Why circumcision is a biomedical imperative for the 21st century

Brian J. Morris

Summary

Circumcision of males represents a surgical ''vaccine'' against a wide variety of infections, adverse medical conditions and potentially fatal diseases over their lifetime, and also protects their sexual partners. In experienced hands, this common, inexpensive procedure is very safe, can be pain-free and can be performed at any age. The benefits vastly outweigh risks. The enormous public health benefits include protection from urinary tract infections, sexually transmitted HIV, HPV, syphilis and chancroid, penile and prostate cancer, phimosis, thrush, and inflammatory dermatoses. In women circumcision of the male partner provides substantial protection from cervical cancer and chlamydia. Circumcision has socio-sexual benefits and reduces sexual problems with age. It has no adverse effect on penile sensitivity, function, or sensation during sexual arousal. Most women prefer the circumcised penis for appearance, hygiene and sex. Given the convincing epidemiological evidence and biological support, routine circumcision should be highly recommended by all health professionals. ***BioEssays*** **29:1147–1158, 2007. © 2007 Wiley Periodicals, Inc.**

Introduction

Circumcision is the removal of a simple fold of skin—the ''prepuce'' (or ''foreskin'')—that covers the glans (head) of the flaccid penis (Fig. 1). It is extremely common, 25 circumcision being performed per minute worldwide.[1] It is also quite simple to perform. Globally over 25% of men are circumcised.[2] Such a high rate for elective surgery involving the genitalia suggests important net benefits. When humans roamed naked on the African savannah, the prepuce protected the glans penis. But once humans started to cover the genitals with clothing, that benefit was lost, and the adverse effects of retaining the prepuce—suboptimal hygiene, infections and irritation from sand—no doubt triggered its removal. This then became ritualized, making circumcision a tradition in practically all indigenous peoples of equatorial and hot countries, spanning the globe, from Australia, the Pacific Islands, the Middle East, Indonesia, to the Americas.[3] Today in the USA, where medical knowledge and expertise are high, over 1.2 million newborn boys get circumcised each year[4,5] and is rising.[6] Those not circumcised are mainly immigrants from cultures in which circumcision is unfamiliar (Hispanic, European and Asian). Many then adopt local practise by having their sons circumcised. A recent representative study by the US Centers for Disease Control (CDC) found the rate is 88% in whites, 73% in blacks, 42% in Mexican-Americans and 50% in others (79% overall).[7] For Australian-born men, the rate is 69%, although is only 32% in those aged 16–20.[8] In the Middle East 100,000 Jewish and 10 million Muslim circumcisions are performed each year, and in Africa the number is 9 million.

The benefits of circumcision have in recent times grabbed headlines owing to its striking protection against heterosexual acquisition of HIV. But this is only a small component of the overall net benefit in most developed countries. The many diverse benefits extend from cradle to grave, not just in males, but also their sexual partners. Many workers tend to be familiar with the benefits in their own narrow specialty, but not always the totality of benefits. The latter are detailed in recent reviews[9,10] and listed in Table 1. Here I will emphasize the biological aspects that make the prepuce a health hazard and summarize the risks to public health.

School of Medical Sciences and Bosch Institute, Building F13, The University of Sydney, Sydney, New South Wales 2006, Australia.
E-mail: brianm@medsci.usyd.edu.au
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Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; HPV, human papillomavirus; RCT, randomised controlled trial; STIs, sexually transmitted infections; SIL, squamous intra-epithelial lesion; PIN, penile intraepithelial neoplasia; UTI, urinary tract infection; WHO, World Health Organization.

HIV infection

Sexual transmission of HIV requires this virus to penetrate epithelial tissue. The inner lining of the prepuce provides such an access route. This is because it is a mucosal epithelium and its protective keratin layer is very much thinner than in the outer prepuce and glans penis.[11] Histologically, this tissue resembles the lining of the nasal passages and vagina, which are major targets for infection by micro-organisms. In addition, the uncircumcised penis is more susceptible to minor trauma and ulcerative disease, and the preputial sac serves as a reservoir for pathogenic organisms present in the pool of smegma (a whitish film consisting of neutral lipids, fatty acids, sterols and exfoliated cells) that accumulates beneath the

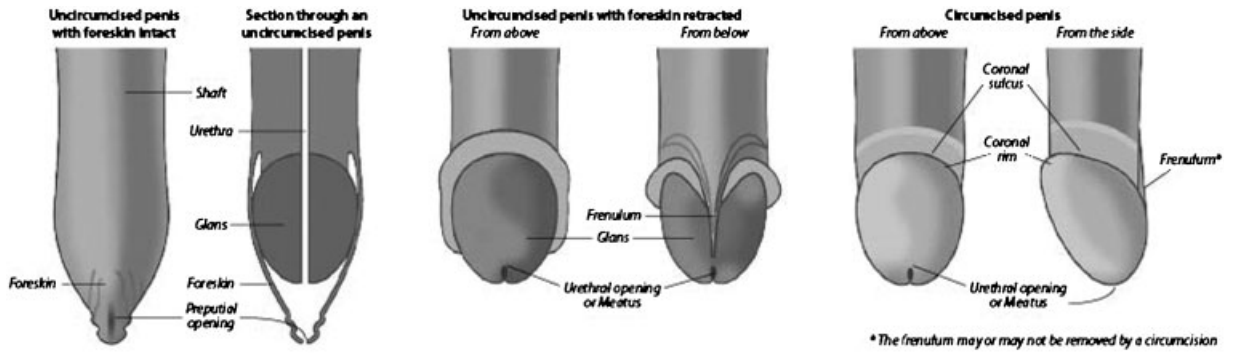

Figure 1. The uncircumcised and the circumcised penis, annotated to show the different parts.

Table 1. Why risks from not circumcising exceed risks of circumcision by over 100 to 1

Risks for not circumcising

Condition	Fold increase	NNT
Urinary tract infection	10	50
Pyelonephritis	5	100
With concurrent bacteraemia		1000
Childhood hypertension		1500
End-stage renal disease		13000
Prostate cancer	1.5–2	6
Balanitis	3	10
Phimosis	infinite	10
Syphilis	3	200
HIV infection	3–8	1000
Penile cancer	>20	1000
In female partner:		
Cervical cancer or chlamydia	5	100
Thus risk of developing a condition requiring medical attention = 1 in 3		

Risks for circumcision

Condition	Fold increase	NNH
Local bruising at site of injection of local anaesthetic (if dorsal penile nerve block used)	0.25*	4
Infection, local	0.002	600
Infection, systemic	0.0002	4000
Excessive bleeding	0.001	1000
Need for repeat surgery (if skin bridges or too little prepuce removed)	0.001	1000
Loss of penis	Close to 0	1 million
Death	0	Virtually zero
Loss of penile sensitivity	0	Zero
Thus risk of an easily-treatable condition = 1 in 500 and of a true complication = 1 in 5000		

Values are based on statistics for USA (see[125] for refs used for source data). NNT, number needed to treat, i.e., approximate number of males who need to be circumcised to prevent one case of each condition associated with lack of circumcision; NNH, number needed to harm, i.e., number that need to be circumcised to see one of each particular (mostly minor) adverse effect.

*The minor bruising (from this method only) disappears naturally without any need for medical intervention, so is not included in overall calculation of easily-treatable risks.

prepuce.[9] Because of the potential for infection these pose, the mucosal epithelium has a high prevalence of immune system cells: CD4+ T cells, Langerhans cells and macrophages. These represent 22, 11 and 2%, respectively, of the total cell population.[12] For the external prepuce and the rest of the penis, these figures are 2, 1 and 0.7%, and for the cervical mucosa are 6, 2 and 1%.[12] Although the urethra is a mucosal surface, Langerhans cells are absent,[11] and this is not a common site of HIV infection.

