Gerd Gross
Stephen K. Tyring *Editors*

Sexually Transmitted Infections and Sexually Transmitted Diseases

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Gerd Gross • Stephen K. Tyring
(Editors)

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Foreword

"Medicine, to produce health, has to examine disease, and music, to create harmony, must investigate discord." Plutarch (AD 46–120), Translation by John Dryden (1631–1700).

Strictly speaking a foreword or preface are introductory remarks, especially by another than the author of the book. Dear reader, please excuse this once, the foreword from a contributor to this work. This field of medicine which examines pathology, clinical studies, sociology, diagnosis, prevention and treatment of an aspect of one of the results of humanity, the erotic or sexual life, has been much studied. But its passage ensues. Thus in the nature of endeavours of mankind, the study of sexually transmitted infections and sexually transmitted diseases will need to continue. This work the result of five years labour by two editors from two continents has resulted in sixty-three chapters, the products of many more minds cooperating and writing about the essentials of studies, research and clinical observation of the subject to instruct the reader who wishes to learn more about sexually transmitted infections and sexually transmitted diseases.

By the time one is asked to write a foreword, realisation dawns of the rapid passage of professional life. It seems not long ago but in fact it was almost fifty years when as a medical student at Charing Cross Hospital, London, who realised he did not know how to make a Gram stain, a prerequisite in the bacteriology final exams in those days, he ventured into the department for venereal diseases where not only did he learn how to pass his practical, but learned about those the same age as himself who were treated with devotion, respect and the best contemporary knowledge of the subject. This time the summer of 1964 made me want to study sexually transmitted diseases for my career. Little did I know then what a wonderful journey it would be for the rest of my life. Dear reader, especially for those at the start of their professional journeys, I hope aspects of this book will also make you think you would like to help others by devoting some of your energy and intellect to adding to the corpus of knowledge about sexually transmitted infections.

Since then so much has been added to sexually transmitted infections. Syphilis had been studied for five hundred years. We thought it would become a rare disease. We realise now we were mistaken and it weaves into all the other sexually transmitted infections. Antibiotic resistance in gonorrhoea has increased as would be expected but applied research into effective chemotherapy has lagged. Knowledge of Chlamydia

trachomatis at that time only known to a few is now an everyday matter, but it affects the fertility of so many young people. The diagnosis of microbial infection has been enormously furthered by techniques of applied DNA hybridisation. We had no cure and little understanding of the effects of genital herpes. There is still so much to be done in that field. We were beginning to understand the complexity of human genital papilloma virus infection. We were at the start of its relationship in some aspects to cervical and ano-genital neoplasia. The vaccine was many years away. In the 1970s, the sexual aspects of hepatitis B and then later the other hepatitises were established. A visit to San Francisco in 1975 was enough to show me how public health medicine took as a matter of serious concern, enteric diseases transmitted through sexual contact in men who had sex with men.

Then AIDS came to the Western World. For those of us in the field at the time we saw for the first time in the post-antibiotic era our fellow humans terribly suffering from a disease which at the start we did not know the cause. We saw ambulant patients, in my country mostly previously healthy men and later women and infants, visibly failing in health in front of us before dying. For all of us deep into our specialty, we saw dying patients, friends, loved ones, colleagues, for AIDS spared very few infected with the human immunodeficiency virus (HIV) in its early years. No specialty can work in isolation. The epidemic of HIV brought in extra magnificent and welcome minds and manpower into sexually transmitted infections. It introduced much needed governmental, international aid and private finance for prevention, and applied research. It rapidly brought the might of the pharmaceutical industry to manufacture within a comparatively short time highly active anti-retroviral therapy. Yet in that field so much more still needs to be done. I have travelled much to continents outside the West to see what devastating effects HIV/AIDS has on developing countries not only in the loss to human life but to the structure of countries and their social and economic well-being. So much still needs to be done.

Our knowledge of prevention of sexually transmitted infections is still in its infancy. There is far more to be done in the field of the development of immunisation to prevent sexually transmitted infections. In nineteenth century Europe there was a concept of immunisation for syphilis. This has not yet been achieved.

A glory of this work has been German–American cooperation in medical science. This follows a long and hallowed tradition in Europe and America. In the nineteenth century post-graduate students flocked to Vienna and Berlin to learn from the great men of medicine in those times. One such was the great William Osler, though born in Canada and making his career as a professor at Johns Hopkins and Oxford. In Vienna they would learn dermatology still a basic specialty of sexually transmitted infections from masters such as Hebra, Sigmund, Neumann and Kaposi. In Berlin the pupil would learn from the giants of general medicine and pathology such as Traube, Frerichs, Johannes Muller and Rudolph Virchow. It was not only in medicine that this cooperation flourished. Bismarck was much influenced by various friendships with American intellectuals of his day. Even the catastrophe of 1933 meant that American medical science would be enriched by refugees from Germany and Austria. However we must not forget this work is truly international from some of the best minds in the subject from around the world.

The editors Gerd Gross and Stephen Tyring are to be congratulated in seeing their concept reaching fulfilment. It is not an easy task to shepherd the contributors of a post-graduate medical comprehensive multi-authorship book towards finalisation of

their copy in not too long a time. It is a happy achievement for all authors in such a book to have written their allotted chapters to the best of their ability. One so much hopes this book will encourage and assist towards knowledge of sexually transmitted infections and sexually transmitted diseases.

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Preface

Sexually transmitted diseases (STDs), previously known as venereal diseases, have been a topic of major concern for centuries as they are considered very important risk factors for morbidity and mortality both in poor and in industrialised countries.

Great steps have been made during the last two centuries to combat STDs. The introduction of penicillin was a major breakthrough in the treatment of syphilis. In the late twentieth century HIV was documented as the cause of AIDS, and the association between genotypes of HPV and genitoanal cancer was documented. These events paved the way to the production of many classes of antiretroviral drugs and to the development of prophylactic HPV vaccines.

