Is Routine Circumcision Indicated in the Newborn?

An Affirmative View

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Neonatal circumcision can prevent urinary tract infections, pyelonephritis, and its ensuing end-stage renal disease (chronic pyelonephritis). Studies from Sweden show that the overall incidence of urinary tract infection in male infants is highest in the newborn.[1] At no other time is the incidence of urinary tract infection greater in male than in female patients. The same is not true in the United States if the infant is circumcised.

URINARY TRACT INFECTIONS

Following the statement by the American Academy of Pediatrics that there "is no absolute medical indication for the routine circumcision of the newborn,"[2] a study by Ginsburg and McCracken[3] showed that 95% of all boys with urinary tract infections during the first year of life were uncircumcised. Wiswell et al[4] later reported on over 400,000 infants studied by suprapubic urine aspirates. They found that while the incidence of urinary tract infection in circumcised boys was 0.1%, in the uncircumcised boys there was a tenfold increase to a 1% rate of infection. The 1% rate of infection has been questioned, but in Finland, where circumcision is almost never done, an epidemiologic study shows essentially the same rate.[5] Although the mothers of infants not circumcised in the study by Wiswell et al were routinely instructed on cleansing of the foreskin without forceful preputial retraction, infection was not prevented, as was previously suggested.

The infant at birth has no natural bacterial flora. Very soon after birth, however, the baby is colonized with both aerobic and anaerobic intestinal flora. These bacteria are most often transferred from the mother during birth or soon thereafter,[6] or the baby may become colonized with bacteria present in the environment if it is cared for in a nursery.[7] The mucosal surface of the prepuce of the male infant also becomes colonized within the first days of life by bacteria that he may share with his mother. One study suggests that such colonization may lead to urinary tract infection.[8] When mothers had bacteriuria during pregnancy, 24% of their infants were bacteriuric after delivery, and 3% of these developed clinical pyelonephritis; in a control group, only 0.2% of infants from nonbacteriuric mothers developed pyelonephritis. While this study may be criticized because it relied on voided urines for culture, the clinical diagnosis of acute pyelonephritis is hard to deny, and all patients, including control patients, were studied in the same way.

Several outbreaks of urinary tract infection in premature or neonatal nurseries have been reported.[9,10] In the most recent epidemic, personnel working in the nursery were shown to be colonized by the same *Escherichia coli* that caused pyelonephritis in the infants, either while the infants were in the nursery or at some time in the ensuing months, during which time their gastrointestinal tract continued to be colonized by the same bacteria.[11]

Lincoln and Winberg[12] long ago showed that the bacteria causing urinary tract infection in infant boys were present on the prepuce, and later studies by Bollgren and Winberg[13] showed that the prepuce becomes heavily colonized with *E coli* soon after birth. *E coli* colonization was confirmed by Hallett and colleagues,[14] who found that bacterial colonization of the prepuce was common until the age of 5 years. Wiswell et al[15] in a recent study has shown that at birth urethral cultures for Enterobacteriaceae are positive in over 30% of infant boys. The incidence of positive urethral cultures increased after birth in uncircumcised boys, while it decreased in circumcised boys.

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The complications of circumcision are minimal and occur at a low frequency (0.06% to 0.2%). No more than two to three deaths per year can be attributed to circumcision.[16] It appears that mortality from acute pyelonephritis in the uncircumcised population is greater. Indeed, Littlewood[17] reported early in the 1970s that as many as 11% of children who have a urinary tract infection during the first month of life may die of it, although the number of deaths in the present antibiotic era is much lower. The most recent report[16] shows two deaths from urinary tract infection in a study of 35,929 uncircumcised boys and no deaths in over 100,000 boys circumcised during the same study period. Studies by both Speert[18] and King[19] of different populations (each over 500,000) showed only one death attributable to circumcision.