Antigen-presenting cells in the mucosa of the inner prepuce[13] are a primary target for HIV infection in men.[14] Whereas such immune system cells usually offer protection from infectious micro-organisms, in the case of HIV they act as a "Trojan horse", serving as portals for HIV uptake via CD4 receptors and cofactors such as chemokine receptors CCR5 and CXCR4 present in high density in cells, in particular Langerhans cells,[9] in the mucosa.[12] Uptake of HIV by the mucosal, but not the external, preputial lining has been demonstrated in explant culture.[12] This work showed 301 copies of HIV per 1000 cells as opposed to zero, in internal and external tissue, respectively, one day after exposure.[12] For the cervix there were 30 copies, i.e., the mucosal inner prepuce was 10 times more susceptible to HIV.[12] Similar findings have been obtained after application of SIV to the prepuce of monkeys.[15]

Although cells with HIV receptors CD1a, CD4, CCR5, CXCR4, HLA-DR and DC-SIGN are present in penile epithelia in general, HIV only attaches to those it can access. CD1a-positive Langerhans cells are closest to the surface, whereas T cells are located in the submucosa. The Langerhans' cells, moreover, send dendritic projections up between keritanocytes to the epithelial surface, these processes being particularly superficial in the inner prepuce (4.8 μm) compared with the outer (20 μm)[11] (Fig. 2). c-type lectins, such as langerin, can then bind, internalize and transport HIV to regional lymph nodes.[16] Other mechanisms are, however, more important than langerin in viral internalization.[17] Moreover, direct, Langerhan cell independent, infection of T cells by HIV takes place as well.[17] It is nevertheless possible that the success of HIV in establishing a systemic infection may depend on its early interaction with Langerhans cells.[17] Unless depleted by viral overload, langerin could help prevent infection.[18]

During sexual arousal, the vulnerable inner epithelium becomes stretched halfway down the penile shaft (Fig. 3). This further diminishes its already thin layer of keratin and, during penetration, the inner prepuce becomes exposed directly to infected secretions of the receptive partner. Having been infected, the preputial cavity offers a hospitable environment for an infectious inoculum, so facilitating transmission during sex with subsequent sexual partners.

Since HIV risk is lower in circumcised men who have more frequent, as opposed to less frequent, sexual exposure, it has been suggested that repeated contact may induce additional protection via an immune response to subinfectious inoculums.[19] This may involve the small area of exposed urethral mucosa, or more likely the meatus, which unlike the urethra does contain a small number of HIV receptors.[11] In addition, mucosal alloimmunization has been suggested as a protective factor against HIV.[20]

Virtually all of the 40, mostly observational, studies conducted worldwide since the 1980s have shown that

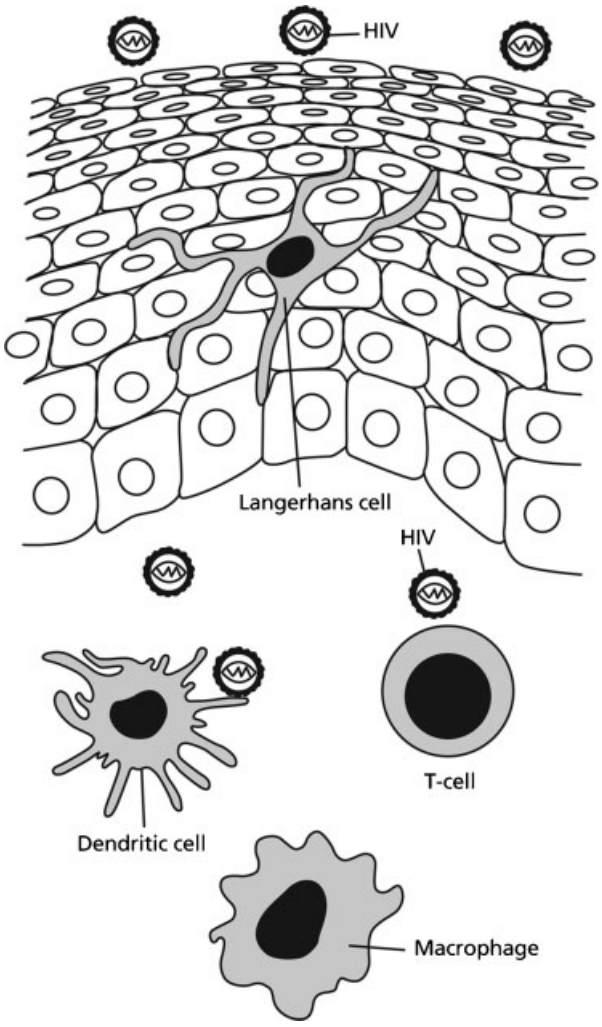

Figure 2. Typical location of HIV target cells in the inner epithelial lining of the prepuce, showing proximity of Langerhans cells, in particular their dendrites, to the surface. According to Scott McCoombe (personal communication) 'Langerhans cells are very active antigen samplers that cover a huge surface area and are constantly moving between epithelial cells. The processes extend closer to the surface than [in his paper, Ref. 11] owing to a 0.5–1 h delay while being transported on ice to the Lab'. McCoombe's recent work shows HIV penetrating to near Langerhans cell processes.

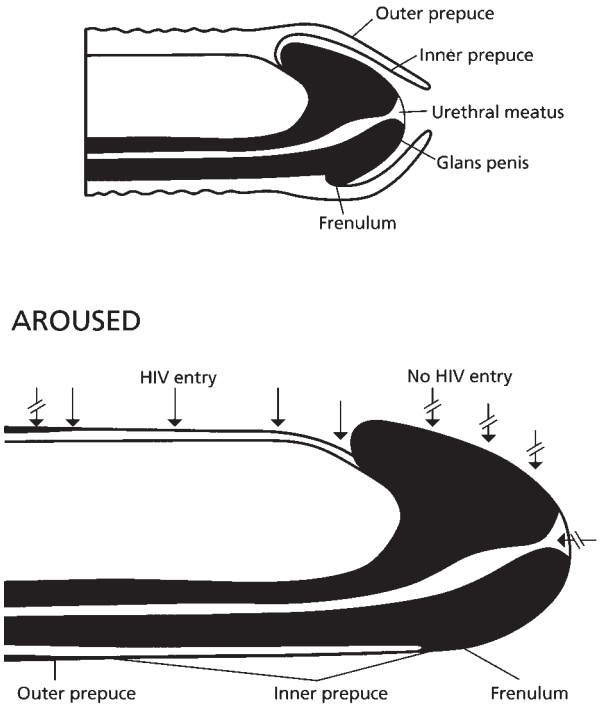

Figure 3. Illustration of how the inner lining of the prepuce becomes exteriorized during an erection so as to become exposed directly to HIV in biological fluids of an infected sexual partner. (Modified from Ref. 11.)

circumcision provides a 2- to 8-fold protection against HIV infection.[10] The per-protocol findings from three large randomized controlled trials (RCTs), that were all stopped early so that circumcision could be offered to the control group, found that circumcision led to a 56–75% risk reduction.[21–23] In March 2007 the WHO therefore endorsed circumcision as an important additional weapon in the fight against AIDS. The WHO, UNAIDS and others have done projections estimating the millions of lives that will be saved by implementation of circumcision, which has been equated to an effective vaccine.[24] It could potentially "abort the epidemic".[25] Cost-effectiveness estimates are, moreover, substantial.[25,26]

Although condoms reduce risk by 80–90% when always used,[27] they are not infallible, nor used universally, and do not protect during foreplay when the inner prepuce may come into contact with infected fluids. Circumcision in contrast is once only, so does not need to be applied each time sex is contemplated, is permanent, and when coupled with condom use should virtually guarantee complete protection from infection by HIV. Curiously, contrary to contemporary wisdom, a review of 10 studies in Africa found no association between condom use and reduced HIV infection; one study in fact found condom use was associated with higher HIV infection![28]

Other sexually transmitted infections (STIs)

Ulcerative STIs

Circumcision affords substantial protection from syphilis (*Treponeum pallidum*), chancroid (*Haemophilus ducreyi*), and, in some studies, herpes simplex virus type 2 (HSV-2).[2,9,10] The warm moist environment under the prepuce favours bacterial replication. The delicate inner lining's mucosal nature and risk of tearing it and the frenulum during intercourse are other factors. Chancroid is more likely to present on the inner and outer prepuce, whereas syphilis and HSV-2 tend to infect the genitalia more widely.

