ABSTRACTS

Wednesday, December 17, 2008

09:00 – 10:45 Session 1: Travel Medicine

An inactivated cell culture derived JEV vaccine (IC51) towards worldwide licensure

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Japanese encephalitis is the most common viral encephalitis in Asia with 30% case-fatality rate. The use of mouse-brain derived JE vaccines available to travelers was limited for safety concerns. IC51 is an alum containing JE vaccine produced on Vero-cells without thimerosal or gelatin. Seroconversion rate after to 2 IC51 doses was 98 % (95% after 3 JE-VAX® doses) with persisting immunity at 12 months in 83% of subjects. IC51 safety was comparable to placebo; IC51 local tolerability was more favorable than JE-VAX®. Similar results were obtained in a pediatric population with 2 reduced doses IC51. Co-vaccination with hepatitis A vaccine did not interfere with immunogenicity. Licensure for IC51 is expected in Australia, Europe and in the USA in the near future.

Malaria incidence in Israeli travelers to Latin America: implications for malaria chemoprophylaxis

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Most Latin America countries are considered as malaria endemic countries and thus authorities such as The Center for Disease Control and Prevention (CDC), and the World Health Organization (WHO) recommend malaria prophylaxis for travelers to most Latin America countries. Latin America is a popular tourist destination for Israeli travelers, where there are approximately 51,000 visits annually. We reviewed all malaria cases reported to the Ministry of Health which were acquired by Israeli travelers to this region. We defined a country where malaria was acquired based on the following: if the traveler visited a single country, this was the country where malaria was acquired; for stays in more than 1 country, in the case of *P. falciparum* infection, countries visited within 6 weeks preceding the illness were considered as the acquisition areas and in the case of *P. vivax* infection, all of the countries visited during the trip were considered places of

possible acquisition. During the period from 01/01/1995-31/12/2005, 683 imported malaria cases were reported to the Ministry of Health in Israel. Of these cases, 467 were imported from Africa, 90 from Asia, 17 from Oceania, 7 from the Middle East (3 of them were probably contracted in Israel), and 36 were from Latin America. Among the 36 cases acquired in Latin America, 28 were from South America (*P. vivax* = 22 and *P. falciparum* = 6) and 8 from Central America (all *P. vivax* infection). Thus, the overall estimated malaria attack rate in Israeli travelers to Latin America is around 6.4 malaria cases per 100,000 travelers. The estimated attack rate of *P. falciparum* infection is ~ 1.1 cases per 100,000 travelers, while of *P. vivax* infection is ~ 5.3 cases per 100,000 travelers. In a telephone survey among randomly selected travelers who visited our clinic, only 14.3% had reported taking any malaria prophylaxis while traveling to Latin America. Based on the data above and assuming 100% efficacy of prophylaxis against *P. falciparum*, we calculated that 80,000 travelers have to be treated in order to prevent 1 case of *P. falciparum* malaria. Thus, consideration should be given, where feasible, to refining international recommendations on malaria prophylaxis, such that limited high risk areas are identified for chemoprophylaxis, and persons traveling to low-risk areas spared the need for taking anti-malarial drugs.

Controversies in vaccinations for travelers to developing countries

Michael Giladi

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Travel medicine standards are increasingly based on evidence and are moving away from reliance on the opinion of experts. As a young discipline, however, expert opinion and experience still dominate many of the topic areas. It is therefore not surprising that disagreements on vaccination policies between health authorities such as the Israeli Ministry of Health, the USA CDC, the WHO or commercial travel medicine resources such as Travax, often exist. Disagreements and controversies are most prominent when the vaccines under discussion can cause serious side effects, including death. This presentation will focus on the controversies related to the Japanese encephalitis, yellow fever and meningococcal meningitis vaccines.

Vaccines: when a booster is needed?

Michal Chowers MD

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Different types of vaccines and vaccination protocols which result in variable immunity outcomes are used in clinical practice. Live attenuated vaccines contain living organisms which continue to multiply in the body until their proliferation is contained by pathogen-specific antibodies resulting from activation of the adapted immune system. This sequence of events mimics natural infection and is believed to confer lifelong immunity. In contrast, most vaccines containing nonviable organisms do not confer lifelong immunity and require booster vaccinations in order to maintain protective antibody levels. The requirement for the different vaccination schemes and the scientific basis for these requirements will be discussed.

The role of travel medicine in exploring helminthic diseases

Eyal Meltzer

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Helminthes were the earliest infectious agents recognized by humans. However, despite their high prevalence, until the early 20^{th} century there was little recognition of the acute manifestations of helminthic diseases. Due to their complex life cycle, many helminthes are associated with different symptom complexes at particular phases after infection. The spectrum of symptomatology, the laboratory and imaging findings of many conditions are still unknown. There are a number of reasons limiting the study of acute helmnthic diseases in endemic countries, however travelers are a suitable study population. Most diagnostic techniques however target late stages of worm development and have only been validated in endemic populations. The differences between these populations, the drawbacks of current diagnostic techniques and the prospect of a diagnostic revolution in the near future will be discussed, through several examples. Schistosomiasis represents a helminthic disease where the acute syndrome is well characterized, and current diagnostic methods are adequate (if not ideal); hookworms present with a clinically recognizable symptom complex, but with no available diagnostic means, while for Strongyloides the very nature of the acute syndrome remains to be elucidated.

