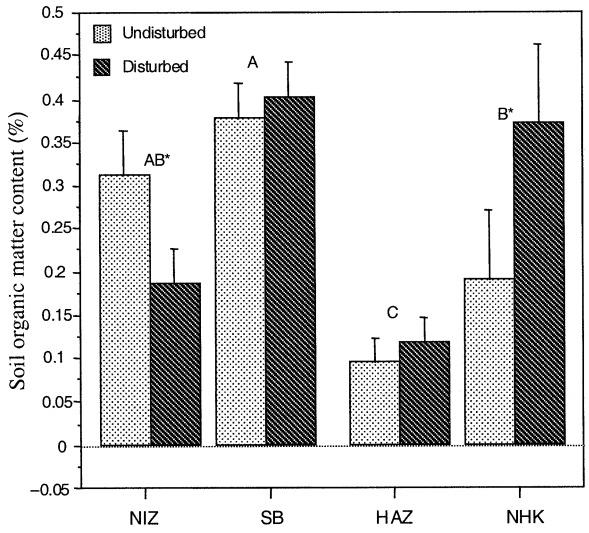

FIG. 6. Comparison of soil organic matter content (%) in active *P. obesus* burrows between disturbed and nondisturbed habitats in the five study sites. Values are means + 1 SE. Asterisks (*) indicate significant differences between habitats (planned comparison, $P < 0.05$). Significant differences between sites are indicated by different letters above the bars (Bonferroni/Dunn means comparisons, $P < 0.0005$).

TABLE 3. Effect of human activity on Chenopodiaceae plant characteristics.

Plant characteristic	Disturbed habitat	Undisturbed habitat	*P*
Percent cover	15.4	13.7	NS
Bush volume (m^3)	16.8	12.3	NS
Bush transparency	0.65	0.61	NS
Lushness	1.82	1.49	0.009
Proportion cover	0.62	0.51	0.049

Note: Significance values indicated are those of habitat effect resulting from two-way ANOVA testing the effect of habitat, site, and their interaction on each plant characteristic.

± 0.131% vs. 1.183 ± 0.27%, respectively; paired $t = 1.363$, $n = 37$, $P = 0.2$) or organic matter content (0.598 ± 0.327% vs. 0.457 ± 0.166%, respectively; paired $t = 0.386$, $n = 27$, $P = 0.703$).

The effect of anthropogenic disturbance on Chenopodiaceae plants and its consequences for host abundance

Habitats differed significantly only with respect to lushness and the proportion of chenopod plants. Plants tended to be, on average, more lush and predominantly composed of Chenopodiaceae plants in the disturbed habitat (Table 3). Fat sand rat abundance was positively correlated only with plant lushness (Table 4), which is assumed to be indicative of plant quality. Due to variance heteroscedasticity we conducted a separate weighted regression for lushness alone and got a much better fit (*Psammomys obesus* density = 0.815 × lushness + 1.12, $r^2 = 0.746$, $P = 0.0009$).

The spatial distribution and dispersion of P. obesus *burrows around Hazeva*

A significant positive correlation was found between expected (on the basis of external activity marks) and observed burrow activity ($y = 0.82x - 0.356$, $n = 25$, $r = 0.886$, $P < 0.0001$). This result confirms the reliability of these activity marks as indicators of *P. obesus* burrow activity.

No significant relations were found between distance from the settlement and total burrow (active and nonactive, combined) density per sampling unit ($n = 217$, $r = 0.072$, $P = 0.293$). Active burrow density also did not change significantly with distance, although a negative trend existed in the expected direction ($n = 192$, $r = -0.128$, $P = 0.076$). A significant negative correlation was found between distance from settlement and the proportion of active burrows ($n = 100$, $r = -0.439$, $P < 0.0001$).

