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The Evolution of Infectious Agents in Relation to Sex

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Danielsson

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Issue: *The Evolution of Infectious Agents in Relation to Sex*

Dedications

We dedicate this volume to the memory of several individuals, from different countries and disciplines, each of whom has contributed in many ways to the conception and realization of this, the first symposium on the evolution of infectious agents in relation to sex.

E. Russell Alexander, MD (United States) pioneered the epidemiology and population biology of many infectious agents, focusing on their deleterious effects on reproduction and progeny fitness.

Robert A. Good, MD, PhD (United States) authored many of the concepts and substantiating evidence related to the phylogeny and ontogeny of the multivaried immune systems in animals and humans, as well as to many practical immune interventions.

J. David Oriel, MD (United Kingdom) emphasized early on the need to study in animals, as well as in humans, the basic and practical clinical and public health aspects of infectious agents that assume sexual transmission.

Darryl Reanney, PhD (Australia) designed sentinel applications of the developing molecular genetic technologies to our understanding of the evolution of infectious agents, particularly viruses.

Ragnar Sohlman, chemical engineer (Sweden), as executor of the will of Alfred Nobel, successfully struggled to secure Nobel's unique legacy to the world. Sohlman also helped to preserve, for more than a century, the Nobel Mansion, which housed our symposium.

We also wish to honor **James H. Steele, DVM, MPH**—the father of veterinary public health in the United States and founder of the World Veterinary Epidemiological Society. Fortunately for us, Dr. Steele has helped to contribute to these proceedings—at the age of 98!

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Darwin meets Nobel

Björkborn Mansion,
Alfred Nobel's last home in Sweden



CREATIVITY, INNOVATION, DISCOVERY

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Preface for *The Evolution of Infectious Agents in Relation to Sex*

Charles Darwin's thoughts and writings have provided much of the basis for the understanding of evolutionary principles, and Alfred Nobel is the icon of the technological advances of their days. Together, they represent two of the most influential creators, innovators, and discoverers of the 19th century. The most recent "Golden Age" of evolution, has been propelled, particularly during the last two decades, by major advances in technology, providing us with information beyond even the imagination of Darwin and Nobel. Although neither of these giants is usually connected with the world of infectious agents, historical research has revealed that Darwin was well aware of the growing knowledge of microbes (he even believed that his stomach problems might have been caused by bacteria[a]). Similarly, Alfred Nobel's understanding of the contemporary field of bacteriology led him to state that "the conquest of scientific research and its ever expanding field awake in us the hope that microbes—of the soul as well as of the body—will gradually be exterminated, and that the only war humanity will wage in the future will be war against these microbes."[b]

In early 2009, our half-century common journey (see Introduction) led us to explore the possibility of organizing a symposium on the evolution of infectious agents that are sexually transmitted. Where and when would it be held—to also symbolize a meeting of Darwin and Nobel? It so happened that the bicentennial celebration of Darwin's birthday had just been held, and the celebration of Nobel's birthday is held yearly at his mansion, near Örebro, Sweden, on October 21. We pursued the possibility of holding the symposium as part of Nobel's birthday celebration at Björkborn Mansion and secured the site for October 21–23, 2010. With the help of many individuals, we also obtained the participation of over 30 participants from six different countries. Nobel's estate, comprising his laboratory and artifacts of his personal life and legacy, as well as a conference center, provided a most appropriate setting for the many interdisciplinary, intellectual, scientific, and social interactions that took place during the symposium.

This volume reflects the international/interdisciplinary exchanges on the newer evolutionary perspectives and more recent technological advances, together with the growing knowledge regarding the commonality and divergence of those animal and human infectious agents that can be sexually transmitted.

Dan Danielsson
University Hospital, Örebro, Sweden

André Nahmias
Emory University, Atlanta, Georgia

[a]Wainwright, M. 2009. Historical perspectives: Charles Darwin and microbes. *Microbiol.* **10**(2): 32–35; O'Malley, M. 2009. What did Darwin say about microbes, and how did microbiology respond? *Trends Microbiol.* **17:** 341–347.