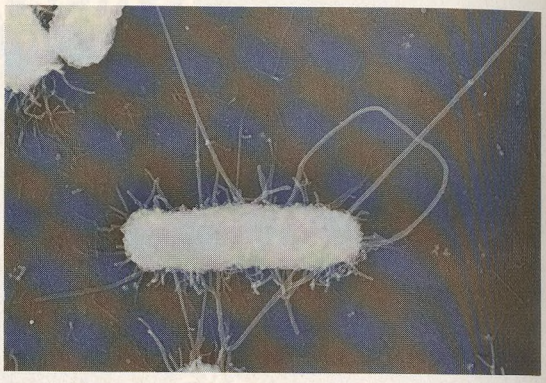

Figure 1. P-fimbriated *E coli*. Shadow cast with platinum-carbon. Transmission electron-microscope ×48000.

MECHANISMS OF BACTERIAL ADHERENCE

Bacterial colonization of mucosal surfaces has been found to be a necessary event preceding any infection other than those associated with wounds or instrumentation. A surface energy theory has been devised to explain the initial events that can lead to bacterial adhesion to mucosal surfaces.[20] While the negative charge on both bacteria and epithelial cells tends to repel the cells as they approach each other, the cells are attracted to each other when they are more than 10 nm apart. When closer than that, these charges tend to repel adhesion until a separation of less than 1 nm is achieved, at which time irreversible attachment will occur.

Bacteria normally do not have sufficient kinetic energy to come this close to epithelial cells. Attachment therefore occurs only if bacterial fimbriae or some other surface adhesin is present. Bacterial fimbriae, hairlike extensions from the surface of bacteria having a radius of 2 to 10 nm, are not repelled so much as bacteria, whose radius is approximately 250 nm. Fimbriae therefore are often responsible for bacterial adherence. Nonspecific factors such as hydrophobicity favor adhesion, since both bacteria and cell membranes are hydrophobic. As the cells come together, water is displaced, yielding a net free energy decrease, which is favored in nature, where energy cannot be expended needlessly.

Whatever the mechanism, once the adhesin and cell surfaces have come in contact, there is a specific, irreversible receptor-ligand interaction, with the cell acting as the receptor and the fimbriae acting as the ligand. On some bacteria such as *Salmonella*, there are, in addition to the fimbriae, carbohydrate polymers that effectively bridge the gap between the repulsive forces.[21]

PATHOGENESIS OF ACUTE PYELONEPHRITIS

Adherence has been most extensively studied for *E coli*, the causative organism in most urinary tract infections. Specific adherence by means of P fimbriae has been shown both in children and adults with nonobstructive acute pyelonephritis (Figure 1).[22–24] These fimbriae are so named because they are frequently associated with pyelonephritis, and the receptor for these fimbriae is the P blood group antigen.[25] This antigen is a glycolipid of the cell wall, the minimal specific urothelial cell receptor being the disaccharide moiety α-gal-1-4-β-gal.[26] Bacterial adherence by means of fimbriae and colonization first occurs in the intestinal tract, then colonization of either the perineum or prepuce, followed by urethral colonization and ascending urinary tract infection.

It should be emphasized that colonization is an asymptomatic event. It precedes symptomatic infection in both children and adults. Ascent from the periurethral area into the urethra and bladder may occur only because of an increase in numbers of colonizing bacteria, or may perhaps be assisted by mechanical factors, much as "honeymoon cystitis" often follows intercourse in adult women. Studies by Wiswell et al[15] have shown that *E coli* commonly colonize the prepuce, and the incidence of positive urethral culture for *E coli* increases in the absence of circumcision while it decreases in circumcised boys. In vitro studies of adherence to the prepuce showed that nephropathogenic P-fimbriated *E coli* adhere to the mucosal surface better than nonpathogenic *E coli* (Figure 2).[27] This finding is important, as P-fimbriated *E coli* are causative in over 95% of the cases of acute pyelonephritis in children.[23,24] Experimental studies with P-fimbriated *E coli* have shown that monkeys have the same urothelial

Figure 2. P-fimbriated *E coli* adherent to mucosa of foreskin. Scanning electron-microscope ×18000.

cell receptor as does man.[28] These P-fimbriated *E coli*, once in the bladder of the monkey, have been shown to ascend the urinary tract even in the absence of any anatomical abnormality, such as reflux, and produce acute pyelonephritis.[29] Thus it can be assumed that by this mechanism pyelonephritis may occur in the male neonate, as Winberg et al have shown that only one third of the infants with acute pyelonephritis have vesicoureteral reflux.