Sand rat burrow dispersion was confirmed as highly aggregated by both indices in both disturbed and undisturbed habitats. Burrow distribution conformed with the negative binomial distribution only in the disturbed habitat (Table 5). When we compared the proportion of sampling units that contained at least one host burrow (hereafter ''occupied units'') between disturbed and undisturbed habitats, we found that in the disturbed habitat only 29.3% of the sampling units were occupied compared with 69.5% in the undisturbed habitat (contingency table: $G = 32.5$, df = 1, $P < 0.0001$). On the other hand, there was a nonsignificant trend suggesting that within occupied units aggregate size is slightly bigger in the disturbed than in the undisturbed habitat (mean ± 1 SE; 7.44 ± 1.07 vs. 5.343 ± 0.469 burrows; Mann-Whitney $U = 779.5$, $P = 0.107$).

TABLE 4. Multiple regression testing the relations between *P. obesus* abundance and plant lushness and proportion coverage of Chenopodiaceae plants (Prop. Chen.).

	Coefficient	SE	*t*	*P*
Intercept	0.558	0.884	0.632	0.5302
Lushness	0.905	0.418	2.166	0.0345
Prop. Chen.	0.605	0.860	0.703	0.487

Note: Model $R^2 = 0.097$, $n = 59$.

DISCUSSION

A prerequisite for the establishment of a disease hot spot in vector-borne zoonoses is the coincidence, in time and space and in sufficient numbers, of the pathogen, the host, and the vector (Sousa and Grosholtz 1991). The study of the environmental attributes that promote such a coincidence, termed by Pavlovsky (1966) ''landscape epidemiology,'' provides the basis for defining environmental risk factors and facilitates the development of a sensible control strategy. In this study we applied this approach to determine whether anthropogenic disturbance induces ecological changes that promote the establishment of a hot spot for CL.

To integrate the results of this study, we constructed a conceptual model of the zoonotic system of CL (Fig. 7), which depicts the structure and main processes operating in this system, and results in self-enhancement of infection risk to humans, as suggested by this study.

A conceptual model of the zoonotic system of CL

The model is constructed as a set of interacting flow diagrams (FD) (Fig. 7). Rectangles represent state variables, arrows represent flows, and ellipses represent

TABLE 5. Comparison of the spatial dispersion of sand rat burrows (in units of sand rat burrow density per 100 m of transect segment) between disturbed and undisturbed habitats in Hazeva.

Habitat type	*N*	Mean	*I*	*k*
Disturbed	92	2.19	9.35**	0.124
Undisturbed	105	3.71	4.63**	0.672**

Notes: Spatial dispersion was assessed by calculating *I*, the coefficient of dispersion (variance/mean ratio) and *k*, the negative-binomial distribution exponent. Departure from random and negative-binomial dispersion was tested using index of dispersion of χ^2 goodness-of-fit tests (Krebs 1999), respectively.