[b]Cited in the Nobel Prize address by Ahmed Zewail, Egypt, (Chemistry) 1999; however, as discovered since Nobel's time, many "microbes" have been shown to be beneficial to their hosts.

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Acknowledgments

We would like to thank the staff of the Nobel Mansion at Björkborn, Karlskoga, Sweden, and particularly Nobel "himself"—Mr. Peter Sundh—an actor who gave the participants a memorable impersonation of Alfred Nobel and a narrative of his last years in his mansion and laboratory. We also wish to thank the University of Örebro, the Örebro County Council, and the Clinical Research Unit of Örebro University Hospital for financial support of the symposium, including accommodations and several extraordinary social evenings. Also greatly appreciated was the support of the Department of Pediatrics and Professor Raymond F. Schinazi, Emory University, Atlanta.

We extend our deepest gratitude to the vice chancellor of Örebro University, Jens Schollin, professor of pediatrics, who gracefully welcomed the visitors and participated in our meeting. We are also deeply indebted to the organizing committees in Örebro and Atlanta, instrumental to the meeting's success: Monica Wettler, Magnus Unemo, Jacque Muther, Margareta Jurstrand, Hans Fredlund, and Per Olcen. Thanks also go to the presenters, chairs, and participants who contributed their expertise, wisdom, and wit, making this meeting a most informative, exciting, and unforgettable experience. We also greatly appreciate the publication assistance of the editorial staff of *Annals of the New York Academy of Sciences.*

Dan Danielsson
University Hospital, Örebro, Sweden

Susa Beckman Nahmias and André Nahmias
Emory University, Atlanta, Georgia

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Introduction to *The Evolution of Infectious Agents in Relation to Sex*

Practical wisdom is of the particular which becomes graspable with experience.
Aristotle

There is a time to divide and a time to unite.
André Lwoff—French Nobelist

Theme of the symposium

These proceedings of the conference "The Evolution of Infectious Agents in Relation to Sex" represent a compendium of the many relevant basic and technological advances in our ever-increasing knowledge acquired particularly over the past decade. The evolutionary perspectives help to unite a number of very diverse infectious agents that can assume the sexual mode of transmission, with either common or limited frequency, in humans and animal species (classified in Tables 1 and 2, see below).

In several respects, this symposium represents a sequel to Darwin's second opus in 1871 entitled *The Descent of Man, and Selection in Relation to Sex*,[1] the Nobel symposium in 1987 on the "Evolution of Sex,"[2] as well as a pioneer review on the evolution of sexually transmitted infections (STIs) in 1996 by a team led by Janis Antonovics.[3] A major expectation was also that evolutionary considerations could provide new insights on the more practical approaches to prevention and treatment, improving our ability to be better prepared for the impact that such emerging and re-emerging infectious agents are having currently, and that are likely to have in the future.

Conception of the symposium

Our common basic and practical experiences led us to the eventual concept for, and realization of, this international and interdisciplinary meeting. For many years, we have appreciated the need to *divide* and *unite*, and have tried to follow the Aristotelian admonition to apply practical wisdom to our various efforts. To illustrate the process that led up to this symposium, we will briefly narrate our evolving and developing personal journeys from our many decades of collaboration.

We first met in the 1960s—at the Communicable Disease Center (CDC) and at Emory University in Atlanta, and later in Örebro, Sweden—discovering a commonality in our basic and applied training and interests in the microbiology, immunology, and epidemiology of infectious diseases. Independently, we had also developed earlier in our careers a mutual desire to bridge the various disciplines, particularly those related to sexually transmitted infectious diseases and several of their causal infectious agents: DD—involved mostly studying bacteria, particularly those that can affect reproductive fitness, for example, gonococci and chlamydia; and AN—researching several

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viruses causing diseases in the fetus/infant, for example, herpes simplex and cytomegalovirus, and also (as an epidemiologist in the CDC Veterinary Public Health Laboratory) investigating various infectious agents affecting animals.

