GONORRHOEA: PAST AND PRESENT

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Man is the only natural host for Neisseria gonorrhoeae and the pain, guilt, recriminations and long term complications of gonococcal infection are well recognised. Although often stated that gonorrhoea has infected mankind since ancient times there is little objective evidence to support this. One of the earliest quoted references occurs in the book of Leviticus, chapter 15, verse 2-"When any man hath a running issue out of his flesh, because of his issue he is unclean'. Whilst it is possible that this refers to gonococcal urethritis (or non-specific urethritis) the affected part is not specifically named in the scripture.

Over several millennia the clinical features of gonorrhoea were slowly elucidated and theories of aetiology developed, contrasting with the rapid advances possible in more modern times. In a little over a decade another sexually transmitted disease, AIDS, has had its cause identified, clinical features characterised, detailed immunology studied and effective treatments developed although no cure found as yet. Indeed it is interesting to note that more is known about the immunology and molecular epidemiology of HIV than is about N. gonorrhoeae.

RECOGNITION OF THE CLINICAL FEATURES OF GONORRHOEA

Urethral discharge appears to have been well recognised by both the Romans and Greeks. The Roman scholar Celsus (25BC-AD50) called it profusio semens and described it as 'a fault in the genital region called the shedding of semen. It occurs without sexual desire or erotic dreams and in such a way that in time the patient is consumed by wasting'. It was Galen (AD130-200), a Greek physician, who first used the word gonorrhoea (from the Greek gonor: semen and rheo: to flow) and wrote: 'Gonorrhoea is an unwanted excretion of semen which you may also call involuntary; or be be more precise you might say a persistent excretion of semen without erection of the penis'. Whether these discharges were truly gonorrhoea or less clear since neither author mentioned the dysuria and inflammation often associated with infection nor alluded to the concept of infectiousness or the development of complications such as urethral stricture.

In the 9th century Arabic culture had become the dominant force in medicine and both Rhazes (860-932) and Ibn Sina (980-1037) wrote of urethral discharges which they treated with urethral irrigation; this formed the mainstay of therapy for the subsequent nine hundred years. In the 16th century the term claps was first used and, although the origins of the word are obscure, it may relate to the name of the flats frequented by prostitutes in Paris called clappiers.

In the 18th century two of the great figures in the history of venereology made their contribution—John Hunter and Benjamin Bell. Hunter (1728-1793) was born near Glasgow and trained in medicine in London where he was elected a surgeon at St George's Hospital after a brief period in the army. He worked there until his death from ischaemic heart disease, said to have been precipitated by an acrimonious hospital board meeting. Bell (1749-1805) came from a more educated background than Hunter and, after training at Edinburgh, became a Fellow of the Royal College of Surgeons of Edinburgh in 1771. The two men did meet and appeared to get on well. Their detailed clinical descriptions of gonorrhoea and its complications were impressive although the conclusions they reached were not always correct and indeed they often disagreed with each other. Infection in women received scant attention from physicians around this time with the exception of blaming those of 'loose moral virtues' for the spread of infection. Gonococcal infection in women is generally less acute than in men and this, in addition to the difficulties in performing an adequate examination, may have made detailed study difficult. The problems associated with performing a pelvic examination were described by John Burns, a Scottish obstetrician, who wrote 'it is usual for the room to be darkened and the bed curtains drawn during an examination ... it should never, if possible, be proposed or made whilst an unmarried lady is in the room'. In addition a vaginal discharge was not considered pathological and it was not until the late 19th century that Ricord reintroduced the speculum to facilitate vaginal examination.

The clinical syndrome of pelvic inflammatory disease (PID) was recognised in women but physicians generally did not link it to gonorrhoea although one notable exception was Bell, who suggested that infection could spread to the upper genital tract. It was Noeggerath (1827-1894) who subsequently proposed that asymptomatic gonococcal infection in women could progress to PID with associated pelvic pain and infertility, but when he presented his findings to his contemporaries they strongly disagreed and it was not until the gonococcus was isolated that he was proven to be correct.