** $P < 0.01$.

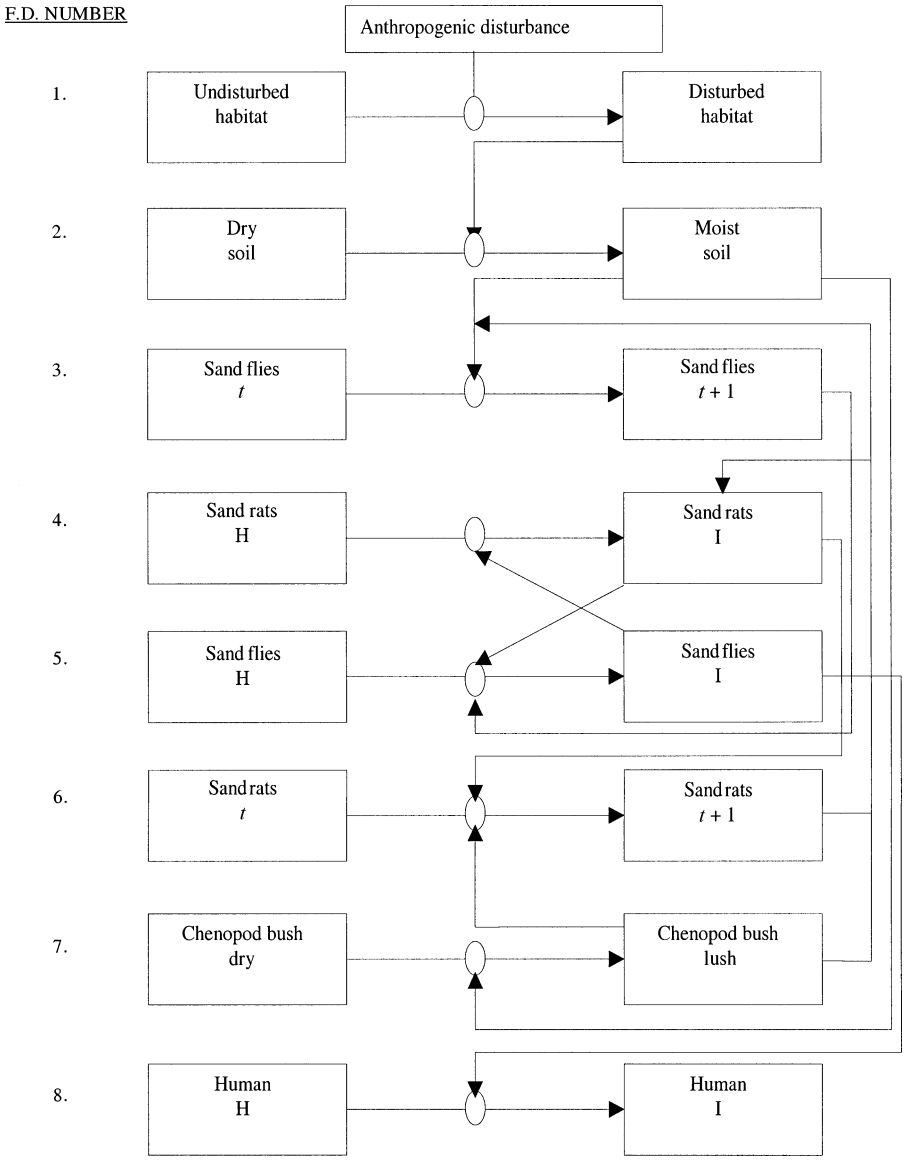

FIG. 7. A conceptual model of the zoonotic system of CL. Rectangles represent state variables, arrows represent flows, and ellipses represent controllers (H = healthy, I = infected, FD = flow diagram, t = time).

controllers. Results show that disturbances (FD1) arising from a variety of human activities such as construction, military training exercises, agriculture, etc., appear to have one common denominator: water addition (FD2). Soil moisture is, on average, higher in the disturbed habitat (Fig. 5) and so is sand fly density (Fig. 3). Both soil moisture and organic matter content are positively associated with sand fly occurrence. Yet, since only soil moisture varies consistently with sand fly density across habitat types, we conclude that anthropogenic disturbance affects sand fly abundance via its effect on soil moisture and not on soil organic matter content. For the vector, increased soil moisture provides better breeding, sheltering, and feeding conditions (*P. papatasi* is partially nectivorous) (Killick-Kendrick 1999), and was shown, in this study and others (Schlein et al. 1984, Zherkhina et al. 1990, Yuval 1991), to be positively associated with vector abundance. This positive effect of soil moisture on sand fly abundance is depicted as the effect of moist soil (in FD2) on sand fly population dynamics (FD3). The relation between soil moisture content and sand fly abundance, however, differs among sites. In Nizzana, the slope is two orders of magnitude greater than in the Arava valley, and one order of magnitude greater than Sede-Boker (Fig. 4), suggesting the involvement of another factor that differentially enhances the relations between soil moisture and vector abundance. Soil organic matter content is probably not that factor, since it is ranked inconsistently with respect to sites (Fig.

6). An alternative explanation may simply be that climate is most favorable for *P. papatasi* sand flies in Nizzana. Sede-Boker, located at a higher elevation, may be too cold, while the Arava valley may be too hot (Table 1). Climate, therefore, might interact with soil moisture to produce the observed differential response.