An early result of our interactions was a three-day symposium, "Genital Infections and Their Complications," held in Stockholm in 1974—organized by DD and in which AN participated.[4] Our laboratory and epidemiological interests prompted each of us to apply established and new technologies to various basic and practical issues that focused on the *separation* of bacterial and viral agents into types and subtypes, for example, as exemplified by DD's serological differentiation of gonococci[5] and AN's differentiation of herpes simplex viruses into type 1 and type 2.[6] The evolutionary perspective *uniting* the 70+ herpesviruses in animals and humans was expanded to all known viruses in a comprehensive review entitled "The Evolution of Viruses,"[7] written by AN in 1977 together with Darryl Reanney, an Australian molecular biologist, and further developed at several workshops at the International Congresses of Virology in the 1970s and 1980s.

Various influences led DD and AN to also study the interactions of commensal agents associated with several diseases: the extensive microbiota in the gut and vagina in relation to bacterial vaginosis in women, and their relation to necrotizing enterocolitis and several intrapartum infections in newborn infants. DD contributed to the immune aspects related to such agents in the *Immunology of Human Infections* (coedited by AN with Rich O'Reilly), which also included reviews on STIs.[8] Our immunological interests led to an involvement with newer technological advances, including ELISPOT—a method that permits enumeration of lymphoid B cells that produce, in the peripheral blood, immunoglobulins of a different class, or subclass, that are antibodies to various agents. The method provided new information on what is now known as evolution–development (EVO-DEVO), linking phylogeny and ontogeny[9] (see also chapter in these proceedings[10]).

By 1985, with several colleagues, AN identified the earliest known HIV-1 in the world in stored sera collected in 1959 from the Belgian Congo (Zaire, now DRC).[11] Over a decade later, molecular genetic analyses of viral fragments in that stored serum specimen demonstrated its relationship to the different HIV-1 clades, helping to date the entry of HIV-1 in humans, as well as its geographic spread.[12] In 1987, AN and DD teamed up to organize a symposium in Atlanta called "AIDS in Children, Adolescents, and Heterosexual Adults,"[13] sponsored by the International Interdisciplinary AIDS Foundation they had helped found earlier in Geneva. In turn, DD organized a Berzelius symposium on the major worldwide STDs in 1989, which included discussions on their transmission, molecular biology, and methods of epidemiological control and prevention.[14]

Over the years, we expanded our interests to the evolution of a greater number of STI agents, with presentations to various groups. We became, belatedly, aware of a paper published in 1996 by the team of Janis Antonovics (then at Duke University), providing a comprehensive assessment of the many STI agents then known, not only in animals and humans, but also in plants.[3] The review was prescient, but somewhat premature, as the knowledge of the molecular biology and other aspects of these agents and their hosts was still generally limited. The years since have indeed provided a vast amount of new relevant evolutionary basic knowledge, together with an almost logarithmic growth in molecular and other technologies—providing the means of identifying a greater number of infectious agents, their genomics, phylogeny, and other relevant information of evolutionary and developmental import. Even though we had contemplated many times over the years writing a comprehensive review, we concluded, by the summer of 2009, that two people could not do justice to a subject that encompasses such a large number of diverse aspects. We imagined (as noted in the Preface) that creativity, innovation, and discovery that linked Darwin to Nobel could be realized best in Alfred Nobel's last home and laboratory—at his mansion in Björkborn, Sweden. We then consulted with colleagues from many different disciplines and developed an agenda for presentations over a two-and-a-half-day meeting that would cover three main goals:

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1. introducing general evolutionary and relevant topics from an interdisciplinary *unifying* perspective;
2. presenting talks on selected *separate* individual infectious agents (viruses, bacteria, and parasites) that would include (a) almost all of the agents in humans that primarily use the sexual route of transmission (STI agents), and some of those sexually transmissible (STxI) agents that have other primary transmission routes; and (b) those agents in nonhuman mammals, including primates, which have lessons to contribute to the one health–one medicine concept, unifying veterinary and human medicine and public health (see Tables 1 and 2); and
3. addressing how the evolutionary knowledge and questions developed could be translated to the more practical clinical and public health modalities of diagnosis, prevention, and treatment.