Neonatal pyelonephritis is a serious disease and is associated with bacteremia in 30% to 40% of the cases.[1,3] This high incidence of bacteremia has led to a misunderstanding in the past that pyelonephritis in the male neonate must be due to a blood-borne route of infection. Neonatal urinary tract infections occur in uncircumcised, but not in circumcised, infants; therefore, preputial bacterial adhesion and colonization leading to ascending urethral infection is the means by which acute pyelonephritis occurs in the newborn (Figure 3). Since the incidence of circumcision is approximately 80% in this country, urinary tract infections in uncircumcised boys cannot be considered random events.

END-STAGE RENAL DISEASE

In addition to the significant morbidity and even mortality caused by acute pyelonephritis, one must consider the morbidity and mortality that result from renal scarring, which can occur following pyelonephritis in the infant. It appears that those infections occurring in the first years of life most often lead to significant renal scars. Renal scarring may occur, however, if acute pyelonephritis is inadequately or improperly treated at a later age. Indeed, the

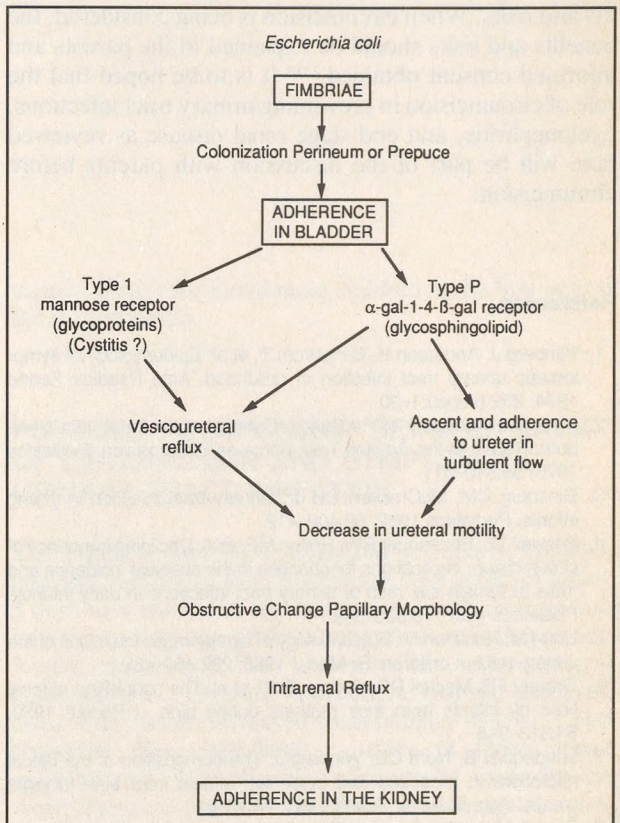

Figure 3. Pathogenesis of pyleonephritis.

studies of Winberg et al[1] in infants and Smellie et al[31] in adolescent children have shown that undiagnosed and untreated infections, whether in infancy or later, lead to an increase in renal damage.

Considering the 1% frequency of urinary tract infections in uncircumcised infants, it would be expected that if circumcision were no longer done in this country, 20,000 cases of acute pyelonephritis might occur annually. It has been estimated that 10% to 15% of all cases of acute pyelonephritis in the infant lead to renal scarring. Of these, 2% to 3% will develop renal insufficiency.[1] Indeed, up to 20% of all children or young adults with end-stage renal disease have been reported to have chronic pyelonephritis as the cause.[32,33] The overwhelming evidence therefore leads to the conclusion that the common American practice of neonatal circumcision is an important prophylactic operation, even though the practice was not previously well founded. Of interest, after a rigorous review by a special task force, the American Academy of Pediatrics has changed its previous policy. It now states that "newborn circumcision has potential medical bene-

fits and risks. When circumcision is being considered, the benefits and risks should be explained to the parents and informed consent obtained."[34] It is to be hoped that the role of circumcision in preventing urinary tract infections, pyelonephritis, and end-stage renal disease as reviewed here will be part of the discussion with parents before circumcision.