11:15 – 13:00 Session 2: Tropical Medicine

Leptospirosis in Israeli Travelers

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Introduction: Travel related leptospirosis is emerging as an important entity in developed countries. We present a national retrospective study of cases with travel related leptospirosis.
Results: During the years 2002-2008, 36% (17/47) of all leptospirosis cases in Israel were travel related. Detailed clinical data was available for fifteen patients.
Exposure occurred in South East Asia in 76%. Mean age was 29±10 years and 94% were male. Most of the patients (86%) were infected during water related recreational activities. The mean incubation period was 10±3 days. Common symptoms were fever 15/15 (100%) and headache 13/15 (86%). Conjunctivitis was present in only 4/15 (26 %) patients. All patients were hospitalized. Severe disease was present in 9/15 (60%) patients, of them six patients were infected with serogroup Icterohaemorrhagia. None of the patients died and all had complete recovery.
Conclusions: Travel related leptospirosis was mostly acquired in SE Asia. Leptospirosis manifested as multiorgan failure in a significant number of the patients, mostly infected with serogroup Icterohaemorrhagia. Some of the patients did not recall water exposure. Thus, leptospirosis should be suspected in any traveler with undifferentiated febrile illness even when water exposure in not reported. Many travelers with mild self limiting illness remain undiagnosed and disease burden is probably underestimated. Travelers should be educated about the associated risks in water exposure.

African tick bite fever: 8 cases of female Israeli travelers returning from a South African jeep expedition

Drorit Attias and Eli Schwartz

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Introduction: African tick bite fever (ATBF) is a tick-borne disease, caused by *Rickettsia africae*, belonging to the spotted fever group. The disease is imported mainly by travelers from sub-Saharan Africa. Most patients are infected during wild game safaris and bush walks. In a recent GeoSentinel study, spotted fever group rickettiosis was the second most commonly diagnosed febrile disease in returned travelers from sub-Saharan Africa. The disease is characterized by acute fever, headache, myalgia, regional lymphadenitis and one or several eschars. Incubation period is from 5 to 10 days. Most cases are mild and self limited, however treatment with Doxycyline is usually associated with rapid recovery. No fatal cases were reported. Among Israeli travelers, there was only one case report of ATBF. We report a series of cases of ATBF among female Israeli travelers to South Africa. Methods: 671 women in 13 consecutive journeys participated in the "Desert Queen 2008", which were jeep expeditions to the area of Kwazulu Natal, South Africa, from May to August 2008. After an index case was diagnosed, all participants were instructed to contact us if they had symptoms of fever or skin lesions after returning from the expedition. The suspected case underwent physical examination and serology was sent. **Results:** Eight cases of ATBF were diagnosed on the basis of clinical findings. The time lag from returning to onset of symptoms ranged from 3 to 10 days. All patients had fever and typical eschars. Other findings were macular rash, regional lymphadenopathy, headache, myalgia and arthralgia. Non-specific Rickettsial serology done in Israel was positive in 2 patients. Specific serlogy for *R. africae* was sent out and is pending. Doxycycline treatment (5-7 days) was given to 6 patients with a rapid response. One pregnant patient did not take antibiotic treatment and her pregnancy course has not been affected (after a 4- month follow-up). Initial diagnoses in some of the patients included: chicken pox in 1 patient, another patient was hospitalized to investigate possible vasculitis. Two participants found ticks on their bodies which were identified as Amblyomma ticks, the vector that transmits ATBF. **Conclusion:** From being a virtually unknown entity in travel medicine only two decades ago, African tick bite fever has since emerged as an important cause of acute febrile illness in travellers to sub-Saharan Africa, in particular to South Africa and neighbouring countries. In Israel, it has rarely been reported, probably due to under diagnosis. There should be a high suspicion of ATBF when patients returning from Africa complain of fever and lesions or rash. Diagnosis is based on specific serology which currently does not exist in Israel, although cross-reaction with assays based on *R. conorii* and *R. rickettsii* antigens occurs. The best period to perform serology in R. africae infection is more than 3 weeks after the onset of symptoms. Treatment with Doxycyline should be considered whenever a case of ATBF is suspected to ensure rapid recovery. Travelers to endemic areas should be informed as to the risk of ATBF and encouraged to follow some preventive measures to minimize tick bites.

Liposomal amphotericin B (AmBisome) for treatment of severe cutaneous leishmaniasis (*L. braziliensis* & *L. tropica*)

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Background: Leishmaniasis is endemic in Israel and usually due to *L. major*, a benign form of the disease. In the last decade we have encountered in Israel more patients with *L. tropica,* which is much more resistant to treatment. In addition, there has been an increased number of imported New World leishmanisis, mostly due to *L. (V.) braziliensis.* The treatment of cutaneous *L. (V.) braziliensis* infection is considered to be systemic pentavalent antimonial compounds (SSG), at a dosage of 20 mg/kg for three weeks. In our experience, treatment failure with this regimen occurs in about 25% of cases. Moreover, this treatment is associated with a significant amount of adverse events, often leading to an interruption of treatment and resulting in a longer treatment time of about 1 month. Therefore, in recent years we have initiated treatment with a short course of liposomal amphotericin compound (AmBisome) with very encouraging results. During the past year, the same protocol was also used for *L. tropica* cases that failed using other treatment options.

Methods: A prospective evaluation was performed on patients who were given AmBisome for severe cutaneous leishmaniasis due to *L. braziliensis* and *L. tropica*, diagnosed by PCR. A dose of 3 mg/kg AmBisome was given for 5 consecutive days, with a 6^{th} dose on day 10. All doses were given in an outpatient setting.

Results: 23 consecutive patients received this treatment for *L. braziliensis* infection. All were returned travelers; most (21/23) were infected in the Amazon region of Bolivia. 18 were male and 5 female; their mean age was 25.8 years (range 21-60 years); one case included mucosal involvement. 5 patients received this treatment for *L. tropica* infection acquired in Israel: 4 males and 1 female, with a mean age of 11 years. All received the same schedule, side effects were very mild and none had to terminate treatment prematurely. Follow-up of more than 12 months in 13 patients revealed no relapse. A comparison of the cost of treatment for AmBisome vs. SSG shows that despite the high cost of AmBisome, the expense for the total treatment with AmBisome is less than with SSG: 45% less if SSG was given in an inpatient setting; 15% less when SSG was given in an outpatient setting.