Realization of the symposium and its eventual publication

Important to the concept of the meeting was the intimate format, with 30 invited presenters and an additional 10 individuals from six different countries, primarily serving as chairs. The schema—*from origin to disease*, presented in the introduction of the symposium—served as a framework for considering the origin and phylogeny of the different infectious agents and their adaptation to the genital econiche and sexual transmission, with their various outcomes in the infected hosts and their progeny (see Fig. 1).

For the general part of the proceedings, we were particularly pleased to have a keynote address by Randolph Nesse[15]—who, with George Williams, pioneered the concept and practice of evolutionary medicine—as well as one by Janis Antonovics on the evolution of sex.[16] As noted in the table of contents, the other relevant general contributions comprise animal–human interactions (one health–one medicine)[17] and the genital econiche, with a focus on its microbiota and bacterial vaginosis.[18] The specific evolutionary–developmental (EVO-DEVO) interactions of the tolerizing mechanisms and responses to STI agents of the "triad"—the mother, placenta, and fetus/infant[10]—is addressed, as is the role of endogenous retroviral genes (ERVs) in reproduction.[19] As an added background for practical, clinical applications of this evolutionary and developmental knowledge, the impact of human, social, economic, and behavioral developments on the STI agents, and their transmission and evolution is included.[20] These general interdisciplinary contributions were followed by the specific evolution of several animal and most human sexually transmitted agents,[19,21] as well as some relevant preventive and therapeutic aspects of evolutionary import.

The large number of contributions and the page limitations of the printed journal led to an updated format for their publication. The contents herein include most of the general subjects, as well as a composite of brief responses from each of the contributors on specific agents in animals and humans, addressing three major issues: (1) What have we learned about the likely origin and phylogeny of the infectious agent up to the time of its establishment in the genital econiche and sexual transmission? (2) What research is needed to provide additional knowledge? (3) What evolutionary questions/answers might aid in providing novel approaches to the clinical and public health issues facing us currently and in the future? In addition, the in-depth articles on each individual animal and human agent discussed will be published during the coming months online.

Expectations

Today, the large group of infectious agents that have assumed the sexual mode of transmission represent a major global problem in both human and veterinary medicine and public health. Improved knowledge from an evolutionary perspective may not only be of import for current