Results of a recent meta-analyses of all studies (from the USA, UK, Australia, Africa, India and Peru) are shown in Table 2. In a New Zealand birth cohort aged 26, HSV-2 seroprevalence was 7% irrespective of circumcision status[29] and a CDC study similarly found no association.[7]

Urethral STIs

In the case of gonorrhea and *Chlamydia trachomatis*, older studies generally report a lower rate, whereas recent data from developed nations show little difference.[9,10] This may be unsurprising, given the site of infection is the urethra.

A longitudinal New Zealand birth cohort study found that to age 25 the uncircumcised had a 3.2-fold higher rate of STI (the frequency of which in this cohort was *Chlamydia* 52%, genital warts 31%, non-specific urethritis 12%, genital HSV-2 10%, gonorrhea 5%) when compared with those who were circumcised, after adjustment for the higher number of sexual partners and of rate of unprotected sex in the 30% who were circumcised.[30] It was concluded that, if all had been circumcised, their rate of STI would have been reduced by 48%. This included *Chlamydia* (OR 2.5; CI 0.73-8.5).

Human papillomavirus: HPV will be dealt with in the next section.

Table 2. Reduction in risk of an ulcerative STI by circumcision

	Number	Relative risk (CI)
Syphilis	14 of 14 studies	0.61 (0.54–0.83) 0.53 (0.34–0.83)*
Chancroid	6 of 7 studies	0.12–1.11†
HSV-2	6 of 10 studies	0.88 (0.77–1.01)

*When circumcision prior to first sexual intercourse.
†Individual study RR.
(Data from Weiss HA, et al. 2006. Sex Transm Inf 82: 101–9).

Penile cancer

This disease has a high morbidity and mortality, as well as serious psychological ramifications.[31] It most commonly presents as invasive squamous cell carcinoma,[31] the incidence of which is over 22 times higher in men who are uncircumcised.[31–33] In the USA it represents 0.3–0.6% of all male cancers.[31] For uncircumcised men in developed countries, lifetime risk of penile cancer is 1 in 600–900,[34] but for circumcised men is only 1 in 50,000–12,000,000.[35,36] The benefit is far greater when circumcision is performed early in life.[31,37]

In underdeveloped countries, the incidence of penile cancer can be 10 times higher and as many as 20% of men can have it.[10,31,34] Like cervical cancer it is caused by high-risk (cancer-causing) HPV. But penile cancer is 10-times less common than cervical cancer.[38]

The penile distribution of HPV is: prepuce 28%, shaft 24%, scrotum 17%, glans 16% and urine 6%.[39] HPVs, most notably high-risk types, are more common in uncircumcised males (see Ref. 40 for references to the various studies). Most notable is a large multination study that found HPV in 19.6% of 847 uncircumcised men, but only 5.5% of 292 circumcised men (overall odds ratio [OR], after adjusting for potential confounding factors = 0.37).[40] In healthy Mexican military men, OR for persistent HPV was 10 times higher in the uncircumcised.[41] A recent meta-analysis showed that circumcision was consistently associated with a significant reduction in penile HPV (OR 0.56, CI 0.39–0.82).[42] High-risk HPVs produce lesions visible only by application of dilute acetic acid to the penis; in contrast low-risk HPVs present as visible warts.[43] The majority of infections are subclinical, and are more prevalent in uncircumcised men with balanoposthitis.[44] Smegma was implicated in an early study,[45] but such findings remain to be confirmed.[46]

Consistent with HPV's sexual transmission, 93% of men whose female partner had a squamous intra-epithelial lesion (SIL) had penile intra-epithelial neoplasia (PIN).[47] Oncogenic HPV was present in 75% of patients with PIN grade I, 93% with PIN grade II and 100% of PIN grade III, which is one step removed from overt penile cancer.[47] PIN has been found in 10% of uncircumcised men, compared with 6% of circumcised men.[47] Most PIN is cleared naturally. HPV has been found in 80% of tumour specimens, 69% having the very high-risk type HPV16.[48] Since not all HPV types were tested for, the rate of HPV is undoubtedly higher.

Condom use lowers HPV infection only slightly.[49]

Phimosis is a strong predisposing factor in invasive penile carcinoma (adjusted OR = 16 in one study[37] and 11 in another[48]). Although other factors, such as smoking,[48] poor hygiene and other STIs may contribute,[50,51] lack of circumcision is the biggest risk factor. Indeed, there is no scientific evidence that improved penile hygiene reduces penile cancer risk in an uncircumcised man.[2] Thus circumcision in early childhood, by eliminating phimosis seen in 10% of men,[52] may help prevent penile cancer.[48]

Prostate cancer

This is the second most common cancer in men and is 1.6–2.0 times higher in uncircumcised men (see Refs 10,53 for references to the various studies). A role of STIs, many of which are higher in uncircumcised men, may explain this relationship.[53] A recent analysis found that in the USA universal circumcision would have reduced the current annual number of prostate cancer cases by 45–67,000 and medical costs by $0.8–1.6B.[53]

Urinary tract infections (UTIs)

UTIs are particularly common in infants, especially those under 6 months of age.[36,54,55] Incidence is strikingly higher in uncircumcised boys (2.5% vs 0.2%). Worldwide, lack of circumcision represents 0.5–1.5 million UTIs annually.[10] An early meta-analysis showed a 12-fold higher incidence in uncircumcised boys (range 5–89 fold),[56] and a meta-analysis in 2005, that included older children, revealed an 8-fold higher rate (CI 5–13).[57] In febrile infants, bacteruria is seen in 36% of uncircumcised boys, but only 1.6% of those who were circumcised, a 22.5-fold difference.[58] Moreover, up to the age of 5 years, 6% of boys in Sydney had had a UTI.[59] The rate, hospital admissions, consequences and costs are, moreover, far greater than in girls.[60] Recurrent UTIs occur in 19% of uncircumcised boys, but in none of the circumcised.[61]

The infection can travel up the urinary tract to affect the kidney. Moreover, in infants, a UTI is more likely to result in renal injury and scarring. Pyonephritis is seen in 34–70% of those with febrile UTI,[62] where UTI is the cause of the fever in 21% of uncircumcised boys, 2% of circumcised boys and 5% of girls.[63] An imaging study found that 50–86% of children admitted with febrile UTI and presumed pyelonephritis had renal parenchymal defects.[64] These persist, and a 27-year follow-up study found elevated risk of hypertension and end-stage renal disease in 10%,[65] meaning ongoing morbidity and costs from an infant UTI.

Bacteria are present under the prepuce of 92% of boys aged 0–6.[66] Moreover, pathogenic fimbriated strains of *E. coli* and *Proteus mirabilis* can adhere to the prepuce.[10,67,68] Additional organisms include other species of coliforms, *Klebsiella, Serratia, Enterococcus* and non-fimbriated *Pseudomonas*.[68–72] These are pathogenic to the urinary tract and pyelonephritogenic.[73,74] Prior to circumcision for medical reasons, uropathogenic bacteria were detected in 52% of boys, but 3 weeks afterwards none were found.[69] In another study, these figures were 64% and 10%, respectively, and it was concluded that periurethral flora originate from deeper preputial regions.[75] That infection persists was shown in a study of boys aged 4–12 (mean 6) years: the 16% with phimosis had clinically significant (≥100,000 cfu/ml) uropathogens and, in those who did not have phimosis, 93% of the 56%

with uropathogenic species had clinically significant colonization.[70] In 82% of uncircumcised, but in virtually no circumcised, males over the age of 15, *Streptococci*, strict anaerobes and genital mycoplasms have been found. Given these are common in the female genital tract, sexual acquisition was probable.[76] Boys with vesicoureteral reflux are at increased risk of UTI and thus renal damage.[77] Since antibiotic prophylaxis is ineffective, circumcision is advocated.[78,79] The presence and transmission to others of *Salmonella typhimurium* is, moreover, prevented by circumcision.[80]

The *E. coli* responsible for UTI form impenetrable, protective ''pods'' on the walls of the bladder, explaining their well-known ability to persist in the face of robust host defences and antibiotic administration.[81]