IDENTIFICATION OF THE CAUSE

Although detailed clinical descriptions appeared in the 18th century the cause of gonorrhoea remained elusive. One of the earliest views was based on the Hippocratic theory that disease arose from humoral imbalance and suggested that gonococcal discharge was the result of semen corrupted by bad humours, possibly originating in the prostate.

In 1689 Louis de Monnier suggested that urethritis resulted from multiple ulcers within the urethra, a not unreasonable if completely unfounded conclusion, given the high incidence at that time of external genital ulcers due to syphilis and chancre. Others including Daniel Turner accepted this explanation and it was not until Hunter published his Treatise on Venereal Disease that the 'ulceration' theory lost prominence.

At the start of the 18th century many scholars considered that gonorrhoea and syphilis were but different manifestations of the same disease caused by a 'venereal poison' (the unisect theory) but gradually others, including Bell, proposed that they were separate disease entities (the dualist theory). Hunter did much to confuse the issue when he performed his famous experiment, reputedly on himself, during which he inoculated his urethra with gonococcal pus from a patient and subsequently developed syphilis, presumably as a result of his patient having a dual infection. Hunter's experiment and his incorrect conclusions would not withstand widespread peer review today, but such was his eminence at that time that many accepted the erroneous unisect theory, and it was not until the end of the 19th century that gonorrhoea and syphilis were generally accepted as separate disease entities.

Swedlund suggested that gonococcal urethritis could occur in two ways: firstly as a result of 'venereal poison' or alternatively following non-specific irritation.
To prove the point he inoculated his own urethra with a solution of ammonia and with the development of a purulent discharge the following morning judged his theory proven. The 19th century venereologist Philippe Ricord (1800–1889) also believed that a variety of factors could lead to gonorrhoea including contact with vaginal fluid, foreign bodies or urethral irritants and also wrote that temperature, diet, alcohol and 'an unnatural size of male organ' could be implicated. Rollet (1824–1894) was one of the first to propose that a specific 'virus' was responsible for gonorrhoea which could be passed between infected individuals. He proved his theory by inoculating human volunteers with gonococcal and other pus in a study slightly more methodological but morally dubious.

With developments in staining techniques and light microscopy Albert Neisser identified Neisseria gonorrhoea for the first time in 1879 using Koch's staining technique on a smear of purulent material. Culture on blood serum gelatin by Leistikow followed in 1880 but even then some doctors remained sceptical about the role of N. gonorrhoeae in the pathogenesis of gonorrhoea, a situation possibly arising from the contamination of the unsellable media by non-pathogenic Neisseria species. Experiments inoculating pure cultures of N. gonorrhoeae into humans eventually silenced those who doubted the pathogenic potential of the gonococcus.

**STRUCTURE OF NEISSERIA GONORRHOEA**

Mapping of the gonococcal genome over the last few years has revealed much about the loci involved in determining the organism's structure and that control mechanisms of these structures are of particular importance not only during the initial attachment of N. gonorrhoeae to the mucosa but also in determining virulence and sensitivity to antibiotics. The pili which project from the surface of gonococci have a central role, probably in combination with Protein II, in adhering to the mucosa before the gonococci can enter the host cell. Pili expression is controlled by four genetic loci: PilA, PilB, PilE and PilS. Antigenic variation of the pili occurs which may evade the effects of the host immune system, and is the result of repeated recombination of pilin DNA from silent (PilS) to expressed sites (PilE) under the control of a promoter which is inhibited by the PilB gene product and activated by the PilA gene product.

In addition to Protein II there are a number of other surface proteins which are of interest. Protein I is the major outer membrane protein and forms a complex with Protein III to produce a porin through which hydrophilic molecules can pass. Protein I appears to be stable both in vitro and in vivo and, using a panel of monoclonal antibodies directed against epitopes on the protein's surface, provides the basis for subdividing the organism into different serovars. Thus changing patterns of infection produced by different strains of gonococci can be described and the introduction of new strains into a region identified. For example, it appears that within a given area homosexual and heterosexual men are infected with different serovars of N. gonorrhoeae.