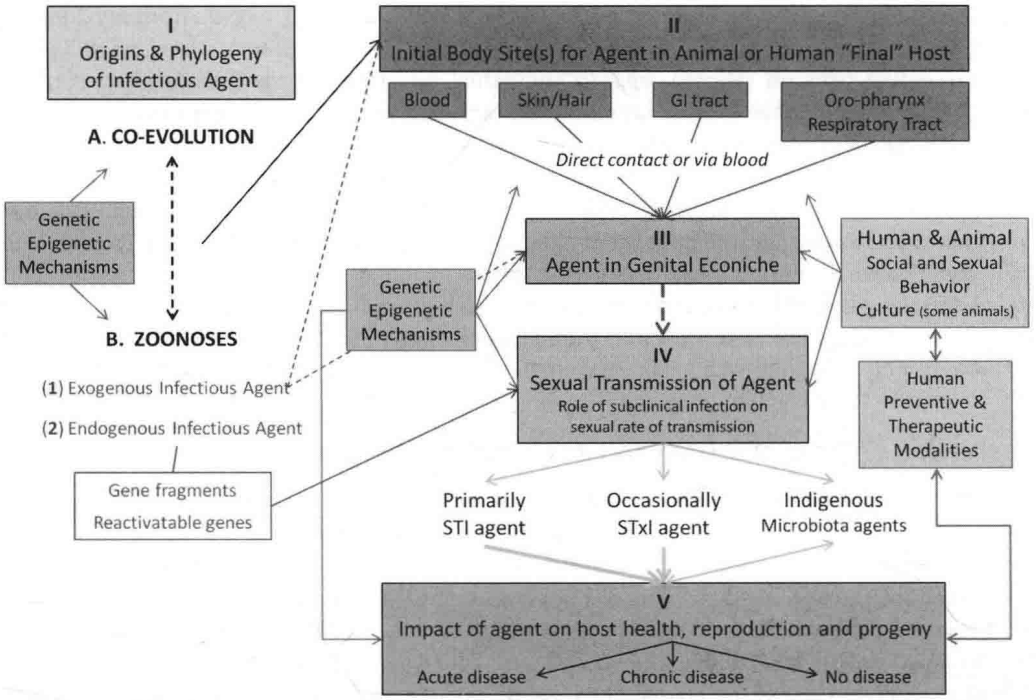

Figure 1. From origin to disease in mammals, including humans. The figure schematizes how infectious agents of similar or different phylogenies may have evolved (I) in the animal and human "final" host (II); then adapted to the genital econiche (III) and sexual transmission (IV), with impact on host health, reproduction, and progeny (V)—under the influence of genetic/epigenetic mechanisms and the impact of human development and interventions. The possible origin (I) of the infectious agent in a particular existing "final" host (e.g., horse or human) is dependent on *time** and the evolution–development of the agent–host relationship—*co-evolution* or as *zoonoses*. (A) *Co-evolution*: most likely, first at various initial body sites, then by adaptation to the genital econiche and sexual transmission in the final host. (B) *Zoonoses*: (1) Exogenous—in which case the agent must be able to be transmitted, not only to a new host—for example, animal to human—but also to adapt subsequently to the genital econiche and be sexually transmitted from human to human; (2) Endogenous—transmitted by maternal and paternal gametes that contain various evolutionary viral elements (EVEs), particularly endogenous retroviral genes (ERVs), which can assist placentation in mammals and may have other possible beneficial effects, or may cause ill-effects, likely modulated by epigenetic mechanisms. **time perspectives*: vertebrates ~500 million years ago (mya); mammals ~120–150 mya; primates: monkeys ~25–40 mya, apes ~7–18 mya, *H. sapiens* hunters and gatherers ~200,000 years ago; agriculture/domestication of most animals and emergence of cities ~5–10,000 years ago.

research and prevention/treatment efforts, but also prove of assistance in case of future emerging and re-emerging agents. It is our hope that readers will be stimulated by the *uniting* evolutionary approaches and can help enlarge the discussion on some of the likely controversial aspects or definitions, such as the inclusion of the "intact" enveloped endogenous retroviruses as STI agents, or the evolutionary–developmental (EVO-DEVO) approaches to the phylogeny and development of infectious agents and innate and adaptive immune responses, as exemplified in humans.[10] We anticipate that these proceedings will lead to continued interchanges with, and between, other workers on some of the newer evolutionary perspectives, which are also intimately linked to, for example, social, economic, and technological developments.[20] We would urge particularly our veterinary medical and public health colleagues to include the uniting evolutionary paradigm to expand basic and practical knowledge within the one health–one medicine interchanges[17] on such common issues as reproductive aspects, vaccines, and antimicrobials.

More generally, we can only wish that many of our younger colleagues will continue in their developing and evolving careers to apply the *united* and the *separate*, the basic and the

practical—modeling themselves after one of the greatest ancient practical biologists, Aristotle, and one of the pioneers of molecular biology, André Lwoff, and to also strive for the creativity, innovation, and discovery that Darwin and Nobel demonstrated in their work.

André Nahmias
Emory University, Atlanta, Georgia

Dan Danielsson
Örebro University Hospital, Örebro, Sweden

Table 1. Sexually transmitted and sexually transmissible infectious agents in humans