Penile candidiasis (thrush) is also significantly less common in circumcised males (OR 0.40).[8]

Inflammatory dermatoses

Balanitis and posthitis:
Inflammation of the glans and of the prepuce, respectively, cause significant pain and are obvious medical indications for circumcision. Balanitis is seen in 11–13% of uncircumcised men, but only 2% of the circumcised.[44,82] In boys it is half as common in the circumcised,[83,84] and in uncircumcised infants only can be caused by group A haemolytic variety of *Streptococcus*.[85] In diabetic men, balanitis and posthitis is seen in 35%.[44]

Other penile skin diseases
Psoriasis, and conditions arising from penile infections, lichen sclerosis, lichen planus, schorrheic dermatitis, and plasma cell (Zoon) balanitis[44,86] are all either much more common or exclusively seen in uncircumcised males. Uncircumcised males (only) can get Zoon balanitis, bowenoid papulosis, and non-specific balanoposthitis.[87] Zoon balanitis is likely caused by mycobacterium smegmatis.[86] Typical symptoms are erythrema (in 100%), swelling (in 91%), discharge (in 73%), dysuria (in 13%), bleeding (in 2%) and ulceration (in 1%).[44] Lichen sclerosis occurs in 4–19% of prepuces,[88] and in older patients this or other inflammatory changes result in phimosis,[89] present in 80% of penile cancers.

Balanoposthitis
Inflammation of the prepuce and glans is particularly common in uncircumcised diabetic men, whose penis is weakened and diminished.[82]

Physical problems

Phimosis
This is a narrowing of the preputial orifice so as to prevent retraction over the glans, and affects around 10% of uncircumcised adolescents and men (Table 3). In men it makes sexual intercourse painful and difficult, and, as an historical anecdote, was why Louis XVI was unable to impregnate Marie Antoinette until he was circumcised years later – the delay having historical consequences.[10]

A ''physiological'' phimosis should be contrasted with pathological phimosis from secondary cicatrization of the prepuce orifice as a result of balanitis xerotica obliterans (BXO). Although once thought to affect only 1% of boys,[90] recent histological examination of the prepuce from 1178 boys circumcised for phimosis found BXO in 40%.[91] Of these, 19% had early, 60% intermediate and 21% a late form of BXO. Incidence peaked at ages 9–11 (76% of cases).[91] Of 41 paediatric BXO cases in Boston, 52% had been referred for phimosis, 13% for balanitis and 10% for buried penis.[92] Of the 46% who were subsequently circumcised, BXO was found in the meatus of 27%. These then required meatotomy or meatoplasty, with 22% requiring extensive penile plastic surgery, including buccal mucosa grafts. Thus BXO can have quite severe and morbid clinical consequences.

Phimosis from whatever cause increases risk of penile cancer.[37,48] Treatment by complete circumcision is the definitive option. Topical steroid creams can be used, but have to be applied frequently for over a month, are not completely successful, can lead to iatrogenic Cushing's syndrome, adrenal suppression, delayed growth, skin atrophy, and do not confer the additional benefits that circumcision provides.[93–95]

Paraphimosis
An inability to return the prepuce after retraction is also cured by circumcision. Paraphimosis can result in partial or complete

Table 3. Incidence of phimosis

Population	Incidence	References
British, aged 5–13	20%	Gairdner 1949. Brit Med J 2:1433–7
Danish, aged 8	8%	Oster 1968. Arch Dis Child 43:200–3
British soldiers	14%	Osmond 1953. J Roy Army Med Corp 99:254
German youths	9%	Saitmacher 1960. Dtsche Gesundheitwesen 15:1217–20
German men	9%	Schoeberlein 1966. Muench Med Wschr 7:373–7
Japan, aged 11–15	23%	Ishikawa & Kawakita 2004. Hinyokika Kiyo 50:305–8
Taiwan, age 13	16%	Ko et al. 2007. J Formos Med Assoc 106:302–7

urinary obstruction, and backward pressure can impede kidney function.

''Accidents''

The prepuce can become entrapped in zippers, leading to swelling and scarring. This is painful and traumatic. The ''bathroom splatter'' of uncircumcised males can be a source of annoyance.

Frenular chordee

A quarter of all uncircumcised males have this.[96] It is caused by an unusually thick and often tight frenulum, which prevents the prepuce from retracting fully. The frenulum can tear during intercourse or masturbation. Scar tissue, being less elastic and generally more fragile, means the tear often recurs, causing pain and bleeding, thus risking infection, and is an impediment to sexual activity. It is solved by frenoplasty, which can be part of a circumcision.

Penile hygiene

This is difficult to achieve in uncircumcised schoolboys.[97,98] Moreover, if uncircumcised men do not perform penile hygiene after sex (rather than rolling over and falling asleep) they increase their risk of STIs.

Smegma increases in adolescence, peaking at age 20–40. Initially it is a white or pale yellow lubricant. Over time it is transformed chemically as it becomes mixed with epithelial cells, dirt and micro-organisms that together form aggregates and generate an offensive odour.[99]

Improved penile hygiene is a major reason for circumcision—82% in one study.[100] In another study, smegma was regarded by 88% as unclean and infected with micro-organisms.[100] Not only is penile hygiene often difficult to achieve, attempts to do so in uncircumcised men can result in dermatological problems. For parents, it is far easier to maintain cleanliness of their son's penis if it is circumcised.

In men in London, inferior genital hygiene behaviour was seen in 26% of the uncircumcised, but only 4% of the circumcised.[101] Medical conditions that impeded retraction of the prepuce for washing could have contributed to the difference. Of the circumcised men 37% washed more than once per day, compared with 19% of the uncircumcised ($P = 0.01$).

Psychological sequelae

There is no adverse psychological aftermath from circumcision. For example, 5-year follow-up of 117 Swedish boys circumcised for medical reasons found 95% were completely satisfied,[102,103] and in the African HIV RCTs 98.5–99.5% were ''very satisfied'' with their circumcision.[22,23]

Geriatric consequences

Not often considered at birth, but which should be,[104] are future problems in the male as an elderly person. The pain of an infected, inflamed or nonretractable prepuce means suboptimal hygiene. If the man is suffering from dementia, adverse reaction to carers attempting genital washing can ensue. Indwelling catheters—required for urinary drainage following prostate surgery, for example—are more difficult to insert and more likely to produce infection in uncircumcised men.

Cervical cancer

Cervical cancer is caused by high-risk HPVs, which initially induce a SIL.[38,105–107] Women with cervical cancer[108] or SIL[47] are more likely to have a partner with PIN. Although lack of circumcision had long been associated with cervical cancer,[10] a large multination study published in 2002 confirmed this connection.[40] It involved 1913 couples in 5 global locations in Europe, Asia and South America. Twenty percent of uncircumcised men had penile HPV as compared with 5% of circumcised men. Penile HPV infection was associated with a 4-fold increase in the risk of cervical HPV infection in the female partner, and cervical HPV infection was associated with a 77-fold increase in the risk of cervical cancer. If the man had had 6 or more sexual partners and was uncircumcised his monogamous female partner was 5.6 times more likely to have cervical cancer than was the case for such ''high-risk'' men who were circumcised. Circumcision was also protective in women whose partner had an intermediate sexual behaviour risk index (OR = 0.50). An accompanying editorial stated ''reduction in risk among female partners of circumcised as compared with uncircumcised men may well be more substantial than reported''.[109] A survey of 121 developing countries, moreover, found that circumcision was strongly associated with lower rates of cervical cancer, independent of religion.[110]

HPV is highly infectious and skin-to-skin contact, such as during foreplay or involving areas not covered by a condom, could lead to infection. Condom use in fact afforded only slight protection in the multination study (OR 0.83 vs 0.67).[40] This observation is backed up by a meta-analysis of 20 studies.[111] The uncircumcised men in the study washed their genitals more often after intercourse than did the circumcised, but the circumcised men had better penile hygiene when examined by a physician. It was suggested that in an uncircumcised man the more delicate, easily-infected, mucosal lining of their prepuce when retracted during erection becomes wholly exposed to vaginal secretions of an infected woman (just as for HIV in Fig. 3). Once infected, the man risks infecting any future partner. A prophylactic vaccine against the two most common high-risk HPV types (16 and 18) may prevent up to 70% of cervical cancers if all girls receive it. Universal male circumcision could have a similar impact on cervical cancer

incidence, but would have the added benefit of greatly reducing other conditions as well.