Conclusion: The gained experience using AmBisome treatment for *L. braziliensis* infection shows a very successful and well tolerated treatment and demonstrates the potential of this drug for being the drug of choice for treating *L. Braziliensis* infections. The preliminary results of treating *L. tropica* with AmBisome are encouraging and further evaluation is needed.

False positive malaria diagnosis in cases of acute schistsomiasis

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Rapid malaria diagnostic test is gaining popularity and is in use in many clinics as a prompt and sensitive test for the diagnosis of malaria. The rapid malaria tests utilize polyclonal or monoclonal antibodies directed against select target parasite antigens when present in the blood, and a separate antibody conjugated to an indicator, act to produce a visible line. The sensitivity is similar to thick smear (especially for *P. falciparum* infection), however unlike the thick smear that requires an experienced laboratory technician and takes several hours to be completed, the rapid test is a simple test that does not require professional skill, and is completed within few minutes. False positive results are rarely reported and are usually due to non-specific antibody reactions such as rheumatoid factor. Herein we report a series of clinical cases of acute schistosomiasis due to *Schistosoma japonicum* (probably *S. mekongi*) in 4 members of a family returning from a trip to Laos. The diagnosis of acute schistosomiasis was based on a typical clinical presentation, accompanied by positive serology and followed by detection of *S. japonicum* ova in stool samples. As a part of post- travel medical evaluation, a rapid malaria test was performed and was positive in all four family members. Malaria smears and malaria PCRs were negative in all. Further investigation showed that the malaria test was positive in whole blood and in serum, in a "Binax" assay that is based on the malaria specific HRP (Histidine- Rich Protein), but was negative with the rapid tests that are based on malaria specific LDH. (Optimal, are stat). Rheumatoid factor was negative in all. Interestingly, sera of patients with acute schistosomiasis who were infected in Africa (*S. mansoni*) were negative for all rapid malaria tests. o the best of our knowledge, this is the first report of such a phenomenon.

Innovation in diagnosis of gastro-intestinal protozoan parasites

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Diarrheal diseases are extremely common in developed and developing countries and are major causes of morbidity and mortality, affecting millions of individuals each year. The need to diagnose protozoan parasites among the known etiologies of GI clinical symptoms is well recognized. The most common intestinal protozoan parasites infecting humans worldwide are considered to be *Entamoeba histolytica*, *Giardia lamblia*, *Blastocystis hominis, Dientamoeba fragilis* and *Cryptosporidium spp.* Laboratory detection of gastrointestinal parasites is relying on microscopic examination of stool

samples and water concentrates, as well as enzyme immunoassay (EIA) tests. Utilizing the microscopic examination usually results in under-detection of the GI parasites on one hand, while usage of EIA is often not cost-effective on the other hand. Savyon is currently engaged with developing an approach aiming to respond to the unmet needs and to the current limitations in this field. This approach includes 3 major aspects: (1) the ability to detect the panel of all the above 5 organisms in one test kit, (2) the possibility to carry out the diagnosis in two steps – first, simultaneous detection of these organisms without distinguishing between the different species for screening of large number of specimens, and second, distinctive detection of the specific etiology in the positively-found specimens, and (3) the ability to apply EIA diagnosis in formalin-preserved specimens for all the mentioned parasites. The presented work is a paradigm of an innovative approach that is expected to be an important advance in improving the diagnosis of protozoan parasites in GI symptomatic patients, enabling the appropriate treatment, and saving healthcare costs.

09:00 – 10:45 Session 3: Leishmaniasis

Molecular diagnosis of *Leismania* infections in a non-endemic setting

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The increasing trend of imported cutaneous and visceral *Leishmania* infections is a challenge for the diagnostic laboratory in a non-endemic setting. Traditionally the diagnosis relies on extensive microscopic examination by experienced personal of biopsy material or bone marrow being time-consuming and sometimes very difficult. The unsurpassed sensitivity and specificity of nucleotide amplification methods (e.g. PCR) offer a worthwhile diagnostic alternative and the possibility of species differentiation which is of importance in the choice of treatment. The taxonomy of the *Leishmania* species is complex and the nomenclature of the different species (complexes) is subject to change. Therefore, it is sometimes difficult to compare different differentiation techniques. In our laboratory a genus specific real-time assay on the Small Sub Unit rRNA gene is used for detection. Depending on the travel history, additional RFLP-PCR methods targeting ITS, HSP70, T2B4 repeat, and/or Mini Exon are employed for species (complex) differentiation. In this presentation an overview and some examples on the application of these methods will be given.

Arginine transport via LdAAP3 in *Leishmania donovani* is regulated by amino acids availability and the polyamine pathway

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Arginine is an essential amino acid for the human pathogen *Leishmania* but not to its host. Thus, the mechanism by which these organisms regulate cellular homeostasis of this amino acid is critical for its survival and virulence. In a previously conducted study we cloned and functionally characterized a high affinity and specificity arginine transporter in *L. donovani*, LdAAP3, and suggested that it is the major supplier of extracellular arginine to parasite cells (1). Here, we investigated the relationships between arginine transport via LdAAP3 and its availability in *L. donovani* promastigotes. We found that starving promastigotes to amino acids decreased the cellular level of most amino acids including arginine. Amino acid starvation increased arginine uptake in promastigotes 5-fold within 4 hours, and was followed by an increase in the abundance of both LdAAP3 mRNA and protein and as a result up-regulated arginine transport. Disconnecting the polyamine biosynthesis pathway from its precursor, arginine, caused a significant decrease in the rate of transport of this amino acid. This was achieved using *L. donovani* mutants that lack the genes that encode for ornithine dexarboxylase and Spermidine synthase (2). Cumulatively, we found that LdAAP3 expression and activity changed whenever the cellular level of arginine changed. We propose that promastigotes have a signaling pathway that senses cellular concentrations of arginine and subsequently activates a mechanism that regulates LdAAP3 expression. Interestingly, this phenomenon of *L. donovani* LdAAP3 response to amino acid availability resembles that of the mammalian cation amino acid transporter 1 (CAT1), but not arginine transport in yeast or fungi. Thus, we hypothesize that *Leishmania* mimic hosts' response to amino acid availability in order to improve virulence.

