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## **Infectious Diseases and Their Control - Past, Present, and Future**

### **A cross-disciplinary workshop by BGU Faculty and Students**

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## **Abstracts**

### **Recent History of Viral Hepatitis**

Michael L. Alkan, Medical School for International Health

For a long period of time, it was believed that viral hepatitis had two faces. One came in outbreaks, with a short incubation period and a relatively mild clinical course, without any sequelae. The other form was sporadic, prolonged, and followed by severe liver damage. During World War II, many soldiers who received plasma transfusions suffered from the latter form, justifying the name "Serum Hepatitis".

Pediatrician Dr. Saul Krugman observed that in his patients, who were all children with special needs hospitalized at the Willow Brook Institution, both forms of hepatitis were common. He started a research project, and deliberately infected the children with both types of the disease, ascertaining that they were two distinct diseases, caused by two different viruses.

Dr. Baruch Blumberg, a geneticist, tried to identify different human races by their blood proteins, using as antibodies serum from multi-transfused subjects. He got a positive result with the blood of an Australian Aborigine, and named it "Australian Antigen". This antigen was found by Krugman to correlate with severe hepatitis rather than with Australians, giving us a diagnostic tool for this type of hepatitis, from then on called Hepatitis B. The road to the development of a vaccine was now open.

The detection of viral particles in the feces of American GIs in Formosa who developed mild hepatitis led to the availability of both a diagnostic test as well as a Vaccine against this type of hepatitis, called Hepatitis A.

Sophisticated RNA studies defined the cluster of "Non-A-non-B" cases as a different virus, named Hepatitis C, for which we do not have a vaccine yet.

Conclusion: In the 20<sup>th</sup> century, viral hepatitis has become a vaccine-preventable disease through research which is coined "Unethical" in the 21<sup>st</sup> century.

## **Forgetting and Remembering the Great Flu of 1918-19**

Guy Beiner, Department of General History

The influenza pandemic of 1918-1919 is considered the greatest killer of all time and yet memory of the 'Great Flu' was overshadowed by the large-scale remembrance of the Great War that preceded it. There has been practically no public commemoration of the millions of casualties of the epidemic. The little-known socio-cultural history of its forgetting exposes a striking dissonance between remembrance in private and public silence. Recent epidemic scares have ignited new-found interest in the topic and this rediscovery has encouraged several expressions of cultural remembrance.

## **Infectious Disease Ethics: Some Conceptual Challenges**

Shlomo Cohen, Department of Philosophy

Infectious disease ethics has been virtually absent from the central, formative discussions in the first couple of decades of the discipline of bioethics. However, the prevention and treatment of infectious disease raise special ethical concerns. It has been argued recently that these special concerns show the need for a new conceptual framework or paradigm for bioethics. The basic argument for a new ethical paradigm will here be presented and discussed critically.

## **Controversies over Bacteria as Causes of Infectious Diseases: The Case of Ferdinand Cohn, Founder of Microbiology**

Ute Deichmann, Jacques Loeb Centre for the History and Philosophy of the Life Sciences

Until the 1890s, epidemics were mainly explained by environmental factors such as local pollutions. Micro-organisms, including bacteria, were widely believed to occur in multiple forms, generated spontaneously from non-living material. I will show that, starting in the 1860s, this theory was most strongly contradicted by botanist Ferdinand Cohn, who, guided by careful observations and his discovery of bacterial spores, promoted the idea that bacteria have definite forms and generate only from others of the same kind.

Cohn's theory was later adopted by Robert Koch, the founder of modern bacteriology, and became the basis of the concept of bacteria as causes of infectious diseases. The theory of environmentally-caused infectious diseases, most forcefully promoted by hygienist Max Pettenkofer, lost credibility after Koch's theory proved to be successful during the 1892 cholera epidemic in Hamburg. But subsequently a modified version of Pettenkofer's theory gained ground, and after the German defeat in 1918, Jewish bacteriologists who comprised the majority of German bacteriologists, were discriminated against as "hunters of bacilli".