By subdividing N. gonorrhoeae on the basis of differences in membrane structure or nutritional requirements (auxotyping) it is also possible to find associations between different strains of infection and their clinical presentation. Thus infections in women which spread up the genital tract to produce pelvic inflammatory disease often have an outer membrane deficient in Protein III while strains associated with disseminated infection tend to be of the Protein IA group and have the AHU- auxotype indicating a need for arginine, hypoxanthine and uracil in culture. These physical properties of the gonococcus may also influence the magnitude of the host immune response to infection with differences noted in complement activation and chemotaxis of neutrophils. Thus the presenting symptoms of gonorrhoea reflect a balance between the physical structure of the strain of gonococcus and the individual host's response to infection.

**TREATMENT**

The large number of therapies available for the treatment of gonorrhoea were, as might be expected, in inverse proportion to their effectiveness. Le Monnier proposed that his patients urinate into warm cows milk or soak the genitals in warm water for several days but other options included bleeding with leeches and herbal potions. Up until the 18th century mercury was also widely advocated and even after it was recognised that syphilis and gonorrhoea were separate diseases it was still occasionally used as 'prophylaxis'. Patients were generally advised to avoid sexual intercourse and, as is the case today, this advice appears to have been widely ignored.

Urethral lavage was recommended by many physicians including John of Ardenne (1306–1390) who used 'milk of a woman, a little sugar, oil of violet and barley water' as the irrigating fluid. By the 18th century Bell was using zinc sulphate solution but recognised that epididymitis and prostatitis could result from irrigation of the urethra. Alternative solutions included silver nitrate and potassium permanganate which were suspended in a container at some height to create a head of pressure enabling the irrigation to be performed once or twice a day for up to two weeks.

After the recognition of N. gonorrhoeae, stained smears were used as a test of cure often preceded by the patient drinking a draught of beer or champagne to stimulate any latent infection.

Heat was believed to kill the gonococcus and a variety of electrically heated bougies and electrodes were devised for this purpose. Alternatively fever therapy, similar to that used for syphilis, was advocated for the complications of gonorrhoea and was reported to be particularly effective for gonococcal arthritis. The patient was placed in a hyperthermia cabinet until attaining a rectal temperature of 41°C which was maintained for several hours. Attempts at vaccination centred around injecting increasing doses of infected material, supplied either by the patient or cultured previously, which perhaps not surprisingly were not very successful.

Urethral strictures were a cause of considerable morbidity and one of the first reports of urethral dilatation comes from an Italian surgeon, Antonio Guainerio, in the 15th century. Initially bougies were crude devices which often resulted in significant trauma to the urethra and bladder but with the incorporation of a single or double loop they became easier to pass. Unlike today dilators would generally be left in situ for several days only being removed to permit the patient to urinate. The introduction of urethroscopy by Desmormeux in 1853 permitted direct visualisation of urethral pathology including strictures but until the electric light was introduced early instruments were unsatisfactory.

In 1935 Domagk reported the first use of Protonsil, an azo dye, which had activity against streptococcal infections. The active component of Protonsil was
sulphanilamide and this early sulphonamide was first used to treat gonorrhoea in 1937.23 Sulphonamides were never 100% effective against N. gonorrhoeae and resistance quickly developed becoming a major problem by 1944.24 Penicilllin was first used to treat gonorrhoea in 1930 by Paine, a chemist in Sheffield, who cured two babies with ophthalmia neonatorum.25 Gonococcal urethritis was shown to respond to penicillin in 1943 and soon became established as the treatment of choice.26

SEQUELAE OF GONORRHOEAE

Local spread of infection and chronic inflammation were common in the pre-antibiotic era and resulted in chronic urethral discharge, epididymitis and urethral stricture. The time delay between the onset of gonorrhoea and development of the stricture led some physicians, including Hunter, to believe the two were unrelated and other causes such as urethral caruncles, tumours of the corpus cavernosa or prostatic disease were suggested.22 Bell had no doubt of the importance of gonococcal infection stating ‘urinary obstruction often follows clap’ but it remains unclear how often it was the astringent substances used for urethral lavage that led to stricture formation rather than the infection itself.

Chronic prostatitis was often ascribed to gonorrhoea but the bacteriological basis for this remains doubtful even today. The incidence of pelvic inflammatory disease around this time is difficult to estimate as it is often asymptomatic but gonorrhoea is likely to have been a major cause of infertility, pelvic pain and chronic ill health prior to the introduction of penicillin.