1. Shaked-Mishan, P., Suter-Grotemeyer, M., Yoel-Almagor, T., Holland, N., Zilberstein, D., Rentsch, D. (2006) Novel high affinity arginine transporter from the human parasitic protozoan *Leishmania donovani*. *Mol. Microbiol.* 60, 30-38.

2. Roberts, S.C., jiang, Y., Jardim, A., Carter, N.S., Heby, O., and Ullman, B. (2001) Genetic analysis of spermidine synthase from Leishmania donovani. *Mol. Biochem. Parasitol.* 115: 217-226.

Molecular and functional characterization of proline and lysine transporters from *Leishmania donovani*

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We identified and functionally characterized two amino acid transporter genes from *Leishmania donovani*, *Ld*AAP24 and *Ld*AAP7 that are members of the amino acid/auxin superfammily. Heterologous expression of these genes in *Saccharomyces cerevisiae* mutants revealed that *Ld*AAP7 encodes a lysine transporter and *Ld*AAP24 encodes a proline transporter. *Ld*AAP7 protein obtains high affinity (Km=2 μM) and specificity for lysine while *Ld*AAP24 has lower affinity (Km=200 μM) and specificity but higher capacity for proline. The activity of *Ld*AAP7 was sensitive to external pH with optimum activity at acidic pH. *Ld*AAP24 was less sensitive to external pH with a small peak at natural pH. Fusing these proteins with GFP revealed that both transporters are localized to the plasma membrane of promastigotes. Interestingly, starvation had no effect on lysine transport and *Ld*AAP7 level of expression, even though it increases transport of arginine and the expression of its transporter (*Ld*AAP3). *Ld*AAP24 specificity and activity resembled proline transport system C that is active only in promastigotes. This work is the first to describe the genes for proline and lysine transporters in trypanosomatids.

Evaluation of a new sensitive diagnostic method for detecting anti-leishmanial antibodies in patients sera using chemiluminescence and optical fiber immunosensor (OFIS) assays

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Background: Leishmaniasis is a vector- borne disease caused by a flagellated protozoan parasite of the genus *Leishmania*, which affects both humans and animals. Several serological tests (IFA, ELISA, IMB) are available, each with its limited sensitivity and specificity. Also, early infection with cutaneous leishmaniasis (CL) is associated with a low level (occasionally undetectable) of antibody activity. Therefore, the development of a highly sensitive, economical and simple technique might be highly useful for diagnosis of the disease. **Aims:** To apply the chemiluminesence-ELISA and an optical fiber immunosonsor (OFIS) based on chemiluminesce for the diagnosis of leishmaniasis, using highly sensitive and specific *Leishmania* antigens. **Methods:** Three serological assays were compared, including: colorimetric-ELISA, Chemiluminesence-ELISA and OFIS

using sera from CL patients and other parasitic diseases. Leishmanial antigens were prepared from promastigotes, and partially purified antigens were obtained using physical and molecular techniques. **Results and Conclusions:** Using total *Leishmania* soluble antigens indicated that the chemiluminesence-ELISA is superior (x30 more sensitive) than the colorimetric-ELISA. The highest sensitivity (x60) was observed with the OFIS, as compared to the colorimetric-ELISA. However, high cross reactivity was observed with sera from malaria, toxocarosis and strongiladosis patients. No cross reactivity was demonstrated with sera from patients suffering from amoebiasis, giardisis, toxoplasmosis, echinococosis, enterobiasis, schistosomosis, strongiladosis or *Hymenolepis nana* infection. Analysis of the crude antigen by WB indicated the presence of a low MW (12kDa) band that reacted specifically with all of the CL patient's sera examined, without any cross reactivity with other diseases. However, using this antigen (eluted from the gel) in all the 3 assays yielded a very low serological reaction. The present study suggests that the OFIS technique is highly sensitive for the detection of anti-leishmanial antibodies in humans. However, further studies using highly purified antigens are required to clarify the usefulness of the OFIS technique for diagnosis of the disease.

A preliminary mathematical model of the dynamics of the *Leishmania* parasite amongst migrating populations of rock hyrax

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BACKGROUND: The rock hyrax (*Provacia capensis*) has been implicated as a host reservoir for the *Leishmania* parasite in recent outbreaks of leishmaniasis in northern Israel. Little is known of how the ecology of the hyrax may influence transmission of leishmaniasis to humans, but studies of other mammalian hosts in the Negev have indicated that anthropogenic environmental changes may have a role in the epidemiology of the disease. We have begun modeling the spatial behavior of the hyrax, and its effect on the transmission of the parasite between hyrax populations. To do this, we have drawn together two observations: (1) the building of new residential neighborhoods in the Galilee generates boulder piles that provide ideal sites for hyrax dens, and (2) preliminary field studies indicate that family groups of hyrax can make use of multiple dens, migrating between different sites, possibly following depletion of resources. METHODS: We have built a mathematical model of the interaction between two hyrax populations rotating between different den sites, where cross infection between the populations is dependent on the distance between them. By varying the distances between suitable den sites, we simulated the proliferation of anthropogenic boulder piles. RESULTS: The model shows epidemic peaks, during which the number of infected animals rises significantly above the endemic level. These peaks correspond to episodes when the two populations move closer together. It is from these infected animals that the sandfly vector (*Phlebotomus spp.*) acquires the parasite, and subsequently transmits it to

humans. CONCLUSIONS: If the model results are empirically validated, these peaks in hyrax infection could be a contributing factor to future outbreaks amongst human populations living in close proximity to hyrax dens.