Chlamydia trachomatis in women

A study involving 305 couples in 5 countries found an increase in risk of *C. trachomatis* of 5.6-fold if the male partner is uncircumcised.[112] The corollary to this is that circumcision reduces risk by 82%. Data were identical for women who had only ever had one sexual partner. *C. pneumoniae*, which is not sexually transmitted, was of equal frequency in each group, so supporting the biological plausibility of the observation.

HPV is the most common and *C. trachomatis* is the world's 2nd most frequent STI, the latter being the most common bacterial STI: 92 million new cases annually, 3 million being in the USA (where annual cost for care = $2 billion).[113] Incidence is, moreover, rising. *C. trachomatis* causes pelvic inflammatory disease that can lead to infertility, ectopic pregnancy and pelvic pain. It is a co-factor in HPV-induced cervical cancer and HIV transmission in women and men. In men *C. trachomatis* can cause infertility, prostatitis and urethral blockage.

Entrapment of a higher infectious load by the prepuce, and subsequent delivery of this to a subsequent partner, may explain the higher transmission risk.[112]

HSV-2 in women

A study in Pittsburgh amongst 1207 women aged 18–30 years having an overall HSV-2 seroprevalence of 25% found that history of sexual intercourse (ever) with an uncircumcised male greatly increased their risk of HSV-2 infection (OR = 2.2; CI 1.4–3.6, after multivariate logistic regression analysis).[114] The high prevalence of HSV-2 worldwide highlights the need to ameliorate risk factors. Circumcision should thus help reduce transmission.

Sensitivity, sensation and socio-sexual aspects

Sensitivity of the flaccid penis differs little between circumcised and uncircumcised men.[10,115,116] The more important issue of penile sensation during sexual arousal was addressed in a recent thermal imaging study which found no difference.[117] In fact sensitivity decreased similarly in both groups during arousal! Baseline penile temperature was lower in the uncircumcised men, in whom the monitor was under the prepuce, just below the glans.

Credible research has, moreover, found no association between circumcision status and failure to enjoy sex.[118,119] Erectile function scores were unchanged after circumcision of adult men.[120] And intravaginal latency times were no different (6.7 versus 6.0 min in circumcised versus uncircumcised men, respectively) in a study of 500 couples in the USA, UK, Netherlands, Spain and Turkey.[121]

The US National Health and Social Life Survey, involving over 1400 men, found the uncircumcised were more likely to experience sexual dysfunctions.[122] In an Australian survey of 16–60 year-olds, problems in the uncircumcised were greater—this included pain at any age and erectile dysfunction in 27% aged <50.[8] Circumcised men had more liberal attitudes[8] and enjoyed a more elaborate sexual lifestyle.[122] Women's preference for the circumcised penis for sexual activity, appearance and hygiene is one reason.[120,122,123]

Males in higher socio-economic-educational categories in the USA, UK and Australia have higher rates of circumcision.[10,122,123]

Circumcision methods

Various devices are used to protect the penis during excision of the prepuce in infants. The most commonly used are the PlastiBell (Fig. 4), the Gomco clamp and the Mogen clamp. Each has advantages and disadvantages. Whereas the PlastiBell must remain in place after the boy goes home, and falls off several days later, use of the metal clamps means completion of the circumcision on the day. An anaesthetic is imperative. A local, rather than a general, is all that is required, coupled with a sedative in older children and men. Local anaesthetic methods include ring block, dorsal penile nerve block (both injections) and the application of EMLA (lidocaine/prilocaine) cream. Nevertheless, a general anaesthetic can often be preferred by surgeons for techniques in men that take longer, such as the sleeve-resection technique.[124]

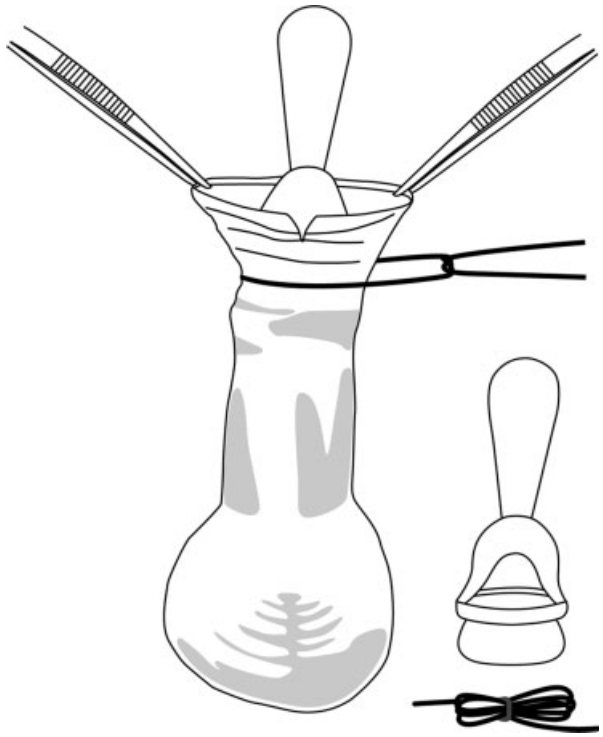

Figure 4. The Plastibell device and its use for infant circumcision. (Modified from Ref. 124.)

A method developed by Dr Terry Russell for infants (www.circumcision.com.au) involves application of EMLA for *2 hours* prior tying on the PlastiBell device. The anaesthesia lasts 6 hours in total, making the procedure completely pain-free. Russell reports only minor complications from 18,000 circumcisions that he has done, except for transient methaemoglobinaemia in one infant, and this resolved spontaneously without intervention. In a different variation, Dr Sam Kunin injects anaesthetic between the outer and inner prepuce, prior to circumcision by Gomco clamp (www.samkuninmd.com).

Best time to circumcise

For optimum health benefit, cosmetic result (no stitches), simplicity, speed, convenience and cost, infancy is the ideal time to perform a circumcision. When performed in the adult male, the man should abstain from sex for 4–6 weeks and realize that final cosmetic appearance requires several months.

Complications

These vary according to technique used and skill of the operator.[10,125] For 1 in 500 infant circumcisions, there may be slight bleeding (easily stopped by pressure or, for 1 in 1000, stitches), need for repeat surgery (1 in 1000), or a generalized infection (1 in 4000). True complications requiring hospitalization occur in only 1 in 5000. Mutilation or loss of penis is unheard of by competent medical practitioners these days. Family history of haemophilia requires special preoperative treatment. In men circumcised by an experienced operator minor bleeding or infection, easily treated, occur in 2–3%. This is reduced to $<$1% after 400 circumcisions.[126]

Fictions

Various myths abound concerning circumcision. Emotive arguments, such as ones prevalent on anti-circumcision internet sites, are not supported by current scientific evidence. What remains is nebulous, convoluted legalistic discourses such as consent or ''human rights'' issues, which can be similarly levelled against vaccination and other interventions that are in the best interests of infants and children. The claim that circumcision was popular in the Victorian era as a cure for masturbation had no common currency at that time. For example, the purported ''evil'' of masturbation occupies much of the early 20th century book ''Youth and Sex'', but circumcision (quite common at the time) is not mentioned.[127] Felix Bryke's then well-known book on circumcision completely rubbishes the idea,[3] and Whitla's ''Dictionary of Treatment'' does not list ''circumcision,'' whereas, under ''masturbation,'' only suggests performing circumcision if irritation from a tight prepuce is responsible.[128] But just as today, the Victorians recognized circumcision in prevention of phimosis, penile cancer, syphilis and other STIs. For an exposé of the anti-circumcision movement see Ref. 10.

