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Geographic and Epidemiologic Analysis of the Cutaneous Leishmaniasis Outbreak in Northern Israel, 2000–2003

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ABSTRACT: **Background:** The incidence of cutaneous leishmaniasis in northern Israel began to rise in 2000, peaking at 41.0 per 100,000 in the Kinneret subdistrict during the first half of 2003.

Objectives: To examine the morbidity rates of CL in northern Israel during the period 1999–2003, which would indicate whether new endemic areas were emerging in this district, and to identify suspicious hosts.

Methods: The demographic and epidemiologic data for the reported cases (n=93) were analyzed using the GIS and SPSS software, including mapping habitats of suspicious hosts and localizing sites of infected sand flies.

Results: The maximal incidence rate in the district was found in the city Tiberias in 2003: 62.5/100,000 compared to 0–1.5/100,000 in other towns. The cases in Tiberias were concentrated on the peripheral line of two neighborhoods, close to the habitats of the rock hyraxes. Sand flies infected with *Leishmania tropica* were captured around the residence of those affected. Results of polymerase chain reaction were positive for *Leishmania tropica* in 14 of 15 tested patients.

Conclusions: A new endemic CL area has emerged in Tiberias. The most suspicious reservoir of the disease is the rock hyrax.

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KEY WORDS: cutaneous leishmaniasis, outbreak, epidemiology, Israel, hyrax, sand flies

Cutaneous leishmaniasis, caused by Leishmania parasites, is an endemic worldwide disease with about 1.5 million cases occurring each year [1]. During the period 1993–2000 the global incidence rate increased by 500% [2]. Urbanization and the development of new neighborhoods close to nature areas contributed to this rise in morbidity [3-7]. The disease is usually zoonotic with a variety of rodents and other mammals serving as the disease reservoir [2,8,9].

The rock hyrax, a small thickset herbivorous mammal, is the suspected disease reservoir in Kenya, Namibia and some areas in Israel, with accumulating evidence supporting the notion that hyraxes in these areas are the reservoir host of *Leishmania tropica* [5,10-13]. Sand flies (the disease vector) transfer the Leishmania from the infected reservoir host to humans. The lesions that develop in the bite area, mainly the face and limbs, are cosmetically damaging, may be prolonged [6,9,14,15] and may result in atrophic scars [9].

L. tropica, as compared to *L. major*, is characterized by higher severity, longer course (up to a year and a half), resistance to routine therapies, and a chronic or relapsing clinical presentation [5,6,10,16]. Some cases need intravenous sodium stibogluconate therapy, often resulting in serious adverse effects requiring hospitalization [6,16,17]. In endemic CL areas *L. tropica* may cause visceral leishmaniasis [5], a highly fatal disease particularly in children and immunocompromised patients [19].

CL in Israel is an endemic disease and only a few patients contract the disease abroad. The incidence of CL during the period 1961–2000 was 0.13–7.0/100,000 [4]. During the period 1995–1998 endemic areas of CL were identified in northern Israel near the Sea of Galilee (Kinneret) [5]. In 2000 the incidence of the disease in the Kinneret subdistrict began to rise, reaching the highest level in the country – 41.0/100,000 – in the first half of 2003 [20].

In 2003 we carried out an epidemiologic survey to define the demographic characteristics of the affected CL patients and identify the possible animal reservoir. Results of this survey were then translated into an intervention program aimed at reducing the disease burden. The Northern District data of the CL database show that during the years that followed, CL incidence rates in Tiberias fluctuated, with an overall decreasing trend: 20.0–39.9/100,000 during 2004–2006 and 15.1–22.6/100,000 during 2007–2008. More details pertaining to the association between the intervention program and the disease reduction will be described in a separate article.

MATERIALS AND METHODS

The study was conducted in northern Israel, a region comprising five subdistricts with a population of about 1,100,000. Eligible for this study were all CL cases diagnosed in northern

CL = cutaneous leishmaniasis

district residents who had been reported to the Ministry of Health during 1999–2003.