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An Opposing View

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Information published in the last 5 years suggests a possible association between being uncircumcised and increased risk for urinary tract infection in the first year of life.[1–4] Largely because of these data, the American Academy of Pediatrics convened a task force on circumcision, which released its findings in March of 1989. This group stated that circumcision "may result in decreased incidence of urinary tract infection. However, in the absence of well designed prospective studies, conclusions regarding the relationship of urinary tract infection to circumcision are tentative." They concluded: "When circumcision is being considered, the benefits and risks should be explained to the parents and informed consent obtained."[5]

Alan Brett[6] has recently written an editorial entitled "How Should Practicing Physicians Interpret the Published Data for Patients?" Although his subject matter is different from that of this paper, in addressing the question his title poses, Brett offers the reader some observations and approaches that are highly useful here: "Intervention based on risk factors differs qualitatively from treatment of already manifest disease. It offers specific people therapeutic manipulations on the basis of statistical risk, not existing illness. . . . As long as a recommended type of behavior (intervention) is at worst harmless, it may be ethically proposed without *unequivocal* proof of benefit; the possibility of benefit may suffice." He notes that a strongly interventionist perspective may color the published findings of large trials, and he suggests three perspectives from which to interpret the data to patients: (1) the relative differences between cases and controls, (2) the absolute differences between cases and controls, and (3) those without the morbid event and those who, having had the intervention, still experience the morbid event.

This general approach is used in the review that follows, in which the prepuce (foreskin) as a risk factor for urinary tract infection in male children in the first year of life is considered.

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POSSIBLE RELATIONSHIP BETWEEN LACK OF CIRCUMCISION AND SYMPTOMATIC URINARY TRACT INFECTION

The available data are summarized in Table 1. Ginsberg and McCracken[7] in 1982 described a case series of infants 5 days to 8 months of age hospitalized with urinary tract infections. Sixty-two of these subjects were male and only 3 were circumcised. This finding led the authors to conclude that it is "tempting to speculate that the uncircumcised male has an increased susceptibility to UTI." Subsequently there has been a series of three papers published by Wiswell and colleagues[1–3] from Brooke Army Hospital and various other army hospitals using retrospective cohort methods for children hospitalized with urinary tract infection in the first year of life. The suggestion emerging from these data is that there is a 10- to 20-fold increase in risk for urinary tract infection in the uncircumcised male infant in the first year of life. Only crude analyses are presented for the comparison of urinary tract infection rates in circumcised vs uncircumcised infants. No attempt was made to control for age, race, education, or income in these analyses. When this omission was pointed out to the authors, they replied that "what we found in our study population was that the circumcision frequency rate did not significantly vary between socioeconomic groups." No data have been produced, however, to document this assertion.[8]

To be convincing, the authors would need to present the data with an adjustment for those socioeconomic factors of significance, especially in view of the report from the National Health Examination Survey of 6768 boys 12 to 17 years old who were examined during the 1966–1970 examination cycle. Circumcision rates were 75% overall, but there were absolute differences ranging from 30% to 60% by income and education and between blacks and whites.[9] The role of these factors could be important, since other health-seeking behaviors are quite likely to vary with them. For example, uncircumcised children

TABLE 1. DATA SUGGESTING POSSIBLE RELATIONSHIP BETWEEN LACK OF CIRCUMCISION AND INCIDENCE OF URINARY TRACT INFECTION (UTI)