Emerging cutaneous leishmaniasis in Northern Israel

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In Israel cutaneous leishmaniasis (CL) is emerging in several new foci. Between 2001-2003, CL cases from foci near in the Kineret region were shown to be caused by two different *Leishmania tropica* strains. Parasites from the northern focus (Amnun) were antigenically similar to *L. major* and *Phlebotomus* (*Adlerius*) *arabicus* was incriminated as their vector with 5% infected females. In Tiberias *P.* (*Paraphlebotomus*) *sergenti* (10-20% infected) was the only vector. Between 2006-2008, 72 CL cases from rural areas near Beit She'an were diagnosed as caused by *L. major*. Fifteen of 94 voles (*Microtus guentheri*) collected in Sde Eliyahu near patients' homes were shown by PCR to harbor *L. major* DNA, and *P. papatasi*, the known vector of *L. major*, was the most abundant sand fly species in the area. Emergence of new CL foci in Israel is probably caused by the encroachment of hyraxes upon human habitation (*L. tropica*) and the proliferation of voles in agricultural fields near villages (*L. major*). The adaptation of parasites to new, highly-susceptible vectors (*L. tropica/P. arabicus*) or host species (*L. major/M. guentheri*), also plays a role.

11:15 – 13:00 Session 4: General parasitology

A. Parasite Resistance

Switching virulence genes - the malaria parasite perspective to achieve resistance against the human immune attack.

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The deadliest form of human malaria is caused by the protozoan parasite *Plasmodium falciparum* affecting millions worldwide every year. *P. falciparum* virulence is attributed to its ability to evade the human immune system by modifying the host red blood cells to

adhere to the vascular endothelium and to undergo antigenic variation. The main antigenic ligands responsible for both cytoadherence and antigenic variation are members of the ***P. falciparum*** **E**rythrocyte **M**embrane **P**rotein-**1** (PfEMP1) family. These polymorphic proteins are encoded by a multi-copy gene family called *var*. Each individual parasite expresses a single *var* gene at a time, maintaining the remaining ~60 *var* genes found in its genome in a transcriptionally silent state. As the antibody response against the single PfEMP1 expressed develops, small sub-populations of parasites switch expression to alternative forms of PfEMP1, avoid the antibody response and re-establish the infection. The ability of the human malaria parasite *P. falciparum* to switch expression to different variants within its repertoire of antigenic surface proteins enables it to evade the immune system of its host and to sustain long-term, chronic infections. We studied *var* gene switching *in vitro* in order to identify if transcriptional switches favor the expression of particular subgroups of *var* genes and if *var* gene activation within a clonal population of parasites follows a pre-determined order. We show that transcription of *var* genes located in the central regions of chromosomes is remarkably stable and without selection these genes rarely undergo transcriptional switches. In contrast subtelomericaly located *var* genes exhibit a more dynamic switching pattern with clonal parasite populations readily switching to alternative *var* loci. We confirmed these observations by generating transgenic parasites carrying drug selectable markers in subtelomeric and central *var* loci. To investigate if *var* gene activation within an individual parasite follows a pre-determined order, we generated all transgenic parasites in the same clonal background. We show that after selection for activation of either subtelomeric or central *var* loci, populations of parasites with completely different *var* gene expression profiles develop over time, thus providing an explanation for how a parasite population can exhibit heterogeneous patterns of *var* gene activation despite the uniform bias towards expression of *var* genes with low off rates.
[#] these authors contributed equally to this work

***Leishmania major*: Anti-leishmanial and mechanism of activity of *Nuphar lutea* extract against promastigotes and intracellular amastigotes**

Lital Ozer[1], Jacob Gopas[1,2], Avi Golan-Goldhirsh[3], Ruth Sneir[1], and Joseph El-On[1]

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Background: Leishmaniasis, a major tropical disease caused by protozoan parasites of the genus *Leishmania*, is still affecting both humans and animals worldwide. Plant-derived products have long been valuable sources of medical agents. In our previous study, none of the 45 Israeli plant extracts examined totally eliminated the intracellular amastigotes, except one, *N. lutea* that was almost as effective as paromomycin - the gold

standard drug against the disease. The aim of this study was to isolate and to characterize the leishmanicidal compound(s) of *N. lutea* against *Leishmania major* promastigotes and intracellular amastigotes in peritoneal macrophages and to evaluate its mechanism of toxicity. **Methods:** Water and 50% methanolic plant extracts were prepared from the leaves and stems of the *plant N. lutea* collected at natural water habitats, in central Israel. The *in vitro* anti-leishmanial activity against free living promastigotes (28°C) and intracellular amastigotes in C3H mouse macrophages (37°C) was determined by microscopic examination and by using a colorimetric method (XTT). NF-κB activity was determined by EMSA and western blot, oxidative burst activity was evaluated using NBT assay and isoenzymes (lysozyme, β-galactosidase) activity was analysed by colorimetric methods. **Results and Conclusions:** Both, the crude (IC_{50}=2±0.12 μg/ml; ID_{50}=0.65±0.023 μg/ml; LD_{50}=2.1±0.096 μg/ml, STI=3.23) and the semi-purified extracts (IC_{50}=0.033±0.002μg/ml, ID_{50}= 0.087±0.003 μg/ml, STI=3.33) of *N. lutea* totally eliminated the intracellular *L. major* amastigotes within 3 days of treatment. The active compounds were found to be thermo-stable alkaloid(s), free of charge and resistant to methanol, dichloromethane and xylene treatment. Chromatography on a silica gel column yielded a variety of sesquiterpene thioalkaloids [(6-hydroxythiobinupharidine, 6,6 –dihydroxythiobinupharidine and 6-hydroxythionuphlutine B (nupharidine)] of ~500 kDa. The anti-leishmanial activity was shown to be mediated through the activation of the nuclear factor NF-κB (elevated NO production), but not through oxidative burst or isoenzymes (lysozyme, β-galactosidase) elevated activity. The present study suggests that *N. lutea* might be of a potential source of anti-leishmanial compounds.