DATA COLLECTION AND VARIABLES DEFINITIONS

Several data sources were used:

- Individual notification forms completed by the diagnosing physicians and including the patient's demographic data, address, diagnosis and laboratory test results
- Epidemiologic investigation questionnaires, routinely filled in by the subdistrict's health department team and including additional data on the clinical manifestations, date of disease onset, places visited during the year prior to disease onset, and information on mosquito bites and the presence of animals around the patient's residence
- Data collected from the Ministry of Environmental Protection on the location of traps used to collect sand flies infected by Leishmania
- Information from the National Parks Protection Authority and the municipality veterinarian regarding the location of the rock hyrax habitats in Tiberias
- The Central Bureau of Statistics denominator data used for the calculation of CL incidence rates
- The patients' polymerase chain reaction results, which were obtained from the Leishmaniasis Reference Laboratory (Kuvin Center for the Study of Infectious and Tropical Diseases, IMRIC, Hebrew University-Hadassah Medical School, Jerusalem) that carried out PCR diagnosis and Leishmania species typing.

In order to monitor the CL morbidity and enable integration of data received from the above sources into one database, computerized software, based on SQL SERVER, was developed. The following definitions were used:

- The place where the disease was contracted was determined by the district's epidemiologist, taking into account the information about visiting endemic areas, as in the questionnaire received from the relevant subdistrict's epidemiologic team. For those not visiting any endemic area the place where the disease was contracted was assumed to be the city or township of the patient's residence.
- The time of disease onset was defined as the date of appearance of the first signs (i.e., nodules or macula) reported by the patient in the epidemiologic questionnaire. This information was later used for calculation of the CL incidence rates, rather than the date of reporting to the Ministry of Health.

STATISTICAL PROCESSING AND GEOGRAPHIC ANALYSIS

The demographic and epidemiologic data of the study population was exported from the CL database into GIS and SPSS software.

IMRIC = Institute for Medical Research Israel-Canada
PCR = polymerase chain reaction

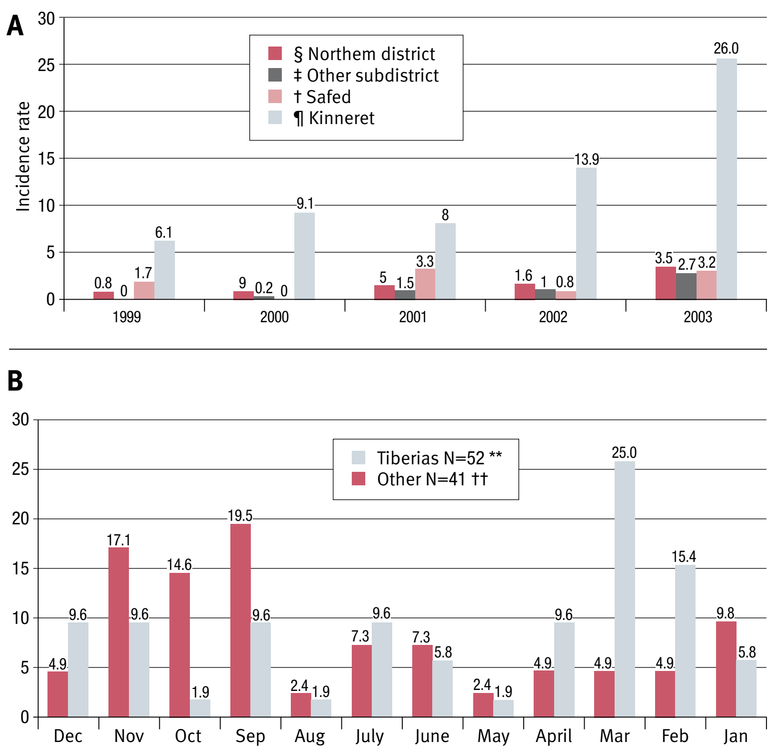
Incidence rates were calculated by geographic area. Associations between age and gender and the place where the patient contracted the disease were examined using the chi-square test. Student's *t*-test was used for comparing groups regarding continuous variables, and the one-way ANOVA test was used for comparing differences among more than two groups.