We now have a far better understanding of numerous sexually transmitted infections. Recent developments in diagnostic techniques not only have permitted more accurate diagnosis but also have widely improved our understanding of the natural history of STDs. It is only through such understanding that the feasibility of specific therapies and preventive methods can be determined, but much remains to be learned regarding STDs.

When planning this text an important consideration was to identify the audience to whom it is directed. It should be of value to the widest audience of physicians and scientists interested in sexually transmitted infections and STDs. However it is not intended only for clinicians and laboratory scientists. It is not a compendium of diseases and information about how they should be treated. Rather it attempts a synthesis of these areas, discussing the clinical, diagnostic, epidemiologic, pharmacologic, molecular biologic and immunologic interrelationships of pathogenic agents, antibiotics, antifungals, antivirals and disease.

The book is intended for those who will most need it in the coming years: the medical student and resident who are interested in infectious diseases, the clinician who diagnoses and treats STDs and the microbiologist who will advance new developments in the field.

We hope that the text will be of interest to readers who are concerned in any way with patients suffering from STDs and associated public health problems, e.g. physicians, nurses, counsellors, students, laboratory personnel, public health workers and politicians. It is also intended for the research scientist who hopefully will be encouraged to do further work in the field of STDs and sexually transmitted infections.

In order to reach such a wide and diverse audience, all aspects of sexually transmitted infections and STDs are covered in this text. We are grateful to the contributors from all parts of the world with their different backgrounds and recognised expertise compiling this manifold book.

There are many instances of overlap in the book, but this is not considered to be undesirable. In many instances it is done for completeness and emphasis. The reader will notice that the individual chapters vary somewhat in terms of length, organization and style. These variations arise from the differing natures of the topics being discussed. We have decided to maintain these differences, since the state of the art varies widely from one area to another.

This book not only covers diagnosis and treatment, but also emphasizes prevention. Education is the cornerstone of prevention and is the goal of this book. Recently the first vaccines to prevent STDs, i.e. for hepatitis B and HPVs, have been added to the list of preventative interventions ranging from condoms to abstinence. It is anticipated that vaccines to prevent other STDs will be added to this list in the future. Education regarding both prevention and treatment should result in better control of STDs. We hope that the book will contribute to increased awareness and knowledge of sexually transmitted infections and STDs emphasizing their important role in human medicine.

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The Editors

Contents

Part I

Basic Elements

History of Sexually Transmitted Infections

1

Michael Waugh

Core Messages

- A basic knowledge of the history of sexually transmitted infections (STIs) is important not only for professionals but also for the general public.
- This knowledge enables the reader to understand the development of STIs, which have had such an enormous impact on the behaviour and health of the human race. This history has been studied and written about by medical and general historians for 500 years.
- STIs have been described since the beginning of recorded history in Europe and Asia, in handwritten manuscripts until the invention of the printing press by Gutenberg in 1454. The history of STIs for the next 500 years followed the growth of medical and scientific discoveries and thus knowledge. STIs were affected by many human activities: travel, trade, war, colonial expansion, migration, industrialization, increasing public education, prostitution, the emancipation of women, slaves, and men who have sex with men.
- This chapter describes the history of STIs from the ancient times of gonorrhoea, into the era of syphilis and all the other sexually transmitted diseases, and now HIV/AIDS.

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1.1 Definition

In this chapter, a sexually transmitted infection (STI) is defined as an infection passed from one person to another as a result of a sexual act. This definition includes sequelae passed from an infected mother to a child (congenital infection).

1.2 Aims

This chapter aims to give a concise history of STIs from ancient to modern times. It comprises the following historical eras:

1. The ancient times prior to the outbreak of syphilis in sixteenth-century Europe.
2. The development of the concept of venereal diseases (VD) until nineteenth century.
3. The development of a scientific basis for sexually transmitted diseases (STDs) from the nineteenth century.
4. The impact on society before and after the discovery of AIDS.
5. Scientific achievements since the advent of chemotherapy.

1.3 Sexually Transmitted Infections in Ancient Times

There are records of STIs – most notably urethral discharge that was probably gonorrhoea – from the earliest times [1]. For example, STIs have been

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described in the Ebers papyrus [2]; the Old Testament in Leviticus 15:2–33 ("The running issue," "Clothing needing washing as did the man himself," "All infected persons had to keep themselves apart from others for 7 days," "and if any man's seed of copulation go out from him then he shall wash all his flesh in water…the women also with whom man shall lie with seed of copulation…", "And the women if she have an issue she too…and she shall be put apart for 7 days") [1]. The Greek and Roman authorities described STIs, including Hippocrates, Celsus, Galen (who gave us the word *gonorrhoea*, meaning a flow of semen), Arateus of Cappadocia (who distinguished vaginal gonorrhoea from simple discharge), and Soranus (who described the condition) [1]. The Golden Age of Islam (900–1100 AD) [3] is exemplified by Abu Ali al Hussein ibn Sina Avicenna (980–1037), who was less remarkable as a physician than as a philosopher and physicist. His gigantic Canon of Medicine (al-Qānūn fī'ṭ-Ṭibb), which dealt with the whole of systemic medicine, recommended irrigations for urethral discharge. Later, Maimonides of Cordoba (1135–1204), who spent most of his active life in Cairo, in "Aphorisms" described gonorrhoea as fluid escaping without erection or feeling of pleasure, doughy, and the result of disease including amorousness and excesses [4].

During the Middle Ages in Europe, advances in the knowledge of gonorrhoea were made. Roger of Salerno (1180) and William of Salicet (1210–77) wrote on the causality and natural history of gonorrhoea; John of Gaddesden (1280–1361) recognised urethritis, epididymitis and vaginitis [1]. The contagiousness of gonorrhoea was generally recognised, as shown by rules for preventing infected prostitutes from plying their trade in Southwark, London in 1162 [1], Avignon in 1347 [1, 5], and Hamburg, Strasbourg, Cologne and Ulm in the eleventh to fifteenth centuries [6].