Future

The evidence for benefits are now so strong that further research is likely only to confirm and fine-tune what is already known. Since the gold-standard—the RCT—has firmly established the role of the prepuce in HIV acquisition, should RCTs be conducted for all other conditions and infections that circumcision prevents? In the case of UTIs the evidence is so striking and unidirectional that no ethics committee would allow a RCT. For penile cancer, not only is the evidence overwhelming, but a RCT would take many decades. Prostate cancer would benefit from a RCT, but again would require decades for results to emerge. For conditions in women, a RCT would of course be unworkable.

It would also be of interest to ascertain the overall net benefit on average in various settings by integrating the data on all conditions prevented. Such a number could then be compared with the risks. I have done this in a crude manner in Table 1, but a much more expert epidemiological analysis is sought.

Lastly, now that we know the news on circumcision is virtually all good, the major challenge is educational, so that this message is converted into policy and practice. In this regard, there has to date been a curious conjunction of dichotomous forces—namely the anti-circumcision movement and conservative medical bodies whose policies, often driven by a small subset of paediatricians, have been less than helpful to public health on this matter. As a result rather than ''evidence-based medicine'' what is occurring all too often at the patient interface is ''ignorance-based medicine'' or worse, ''prejudice-based medicine.'' This must change.

Conclusion

The prepuce poses a risk of genital infection to a man and his sexual partner(s). It helps trap and transmit infectious agents. It also predisposes the male to a vast array of other problems. Over their lifetime, one in three uncircumcised males will develop a condition requiring medical attention. The risk of experiencing each of these is listed in Table 1. In contrast, the only risk for circumcision is the procedure itself, where overall chance of an (easily treatable) adverse event is quite low (Table 1). Local anaesthesia is advocated for all ages. Infant circumcision can, moreover, be completely pain-free, both during and after. Use of the PlastiBell device means the prepuce is not ''cut'' off. In experienced hands, risk can be close to zero. Therefore, when considering the overwhelming medical evidence circumcision is mandated.

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References

1. Hammond T. 1999. A preliminary poll of men circumcised in infancy or childhood. BJU Int 83:85–92.
2. Moses S, Bailey RC, Ronald AR. 1998. Male circumcision: assessment of health benefits and risks. Sex Transm Inf 74:368–373.
3. Bryk F. 1882. Circumcision in Man and Woman - Its History, Psychology and Ethnology. (Die Beschneidung bei Mann und Weib), pp. 174–177. Berger D, German translator. 1934. New York: American Ethnological Press; 1882. 342 p.
4. National Center for Health Statistics of the Department of Health and Human Services. 2003. Trends in Circumcisions Among Newborns http://www.cdc.gov/nchs/products/pubs/pubd/hestats/circumcisions/circumcisions.htm.
5. Stang HJ, Snellman LW. 1998. Circumcision practice patterns in the United States. Pediatrics 101:E51–E56.
6. Nelson CP, Dunn R, Wan J, Wei JT. 2005. The increasing incidence of newborn circumcision: data from the nationwide inpatient sample. J Urol 173:978–981.
7. Xu F, Markowitz L, Sternberg M, Aral S. 2006. Prevalence of circumcision in men in the United States: data from the National Health and Nutrition Examination Survey (NHANES), 1999–2002. XVI International AIDS Conference:Abstract no. TUPE0395.
8. Richters J, Smith AM, de Visser RO, Grulich AE, Rissel CE. 2006. Circumcision in Australia: prevalence and effects on sexual health. Int J STD AIDS 17:547–554.
9. Alanis MC, Lucidi RS. 2004. Neonatal circumcision: A review of the world's oldest and most controversial operation. Obstet Gynecol Surv 59:379–395.
10. Morris BJ. 2007. Benefits of circumcision: medical, health and sexual. [Review] http://www.circinfo.net (over 400 refs).
11. McCoombe SG, Short RV. 2006. Potential HIV-1 target cells in the human penis. AIDS 20:1491–1495.
12. Patterson BK, Landy A, Siegel JN, Flener Z, Pessis D, et al. 2002. Susceptibility to human immunodeficiency virus-1 infection of human foreskin and cervical tissue grown in explant culture. Am J Pathol 161: 867–873.
13. Hussain LA, Lehner T. 1995. Comparative investigation of Langerhans cells and potential receptors for HIV in oral, genitourinary and rectal epithelia. Immunology 85:475–484.
14. Szabo R, Short RV. 2000. How does male circumcision protect against HIV infection? Brit Med J 320:1592–1594.
15. Miller C. 1998. Localization of simian immunodeficiency virus-infected cells in the genital tract of amle and female rhesus macaques. J Reprod Immunol 4:331–339.
16. Turville SG, Cameron PU, Handley A, Lin G, Pohlmann S, et al. 2002. Diversity of receptors binding HIV on dendritic cell subsets. Nat Immunol 3:975–983.
17. Boggiano C, Littman DR. 2007. HIV's vagina travelogue. Immunity 26:145–147.
18. de Witte L, Nabatov A, Pion M, Fluitsma D, de Jong MA, et al. 2007. Langerin is a natural barrier to HIV-1 transmission by Langerhans cells. Nat Med 13:367–371.
19. Wawer MJ, Reynolds SJ, Serwadda D, Kigozi G, Kiwanuka N, et al. 2005. Might male circumcision be more protective against HIV in the highly exposed? An immunological hypothesis. AIDS 19:2181–2182.
20. Peters B, Whittall T, Babaahmady K, Gray K, Vaughan R, et al. 2004. Effect of heterosexual intercourse on mucosal alloimmunisation and resistance to HIV-1 infection. Lancet 363:518–524.
21. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, et al. 2005. Randomized, controlled intervention trial of male Circumcision for reduction of HIV infection risk: The ANRS 1265 Trial. PLoS Med 2(10 pages):e298.
22. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, et al. 2007. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet 369:643–656.
23. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, et al. 2007. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet 369:657–666.
24. Williams BG, Lloyd-Smith JO, Gouws E, Hankins C, Getz WM, et al. 2006. The potential impact of male circumcision on HIV in Sub-Saharan Africa. PLoS Med 3:1032–1040.
25. Gray RH, Li X, Kigozi G, Serwadda D, Nalugoda F, et al. 2007. The impact of male circumcision on HIV incidence and cost per infection prevented: a stochastic simulation model from Rakai, Uganda. AIDS 21: 845–850.
26. Kahn JG, Marseille E, Auvert B. 2006. Cost-effectiveness of male circumcision for HIV prevention in a South African setting. PLoS Med 3: 2349–2358.
27. Halperin DT, Steiner MJ, Cassell MM, Green EC, Hearst N, et al. 2004. The time has come for common ground on preventing sexual transmission of HIV. Lancet 364:1913–1915.
28. Slaymaker E. 2004. A critique of international indicators of sexual risk behaviour. Sex Transm Infect 80:ii13–ii21.
29. Dickson N, van Roode T, Paul C. 2005. Herpes simplex virus type 2 status at age 26 is not related to early circumcision in a birth cohort. Sex Transm Dis 32:517–519.
30. Fergusson DM, Boden JM, Horwood LJ. 2006. Circumcision status and risk of sexually transmitted infection in young adult males: an analysis of a longitudinal birth cohort. Pediatrics 118:1971–1977.
31. Micali G, Nasca MR, Innocenzi D, Schwartz RA. 2006. Penile cancer. J Am Acad Dermatol 54:369–391.
32. Schoen EJ, Oehrli M, Colby CJ, Machin G. 2000. The highly protective effect of newborn circumcision against invasive penile cancer. Pediatrics 105: http://www.pediatrics.org/sgi/content/full/105/3/e36.
33. Schoen EJ. 1991. The relationship between circumcision and cancer of the penis. CA Cancer J Clin 41:306–309.
34. Kochen M, McCurdy S. 1980. Circumcision and risk of cancer of the penis. A life-table analysis. Am J Dis Child 134:484–486.
35. Wiswell TE. 1995. Neonatal circumcision: a current appraisal. Focus Opin Pediat 1:93–99.
36. Wiswell TE. 1997. Circumcision circumspection. N Engl J Med 36: 1244–1245.
37. Tsen HF, Morgenstern H, Mack T, Peters RK. 2001. Risk factors for penile cancer: results of a population-based case-control study in Los Angeles County (US). Cancer Causes Control 12:267–277.
38. Morris BJ, Rose BR. 2007. Cervical screening in the 21st century: the case for human papillomavirus testing of self-collected specimens. Clin Chem Lab Med 45:577–591.
39. Weaver BA, Feng Q, Holmes KK, Kiviat N, Lee SK, et al. 2004. Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. J Infect Dis 189:677–685.
40. Castellsague X, Bosch FX, Munoz N, Meijer CJLM, Shah KV, et al. 2002. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med 346:1105–1112.
41. Lajous M, Mueller N, Cruz-Valdez A, Aguilar LV, Franceschi S, et al. 2005. Determinants of prevalence, acquisition, and persistence of human papillomavirus in healthy Mexican military men. Cancer Epidemiol Biomarkers Prev 14:1710–1716.
42. Castellsague X, Albero G, Cleries R, Bosch FX. 2007. HPV and circumcision: A biased, inaccurate and misleading meta-analysis. J Infect (Epub ahead of print Apr 10).
43. Katelaris PM, Cossart YE, Rose BR, Thompson CH, Sorich E, et al. 1988. Human papillomavirus: the untreated male reservoir. J Urol 140: 300–305.
44. Kohn F-M, Pflieger-Bruss S, Schill W-B. 1999. Penile skin diseases. Andrologia 31:3–11.