A GIS layer was created for all study cases based on the following data: residence and site of disease contraction as well as the year the first signs appeared. Regarding Tiberias, an additional two GIS layers were created for mapping out the habitats of rock hyraxes and sand-fly traps. All three layers were then matched to examine the degree of their overlap.

RESULTS

The district incidence rate of CL was more than four times higher in 2003 than in 1999 [Figure 1A]. The rate in the Kinneret subdistrict increased from 6.1 per 100,000 to 26.0

Figure 1. [A] Incidence rate (per 100,000) of cutaneous leishmaniasis in northern Israel by subdistrict, 1999–2003. **[B]** Distribution (%) of CL cases: Tiberias vs. other locations, by month of disease onset during 1999–2003 (N=93).



¶ Population of the Kinneret subdistrict during 1999–2003: 97,720–102,326.
† Population of the Safed subdistrict during 1999–2003: 118,215–124,938.
‡ Population in the remaining subdistricts during 1999–2003: 97,720–102,326.
§ District population during 1999–2003: 1,058,736–1,142,546
¶¶ Disease contracted in Tiberias
†† Disease contracted in other places

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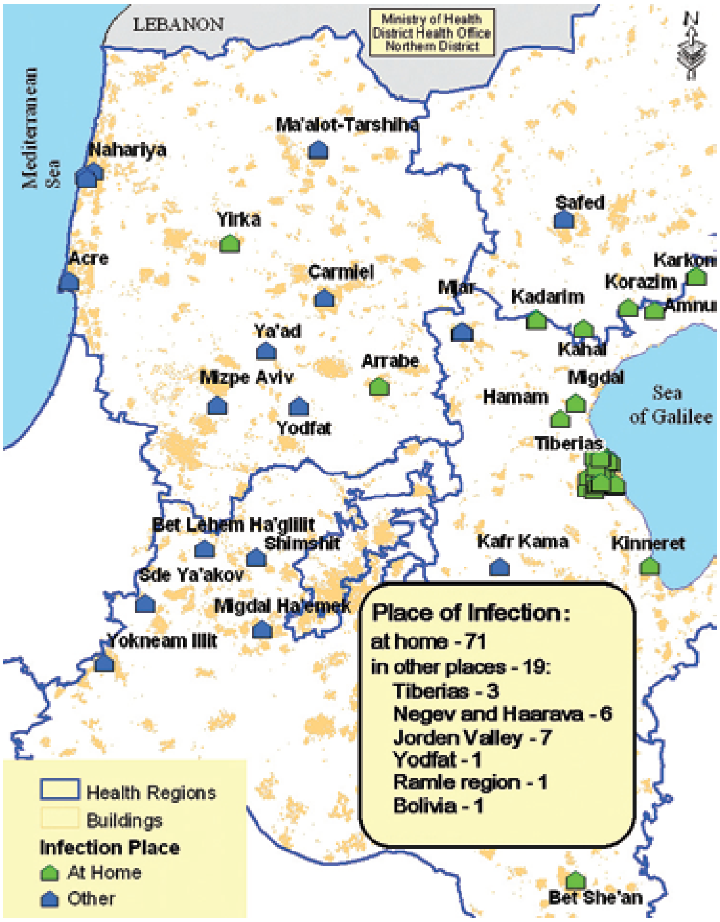
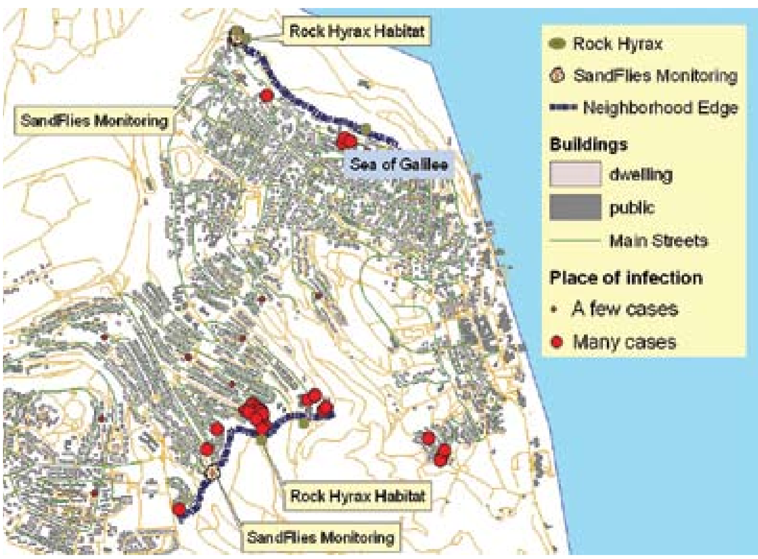
Map 1. Geographic distribution of the CL cases in the northern district according to place of residence and place of disease contraction, 2000–2003