Sexually transmitted (STI) agent[a]	Diseases	Sexually transmissible (STxI) agent[b]
Viruses		
Herpes simplex virus (HSV) type 2	Genital herpes	Genital HSV-1
Human papilloma viruses (HPV)—several distinct genotypes	Genital warts; cervical, anal, oral cancer	Hepatitis B virus Hepatitis C virus HTLV-2 retrovirus
Human immunodeficiency viruses (HIV-1 & -2)	AIDS	Cytomegalovirus Epstein-Barr herpesvirus
Germ cell–transmitted human transposable elements, including "intact" endogenous retroviral enveloped genes	Development of placental trophoblasts and brain; autoimmune, CNS, and other diseases?	Herpesvirus 8 (Kaposi's sarcoma) Hepatitis A, D, and G Molluscum contagiosum poxvirus
Bacteria		
Treponema pallidum	Syphilis	Group B streptococcus
Neisseria gonorrhoeae	Gonorrhea	Meningococcus
Chlamydia trachomatis (several serovars)	Multiple diseases, including lymphogranuloma venereum	*E. coli* Salmonella
Klebsiella granulomatis	Granuloma inguinale	Shigella
Hemophilus ducreyi	Chancroid	Campylobacter
Mycoplasma genitalium	Urethritis/cervicitis	Intestinal helicobacter *Hemophilus haemolyticus* Mycoplasma and ureaplasma Other indigenous flora of the genital tract
Yeast		*Candida albicans* and other species
Protoazoa		
Trichomonas vaginalis	Trichomoniasis	Amoeba and other intestinal protozoa
Ectoparasite		
Pthirus pubis	Pubic lice	Scabies

[a]STI agents: transmitted primarily by sexual contact.
[b]STxI agents: occasionally transmitted sexually, with other primary mode(s) of transmission.

Table 2. Sexually transmitted and sexually transmissible infectious agents in mammals[a]

	Sexually transmitted (STI) agent[b]	Sexually transmissible (STxI) agent[c]
Primates	Macaque venereal papilloma[b]	Bonobo STLV (homology to HTLV-2)
	Colobus monkey venereal papilloma	Bonobo and Troglodyte chimpanzee Genital alpha herpesviruses
		Macaque alpha *herpesvirus simiae* (B virus)
		Baboon alpha *herpesvirus papio*
		Simian treponeme
		Simian immunodeficiency viruses
Other mammals	Equine coital/exanthema herpesvirus (EHV3)	Equine alpha herpesvirus (EHV1—abortus virus)
	Equine *Trypanosoma equiperdum*[d]	Equine *Hemophilus equigenitalis*
	Equine *Taylorella equigenitalis*	Equine salmonella
	Bovine *Trichomonas fetus*	Bovine alpha herpesvirus 1 (BHV1, infectious pustular vaginitis)
	Bovine *Vibrio fetus venerealis*	Bovine alpha herpesvirus 5 (BHV5)
	Bovine *Campylobacter fetus venerealis*	Bovine papillomaviruses
		Bovine mycoplasma and ureaplasma
		Bovine chlamydia
		Bovine, ovine, porcine, canine brucellosis
	Caprine herpesviruses	Ovine chlamydia
	Ovine and caprine venereal orf (poxviruses)	Ovine ureaplasma
		Ovine salmonella
		Suis alpha herpesvirus (pig pseudorabies)
	Transmissible canine venereal tumor	Canine herpesvirus (CaHV1)
	Koala *Chlamydia pecorum*	Rabbit *Treponema cuniculi*
		Otarine gamma herpesvirus (OTHV1) (Sea lion)
		Bottle-nose dolphin gamma herpesvirus
	Germ cell–transmitted transposable elements, including intact endogenous retroviral-enveloped genes of mice, rabbits, marsupials, primates, and other mammals—important when reactivated in the development of the placenta, but may also cause ill-effects, e.g., in the koala.	

[a]There are most likely many more STI or STxI agents in mammals not yet identified or characterized because of lack of visible disease manifestations, epizoonotic information, or relevant outbreak studies. Agents transmitted by artificial insemination are noted in the chapter by Currier and Steele.[17] Infectious agents in plants, insects, fish, amphibians, and birds, classified according to frequency estimates of sexual transmission, were earlier reviewed by Lockhart *et al.*[3]

[b]STI agents, transmitted primarily by sexual contact.

[c]STxI agents, occasionally transmitted sexually, with other primary mode(s) of transmission.

[d]Agents in bold are *not* phylogenetically related to any known agents associated with sexual transmission in humans.

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The Evolution of Infectious Agents in Relation to Sex

ISSUE EDITORS

André Nahmias,[a] Dan Danielsson,[b] and Susa Beckman Nahmias[a]

[a]Emory University, Atlanta; [b]University Hospital, Örebro, Sweden

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