Other STIs, including scabies and pediculosis pubis, have also been recognised since ancient times [4], although the concept of different causes for skin diseases has only developed in the last 300 years [7]. Genital human papilloma virus infection (HPV; i.e., genital warts) have been recognised for 2000 years [4, 8]. Anal warts resulting from anal intercourse were exemplified by Juvenal in his satires. Much later, they were described by the English surgeon Richard Wiseman in 1676 [9] and the French physician Jean Astruc in 1736 [10].

1.4 The Development of the Concept of Venereal Diseases Prior to the Nineteenth Century

The Renaissance showed that any change in medical knowledge is as much influenced by outside social, geopolitical and economic forces as it is from within medicine [11]. So it was with venereal diseases (VD). Syphilis is among the most interesting of diseases from a historical standpoint, not only because of arguments about its origin, but because of its influence on morality and measures towards public health [4, 8, 10, 12]. Its origin has been controversial. The pre-Columbian view is that syphilis was endemic in Europe before the invasion of Italy by Charles VIII in 1494, and with the disbandment of mercenaries it spread sexually all over Europe [4, 8, 13].

The Columbian (Americanist) view is that syphilis was acquired by the sailors of Christopher Columbus and spread after 1493 through Europe [10]. Both these views have their advocates, who usually claim skeletal remains from America or Europe (now aided by genotyping) to further their arguments. Another idea is that of Hudson (1946) [14], who emphasized the evolutionary relationships of yaws, pinta, endemic syphilis, and sporadic syphilis. He regarded them as variants of the same disease that originated in sub-Saharan Africa.

There is a great amount of literature not only on syphilis's effect in Italy [11, 13, 15], but also on its progress, discoveries and consequences throughout Europe [4, 8, 16] after 1494. By the end of the fifteenth century, most of its immediate consequences, including congenital syphilis [17, 18], had been described.

However, some controversies surrounded syphilis for many years. The Diet of Worms (7th August 1495) was the first printed document to mention this new severe disease: "There have been severe diseases and plagues of the people, to wit 'bösen Blattern' which have never occurred before nor been heard of within the memory of man" [15]. In the Latin translation, this new type of disease [12], "bösen Blattern," is called *Malum Francicum* – a French name that is still used today in many countries of Asia (farengi) [19]. The French called it the Neapolitan disease [12]. By some, syphilis was considered to be a pox due to the wrath of God [4, 8, 12] and a punishment for immorality. Even astrological explanations were given for it [12, 13].

However, the venereal origins of syphilis were quickly realised and bluntly stated by Andrew Boord in 1547: "It may come when one pocky person doth synne in lechery the one with another. All the kyndes of the pockes be infectiouse" [4]. The term *venereal disease* (lues venerea) was used by Jacques de Bethencourt of Rouen in 1527 [4, 8, 10, 12]. In 1530, Girolamo Fracastoro of Verona [20] wrote "Syphilus sive morbus gallicus"; a swineherd or shepherd was thought smitten with the disease when he refused to make sacrifices to Apollo [4]. Guaiacum, a wood recently imported from South America, was popularised as a treatment because of its sudorific properties by Fracastoro [12]. Also used was mercury in ointment, pill and fumigation forms. It had been used in scabies grossa in Italy for hundreds of years after being inherited from Arabic medicine, so it continued to be used for the new disease syphilis [13].

Cautery of the primary sore was also utilised as treatment, as shown on contemporary watercolours [11]. It has erroneously been taught that Gabrielle Fallopius (1523–1562) [11, 16] recommended the condom as a preventive measure. In fact, Fallopius recommended that his students at Padua prevent contagion by making a wash using active ingredients of guaicum, mercury, copper and gentian root; this wash was to be applied in a bag at the bottom of one's culottes after coitus [16]. He described the typical indurated primary sore and also noticed syphilis was more frequent in men with long prepuces [11, 12, 16], as well as being rare in Jews (who were of course circumcised). It was actually Daniel Turner (1717) who advocated the use of the "condum" (Latin for "condere to protect") to prevent from VD [21].

Jean Fernel (1506–1588) rejected the Galenic concept that genital lesions were secondary to humoral disorders arising in the liver. He taught that morbus Gallicus was caused by a virus usually acquired through intercourse. He stated that midwives may contract it through the hand and the wet nurse through her nipple. He also noted that oral and anal moist lesions were contagious and that the virus could not pass through intact skin. He taught about a long incubation period, prolonged latency, and exacerbations. He also referred to lues venerea- venereal plague (De lues venereae curatione perfectissimo, 1556) [4, 8, 10, 16]. The confusion between the causation of syphilis and gonorrhoea seems to have been compounded by Paracelsus (1493–1531), who called morbus gallicus "French gonorrhoea." He divided it into states–simple and virulent, which developed constitutional symptoms [12, 17]. This was the start of two viewpoints on the diseases: monists [10, 22] believed that gonorrhoea and syphilis were part of the same disease, whereas dualists [23, 24] thought they were separate.

Lancisi (1654–1720) posthumously correlated dilatation of the heart with syphilis "aneurysma gallicum" in 1728 [25]. In the same year, Boerhaave (1668–1738) in Leiden implicated syphilis as a cause of cardiovascular disease as well as considering it to be part of generalised neurological decay [4]. In 1736, Jean Astruc (1684–1776), in "De morbis veneriis libri sex," summarized all there was to know about VD to that time. He believed in its American origin, but shared the belief of the monists [10]. He provided clinical descriptions of several conditions, including genital herpes, condylomata acuminata, phimosis, and balanoposthitis.

Van Swieten (1700–1772), a pupil of Boerhaave called to Vienna after 1749, popularised more liberal treatment of syphilitics, as well as the introduction of graduated dosage with mercury to prevent side effects such as oversalivation (ptyalism), the shakes (tremors), and renal disease [4].