Map 2. Geographic mapping of the CL cases according to the year and the Infected patient's place of residence in Tiberias, 1999–2003



per 100,000; in the Safed subdistrict it increased from 1.7 to 3.2/100,000 and in the rest of the region it remained low. In the Kinneret subdistrict, the highest incidence rate was in Tiberias, reaching 62.5/100,000 in 2003 compared to 10.0/100,000 in 2002. Overall, 93 northern district inhabitants were infected with CL in 1999–2003, of whom 90 underwent an epidemiologic investigation and 3 refused to cooperate. The geographic mapping of the 90 cases [Map 1] displayed small clusters of leishmaniasis near the Sea of Galilee and a new endemic area in Tiberias. Of these 90 cases 71 (76.3%) were infected at their place of residence (52 in Tiberias, 7 in six settlements* near Tiberias, 9 in three endemic settlements near the Sea of Galilee, 3 in settlements of Acre and Jezre'el subdistricts, and 19 in other endemic areas. Of the 59 CL patients from Tiberias and surroundings 15 underwent PCR testing for Leishmania and 14 were found positive for *L. tropica*.

The epidemiologic investigation of the Tiberias foci patients revealed that none of them visited any known endemic areas during the year prior to disease onset. Using GIS analysis, the CL cases were mainly found on peripheral lines of the two infected city neighborhoods [Map 2]. The habitats of the rock hyrax and the traps with the highest rate of sand flies infected with *L. tropica* were also located on the same line [Map 2]. The percent of infected flies in these traps was 19 versus 1–5% in the other sites of Tiberias that were investigated. The 2003 incidence rate in these two neighborhoods reached 145.9 per 100,000 (24 of 16,452 inhabitants).

DISTRIBUTION OF CASES BY GENDER

Fifty-one of the 90 patients (56.7%) were males and 39 (43.3%) were females. Similar proportions of males and females were observed among patients infected in their place of residence (49.3% vs. 50.7% respectively), whereas a significantly higher proportion of males as compared to females were observed among patients infected elsewhere (84.2% vs. 15.8% respectively) ($P = 0.006$).

DISTRIBUTION OF CASES BY AGE

Most of the 19–49 year old patients (78.9%) were infected outside their place of residence [Table 1]. The patients in the other age groups were mainly infected near their place of residence.

THE POSSIBLE DISEASE RESERVOIR

Among 71 patients who were infected at their place of residence, 20 (28.2%) reported the presence of rock hyraxes near their residence [Table 1].