The incidence of disseminated gonococcal infection (DGI) in the pre-antibiotic era was also difficult to estimate since the constellation of arthritis, tenosynovitis and skin rash was probably often misdiagnosed before bacteriological confirmation was available. Even today over half such cases have sterile culture of synovial fluid and blood and diagnosis depends on mucosal cultures and the clinical features. Fortunately even without treatment gonococcal arthritis usually improves without causing permanent damage to the joint.3 It is therefore likely that some features of DGI are mediated through an immunological mechanism rather than direct bacterial invasion27 although despite this there is usually a rapid response to antibiotics and the strains involved are usually highly penicillin sensitive.

GONORRHOEAE IN THE POST ANTIBIOTIC ERA

Although one of the commonest infections in the early part of this century the incidence of gonorrhoea fell dramatically with the introduction firstly of sulphonamides28 and subsequently penicilllin29 but even prior to this it had been demonstrated that infection in soldiers could be reduced substantially by instituting a policy of health education and better recreational facilities combined with a non-judgmental approach.30 Unfortunately this happy situation was not to last and a slow but inexorable rise in the number of infections occurred in the late 1960s and 70s from around 60/100000 to over 100/100000 in the UK and from 110/100000 to 450/100000 in the US.28 This occurred largely as a result of the changes in society’s attitude to sex associated with the introduction of the oral contraceptive pill, the changing role of women in society and increasing mobility of the population.31 Associated with these social changes, an increase in premarital sex and first sexual contact at an earlier age, more infections were diagnosed in women.32–34 The advent of the AIDS epidemic and associated publicity encouraging safer sexual practices were undoubtedly important factors in the more recent decline in infections observed not just in Britain but in many Western countries,35,36 but it is worth noting that the decline started a few years before HIV hit the headlines suggesting that the population was already receptive to the safe sex message. Whatever the combination of factors responsible, the decline in gonorrhoea has been striking—in Edinburgh a 15-fold fall occurred between 1984 and 1994 from 821 cases to just 54 and at St Mary’s Hospital, London a 6-fold decline between 1980 and 1991 from 3600 to around 600 cases.35 Over a similar period (1975–1984) the number of reported cases of gonorrhoea in the US only declined by 12% (999 937 to 875 556) but variation in reporting rates from private physicians make the American figures difficult to interpret.36 Similar trends have been seen in many other Western countries. The prevalence of gonorrhoea in the Third World remains much higher. Although accurate data is more difficult to find for these regions population rates in the order of 7–10% are not uncommon and appear to be rising.73–40 The increased risk of HIV transmission associated with the presence of other sexually transmitted agents, including gonorrhoea, is of particular relevance in Third World countries and highlights the need for co-ordinated control programmes targeted against the full range of sexually transmitted infections.

More recently there have been reports of increasing numbers of infections in the West particularly in homosexual men, suggesting that this group is once again placing itself at risk for HIV infection.35 Given the often unpredictable course and extent of infection that have occurred in the past and the versatility of N. gonorrhoeae as a pathogen41,42 combined with the vagaries of human sexual behaviour it is still premature to sound the death knell of the gonococcus.

The clinical presentation of gonorrhoea comprises a spectrum including disseminated gonococcal infection (DGI), the Curtis–Fitz–Hugh syndrome (perihepatitis), pelvic inflammatory disease, epididymitis, genital discharge and asymptomatic infection. In the UK complication rates are low and in the vast majority of cases infection is localised to the genital tract. In other areas however local and systemic spread of infection remains common, not just in the Third World but also in areas such as the US where DGI remains the commonest cause of newly diagnosed arthritis requiring hospitalisation.19 Asymptomatic infection is more common in women accounting for up to three-quarters of infections. Pharyngeal or rectal gonorrhoea also is often asymptomatic and thus women and homosexual men may comprise an important core of infected individuals responsible for the persistence of infection within a community and suitable for targeted screening programmes.