John Hunter (1728–1793) wrote "A Treatise on the Venereal Disease" in 1786, but it was not one of his best works. His error was to adhere to the monist doctrine. In an experiment in 1767, he tried to prove that gonorrhoea and syphilis had a single cause. Gonococcal pus was inoculated onto the prepuce and glans penis. Unfortunately, the inoculum was chosen from a patient suffering from syphilis as well as gonorrhoea. As the inoculum was not put in the urethra, no gonorrhoea, only syphilis, resulted. This caused the faulty deduction that the result depended on the nature of the surface of the inoculum–gonorrhoea for moist surfaces and ulceration for a cutaneous surface [4, 8, 22]. In Edinburgh, Benjamin Bell (1749–1806)–following the teachings of Morgagni (1682–1771) in 1793 (Treatise on gonorrhoea virulenta and lues venerea)–refuted Hunter's ideas after inoculation experiments on students [23]. The French venereologist Philippe Ricord (1800–1889) in 1838 [24] used 2,500 inoculation experiments performed between 1831–1837 to show conclusively that gonorrhoea and syphilis were different diseases (Traité Pratique des Maladies Vénériennes). Although ethical standards in those days were different, when others in France tried similar experimentation on patients, cases were taken before the courts.

After the French Revolution, postreform medical teaching had an immense impact globally [26]. Ricord [8, 12] exemplified this teaching. He was born in Baltimore and obtained a teaching position in Paris from 1831. Ricord was an excellent and witty teacher; he was considerate women with VD and was a proponent of the vaginal speculum. He was also the classifier of syphilis in primary, secondary and tertiary stages, although he still did not recognise the separate entity of chancroid–which was left to his pupil Leon Bassereau (1810–1887) [27]–or that secondary syphilis was contagious. His pupils, such as Paul Diday and Alfred Fournier (1832–1914), were worthy successors to his school and its teaching traditions.

There were some other smaller advances in knowledge in those times. In 1814, Thomas Bateman's fourth edition of "A Practical Synopsis of Cutaneous Disease" described Herpes praeputalis [7], with an excellent clinical description but stating that a practical mistake with serious consequences for the patient would be made if syphilis was wrongly diagnosed for then mercury would be prescribed. In 1818, Benjamin Brodie (1783–1862) wrote a textbook on diseases of the joints [28] and described the syndrome. This was later described by Launois in 1899 [8] and by Hans Reiter (1881–1969) in 1916 [29], with the main triad being urethritis, arthritis and conjunctivitis. In 1835, Wallace (1791–1837) in Dublin introduced potassium iodide into the treatment of syphilis following contemporary interest in the chemistry of the halogens [30].

1.5 The Development of a Scientific Basis for Sexually Transmitted Disease from the Nineteenth Century

The Industrial Revolution brought with it movement of populations into cities, which also contributed to increasing STD rates. The Industrial Revolution also was the lever for advances in engineering and the natural sciences, which would have effects throughout medicine. Nations that considered themselves to be civilised also enabled public health medicine, as well as provided medical education to middle-class citizens to increase manpower for providing these services. The fields of epidemiology and microscopy; the reorganisation of medical education in great centres such as Paris [26], Vienna [31], London [4] and New York; and later advances in microbiology, serology, immunology [31] and organic chemistry led to recognition of causal agents for syphilis, chancroid, gonorrhoea, lymphogranuloma venereum, and advances in the microbiology of STDs–and ultimately cures for them.

1.5.1 Epidemiology

The concept of the nation-state and the regulation by the state of various aspects of a citizen's life meant that the relationship of VD took on a new importance in this era [4]. Parent-Duchatelet (1790–1836) [32] was a pioneer in epidemiology. Posthumously in 1837, he tabulated where prostitutes lived in Paris, where they came from, and their former trades. He also noted that syphilis, gonorrhoea, scabies and uterine cancers were more frequent in them than in other women. This was the start of many epidemiological and sociological studies on the relationships of society, women, prostitution, and VD throughout the nineteenth centuries and to present times. Such studies were highlighted by Flexner (1914) [33] and the British Royal Commission on Venereal Diseases (1916) [34]. Colonial policies on sex and its influence on STDs and society thus needed to be formulated [19].

Chancroid. It was left to Bassereau (1852) [27] to publish his clinically based observations that the sore of chancroid was a separate entity from syphilis and that it did not lead to spread in the body as did syphilis with constitutional symptoms. Augusto Ducrey (1860–1940) [35], working in the department of Paul Gerson Unna (1850–1924) in Hamburg, discovered the organism of chancroid in the pus from its lesions in 1889.

Congenital syphilis. By 1854, Diday [12, 36] had described all that was known on congenital syphilis to that time. From 1857–1863, Jonathan Hutchinson (1828–1913) in London described his triad of interstitial keratitis and labyrinthine disease, which were all later codified by the successor to Ricord in Paris, Alfred Fournier, in "La syphilis heriditaire tardive" in 1886 [4, 12, 36].

Neurosyphilis. Fournier (1875) [4, 37] proposed that syphilis was the cause of general paralysis (GPI), tabes dorsalis, tabo-paresis, and primary optic atrophy. But it was not until 1913 that Hideyo Noguchi (1876–1928)

and Moore [38], who were working at the Rockefeller Institute in New York, were able to demonstrate spirochaetes in the brains of a series of paretics.