SEASONAL CHARACTERIZATION OF THE DISEASE

Significant differences between the patients who contracted the disease in Tiberias and those who contracted the disease else-

*township, kibbutz or moshav

where were noted [Figure 1B]: 40.4% of the patients who contracted the disease in Tiberias became ill during February and March, compared to 9.8% of those who were infected in other locations; 30.7% of the patients who contracted the disease in Tiberias became ill during September–December in comparison to 56.1% of the patients who contracted the disease elsewhere.

DISCUSSION

Taking into consideration the increase in CL incidence in the northern district that occurred from 1999 to 2003, the principal goal of the present study was to examine whether a new endemic focus had emerged in this region. The following arguments support our hypothesis:

- *Geographic distribution of cases alongside nature areas*: GIS analysis of the CL cases occurring in Tiberias revealed the main foci to be on the city outskirts. The patients' residences were adjacent to undeveloped nature areas. In addition, the habitat locations of the rock hyraxes and the traps for the sand flies that were infected with *Leishmania tropica*, as mapped, were found to overlap with the sites that marked the patients' residences. Similar findings were reported by Biton et al. [7], who described a CL outbreak in 32 patients in a newly built area outside Yerucham (a small town in the south of the country). This tendency is known around the world: namely, that new endemic areas of CL appear in neighborhoods invading ecological undeveloped rural areas [3-6]. Indeed, our field investigation revealed the presence of trees, vegetation and rocks, as well as boulders left over from building construction.
- *Findings regarding the possible reservoir*: 28.2% of the CL Tiberias patients reported the presence of rock hyraxes near their area of residence. Rock hyrax families were found by the epidemiologic team in this area. The environmental conditions near two infected neighborhoods were suitable for their habitat. It is known that rock hyraxes live among rocks, rocky cliffs and boulder screes, and eat virtually any type of vegetation [21]. The municipal veterinarian first noted their appearance in 2001, with peak growth in the hyrax population in 2003. A similar increase in CL incidence was observed in this period.
- *Possibility for expansion of the endemic area*: As stated earlier, endemic clusters of CL were described in the northern district (Kinneret) and were studied by Jacobson et al. [5] who identified *Leishmania tropica* in PCR tests of CL patients and female sand flies. Leishmania DNA was positive in 3 of the 29 tested rock hyraxes. The distance between Tiberias and the northern Kinneret foci is only 10–15 km.
- *Contributing weather conditions*: The large number of CL cases in 2003 might be related to the abundance of rain [22] in the area during the 2002–2003 winter. The direct relationship linking humidity, rainfall, vegetation growth, with the increase in the sand fly and the reservoir populations and with CL morbidity has been described in many studies [8,23,24].
- *Patient's epidemiologic data*: Most of the CL patients (78.9%) did not report visits to any known endemic region for a year prior to disease onset. The distribution of the CL patients by gender and age also supports our hypothesis. It manifested in similar proportions (about 50%) of males and females, as well as in the predominance of young and elderly subjects among those contracting their disease in Tiberias. This pattern is described in populated endemic areas [3].

Table 1. Demographic and epidemiologic characteristics of CL patients in northern Israel, 1999–2003

		Place where disease was contracted N (%)			
	Total N (%)	Residence N (%)	Elsewhere N (%)	OR (95%CI)	*P* value
Total	90 (100)	71 (100)	19 (100)		
Gender					
Male	51 (56.7)	35 (49.3)	16 (84.2)	5.5	
Female	39 (43.3)	36 (50.7)	3 (15.8)	(1.46-20.49)	0.006
Age (yrs)					
0–18	29 (32.2)	26 (36.6)	3 (10.3)	0.11 (0.03-0.44)	0.0001
19–49*	29 (32.2)	14 (19.7)	15 (78.9)		
50–77	32 (35.6)	31 (43.7)	1 (5.3)	0.03 (0.004-0.25)	‹ 0.0001
Place of residence					
Tiberias	52 (57.8)	52 (73.2)	0		
Other	38 (42.2)	19 (26.8)	19 (100)		
Disease onset (mos)					
1–4	37 (41.1)	34 (47.9)	3 (15.8)		0.007
5–8	15 (16.7)	13 (18.3)	2 (10.5)		
9–12	38 (42.2)	24 (33.8)	14 (73.7)		
Reported suspicious hosts at their residence					
Rock hyrax		20 (28.2)	NR**		
Mice/Rats		15 (21.1)	NR**		
Mongoose		4 (5.6)	NR**		
Other rodents		8 (11.3)	NR**		
None		24 (33.8)	NR**		