PREVENTION

Preventing gonorrhoea requires a change in the behaviour in the sexually active population who place themselves at risk. Merely providing information in the form of health education is not enough in itself and an additional impetus such as peer group pressure is needed before changes are evident. Condoms are undoubtedly effective when used properly and although their usage has increased following the high profile HIV campaigns of the late 1980s it is estimated that less than half the population use such protection when having sex with a new partner for the first time.43 It also seems likely that any behavioural changes that are
achieved are short lived and unless frequent reminders are provided the population soon returns to their previous activities. Actively tracing the sexual contacts of infected patients, who may be asymptomatic, can also prevent the spread of infection but even with appropriate resources only around half of named sexual contacts are successfully traced and screened for infection.

**ANTIBIOTIC RESISTANCE TO NEISSERIA GONORRHOEAE**

Although virtually all strains of *N. gonorrhoeae* were initially highly sensitive to the effects of penicillin it was not long until low level resistance occurred necessitating an increase in the treatment dose. The decreasing sensitivity occurred as a result of mutations in the chromosomal DNA associated with changes in the affinity of penicillin binding proteins, increased cross-linking of peptidoglycan in the outer membrane and altered expression of outer membrane proteins. A number of different mutations have been described, some leading to selective resistance to penicillin (PenA), whilst others produce multiple resistance to a range of antibiotics including tetracycline and ciprofloxacin (PenB and mtr). When these mutations occur in combination the effect on resistance is several times that expected by summing them individually and in clinical practice this leads to a stepwise increase in resistance which eventually becomes clinically significant.

This contrasts with the single step, high level resistance associated with the acquisition of a penicillinase producing plasmid (PPNG). First described in 1976 in both the USA and UK it was feared that the rapid spread of these highly resistant strains would spell the end of penicillin as an effective therapy for gonorrhoea. Fortunately their incidence have plateaued at about 10–20% in some areas of the UK such as London and also in Edinburgh where despite an initial outbreak they are now a rarity. One would hope that the tight controls on the availability of antibiotics and established network of Genitourinary Medicine clinics within the UK was at least partially responsible for this.

In 1988 high level plasmid mediated resistance to tetracycline (TRNG) was reported which rapidly became endemic in certain areas of Africa. The subsequent need to use more expensive cephalosporins and quinolones to treat gonorrhoea has increased the already considerable problem of controlling sexually transmitted diseases in this area.

It would appear that antibiotic resistance may not always be advantageous to the bacteria and there is a poor correlation between penicillin resistance and the prevalence of individual strains at least in areas where antibiotic pressures are low. Possibly changes in the outer membrane structure associated with resistance also impede the flow of nutrients into the bacteria. Certainly some of the most successful and common strains of *N. gonorrhoeae* are also those which remain highly penicillin sensitive.

The geographical and temporal variation in sensitivity to different antibiotics emphasises the importance of continuous monitoring of resistance patterns and updating of antibiotic policies. Many clinics moved away from penicillin based therapies in the 1980s often to the quinolone antibiotics, such as ciprofloxacin, which have excellent activity against the gonococcus but with the decreased use of penicillins the selective pressure appears to fall and it may be possible to return to less expensive drugs after a period of time. In London, where the geographical origin of gonococcal infections is widespread, ciprofloxacin remains a common first line antibiotic although case reports from the Far East suggest that resistance can develop rapidly to this agent as well. In Scotland penicillin resistance is less of a problem and first line therapy with amoxicillin plus probenecid remains largely effective enabling quinolones to be reserved for infection acquired abroad or infections in homosexual men which tend to be caused by more resistant strains.

**CONCLUSIONS**

The history of gonorrhoea progresses through clinical descriptions of the disease that gave rise to theories about aetiology to the subsequent slow development of effective treatment. The same processes are still used today and although through improved investigative techniques and communication the pace has been greatly accelerated. However the same potential for drawing incorrect conclusions from incomplete or poorly designed studies also remains. Despite the great leaps in our understanding of gonorrhoea in the last two centuries much remains to be discovered.

The effective control of gonorrhoea is dependent not only on having effective therapy but also on health education, availability of diagnostic services, the attitudes of society to sexual activity, screening of high risk groups and the tracing of infected sexual partners. Despite the recent welcome decline of gonorrhoea in Britain it seems likely that this may only be temporary and the remarkable ability of the gonococcus to adapt to its environment will secure its place for the foreseeable future.

**REFERENCES**