Gonorrhoea. Microbiology made amazing progress in the latter part of the nineteenth century, led by Louis Pasteur (1822–1895) and Robert Koch (1843–1910). Using Koch's techniques, Albert Neisser [39] (1855–1916), at the age of 23 in 1879 with a Zeiss Microscope and an Abbe condenser, was able to demonstrate the micrococci of gonorrhoea from cases of purulent urethritis and ophthalmia neonatorum, but reserved his judgement until culture and inoculation experiments had been performed. In 1882, he stated: "Gonococci are absolutely constant in every case of gonorrhoea… and they are not found in any other disease…furthermore, gonococci are the only organisms found in gonorrhoeal pus" [8]. Carl Crédé (1819–92), in 1883 in Leipzig, published his procedure where instillation of 2% silver nitrate prevented ophthalmia neonatorum [40]. Succeeding workers elaborated on diagnostics of gonorrhoea, as summated by Vienna's Ernest Finger (1856–1939) in "Die Blennorrhoe der Sexualorgane und ihre Complicationen" in 1888 [5].

1.5.2 Syphilis: Causation, Serology and the Magic Bullet

Between 1875–1877, Edwin Klebs (1834–1914) in Prague had observed spirochaetes in human syphilitic material and may have transmitted the disease to monkeys [4]. Experimental syphilis was reinvigorated by Elie Metchnikoff (1845–1916) and Pierre E. Roux (1853–1933), who showed that syphilis could be transmitted to chimpanzees [41]. On March 3, 1905, at the Charite in Berlin, dermatologist Erich Hoffman (1868–1959) and protozoologist Fritz Schaudinn (1871–1906) demonstrated spirochaetes (later called *Treponema pallidum*) from preparations of patients with early syphilis with fresh and Giemsa-stained preparations [42]. In the same year, Aldo Castellani (1877–1971) [43], working in Ceylon, described the spirochaete (now *T. pertenue*) in yaws. By 1906, Karl Landsteiner (1868–1943) and Viktor Mucha (1877–1933) were able to demonstrate *T. pallidum* by dark field methods [44].

The earlier work of Jules Bordet (1870–1961) and Octave Gengou (1875–1961) [45] defined the complement fixation test (CFT) in 1901, in which an infection could be diagnosed by finding its antibody in the serum. August von Wassermann (1866–1925) was able to show in 1906 the value of the CFT in the diagnosis of syphilis [46], which was later evaluated by Landsteiner and Rudolf Muller in 1907 [47]. The introduction of the first test for a specific antibody to exclude false-positive results did not come until 1949 with the introduction of the treponemal immobilization test by Robert Nelson and Manfred Mayer [48].

Until the advent of the arsenicals, mercury was still the main treatment for syphilis [12]. In 1895, Adolph Jarisch (1850–1902) [8] from Innsbruck described a phenomenon that was well recognised in patients with secondary syphilis with mercury inunctions, in which the first few hours there was an exacerbation of symptoms. This was later recorded in more detail by Karl Herxheimer (1861–1944) [49].

Paul Ehrlich (1854–1915) had for many years been working on synthetic agents to control trypanosomal infections. In 1909, it was found that 606-arsphenamine (Salvarsan) was effective when given intravenously for syphilis in animals. By 1910, it was found to be effective in the cure of syphilis in humans and was thus the magic bullet – "Therapia sterilis magna" [50].

Malarial therapy was introduced in 1917 for the treatment of GPI by Julius Wagner von Jauregg (1857–1940) an Austrian neuropsychiatrist [51] who had noticed patients improved after being given a controllable source for a fever. It was used later with penicillin until the 1950s. Although not as active as arsenicals, bismuth was found to effective for syphilis by R. Sazerac and Constantin Levaditi (1874–1953) in 1921 [52], and it was used until the 1960s.

1.5.3 Chlamydial Trachomatis Oculogenital Infection

In the 1900s, Neisser had worked on experimental syphilis in orangutans in Java [8]. While there, some members of his team – Ludwig Halberstaedter (1876–1949) and Stanislaus von Prowazek (1875–1915) [53] – also researched conjunctival scrapings from patients with trachoma by inoculating them into orangutan and reporting inclusion bodies (1907). This work was continued by Lindner [54], who reported inclusions in urethral specimens from 3 of 10 men with nongonococcal urethritis.

With the advent of penicillin, it was noticed that some men with urethral discharge did not respond to penicillin. This resulted in the 1950 work of Arthur Herbert Harkness (1889–1970), who recognised nongonococcal urethritis as a separate entity [55]. From 1959, when it was first isolated from genital material *Chlamydia trachomatis* and later recovered from the eyes of a baby with inclusion conjunctivitis and the mother's cervix by Jones and his team at the Institute of Ophthalmology in London [56], the organism has been increasingly recognised and is the most frequent bacterial STD in industrialised countries.

Donovanosis. This tropical STD was described by Kenneth Macleod (1844–1922) of The Indian Medical Service in 1881[57]. Its causality was identified in 1905 by Charles Donovan (1863–1951) [58] from Madras, who identified intracellular bodies from stained biopsies of the granulating lesions. In 1945, members of Goodpasture's team [59] at Vanderbilt University in Tennessee were able to propagate them in eggs. Thus the organism has been named *Calymmatobacterium granulomatis*.

1.5.4 Impact on Society Before and After the Discovery of AIDS

Few diseases have had such an impact on society as STIs. After all, these infections have an enormous impact on those who contract them – both physically and psychologically. If not treated, STIs may cause serious ill health and even death – especially viral STIs, which can develop from HIV to AIDS, from human genital papilloma virus to anogenital cancers, from herpes genitalis to morbidity and recurrences, and from hepatitis B or C to morbidity and mortality through long-term disease of the liver. It has been a short time in human history from from the advent of antibiotics, which to the general public seemingly allowed for instant cure of bacterial STDs, to the discovery of HIV – not withstanding infertility caused by pelvic inflammatory disease or epididymo-orchitis as a result of gonococcal or chlamydial infections. This chapter has already alluded to STIs and their impact on conventional morality. However, if a study is made of great literature in the last 400 years, the argument for chastity for the individual does not seem to make any impact for very long: from Voltaire in *Dictionnaire Philosophique*,"Venereal diseases are like the fine arts – it is pointless to ask who invented them,". to Alexander Pope in *Satires of Dr Donne*, "Time that at last matures a clap to pox-Whose gentle progress makes a calf an ox," and to Henrik Ibsen in *Ghosts*, who had little effect in modern times, "I never asked you for life. And what sort of life have you given me?" Rather the reaction is usually more like James Boswell in the *London Journal*, "When I got home, though, there came Sorrow. Too plain was Signor Gonorrhoea."