Evolutionary adaptation of the CAP binding complex in trypanosomatids to their CAP-4 structure

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Drug treatment for *Leishmania* is limited and toxic, and the need for novel therapeutics is urgent, especially since drug-resistant strains are spreading rapidly. Our goal is to use the unusual molecular features of *Leishmania* as novel drug targets. Protein expression in trypanosomatids is controlled exclusively by post transcriptional mechanisms, as they are transcribed into polycistronic mRNAs that are further processed by trans-splicing and polyadenylation. The Spliced Leader RNA (SL RNA) donates a complex 5' cap structure that in addition to m^7GTP, consists of unusual methylations on the first and fourth bases, as well as 2'-O-methylations on the first four ribose moieties (cap-4). From an evolutionary perspective, the cap-binding proteins in trypanosomatids went through structural changes that allow fitting of the heavily modified cap-4 structure into the cap-binding pocket. The evolutionary diversity of these proteins is further emphasized by the inability of any eIF4E isoform of *Leishmania* to functionally complement the mutated yeast protein, unlike their orthologues from *Drosophila* and *Arabidopsis*. Such changes are also reflected in the structure of the eIF4G of *Leishmania*. Among several candidates in *Leishmania major* (Lm), LmIF4G3 is most likely the basal translation factor in

Leishmania, since it is eluted along with LmIF4E-1 and LmIF4E-4 from affinity columns, binds these proteins in vitro and in vivo, but fails to interact with the mouse eIF4E. LmIF4G3 is a 70 kDa protein that contains the typical MIF4G domain. However, its amino terminus is short and it is not conserved with orthologues from higher eukaryotes. The interaction between LmIF4G3 and LmIF4E-4 was mapped to the amino-terminal domain of LmIF4G3 using the yeast two-hybrid system. This interaction requires the presence of a seven amino acid peptide in the amino-terminus, which bears hardly any similarity to the consensus peptide sequence $Y(X)_4L\O$. However, this LmIF4G3 peptide resembles a parallel peptide sequence in eIF4G of *C. elegans.* In view of these large diversities, the 4E-4G interaction may serve as a novel target for future drug discovery.

In vivo antimalarial activities of synthetic compounds PP-54 and PP-56 in mice infected with *Plasmodium berghei*

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Each year 300 to 500 million people contract malaria with a death toll estimated at 1.5 to 2 million and more than 90 % of the infections happen in Africa (Snow *et al.*, 2005). Beyond the clinical issues, malaria also poses an economic problem as the disability provoked influences negatively on the productivity at work (Sachs and Malaney, 2002). *Plasmodium berghei* (NK 65), a rodent adapted strain was inoculated into albino mice via an intraperitoneal route. The test synthetic compounds, PP-54 and PP-56 were administered to the two groups of mice at effective doses of 50 mg/kg and 10 mg/kg respectively and daily for four days starting 96 hours post-parasite inoculation. The control groups was administered dextrose saline used to dissolve each dose of the synthetic compound and artemisinin was used as a standard drug. Synthetic compounds PP-54 and PP-56 were observed to inhibit *Plasmodium berghei,* parasitaemia development in mice by 40 % and 55 % at 50 mg/kg and 10 mg/kg respectively at day 20 postinfection when compared to untreated experimental controls. The test compounds ameliorated anemic conditions observed in *P. berghei* infected mice as treatment with compounds PP-54 and PP-56 prevented a drastic reduction in PCV values when compared to experimental controls. This accounts for the observed increase in mean survival time of mice postinfection in the treated group. The test compounds indeed possess anti-malarial activity *in vivo* as revealed by microscopic Giemsa stained thin blood smears.

B. Parasitology

Can copper lethal ovitraps be effective against the populations of the Asian tiger mosquito in Israel?

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In 2001 first individuals of a highly invasive mosquito species were found in Ginaton, Israel, the Asian tiger mosquito (*Aedes albopictus*). Today, the mosquito can be found in many parts of Israel. This mosquito species can cause high level of nuisance. It may also inflict risk for public health as it is known to be able to transfer many pathogens, among which dengue and chikungunya. Accordingly, it is very important to examine various techniques to reduce the level of the mosquito populations. Following studies in Florida (e.g. O'Meara et al 1992) and Italy (Romi et al 2000) we decided to examine the effect of copper lethal oviposition traps (hereafter ovitraps) against the populations of the Asian tiger mosquito in Israel. Here we present the results of: 1. Laboratory study on Asian tiger mosquito oviposition site selection with and without the presence of copper in the water; 2. Field results of Asian tiger mosquito oviposition site selection and larval survival with and without the presence of copper in the water; 3. Field observation of a settlement with copper lethal ovitraps treatment. In the lab the Asian tiger mosquito females deposited eggs equally among treatments. In the field, however, the females deposited more eggs in the control (no copper) treatment. Nevertheless, 21% to 31% of the eggs were deposit in ovitraps with copper. Moreover, no pupae were ever noticed in ovitraps with copper both in the field experiment (#2) and in the field observation (#3). This study suggests that lethal ovitraps with copper in an environment kept dry of small pools can reduce the Asian tiger mosquito populations in a treated area.