*Reference group
** Not relevant

In 2006 Svobodova and co-workers [10] confirmed our hypothesis of a new CL endemic area in Tiberias and its surroundings: the identical *L. tropica* serotype was found in rock hyraxes, sand flies and humans. Rock hyrax peridomestic populations, according to the conclusion of that article, are the primary cause of the emergence of CL caused by *L. tropica* in certain regions.

Of the 59 patients residing in Tiberias and its surroundings, 14 had a positive PCR result for *L. tropica*, one was negative and 44 patients were not tested, yet we believe they would have been found positive had they been tested. This belief is supported by the study of Adir et al. [16] who reached the same conclusions in their study describing the clinical course and response to therapy in 49 patients, residents of Tiberias and its surroundings who were diagnosed as having CL during the period September 2002 to March 2004. Of the 27 patients in their study who were tested, 26 were found by PCR to be positive for *L. tropica*; and 50% of all study patients required multiple therapies due to treatment failure or partial response. Most of the cases in Tiberias and its surroundings occurred between January and March, as was the case in the endemic region of Hormozegen in Iran [25].

CONCLUSIONS AND RECOMMENDATIONS

The epidemiologic characteristics of the infected patients, their positive PCR results for *L. tropica*, the geographic distribution of the CL cases and the proximity of their residence to habitats of rock hyraxes and *L. tropica*-infected sand flies support the hypothesis that a new endemic area of CL due to *L. tropica* emerged in Tiberias at the beginning of 2000. Using GIS analysis of the cases, the vector and the hosts are important for characterizing a new endemic area for CL and for indicating the most likely reservoir prior to availability of valid laboratory etiologic data.

We recommend that investigation of any CL outbreak be conducted collaboratively by the Ministry of Health, the Ministry of Environmental Protection and the National Parks Protection Authority, and that a joint database be established that will include data on the vector, the reservoir and human morbidity. We also propose to conduct statistical and GIS morbidity analyses, including mapping of the infected vectors and the suspected hosts, as well as calculating age- and gender-specific incidence rates for identification of target groups. All of the above strategy and data are crucial for planning a multidisciplinary intervention for disease control.