We also showed that vector abundance, but not host abundance, has a major influence on infection prevalence in the reservoir host population, a result concordant with basic vector-borne epidemiologic models, which emphasize vector abundance as one of the major determinants of the vectorial-capacity of a zoonosis (Dye 1992). This is represented in the model by the interaction between sand fly population dynamics (FD3) and infection dynamics within vectors (FD5). The latter affects directly infection probability of the reservoir host (FD4: infection dynamics within the reservoir host), which, in turn, enhances infection probability for the vector, creating a positive feedback loop.

Soil moisture affects positively, indirectly via its effect on plant state (lushness) (FD 7), sand rat population size (FD 6). Sandrat population size is expected to affect sand fly abundance and distribution (the control of FD 6 on FD 3) by 're-activating' abandoned burrows as proper breeding and sheltering sites, and by providing accessible blood meals. Results, indeed, show higher sand fly capture rate in active burrows compared with nonactive burrows. This difference, however, is probably not due to difference in burrow conditions, since no differences were found with respect to either soil moisture or organic matter content between active and nonactive burrows. Sand fly attraction to active burrows is therefore, probably, due to the actual presence of the host itself, possibly via specific cues such as CO_2 emission (Killick-Kendrick 1999). At the plot scale (~30 m radius) we failed to show positive relations between sand rat and sand fly abundance. Yet recent observations show that at the scale of 500 m radius around a given active burrow, active burrow density is a significant predictor of infection probability per individual host, and that these relations are mediated via sand fly but not sand rat dispersal (G. Wasserberg, *unpublished data*).

This complex chain of processes enhances the probability of a vector becoming infected and consequentially enhancing disease risk to humans (FD5 control on FD8). These two processes, i.e., infection dynamics within the vector population and its effect on disease risk within human settlements, are yet to be studied.

Spatial aspects of anthropogenic disturbance

Human activity also affects the spatial distribution of the reservoir host. We found a negative correlation between distance from settlement edge and the proportion of burrows occupied. We suggest that this pattern arises from the effect of anthropogenic disturbances on water addition. Sand rats rarely dig new burrows and tend to reuse old abandoned ones. Between the two trapping sessions only four new burrows were dug within all 60 study plots. Therefore, it is possible that sand rats perceive old abandoned burrows as potential colonization sites, which become inhabitable as host plants recuperate from the previous exploitation. Food plants in the disturbed habitats probably recuperate faster due to the higher soil moisture, leading to higher patch occupancy rates closer to settlements.

In addition to its effect on the distribution of sand rats, human activity has the potential to affect the distribution of sand flies as well. Re-colonization of old burrows by sand rats could 're-activate' these burrows as suitable shelter and breeding sites for the sand flies. Thus, in terms of infection risk to humans, the tendency of higher recolonization rate of old burrows by sand rats next to a settlement not only enhances the infection risk by changing the spatial distribution of the host, but may also enhance the disease transmission rate by increasing the abundance of vectors.

Our observations confirm earlier studies showing aggregated distribution of sand rat burrows (e.g., Daly and Daly 1974, Ilan and Yom-Tov 1990, Fichet-Calvet et al. 2000). However, we found that the degree of aggregation was higher in disturbed than in undisturbed habitat. This pattern probably results from the fact that the majority of the area surrounding the settlement is not suitable for the sand rat due to its use as agricultural fields. Hence, the sand rat population in the disturbed area is highly fragmented. On the other hand, the remaining suitable patches in the disturbed area appear to be of higher quality than their counterparts in the undisturbed habitat, as suggested by the trend of larger aggregates in the disturbed habitat, probably caused by effluents drained from the nearby fields or settlement. The spatial distribution of sand rats in the disturbed area is highly fragmented, but the majority of the suitable habitat patches occur relatively close to the settlement. This pattern of distribution suggests that the sand rat population in the disturbed area is quite fragile, and may constitutes a sink population, which depends on immigration from the surrounding natural source population (Pulliam 1988) for its persistence.