The financial strain put on a nation may be more impactful, considering the cost of STI morbidity to a large section of its young workforce. The final report of the British Royal Commission on Venereal Disease in 1916 demonstrated the high mortality from syphilis, with mortality statistics showing 10% of London working-class males infected; 25% of infantile blindness was found to be due to ophthalmia neonatorum [34]. More recently, Thailand realized in the 1990s that if HIV disease was allowed to spread, apart from mortality, too many of the young productive workforce would be ill, thus causing a drain on the nation's finances apart from it damaging the tourist trade (World Bank, 1997) [60].

AIDS was first recognised in 1981 [61] in men who had sex with men (MSM) in New York and California; thus, it unfortunately was called "the gay plague." However, very soon it was realised that it was also transmitted through infected blood and by birth processes as well as sexually. The greatest numbers of cases have been reported in heterosexuals in sub-Saharan Africa and South Asia, the former being one of the most under-resourced parts of the world [60]. Paradoxically, AIDS has challenged societal attitudes to the morality of sexual behaviour, especially same-sex relationships, the rights of women, the needs of Africa, and international affairs between industrialised donor countries and much poorer countries. It has also acted as catalyst to increase medical and industrial research in basic sciences, pharmaceuticals, health and community education, and very many ethical and social problems that were involved with an epidemic that now is globally pandemic [60].

These pragmatic realities are a profound argument for expert epidemiology of STIs, continued public education to prevent them, the continued use of the condom in all casual sexual encounters, and further research into development of preventive vaccines for STIs – in addition to the presently available hepatitis A, hepatitis B, and HPV vaccines.

1.5.5 Scientific Achievements since the Advent of Chemotherapy

Ehrlich [50] had been a pioneer in treating infectious diseases with synthetic compounds. However, with the exception of treponemata, it was thought that bacteria were not susceptible to chemotherapy. Research on penicillin and sulphonamides was to change this. In 1935, Gerhard Domagk (1895–1964) [62], who was working with IG Farbenindustrie, reported that Prontosil (one of the azo dyes he had tested) was curative against haemolytic streptococcal infections in animals. It was soon shown that the activity of Prontosil was due to the liberation of sulphanilamide, which can be easily manufactured. In 1937, studies on its use in gonorrhoea appeared in Germany, Great Britain, and the United States [63]. By the start of World War II, it was the main treatment of gonorrhoea in all opposing military forces. However, by 1944 resistant strains of *N. gonorrhoea* had occurred in up to 75% of cases [8]. Sulphonamides combined with streptomycin were used in the treatment of nongonococcal urethritis in some cases until the 1970s, or in combination with trimethoprim in the treatment of chancroid, donovanosis, and lymphogranuloma venereum in some instances.

The story of the discovery and development of penicillin is one of the great romances of medicine, with the 1945 Nobel Prize awarded to Alexander Fleming (1881–1955), Howard Florey (1898–1968) and Ernst Chain (1906–1979). The use of penicillin in the treatment of syphilis was first reported by John F. Mahoney (1889–1957) and his team in 1943: "Four patients with primary lesions were treated with 25,000 units of the drug intramuscularly at 4-hour intervals night and day for 8 days. The chancres all became darkfield negative within 16 hours" [64]. Penicillin was also found to be effective in gonorrhoea, although by 1958 it was evident that resistance was developing. In the following years, this became a major problem [8]. Although the resistance of gonorrhoea to most antimicrobials sooner or later was reported, the resistance of *T. pallidum* to penicillin has not yet occurred.

The course of untreated syphilis had been studied in detail in Oslo, Norway by Caesar Boeck (1845–1913), followed up by his successor Bruusgaard, and reported in 1955 by Gjestland [65]. In all, 30% of patients developed complications of one sort or another [8].

In 1932, the US Public Health Service had studied the course of untreated syphilis on black people in Tuskegee, Alabama. This study continued for 30 years. Patients with early syphilis were treated with arsenicals, but the remainder of patients with a history suggestive of syphilis and positive serological tests were left untreated. This study was conducted long after penicillin had been shown to be effective and informed consent was never obtained from the patients [66]. Medical ethics, like most human development, does not remain static. Therefore, any long-term medical research should be monitored for changing attitudes to contemporary ethics.

Tetracyclines have been the mainstay therapy of nongonococcal urethritis (NGU) caused by *C. trachomatis* or *U. urealyticum* since their development and introduction after 1948 [67]. An underrecognised development, which ended years of suffering of women with chronic vaginal discharge caused by trichomoniasis and also paved the way to therapy of anaerobes, was the effectivity of metronidazole [68].

It is always difficult to decide when to finish a history. In this case, this chapter ends before the advent of modern treatment for candidiasis, herpes genitalis, genital HPV infection, and HIV/AIDS, as well as the introduction of effective vaccines for some STIs. However, these topics will be discussed elsewhere in this book.

Take-Home Pearls

- Knowledge about the development of any subject is important, so that one can learn not only about the subject's general impact but also its achievements and failures.
- These achievements and failures may enable the reader to formulate ideas for research that may have impact on scientific progress in sexually transmitted infections (STIs).
- Knowledge of the history of STIs is necessary for historical purposes and future research. Sometimes it is controversial; sometimes contemporary medical ethics are challenged. But without these challenges, knowledge of the past will not help mankind in the future.