## **Should They Be Told? The Historic Debate in Israel on the Question Whether to Inform Former Patients of Irradiation from the 1950s**

Dan Even, Shifra Shvarts, The Moshe Prywes Center for Medical Education

Irradiation treatment of children for a variety of minor ailments such as ringworm and acne were a common practice in the medical world until 1960s. In the United States some four million children were treated with irradiation in this manner. In France, Portugal, Germany, England and Canada tens of thousands of children were also treated with X-rays. In Israel, the largest group of children treated were children who had contracted ringworm, a fungal disease of the scalp.

In the late 1960s, in the wake of research on the extent of damage caused by irradiation for ringworm, 17,000 medical cards former ringworm patients were found in Israel, among whom 10,000 were identified as children. The identification of the children involved was kept secret by the researchers. At the beginning of the 1980s, a public struggle began to pressure authorities to release the names of 'ringworm children' whose medical cards had been uncovered. The struggle to make the names of the 'ringworm children' public became a legal battle and a media issue between researchers in the health system, and politicians and community activists - a clash that continued for close to three decades.

The work at hand describes the historic struggle to reveal the names of ringworm children in Israel, and its results.

The work is based on archival and legal documents, protocols of discussions of the issue and coverage in the Israeli media on this issue.

## **Contagion, Art and Death in Thomas Mann's Writings**

Mark H. Gelber, Department of Foreign Literatures and Linguistics

This presentation analyzes the representation and multiple significations of contagion and disease, as well as death, in literature, focussing on the complex example of one of the great writers of the last century: Thomas Mann. A Nobel-prize winning author who was decisively influenced by Schopenhauer, Wagner and Nietzsche, Mann went into exile with the ascendance of the Nazis to power in Germany. His writings from the beginning of his career to his death are saturated and obsessed with figures and depictions of illness and death to the point of morbidity. At the same time, departing from the 19th-century, romantic fascination with illness as a cause or prerequisite for artistic creation of the first order, Mann's works are sublimely ironic and ambivalent about the various roles of diseases in the artistic and creative processes, while linking them to dangerous political and cultural developments which caused massive destruction and death in Europe in the 20th century.

## **Ebolavirus Never Sleeps**

Leslie Lobel, Shruga Segal Department of Microbiology, Immunology, and Genetics

The world, and Western Civilization as we know it, has been to a large extent shaped by infectious diseases. Indeed, our control, or lack of control, over infectious diseases has played a major role in history. We are in a never ending race with viruses and other infectious agents for survival, and societies today rely on a sophisticated medical establishment to control these diseases in the background of our ever weakening ability to compete on an evolutionary level. In addition, with globalization and global warming we are witnessing the emergence of infectious agents that were previously confined to equatorial regions of the world and now threaten developed societies north and south of the equator.

The survival of humanity is becoming a never ending race to keep up with the ever changing infectious agents that continue to evolve and outrun our capabilities. Ebolavirus, and the current outbreak in West Africa, is an excellent example of this tenet. It is a member of the family Filoviridae, the cause of Ebola hemorrhagic fever (EHF), which has a case fatality rate that ranges from 30-90%. Given the high case fatality rate, high potential for spread with increasing globalization and global warming and the significant biosecurity threat, Ebolavirus has become a high priority target for development of antivirals and prophylactic vaccines. With limited successes in animal models, challenges imposed by Ebolavirus infection mechanisms have hampered development of effective and safe therapies and vaccines for humans. To facilitate development of effective vaccines and therapeutics an understanding of the profile of humoral and cellular immune responses in humans to Ebolavirus infection is key, especially with respect to memory immunity and its persistence over time. Thus far, this knowledge is lacking.

We have studied the profile of the humoral and cellular immune responses in cohorts of human survivors of Filovirus infection and explored specific memory immunity and its persistence over time. This has been accomplished by profiling the sera and lymphocytes of Ebolavirus survivors with individual proteins of Ebolavirus, to identify the targets and specific epitopes of the humoral and cellular immune responses in human survivors. Studies of the humoral and cellular immune responses to these targets over many years has provided insight into the correlates of neutralizing memory immunity in Filovirus survivors, which will be useful as a metric for development of successful vaccines and therapeutics.

## **Culture and Gender Barriers to Prevention of Mother-to-Child Transmission of HIV (PMTCT) Background**

Anita Nudelman, Recanati School for Community Health Professions and the Inter-University Program in African Studies

Despite the progress in scaling up services to eliminate new HIV infections amongst children, many pregnant women living with HIV still do not access the medication. In order to understand the barriers to PMTCT, UNAIDS undertook a study in five high-burden countries: the Democratic Republic of Congo, Ethiopia, India, Nigeria and Uganda.