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References

1. Center for Disease Control and Prevention (CDC). Diseases & conditions. Leishmania Infection (Leishmaniasis), Fact Sheet. [Cited 2007 Sep 11]. Available from: http://www.cdc.gov/ncidod/dpd/parasites/leishmania/factsht_leishmania.htm.
2. Roberts LJ, Handman E, Foote SJ. Science, medicine and the future: leishmaniasis [Review]. *BMJ* 2000; 32: 801-4.
3. Kroeger A, Avila EV, Morison L. Insecticide impregnated curtains to control domestic transmission of cutaneous leishmaniasis in Venezuela: cluster randomized trial. *BMJ* 2002; 325: 810-13
4. Anis E, Leventhal A, Elkana Y, Wilamowski A, Pener H. Cutaneous leishmaniasis in Israel in the era of changing environment. *Public Health Rev* 2001; 29(Pt 1): 37-47.
5. Jacobson RL, Eisenberger CL, Svobodova M, et al. Outbreak of cutaneous leishmaniasis in northern Israel. *J Infect Dis* 2003; 188(Pt 7): 1065-73.
6. Davidson RN. Practical guide for the treatment of leishmaniasis. *Drugs* 1998; 56(Pt 6): 1009-18.
7. Biton A, Namir S, Mosovich B, Vardi D. Cutaneous leishmaniasis: incidental outbreak in a new endemic area. *Harefuah* 1997; 132(Pt 6): 385-7, 448 (Hebrew).
8. Kamhawi S, Arbagi A, Adwan S, Rida M. Environmental manipulation in the control of a zoonotic cutaneous leishmaniasis focus. *Arc Inst Pasteur Tunis* 1993; 70(Pt 3-4): 383-90.
9. American Academy of Pediatrics. [Section 3: Summaries of Infectious Diseases]. In: Pickering LK, ed. Red Book: Report of the Committee on Infectious Diseases. 25th edn. Elk Grove Village, IL, 2000: 365-8.
10. Svobodova M, Votypka J, Peckova J, et al. Distinct transmission cycles of Leishmania tropica in 2 adjacent foci, northern Israel. *Emerg Infect Dis* 2006; 12(12): 1860-8.
11. Richard W, Ashford RW. Leishmaniasis reservoirs and their significance in control. *Clin Dermatol* 1996; 14: 523-32.
12. Ashford RW. The leishmaniases as emerging and reemerging zoonoses. *Int J Parasitol* 2000; 30: 1269-81.
13. Sang DK, Njeru WK, Ashford RW. A possible animal reservoir for *Leishmania tropica s.l.* in Kenya. *Ann Trop Med Parasitol* 1992; 86: 311-12.
14. Davies CR, Croft SL, Sundar S. Leishmaniasis: new approaches to disease control [Review]. *BMJ* 2003; 326: 377-82.
15. Herwaldt BL. Leishmaniasis. *Lancet* 1999; 354(9185): 1191-9.
16. Shani-Adir A, Stephanie K, Rozenman D, et al. Leishmania tropica in northern Israel: a clinical overview of an emerging focus. *J Am Acad Dermatol* 2005; 53(5): 810-15.
17. William HM, Khaldoun M. Cutaneous leishmaniasis: recognition and treatment. *Am Fam Physician* 2004; 69 (Pt 6).
18. Ya'ari A, Jaffe CL, Garty BZ. Visceral leishmaniasis in Israel, 1960-2000. *IMAJ Isr Med Assoc J* 2004; 6: 205-8.
19. Russo R, Laguna F, Lopez-Velez R, et al. Visceral leishmaniasis in those infected with HIV: clinical aspects and other opportunistic infections. *Ann Trop Med Parasitol* 2003; 97(Suppl 1): S99-105.
20. Vinitsky O, Habiballa H, Or A, et al. *Leishmania tropica* – the experience of the Ministries of Health and Environment in northern Israel. Paper presented at the meeting: Leishmaniasis in Israel, Jordan and the Palestinian Authority; October 2003; Sheba Medical Center, Tel Hashomer, Israel.
21. Wild Watch, eyes on the wild, Living library, Mammals. [Cited 2007 Sep 17]. Available from: http://www.wildwatch.com/living_library/mammals-2/hyrax-rabbit-sized-ungulates
22. Israel Weather. [Cited 2007 Sep 17]. Available from: http://www.israelweather.co.il/page2.asp?topic_id=80&topic2_id=127&sub_topic_id=1.
23. Teodoro U, La Salvia Filho V, De Lima EM. et al. Phlebotomine behavior in forest and extraforest environments, in an endemic area of American cutaneous leishmaniasis in northern Paran State, southern Brazil [PT]. *Rev Saude Publica* 1993; 27 (Pt 4): 242-9.
24. Grotto I, Huerta M, Balicer R. Epidemiology of leishmaniasis in the Israel Defense Force. Paper presented at the meeting: Leishmaniasis in Israel, Jordan and the Palestinian Authority; October 23, 2003; Sheba Medical Center, Tel Hashomer, Israel.
25. Zare S, Baghestani S. Cutaneous leishmaniasis in Hormozgan, Iran. *Int J Dermatol* 2001; 40: 629-31.