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Epidemiology of Sexually Transmitted Infections

2

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Core Messages

- Sexually transmitted infections (STIs) are commonplace worldwide and may be caused by bacteria, fungi, protozoa, parasites, or viruses.
- Epidemiology involves the study of incidence and prevalence of disease in large populations as well as detection of the source and cause of epidemics of infectious disease.
- Acute diseases tend to have high incidence and low prevalence; chronic diseases may have high prevalence even if incidence is low.
- Developing nations have the largest proportion of STIs, while most industrialized countries have low or falling rates of infection.
- Prevention is the best tool to decrease morbidity and mortality of STIs.

2.1 Introduction

Sexually transmitted infections (STIs) are extraordinarily commonplace, with an estimated 340 million new cases of "curable" infections occurring each year (see Table 2.1) worldwide in men and women aged 15–49 years [1]. These infections include those caused by bacterial, mycological, and protozoal agents that have been treated by appropriate antibiotics and chemotherapeutic agents for more than 40 years (namely syphilis, gonorrhea, chlamydia, and trichomoniasis). In spite of adequate available therapy, such STIs have continued to be a public health problem in both industrialized and developing countries. In addition to the "curable" STIs, there are also millions of viral STIs that occur annually (including human immunodeficiency virus [HIV], herpesviruses, human papilloma viruses, and hepatitis B viruses) that cannot be eradicated through currently available medication.

The largest proportion of STIs occur in developing nations, led by South and Southeast Asia, followed by sub-Saharan Africa, Latin America, and the Caribbean [2]. An equilibrium has been reached in most industrialized countries with low (and often still falling) rates of infection. In contrast, the equilibrium reached in many developing countries has been with highly endemic levels of disease [3].

STIs are not only a cause of acute morbidity in adults, but may result in complications including male and female infertility, ectopic pregnancy, cervical cancer, premature mortality, congenital syphilis and fetal wastage, low birth weight, and prematurity and ophthalmia neonatorum [3].

Care for the sequelae of STIs accounts for a large proportion of tertiary healthcare costs in terms of screening and treatment of cervical cancer, management of liver disease, investigation for infertility

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Table 2.1 Worldwide incidence of common "curable" sexually transmitted infections

Infection	Worldwide Incidence/ Prevalence
Trichomonas	170–190 million incident cases
Chlamydia	Over 90 million incident cases
Gonorrhea	Over 62 million incident cases
Syphilis	12 million incident cases
Chanchroid	6–7 million incident cases

causes, care for perinatal morbidity, childhood blindness, pulmonary disease in children, and chronic pelvic pain in women [1]. The costs increase further when the cofactor effect of other STIs on HIV transmission is taken into consideration [1, 2]. The economic burden of STIs is huge, especially for developing countries where they account for 17% of economic losses caused by ill health [4].

Many STIs are asymptomatic and therefore can be difficult to recognize and control. Thus, the worldwide incidence of new cases of STIs may be even higher than the estimated 340 million mentioned above. For example, it is estimated that actual reported cases of STIs represent only 50–80% of reportable STIs in the United States, reflecting limited screening and low disease reporting [5].

Several risk factors exist that make certain populations more prone to STIs than others (see Table 2.2). While these risk factors are not shared by all STIs, there are many commonalities. Young age, for example, is a risk factor common to many STIs. Adolescents and young adults (15–24 years old) make up only 25% of the sexually active population, but represent almost 50% of all new acquired STIs [5]. This may be confounded by the fact that this age group is more prone to engage in high-risk sexual activity (another risk factor) than the older population. Other groups known to participate in high-risk sexual activity (such as sex with multiple partners and unprotected sex) include prostitutes, intravenous (IV) drug users, and prison inmates. Not surprisingly, these groups are also known to be at higher risk for STIs than the general population. Additional risk factors for several STIs include lack of male circumcision, low socioeconomic status, and poor hygiene.

Epidemiology is the branch of medicine dealing with the incidence and prevalence of disease in large

Table 2.2 Major risk factors of sexually transmitted infections

Infection	Young Age	High-Risk Sexual Behavior	Low Socioeconomic Status	Poor Hygiene	Other Specific Risk Factors
Trichomonas		X	X	X	Increased age
Chlamydia	X	X			Female gender
Gonorrhea	X	X	X		
Syphilis	X	X			MSM population
Chancroid	X	X		X	Lack of male circumcision
Donovanosis	X	X	X		
Herpes simplex		X	X		
Human papillomavirus		X	X		Bimodal age distribution, lack of male circumcision
HIV/AIDS		X	X		MSM population (in the United States), perinatal infection, IV drug use
Hepatitis B		X			Lack of childhood vaccination, vertical transmission, IV drug use
Molluscum contagiosum	X	X			
Scabies/pubic lice		X	X	X	

populations and with the detection of the source and cause of epidemics of infectious disease. The terms incidence and prevalence are often confused even in scientific literature. Technically, incidence refers to the number of new cases of a disease in a population over a period of time (usually a year). Prevalence, on the other hand, refers to the total number of cases of a disease in a given population at a specific time. Acute diseases or those with high mortality rates tend to have a high incidence and low prevalence, since those who acquire the disease either get better or expire; either way they are unlikely to be infected with the disease at any particular point in time. Chronic diseases may have high prevalence even if incidence is low, as those with the disease never get rid of it and are added to the number of incident cases each year. The remainder of this chapter will focus specifically on several of the most common STIs, for which the epidemiology is best described in previous literature.

2.2 Epidemiological Trends of Common Sexually Transmitted Infections

2.2.1 *Trichomonas Vaginalis*

2.2.1.1 Burden of Disease

Trichomonas vaginalis, a pathogenic protozoan, is the most common nonviral cause of STI worldwide. It is frequently asymptomatic in men, or may cause a short-lived course of nongonococcal urethritis, but it is significant because the parasite is easily transmitted to women during the short period of infection. Women infected with *T. vaginalis* may also be asymptomatic (up to 30% of cases), but the majority experience vaginitis. Additionally, *T. vaginalis* infection may be responsible for significant reproductive health sequelae including pelvic inflammatory disease and adverse outcomes of pregnancy (such as preterm labor and low birth weight) [6, 7]. Perhaps most importantly, *T. vaginalis* infection has been implicated as one of the most important cofactors in amplifying HIV transmission, particularly in the African American population of the United States [8].