Investigators, Location, Year Published	Study Design	Study Period	Definitions	Subjects (N)	Results	Authors' Conclusions
Ginsburg and McCracken[7] Dallas, University of Texas, 1982	Case series	1976–1981	Hospitalized infants 5 d to 8 mo	100 total 62 M	Only 3 M infants circumcised	"Tempting to speculate that the uncircumcised male has an increased susceptibility to UTI."
Wiswell et al[1] Tripler Army Hospital, 1985	Retrospective cohort	1/1/82–6/30/83	Newborns followed retrospectively for 1 y. Endpoint: hospitalized for UTI in first year. Catheterized urine, 37; suprapubic urine, 4. Predisposing anomalies excluded	 2759 F 1919 M, circumcised 583 M, uncircumcised	UTI N % 13 0.47 4 0.21 24 4.12	Uncircumcised boys had 20-fold greater incidence of UTI than circumcised boys
Wiswell and Roscelli[2] Brooke Army Hospital, 1986	Retrospective cohort	1980–1983	Newborns followed retrospectively for 1 y. Endpoint: hospitalized for UTI in first year. Suprapubic urine all M infants, 6 F infants; 2 F infants catheterized. Predisposing anomalies excluded	 1905 F 1575 M, circumcised 444 M, uncircumcised	UTI N % 8 0.42 0 0.00 8 1.80	At least a 10-fold increase in UTI in uncircumcised boys
All army, 1986[2]	Retrospective cohort	1974–1976	Newborns from all army hospitals. Other definitions the same. Suprapubic urine 92% in M infants	 205,212 F 175,317 M, circumcised 41,799 M, uncircumcised	UTI N % 1164 0.57 193 0.11 468 1.12	
All army, 1986[2]	Retrospective cohort	Compares 1974–1976 with 1981–1983	Same definitions and methods	Total M infants 1974–76: 65,336 1981–83: 67,914 Circumcised M 1974–76: 55,821 1981–83: 50,183 Uncircumcised M 1974–76: 9,515 1981–83: 17,731	 172 0.26 230 0.34 89 0.16 37 0.07 83 0.87 193 1.09 Circumcision Rate (%) 1974–76 85.4 1981–83 74.0	Significant increase in the number of infections in boys during last 3 y compared with initial. Unequivocal increase in number of boys with UTIs as the circumcision rate decreased

TABLE 1. CONTINUED

Investigators, Location, Year Published	Study Design	Study Period	Definitions	Subjects (N)	Results	Authors' Conclusions
Wiswell et al,[3] 1987	Retrospective cohort	1975–1984	Same as 1986 all army	Total M infants 1975–79: 106,623 1980–84: 113,152 Circumcised M 1975–79: 89,975 1980–84: 83,688 Uncircumcised M 1975–79: 16,648 1980–84: 29,464	UTI N % 266 0.25 344 0.30 94 0.10 57 0.07 172 1.03 287 0.98 Circumcision Rate (%) 1975–79 84.3 1980–84 74.0	As circumcision rate decreased, there was a significant increase in the total number of infant boys with UTI
Herzog,[4] Boston Children's Hospital, 1989	Retrospective case-control	1985–1986	Case: various definitions of positive urine ($\geq 10^5$/mL etc). Control: negative urine. Predisposing anomalies excluded	M children <12 mo, suprapubic or catheterized urine at illness visit	UTI Yes No Circumcised 0 52 Uncircumcised 36 24 36 76	Results show that infant boys with a UTI are significantly more likely to be uncircumcised ($P < .001$). Odds ratio for case defined as $\geq 10^4$/mL of suprapubic urine was 39
Winberg et al,[12] 1989	International randomized trial of reflux therapy		Case: UTI with significant reflux	600 children	9.9% of subjects from USA are M, but 22.7% from Europe are M	That circumcision is rare in Europe and common in USA suggests reason for difference is noncircumcision in European boys

M - male
F - female

from families with lower income and educational levels might well be brought for medical care at a later time in the progression of their illness, resulting in disproportionate hospitalization rates. It is known that not all children with urinary tract infections in the first year of life are hospitalized; in Herzog's study from Boston Children's Hospital,[4] 19% were not. In addition, the work of Wiswell and colleagues does not take into account the possibility of differences in the health-care-providing behavior of physicians (eg, the use and timing of bag or suprapubic urine collection for diagnosis), which could result in different hospitalization rates between circumcised and uncircumcised male infants. Only population-based or prospective studies conducted in a manner similar to the study of Wettergren and others[10] can address or avoid this potential source of bias.