The enhancement of soil moisture through anthropogenic disturbances can be either direct, through agricultural or domestic effluents (Zherkhina et al. 1990), or indirect via microtopographic changes, such as the construction of dikes or dams (Frayauff et al. 1993), which may cause local, and possibly regional, accumulation of water. Dikes are quite common features that accompany a variety of disturbances generated by human activities (e.g., drainage canal beds, shooting ramps, dams, roadsides, etc.), and appear to be preferred burrow-digging sites for the sand rat; of the sand rat burrows in disturbed plots, 64.5% (207 out of 321) were found on artificial dikes. Furthermore, when we compared the number of burrows located on an artificial

dike to the number of burrows located on the surface of disturbed plots we found significantly more burrows on mounds; paired t test: $t = 2.346$, $P = 0.026$). Apart from the aforementioned effect on food quality, we believe that dikes are a preferred burrow site because they may be easier to dig, protected from flooding, and provide a good observation deck for the detection of predators. Preference of *P. obesus* for dikes as burrow-digging sites has also been reported previously (Algeria: Daly and Daly 1974, Tunisia: Fichet-Calvet et al. 2000).

Conclusions

Ashford (1999) identified two possible mechanisms that may stimulate endemic and localized CL to develop into an epidemic: (1) influx of susceptible human populations into zoonotic areas; and (2) ecological changes that cause an increase in host population size. To this we would add: (3) ecological changes that cause an increase in vector population size. Examples of the effect of human immigration into zoonotic areas are numerous (e.g., Naggan et al. 1970, Giladi et al. 1985, Klaus et al. 1994, Morsy-Tosson et al. 1995, Biton et al. 1997, and see reviews in Ashford 1999, 2000, Oumeish 1999, Saliba and Oumeish 1999, Desjeux 2001). However, evidence for the ecological effect is scarce and circumstantial. The idea that human-induced ecological changes may promote CL outbreaks is not new (Greenblatt 1985, Ashford 1999, Oumeish 1999, Saliba and Oumeish 1999), however, this is the first time that this hypothesis has been empirically studied. In reality, both epidemic processes—influx of susceptible human populations into zoonotic areas and human-induced ecological changes—are probably synergistic in causing the reported outbreaks. This is probably what happened during the last decade in southern Israel. First, military activity in the region has increased following the redeployment of Israeli troops from Sinai in the early 1980s and has continued to grow steadily ever since (Giladi et al. 1985, Wasserberg et al. 2002). Second, following the large immigration wave from the former USSR in the early 1990s, the Negev and the Arava regions have been rapidly developing, both in terms of increased population size and regional development. A situation like this, of human-induced ecological changes favorable to the zoonotic system, coupled with an influx of a large susceptible human population, sets the stage for substantial epidemiological outbreaks such as that reported by Biton et al. (1997) in Yeruham and Wasserberg et al. (2002) in Nizzana.

Our results indicate that humans are not passive victims of their occurrence in disease endemic sites. Instead, humans alter the structure of their environment, thereby initiating a cascading chain of ecosystem processes that promote the establishment of a CL hot spot (Fig. 7). Humans, through their effect on soil moisture availability, affect positively the distribution and abundance of the reservoir host and the vector, thereby affecting the distribution and transmission rates of the pathogen, respectively. Anthropogenic disturbances cause reservoir hosts and sand fly vectors to occur closer to the human settlement and thus humans enhance CL infection risk to themselves. These insights into the structure and function of the CL zoonotic system provide the basis for several potential control measures. Water addition was identified as the main underlying anthropogenic CL risk factor. Therefore local authorities should put special emphasis on managing residential and agricultural effluents, and try to avoid creation of microtopographic disturbances that disrupt the natural drainage systems and may provide favorable habitats for both the host and vector. In addition, sand fly avoidance can be facilitated by increased public awareness of factors that promote CL transmission. In any case, detection and mapping of such risky patches, i.e., occupied sand rat aggregates in habitat patches containing relatively high soil moisture in the vicinity of the settlement, is required as a first step.

The ultimate goal of our research program is to develop a quantitative, mechanistic, spatially realistic model of the CL system that will constitute the framework for the development of a sensible control plan (Mollison and Levin 1995, Mills and Childs 1998). The study described here, which addressed the environmental aspects of the CL zoonotic system in southern Israel, is the first step towards achieving this goal, and demonstrates the importance of applying an ecological approach to the study of epidemiological problems.

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