### **Methods**

Qualitative intensive participatory methods were used, involving women living with HIV as active partners in a rapid assessment process (RAP).

### **Findings and Discussion**

The findings indicate that gender barriers to services for PMTCT are complex and deeply influenced by cultural perceptions of HIV. They are also fueled by socio-cultural norms and practices that foster unequal power relations, as well as HIV-related stigma and discrimination. Key decision makers, at family and community level, influence pregnant women's attitudes and health behavior, including readiness for HIV testing and disclosure. Low level of male partner involvement also negatively affects service access and utilization. Barriers at the health service delivery level include accessibility of services and financial constraints. In addition, health workers' attitudes and the lack of confidentiality often result in women preferring traditional birth assistants. Based on these findings, practical recommendations were elicited.

## **Protein degradation in *Mycobacterium tuberculosis*: Homology and analogy as Achilles heel**

Ziv Roth, Department of Life Sciences

*Mycobacterium tuberculosis* (Mtb) is the deadliest bacterial pathogen. One third of the world's population is estimated to be infected with Mtb and more than ten million cases are chronically active (the vast majority of which are in developing countries). The resulting death toll of Mtb infections is estimated to be about 1.3 million annually, despite global efforts to combat Mtb. Tb can be cured by prolonged (16 months) antibiotic treatment. However, the emergence of multi drug-resistant (MDR) and extensively drug-resistant (XDR) strains has become a major concern in the combat against Mtb. Consequently, attempts have been made to discover novel Mtb targets that can be used for the development of new anti-Mtb drugs.

One such target is the recently discovered ubiquitin-like system. This system, also found in other actinobacterial species, targets proteins for proteasome degradation by conjugating them to an ubiquitin-analog termed Pup (prokaryotic ubiquitin like protein). A recent study in our lab showed that in *Mycobacterium smegmatis* the Pup-proteasome system is upregulated under starvation conditions to promote amino acid recycling. Indeed, *M. tuberculosis* is in constant starvation inside its host. Furthermore, it has been shown that *M. tuberculosis* lacking the Pup-proteasome system loses its virulence. In contrast to the ubiquitin system, which involves several enzymes in the conjugation of ubiquitin to its target protein, in the Pup-proteasome system there is only one enzyme, PafA, responsible for the conjugation reaction of Pup to target proteins. Therefore, PafA is a target for development of novel anti-TB drugs.

## **Evolution of the Translation Machinery in Trypanosomatids as an Adaptive Measure for Leading a Complex Life Cycle**

Michal Shapira, Simi Mellepattu, Dikla Kamus-Elimeleh and Irit Orr

Department of Life Sciences

Organisms from the genus *Leishmania* are part of the trypanosomatidae family, an ancient lineage of eukaryotes. Different *Leishmania* species cause a spectrum of clinical syndromes that range from self-curing skin sores to the lethal visceral disease. Drug treatment has been available for many years but it is toxic and drug resistance is of great concern, especially since safe and effective vaccination is not yet available. Thus the need for novel drugs, especially new drug targets, is urgent. One approach is to rely on cellular and biochemical pathways which are unique to these parasites, and are not shared with their mammalian hosts. Since *Leishmania* are ancient eukaryotes, it appears that many of the molecular pathways which they use are rather diverged from higher eukaryotes. This has become apparent in studies of the machinery which is responsible for translation, i.e. the decoding of instructions in nucleic acids for making proteins. *Leishmania* are digenetic parasites where sexual reproduction in a vertebrate alternates with asexual reproduction in a non-vertebrate. They cycle between sand-fly vectors

and mammalian hosts, experiencing a variety of stress conditions that include dramatic temperature and pH switches, as well as nutritional starvation at specific points in their life cycle. Our studies aim to decipher how they adapt their translation machinery to the changing environments. It appears that *Leishmania* spp. have generated a rich repertoire of proteins that bind RNA in a manner that can advance translation, block it under specific conditions, and provide a protective mechanism to their RNA molecules which are not actively translated, in the form of various RNA granules.