The interventionist sentiment mentioned by Brett is apparent in the writings of the Wiswell group. In the 1986 paper Wiswell and Roscelli[2] reported that there was an "unequivocal increase in the number of male urinary tract infections as the circumcision rates decreased." The actual rate changed from 0.26% to 0.34% in all male infants, comparing the 1974 to 1976 period with the 1981 to 1983 period. The *P* value for this change based on chi-square is .02. It is well known, however, that if large enough numbers are used, statistical significance may be achieved when biological significance is lacking. A more instructive way to examine the change is achieved by calculating the relative risk for urinary tract infection over the two periods. The relative risk then becomes 1.28 for the increase with a 95% confidence interval of 1.09 to 1.52. The lower boundary of this confidence interval very nearly includes unity. This comparison suggests that the effect, if unbiased, is small. While emphasizing the change in total urinary tract infection rates over time, the authors failed to mention a much larger apparent change in the rate of urinary tract infection from time 1 to time 2 in circumcised infants (from 0.16% to 0.07%). The resultant relative risk

for urinary tract infection in circumcised infants in the second period is 0.46 with a 95% confidence interval of 0.33 to 0.63. Since urinary tract infection is a biological event in either circumcised or uncircumcised boys, the rate in either of those subgroups should be relatively constant over time. When this finding was brought to the authors' attention, they suggested that a 0.21% rate for urinary tract infections in 1974 in circumcised boys was aberrant and led to the "erroneous impression" of change mentioned above.[8] In further analyses from this group, the year 1974 has been dropped (see the 1987 publication).[3] Clearly by leaving out the 1974 year, the graphic representation of the data looks better. In further correspondence Wiswell[11] describes the US army hospitals' experience from 1971 through 1986. He reports that the rate of urinary tract infection in their series of circumcised boys has ranged from 0.07% to 0.23% with a mean of 0.1%. One wonders, was the year with the 0.23% rate another aberrant year?

Finally, in the 1987 paper by Wiswell and his colleagues, they reported that urinary tract infection rates in circumcised boys for the years 1975 to 1984 ranged from 0.07% to 0.13%. These rates are said to be "relatively constant."[3] The rates are not constant. Two- to threefold differences in year-to-year rates derived from these large data sets imply problems with the data.

Herzog,[4] from Boston Children's Hospital, in 1989 reports a retrospective case-control study in which cases were found by examining the results of all suprapubic and catheterized urine specimens obtained in the emergency department as a part of illness workup in male children up to 1 year of age. Case patients were defined as those with greater than 100,000 organisms per milliliter. Control patients were individuals with negative urine samples. An attempt was made to control for the effects of age, race, and medical insurance source as a proxy for income. For 36 cases, in which none of the infants was circumcised, and 76 controls, the differences in the circumcision rates between cases and controls were highly significant ($P < .001$). It was reported that "there were no significant differences found in the two groups in age, ethnic group, and type of medical insurance." In 47% of the cases, however, the infants were less than 3 months of age, while only 39% of the control patients were that young; 47% of the case patients were Hispanic, 28% black, and 19% white, whereas the respective percentages for the control patients were 17%, 34%, and 47%; 50% of case patients were on Medicaid insurance compared with 33% of the control group. The overall numbers of subjects in this study are small, so none of the above differences was statistically significant; however, the odds ratio for nonwhite vs white ethnic differences between case patients and control patients was 3.0 (95% confidence interval 1.2 to 7.1), which suggests a true difference. One would be more confident of the results if the statistical analysis had been adjusted for age, ethnicity, and type of medical insurance. Another potential source of bias in this study was the loss of nearly one quarter (23%) of the potential control subjects for whom circumcision status could not be determined. Finally, the general comments about potential biases attributable to health-care-seeking and health-care-providing behaviors raised earlier are applicable to this study as well.

The final piece of evidence presented in Table 1 is reported by Winberg et al[12] from the randomized trial of reflux therapy. Of the 600 children entered into the trial so far with urinary tract infection, 9.9% of the subjects from the United States are male, where most male infants are circumcised, and 22.7% from Europe are male, where most male infants are not circumcised. These results are suggestive of the association between lack of circumcision and urinary tract infection.