45. Pratt-Thomas HR, Heins HC, Latham E, Dennis EJ, McIver FA. 1956. Carcinogenic effect of human smegma: An experimental study. Cancer 9:671–680.
46. Waskett J, Morris BJ. 2007. Re: ''RS Van Howe, FM Hodges. The carcinogenicity of smegma: debunking a myth. J Eur Acad Dermatol Venereol 2006;1046–1054'' - an example of myth- and mythchief-making? (Letter to the Editor). J Eur Acad Dermatol Venereol 21: in press [DOI: 10.1111/j.1468-3083.2007.02439.x
47. Aynaud O, Ionesco M, Barrasso R. 1994. Penile intraepithelial neoplasia - specific clinical features correlate with histologic and virologic findings. Cancer 74:1762–1767.
48. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, et al. 2005. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. Int J Cancer 116:606–616.
49. Baldwin SB, Wallace DR, Papenfuss MR, Abrahamsen M, Vaught LC, et al. 2004. Condom use and other factors affecting penile human papillomavirus detection in men attending a sexually transmitted disease clinic. Sex Transm Dis 31:601–607.
50. Bailis SA. 2000. Circumcision—the debate goes on. Pediatrics 105:682.
51. Maden C, Sherman KJ, Beckmann AM, Huslop TK, Heh OZ, et al. 1993. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. J Nat Canc Inst 85:19–124.
52. Morris BJ. 2003. Circumcision for phimosis and other medical indications in Western Australian boys. (Critical comment). Med J Aust 178:588–589.
53. Morris BJ, Waskett J, Bailis SA. 2007. Case number and financial impact of circumcision in prostate cancer reduction. BJU Int 100:5–6.
54. Koyle MA, Barqawi A, Wild J, Passamaneck M, Furness PD. 2003. Pediatric urinary tract infections: the role of fluoroquinolones. Pediatr Infect Dis J 22:1133–1137.
55. Schoen EJ, Colby CJ, Ray GT. 2000. Newborn circumcision decreases incidence and costs of urinary tract infections in the first year of life. Pediatrics 105:789–793.
56. Wiswell TE, Hachey WE. 1993. Urinary tract infections and the circumcision state: An update. Clin Pediat 32:130–134.
57. Singh-Grewal D, Macdessi J, Craig J. 2005. Circumcision for the prevention of urinary tract infections in boys: a systematic review of randomized trials and observational studies. Arch Dis Child 90:853–858.
58. Hsiao AL, Chen L, Baker MD. 2006. Incidence and predictors of serious bacterial infections among 57- to 180-day-old infants. Pediatrics 117:1695–1701.
59. Craig JC, Knight JF, Sureshkumar P, Mantz E, Roy LP. 1996. Effect of circumcision on incidence of urinary tract infection in preschool boys. J Pediat 128:23–27.
60. Wiswell TE. 2000. The prepuce, urinary tract infections, and the consequences. Pediatrics 105:8602.
61. Conway PH, Cnaan A, Zaoutis T, Henry BV, Grundmeier RW. 2007. Recurrent urinary tract infections in children: Risk factors and association with prophylactic antimicrobials. J Am Med Assoc 298:179–1186.
62. Zorc JJ, Kiddoo DA, Shaw KN. 2005. Diagnosis and management of pediatric urinary tract infections. Clin Microbiol Rev 18:417–422.
63. Zorc JJ, Levine DA, Platt SL, Dayan PS, Macias CG, et al. 2005. Clinical and demographic factors associated with urinary tract infection in young febrile infants. Pediatrics 116:644–648.
64. Rushton HG, Majd M. 1992. Dimercaptosuccinic acid renal scintigraphy for the evaluation of pyelonephritis and scarring: a review of experimental and clinical studies. J Urol 148:1726–1732.
65. Jacobson SH, Eklof O, Eriksson CG, Lins LE, Tidgren B, et al. 1989. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow up. Brit Med J 16:703–706.
66. Agartan CA, Kaya DA, Ozturk CE, Gulcan A. 2005. Is aerobic preputial flora age dependent? Jpn J Infect Dis 58:276–278.
67. Kallenius G, Moillby R, Svenson SB, Helin I, Hultberg H, et al. 1981. Occurrence of P-fimbriated Escherichia coli in urinary tract infections. Lancet ii:1369–1372.
68. Fussell EN, Kaak BM, Cherry R, Roberts JA. 1988. Adherence of bacteria to human foreskin. J Urol 140:997–1001.
69. Wijesinha SS, Atkins BL, Dudley NE, Tam PK. 1998. Does circumcision alter the periurethral bacterial flora? Pediat Surg Int 13:146–148.
70. Tokgoz H, Polat F, Tan MO, Sipahi B, Sultan N, et al. 2005. Preputial bacterial colonisation in preschool and primary school children. Int Urol Nephrol 37:101–105.
71. Glennon J, Ryan PI, Keane CT, Rees JPR. 1988. Circumcision and periurethral carriage of Proteus mirabilis in boys. Arch Dis Child 63:556–557.
72. Wiswell TE, Enzenauer RW, Holton ME, Cornish JD, Hankins CT. 1987. Declining frequency of circumcision: implications for changes in the absolute incidence and male to female sex ratio of urinary tract infections in early infancy. Pediatrics 79:338–341.
73. Wiswell TE, Miller GM, Gelston HM Jr, Jones SK. 1988. Effects of circumcision status on periurethral bacterial flora during the first year of life. J Paediat 113:442–446.
74. Stull TL, LiPuma JJ. 1991. Epidemiology and natural history of urinary tract infections in children [Review]. Med Clin N Am 75:287–297.
75. Gunsar C, Kurutepe S, Alparslan O, Yulmaz O, Daglar Z, et al. 2004. The effect of circumcision status on periurethral and glanular bacterial flora. Urol Int 72:212–215.
76. Serour F, Samra Z, Kushel Z, Gorenstein A, Dan M. 1997. Comparative periurethral bacteriology of uncircumcised and circumcised males. Genitourin Med 73:288–290.
77. Fischbacher CM. 1999. Circumcision of newborn boys. Lancet 353: 669–670.
78. Cascio S, Colhoun E, Puri P. 2001. Bacterial colonization of the prepuce in boys with vesicoureteral reflux who receive antibiotic prophylaxis. J Pediatr 139:160–162.
79. Thiruchelvam N, Cuckow PM. 2005. Effect of circumcision on urinary tract infection after successful antireflux surgery. BJU Int 95:453–454.
80. Sonmez F, Yazici M, Aydin N, Eyigor M, Univar T, et al. 2001. Possible asymptomatic carrier of Salmonella typhimurium in the preputium: a case report. Turk J Pediatr 43:76–78.
81. Anderson GG, Palermo JJ, Schilling JD, Roth R, Heuser J, et al. 2003. Intracellular bacterial biofilm-like pods in urinary tract infections. Science 301:105–107.
82. Fakjian N, Hunter S, Cole GW, Miller J. 1990. An argument for circumcision. Prevention of balanitis in the adult. Arch Dermatol 126:1046–1047.
83. Furgusson DM, Lawton JM, Shannon FT. 1988. Neonatal circumcision and penile problems: An 8-year longnitudinal study. Pediatrics 81:537–541.
84. Herzog LW, Alvarez SR. 1986. The frequency of foreskin problems in uncircumcised children. Am J Dis Child 140:254–256.
85. Orden B, Martin R, Franco A, Ibanez G, Mendez E. 1996. Balanitis caused by group A beta-hemolytic streptococci. Pediatr Infect Dis 15:920–921.
86. English JC, Laws RA, Keough GC, Wilde JL, Foley JP, et al. 1997. Dermatoses of the glans penis and prepuce. J Am Acad Dermatol 37:1–24.
87. Mallon E, Hawkins D, Dinneen M, Francis N, Fearfield L, et al. 2000. Circumcision and genital dermatoses. Arch Dermatol 136:350–354.
88. Downs AM, de Vincenzi I. 1996. Probability of heterosexual transmission of HIV: relationship to the number of sexual contacts. J AIDS 11:388–395.
89. Aynaud O, Piron D, Casanova J-M. 1999. Incidence of preputial lichen sclerosis in adults: Histologic study of circumcision specimens. J Am Acad Dermatol 41:923–926.
90. Rickwood AMK, Kenny SE, Donnell SC. 2000. Towards evidence based circumcision of English boys: survey of trends in practice. Brit Med J 321:792–793.
91. Kiss A, Kiraly L, Kutasy B, Merksz M. 2005. High incidence of balanitis xerotica obliterans in boys with phimosis: prospective 10-year study. Pediatr Dermatol 22:305–308.
92. Gargollo PC, Kozakewich HP, Bauer SB, Borer JG, Peters CA, et al. 2005. Balanitis xerotica obliterans in boys. J Urol 174:1409–1412.
93. Yang SS, Tsai YC, Wu CC, Liu SP, Wang CC. 2005. Highly potent and moderately potent topical steroids are effective in treating phimosis: a prospective randomized study. J Urol 173:1361–1363.
94. Lund L, Wai KH, Mui LM, Yeung CK. 2005. An 18-month follow-up study after randomized treatment of phimosis in boys with topical steroid versus placebo. Scand J Urol Nephrol 39:78–81.