Specific immune response in cattle to immunization with *Neospora caninum* SRS2 DNA and lipopeptides

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Neospora caninum is an apicomplexan coccidian protozoan that represents a major cause of infectious abortions and congenital disease in cattle. Natural or experimental infections of cattle induce cellular and humoral responses, particularly $CD4^+$ T-lymphocyte activation and gamma interferon (INF-γ) secretion. However, up to date, practical

measures to reduce losses have not been achieved. *N. caninum* SRS2 (NcSRS2) was found to be a highly conserved immunodominant antigen and has been associated with immunity to transplacental transmission of parasites in mice. For the present study cattle were selected for MHC class haplotypes shown earlier to respond to SRS2 polypeptides binding to multiple MHC types to activate the cell-mediated immune responses. In order to optimize dendritic cells activation, naïve calves were inoculated with the NcSRS2 DNA supplemented with granulocyte macrophage-colony-stimulating factor (GM-CSF) and Flt3 ligand adjuvant. The synthesized NcSRS2 lipopeptides were mixed with Freund's adjuvant. The $CD4^+$ T-lymphocyte activation and gamma interferon (INF-γ) secretion to immunization of cattle NcSRS2 popypeptides containing cytotoxic T-lymphocyte epitopes followed by booster with lipopeptide-based immunogens were evaluated in immunized and control cattle. The DNA NcSRS2 vaccine alone could not induce T-lymphocyte activation or INF-γ secretion in vaccinated cattle, however subsequent booster with NcSRS2 lipopeptides induced robust NcSRS2-specific immune responses. Compared to control calves, immunized animals produced higher levels of IgG1 and IgG2a. There was no apparent immune response pattern of cattle in association with the MHCI or MHC II haplotypes. This study showed the induction of potentially protective cell-mediated and humoral immune responses in cattle to DNA and lipopeptide subunit antigens of *N. caninum*, and support further investigation of these immunogens for protection against fetal infection and abortion in cattle.

14:14 – 16:15 Session 5: Echinococcosis in Israel

Alexander Markovics- Prevalence of echinococcosis-hydatidosis in Israel

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Echinococcosis caused by *Echinococcus granulosus* is a zoonotic, helminthic infection with worldwide distribution. The infection is very common in many Middle Eastern and Mediterranean countries. In Israel, the prevalence of the infection in both animals and humans, as reported in the last 5 decades, is considerably lower than in neighboring countries. Infection in humans has decreased since 1948 and was mainly diagnosed in new immigrants, while locally acquired infections were rare. A retrospective study of hydatidosis confirmed cases in the Negev region in 1970-79 showed an average annual incidence of 0.68 and 0.75 per 100,000 in Jewish and Arab (Bedouin) populations, respectively. The increased incidence of new human infections in Arab and Druze communities living in northern Israel during 1980–89 prompted a comprehensive epidemiological study. The overall annual incidence of hydatidosis in these populations rose from 1.4/100,000 in 1960 to 7.1/100,000 in 1989. In Yarka, a small town of 8200 inhabitants, 52 cases were diagnosed during this period with an annual incidence of 55/100,000 giving it the second highest incidence of infection ever recorded. High infection rates were also recorded in domestic animals in Yarka – 26 out of 255 sheep examined at local abattoir (10%) and 5 out of 63 dogs (8%). The high infection rate of

dogs in Yarka was confirmed in another survey conducted in 1991-92 when 7 dogs were infected out of 49 examined following arecoline treatment. The high infection rate found in dogs in Yarka contrast with the rarely encountered canine *E. granulosus* in the last 25 years. Autopsy of 362 stray dogs in 1982–83 from three large cities: Tel Aviv, Beer Sheva and Jerusalem, and 236 dogs from Hadera district in 1984 and 1991 as well as fecal examination of 650 dogs from central part of Israel during 1992 – 1999 revealed only two infected dogs in Jerusalem and in Hadera. Post-mortem examination of 72 foxes and jackals in 1982 and over 700 animals in 1998 - 2005 failed to reveal any infection. Low infection with *E. granulosus* has also been reported in cattle. Abattoir data during 1986-94 on more than 500,000 cattle indicated an annual infection rate of 0.06 – 0.16% with an average of 0.105%. A similar infection rate was obtained in a survey conducted during 1986-90 when every condemned organ was examined from 107,315 cows slaughtered in one abattoir. The infection was diagnosed mainly from beef but only rarely from dairy cattle. The origins of the infected cattle showed that more than half (61 out of 111) was from herds grazing on Golan Heights while the majority of the remaining animals were from a few herds grazing in the vicinity of the West Bank and Gaza strip. The low infection rates in dogs and cattle indicate a low contamination with *E. granulosus* eggs in most parts of Israel. The prevalence of hydatidosis in sheep, despite the difficulties in its diagnosis, seems to be higher than in cattle and dogs. The incidence of the infection according to the data collected from the abattoirs between 1995 - 1997 were: 1.8%, 2.0% and 1.3%, respectively. It should be mentioned that the higher rates of infection result from slaughtering animals purchased in the West Bank, where hydatidosis is very prevalent. Misdiagnosis of hydatid cysts in some of the abattoirs may also add to higher infection rates. On one occasion (1995), we examination at Yarka abattoir 183 sheep carcasses from Yarka, Abu-Snan and Kfar Yasif (with an annual reported incidence of hydatidosis of 10.1%) and found cysts in the livers and lungs of 14 animals (7.65%), but hydatid cysts were diagnosed only in 3 sheep (1.64%). A very high rate of infection (35%) was diagnosed at the same time in two sheep flocks from the northern Golan Heights. In our opinion, the prevalence of hydatidosis in sheep raised in Israel is much lower than is reported from abattoirs and a further definitive survey is needed to confirm this. In conclusion, the prevalence of hydatidosis in Israel is very low in intensively raised animals, much higher in grazing animals, especially on pastures close to the West Bank, Gaza and the Golan Heights but could easily become far higher as in Yarka and in the recent years amongst the Bedouin communities in the Negev region.