2.2.1.2 Incidence and Prevalence

The World Health Organization (WHO) estimates an incidence of 170–190 million new cases of *T. vaginalis* infection worldwide each year. However, these estimates may be low, since they are based on wet mounts that are not as sensitive as new polymerase chain reaction (PCR) technology [9]. Extensive data are available regarding the prevalence of *T. vaginalis* infection but can be difficult to interpret due to variation in diagnostic technique, study settings, populations studied, and whether symptoms were present or absent in participants. Overall, prevalence rates have ranged from 5% to 10% in women in the general population to as high as 50–60% in high-risk populations such as prison inmates and commercial sex workers [10]. Prevalence in males similarly has a high degree of variation depending on the population studied, ranging between 0% in low-risk asymptomatic men to 58% among adolescent males at high risk for sexually transmitted diseases (STDs).

An estimated 7.4 million new cases of *T. vaginalis* infection are reported in the United States each year. Prevalence ranges between 2.2% for young women (≤20 years) compared with 6.1% in women ≥25 years. Male prevalence was lower for both age categories, with a reported 0.8% among men≤ 20 and 2.8% in males ≥25 years [6]. In Northern Australia, a study of indigenous women found a similar increase in prevalence with age, although the overall prevalence (25%) was higher than that seen in US studies [6, 11].

Amongst pregnant women in Latin America and the Caribbean, trichomoniasis prevalence rates ranged from 2.1% in Brazil to 27.5% in Chile [12, 13]. In Africa, pregnant females had prevalence rates ranging from 9.9% in the Central African Republic to as high as 41.4% in South Africa [14, 15].

2.2.1.3 Risk Factors

Unlike chlamydia and gonorrhea, young age is not a risk factor for trichomoniasis. Prevalence of *T. vaginalis* infection appears to increase with age for both males and females, possibly due to its frequent asymptomatic nature of the infection and therefore persistence of untreated infections [6].

Studies in developed nations have found high prevalence of trichomoniasis in prison inmates, IV drug

users, and sex workers [6]. A common trend in these three risk groups is that they are more likely to engage in high-risk sexual behavior than the general population. Unprotected sex with multiple partners increases the chance of *T. vaginalis* infection, as with any STD. In a study by Tyndall et al. of IV drug users with high HIV prevalence, 57% of female participants reported more than 100 lifetime partners. Condoms were generally not used with regular partners, used about half of the time with casual partners, and used about 80% of the time with paying partners [16].

There is no doubt that protected sex with a condom helps prevent *T. vaginalis* infection as well as other STIs (see Chap. 55). Sex workers in countries such as Australia, where there is a decriminalized regulated system, have a much lower incidence of trichomoniasis than do street sex workers [17, 18]. This is likely because street sex workers are less likely to use protection than those who work in a regulated brothel.

Other risk factors that have been described include subjects with poor personal hygiene and low socioeconomic status [10].

2.2.2 *Chlamydia*

2.2.2.1 Burden of Disease

Chlamydia trachomatis is responsible for more cases of STD than any other bacterial pathogen, and is therefore an enormous worldwide public health problem. Since asymptomatic infection is common, it can easily be passed unknowingly between sexual partners. In addition to sexual transmission, the organism can be transmitted by droplets, hands, contaminated clothing, flies, and by passage through an infected birth canal.

In females, chlamydia primarily presents as a cervical infection following exposure to an infected partner. Initial infection may either be asymptomatic or cause a self-limited acute inflammatory response. However, repeated or untreated infection may cause chronic inflammation, irreversible tissue damage, and scarring (i.e., pelvic inflammatory disease) that may lead to infertility or increased risk of ectopic pregnancy. There is a four- to sixfold increased risk of pelvic inflammatory disease and a two- to fourfold increased risk of ectopic pregnancy associated with recurrent infections [19].

In men, chlamydia is the commonest cause of nongonococcal urethritis. Almost 50% of men with chlamydia experience urethritis associated with pain and penile discharge, but those with asymptomatic infection may serve as carriers of the disease. Men rarely suffer long-term health problems as a result of chlamydia infection.

Contamination of the hands with genital discharge may lead to a conjunctival infection following contact with the eyes. Babies born to mothers with infection of their genital tract frequently present with chlamydial eye infection within a week of birth (chlamydia "ophthalmia neonatorum"), and may subsequently develop pneumonia.

Worldwide, the most important disease caused by *C. trachomatis* is trachoma that affects the inner upper eyelid and cornea and is one of the commonest infectious causes of blindness (an estimated seven to nine million people are blind as a result of trachoma). The disease is particularly prevalent and severe in rural populations living in poor and arid areas of the world where people have limited access to water and personal hygiene is difficult. In the United States, Native Americans are most commonly infected.

Another disease caused by *C. trachomatis* is lymphogranuloma venereum (LGV), a condition characterized by painful lymphadenopathy. LGV is caused by the L1, L2, and L3 serovars of *C. trachomatis* and begins as a painless ulcer that is usually self-limited. The secondary stage of LGV is the painful lymphadenopathy, most commonly of the inguinal or femoral lymph nodes; these nodes may coalesce to form buboes that can rupture in as many as one third of patients. The tertiary stage of LGV is caused by fibrosis that can result in lymphatic obstruction, edema, abscesses, and strictures.

2.2.2.2 Incidence and Prevalence

The WHO estimates that over 90 million new cases of chlamydia are diagnosed each year [20]. Various studies have estimated that there are four to five million new cases of chlamydial infection each year in the United States alone. Prevalence varies greatly depending on the type of population studied, as several factors (to be discussed in detail below) greatly increase the risk for chlamydia. For example, in the US adolescent female population, prevalence varies from 5% among