95. Zampieri N, Corroppolo M, Camoglio FS, Giacomello L, Ottolenghi A. 2005. Phimosis: stretching methods with or without application of topical steroids? J Pediatr 147:705–706.
96. Griffin AS, Kroovand RL. 1990. Frenular chordee: implications and treatment. Urology 35:133–134.
97. Kalcev B. 1964. Circumcision and personal hygiene in school boys. Med Officer 112:171–173.
98. Oster J. 1968. Further fate of the foreskin: incidence of preputial adhesions, phimosis and smegma among Danish schoolboys. Arch Dis Child 43:200–203.
99. Wright J. 1970. How smegma serves the penis? Sexology 37:50–53.
100. Oh S-J, Kim KD, Kim KM, Kim KS, Kim KK, et al. 2002. Knowledge and attitudes of Korean parents towards their son's circumcision: a nationwide questionnaire study. BJU Int 89:426–432.
101. O'Farrell N, Quigley M, Fox P. 2005. Association between the intact foreskin and inferior standards of male genital hygiene behaviour: a cross-sectional study. Int J STD AIDS 16:556–559.
102. Stenram A, Malmfors G, Okmian L. 1986. Circumcision for phimosis: a follow-up study. Scand J Urol Nephrol 20:89–92.
103. Stenram A, Malmfors G, Okmian L. 1986. Circumcision for phimosis - indications and results. Acta Paediat Scand 75:321–323.
104. Frank R. 2000. A trade-off analysis of routine newborn circumcision. Pediatrics 106:954.
105. Peto J. 2001. Cancer epidemiology in the last century and the next decade. Nature 411:390–395.
106. Walboomers J, Meijer C. 1997. Do HPV-negative cervical carcinomas exist? (editorial). J Pathol 181:253–254.
107. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, et al. 1999. Human papillomavirus is a necessary cause of invasive cervical cancer. J Pathol 189:12–19.
108. Barrasso R, De Brux J, Croissant O, Orth G. 1987. High prevalence of papillomavirus associated penile intraepithelial neoplasia in sexual partners of women with cervical intraepithelial neoplasia. N Engl J Med 317:916–923.
109. Adami H-O, Trichopoulos D. 2002. Cervical cancer and the elusive male factor. N Engl J Med 346:1160–1161.
110. Drain PK, Halperin DT, Hughes JP, Klausner JD, Bailey RC. 2006. Male circumcision, religion, and infectious diseases: an ecologic analysis of 118 developing countries. BMC Infect Dis 6:172.
111. Manhart LE, Koutsky LA. 2002. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. Sex Transm Dis 29:725–735.
112. Castellsague X, Peeling RW, Franceschi S, de Sanjose S, Smith JS, et al. 2005. Chlamydia trachomatis infection in female partners of circumcised and uncircumcised adult men. Am J Epidemiol 162:907–916.
113. Peipert JF. 2003. Genital chlamydial infections. N Engl J Med 349: 2424–2430.
114. Cherpes TL, Meyne LA, Krohn MA, Hiller SL. 2003. Risk factors for infection with herpes simplex virus type 2: Role of smoking, douching, uncircumcised males, and vaginal flora. Sex Transm Dis 30:405–410.
115. Waskett JH, Morris BJ. 2007. Fine-touch pressure thresholds in the adult penis. BJU Int 99:1551–1552.
116. Bleustein CB, Fogarty JD, Eckholdt H, Arezzo JC, Melman A. 2005. Effect of neonatal circumcision on penile neurological sensation. Urology 65:773–777.
117. Payne K, Thaler L, Kukkonen T, Carrier S, Binik Y. 2007. Sensation and sexual arousal in circumcised and uncircumcised men. J Sex Med 4: 667–674.
118. Collins S, Upshaw J, Rutchik S, Ohannessian C, Ortenberg J, et al. 2002. Effects of circumcision on male sexual function: Debunking a myth? J Urol 167:2111–2112.
119. Fink KS, Carson CC, deVellis RF. 2002. Adult circumcision outcomes study: Effect on erectile function, penile sensitivity, sexual activity and satisfaction. J Urol 167:2113–2116.
120. Masood S, Patel HRH, Himpson RC, Palmer JH, Mufti GR, et al. 2005. Penile sensitivity and sexual satisfaction after circumcision: are we informing men correctly? Urol Int 75:62–66.
121. Waldinger MD, Quinn P, Dilleen M, Mundayat R, Schweitzer DH, et al. 2005. A multinational population survey of intravaginal ejaculation latency time. J Sex Med 2:492–497.
122. Laumann EO, Maal CM, Zuckerman EW. 1997. Circumcision in the United States. Prevalence, prophyactic effects, and sexual practice. J Am Med Assoc 277:1052–1057.
123. Williamson ML, Williamson PS. 1988. Women's preferences for penile circumcision in sexual partners. J Sex Educ Hlth 14:8–12.
124. Elder JS. 2007. Surgery illustrated: circumcision. BJU Int 99:1553–1564.
125. Morris BJ, Bailis SA, Castellsague X, Wiswell TE, Halperin DT. 2006. RACP's policy statement on infant male circumcision is ill-conceived. Aust NZ J Publ Hlth 30:16–22.
126. Krieger JN, Bailey RC, Opeya JC, Ayieko BO, Opiyo FA, et al. 2007. Adult male circumcision outcomes: experience in a developing country setting. Urol Int 78:235–240.
127. Scharlieb M, Silby FA. 1913. Youth and Sex. Dangers and Safeguards for Girls and Boys. London: Dodge Publishing Co.
128. Whitla W. 1912. A Dictionary of Treatment - Including Medical and Surgical Therapeutics. London: Bailli'ere, Tindall and Cox, 606 p.