Current status of the diagnosis and control of cystic echinococcosis

Joseph El-On

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Cystic echinococcosis (Hydatidosis) (CE) caused by the larval stage of the tapeworm, *Echinococcus granulosus* is a serious helminth infection that is endemic in Israel. Humans are infected by ingesting the parasite eggs that are excreted in dog feces. Following hematogenous spread of larvae, fluid filled hydatid cysts are formed in various organs, notably the liver and lungs. In humans, CE is diagnosed mainly with imaging techniques such as ultrasonography, radiology, magnetic resonance imaging (MRI) or CT scanning, and is confirmed by positive serologic tests, using *E. granulosus* hydatid cyst fluid as an antigen. Antibody production is dependant on the location in the body, integrity, and vitality of the larval cyst. Cysts in the liver and bone are more likely to elicit antibody response than those in the lungs, brain, and spleen. Patients with senescent, calcified, or dead cysts are generally seronegative. False-positive reactions may occur in persons with other helminthic infections, cancer, and chronic immune disorders. Infection is not necessarily associated with antibody production and negative test results do not rule out the existence of echinococcosis. Some serologic tests can distinguish between antibodies to the alveolar cyst caused by *E. multilocularis* and *CE.* Biopsies are occasionally performed in diagnosis, but involve the risk of cyst leakage or rupture. Detection of antigens and immune complexes in serum are also used, but are not as sensitive as serology. The PCR technique is generally applied for parasite identification and characterization.

Serological examinations: Presently, no single serologic test is considered suitable for the diagnosis of *E. granulosus* infection in humans, and more than one test is required for adequate levels of diagnostic accuracy. Serological examinations include indirect hemagglutination (IHA), indirect immunofluorescence, (IFA), enzyme-linked immunosorbent assays (ELISA), immunodiffusion (ID), immunoelectrophoresis (IEP) and immunoblotting (IMB), with a sensitivity rates of 60% - 90%. Radio-immunoassay (RIA), complement fixation and latex agglutination tests are now rarely applied. Commercial serological kits are available, including IHA (Behring, UK; Fumouze®, France), ELISA (r-biopharm, Darmstadt, Germany). A combination of 2 or more tests is generally recommended to be used to confirm infection. IHA and ELISA are used for antibody detection, immunoblot, and gel immunoelectrophoresis/ immunodiffusion assays that demonstrate antigen A (Arc 5) and antigen B are used to confirm infection. Antigen B, particularly the 8/12 kDa subunits are considered species specific. Cross reactivity (5%-25%) with antigen A may be demonstrated in sera from persons suffering from neurocysticercosis, cancer and chronic immune disorders.

Cellular response: The lymphoproliferative assay is generally used to determine specific anti-echinococcal cellular activity. The test is usually used in seronegative patients to confirm infection. An increase in cellular immune activity was demonstrated in cases

with both progressive hydatid cysts, and in cured patients following complete surgical removal of the hydatid lesion. However, no correlation between the host serological and the cellular immune responses was demonstrated.

Evaluation of treatment results: So far, no accurate measurements to define the curative status of treated hydatid patients are available. In most cases, both imaging and serological examinations are jointly applied for the assessment of treatment results. Following successful radical surgery, antibody titers decline and sometimes disappear; titers rise again if secondary cysts develop. Tests for Arc 5 or IgE antibodies appear to reflect a decline in antibodies during the first 24 months post surgery, whereas the IHA and other tests remain positive for at least 4 years. No correlations between successful therapy and the level of specific IgG and IgM and circulating immune complexes before, during, and months after therapy was demonstrated. Most changes in antibody activity appeared after the first treatment, and repeated treatment did no alter the anti-echinococcal antibody (IgG, IgG4, IgE) activities.

Disease control: Eradication and control of echinococcosis can be achieved. Elimination of stray dogs, treatment of dogs, vaccination of sheep, education and prevention of the access of potentially infective offal to dogs, may decrease the rate of infection and possibly eliminate the disease.

Jacob Nachmias- Medical approach to Echinococcosis

Abstract not available

The surgical approach to hydatid cysts

Amitai Bickel

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The surgical treatment is considered to be the most efficient approach to deal with hydatid cysts. The operation can be done either by radical excision of the whole cyst with or without hepatic tissue, or through conservative approach. The conservative approach includes the eradication of the germinal layer through the protruding hydatid wall without total excision. The next stage includes different alternatives to deal with the remaining cystic cavity. Since the advent of laparoscopic surgery, the laparoscopic approach to hydatid cysts became familiar, using the same principles as for open surgery. We were the first (Department of Surgery, Western Galilee Hospital, Nahariya) to suggest the laparoscopic conservative approach for the treatment of hepatic echinococcosis. Our technique was based on physical theoretical models, as well as on laboratory trials in animals, showing that no spillage could have been detected during surgical manipulations of the hydatid cyst. The initial maneuvers like puncture and aspiration of the cystic contents were done through a novel transparent cannula that was firmly adhered to the cystic wall by vacuum force. Since 1992, we have operated laparoscopically almost 70 hydatid cysts in 40 patients, without major post-operative complications. Recurrence rate

was 7.5%. Our technique is at present a common practice in the surgical armamentarium against intra-abdominal hydatidosis.

Presentation of clinical cases
S. Kivity, E. Leshem & D. Hasin (Abstract not available)