Another line of evidence comes from comparison of symptomatic urinary tract infection rates in different geographical areas of the world. The incidence of symptomatic urinary tract infections in Swedish infant boys is 1.2%[10] (nearly all uncircumcised), a rate comparable to that reported overall by Wiswell[11] of 1.15% for uncircumcised boys. Similar rates in populations of largely uncircumcised boys have been reported from Austria and Germany.[11,13]

Work in recent years on the pathogenesis of urinary tract infections from a number of national and international sources lends biological plausibility to a possible association between lack of circumcision and urinary tract infection. The evidence suggests that infection is the result of gastrointestinal population from the environment by pathogenic organisms (most notably pyelonephritogenic, P-fimbriated *Escherichia coli*) with subsequent colonization of the periurethral area followed by ascending infection. Pyelonephritogenic *E coli* have been shown to colonize the periurethral and fecal flora in nearly 100% of cases of acute febrile pyelonephritis as compared with 10% in healthy controls.[12,14–19] Indeed, if the gut-colonizing bacteria of the newborn are P-fimbriated *E coli* strains, nosocomial outbreaks of pyelonephritis can occur.[20]

The various lines of evidence reviewed above have caused Winberg and coworkers[12] to pose the question, "Is the prepuce a mistake of nature?" They argue that a mistake is improbable, and propose as the explanation that one unphysiological intervention (circumcision) is counterbalancing the effect of another unphysiological state of affairs, namely, the exposure to the microbial environment of the modern maternity unit. They base their hypothesis on four observations. First, in biological settings, when the mother gives birth in the squatting or kneeling position, she rapidly transfers her largely anaerobic and non-*E coli* gut flora to the child during the

TABLE 2. COMMON AND MORE SERIOUS EARLY COMPLICATIONS OF CIRCUMCISION

Investigator	Year Published	Sample Size and Nature of Study	Hemorrhage (%)	Infection (%)	Surgical Trauma (%)*	Total Rate (%)
Gee and Ansell,[27] University of Washington	1976	5521 newborn boys. Record review, complications sought out in whole record	1.07	0.42	0.40	1.9
Metcalf et al,[28] University of Utah	1983	361, including interviewed outpatients	2.0	1.0	1.0	4.0
Harkavy,[29] Georgetown University	1987	4000 newborns	"Notifiable complications, mostly bleeding"			0.06
Wiswell and Geschke[30]	1989	100,157. All army, 1980–1985. Boys <1 mo only. Only if recorded as a complication	0.08	0.07	0.025	0.19

*Surgical trauma in this context includes removal of too much or too little skin, injury to the urethra or glans penis, circumcision in child with hypospadias, wound dehisence, pneumothorax.

process of delivery. Second, the child's gastrointestinal tract is the probable source of bacteria, and the male prepuce becomes heavily colonized with *E coli* during the first few days of life. Third, this colonization arises because *E coli* and P-fimbriated strains, in particular, bind avidly to the prepuce. Fourth, infantile pyelonephritis is due to a P-fimbriated *E coli* strain in about 90% to 97% of cases. Winberg and colleagues suggest two alternative approaches to the problem of urinary tract infections in infants aside from possible protection through circumcision: (1) an experimental approach of attempting to populate the newborn gut with less pathogenic bacteria while in the nursery, and (2) a practical approach of providing strict rooming-in to increase the likelihood of the baby being colonized by maternal strains, as suggested by the work of Bettleheim and coworkers.[21]

In summary, then, the various lines of evidence, ranging from case series reports to retrospective cohort and case-control studies to international geographical comparisons and studies of pathogenesis, suggest an association between uncircumcised status and increased incidence of urinary tract infection. It is clear from the above review that these data do not constitute the "unequivocal proof" required by Brett before proceeding with an intervention that is not harmless (circumcision) directed to the risk of urinary tract infection in the first year of life.

OTHER CONSIDERATIONS, OR WHAT ABOUT ACQUIRED IMMUNE DEFICIENCY SYNDROME?

Simonsen and coworkers,[22] in attempting to explain the different pattern for AIDS transmission in Africa as compared with that of the United States, performed a case-control study on 340 men reporting to a sexually transmitted disease clinic in Nairobi, Kenya. These men had very low rates for homosexuality and intravenous drug use. In an analysis controlling for potential differences in age, marital status, years living in Nairobi, travel outside of Kenya, age at first intercourse, number of lifetime sexual partners, frequency of contact with prostitutes, and lack of circumcision, the relative risk for human immunodeficiency virus positivity was 2.7 for uncircumcised men.[22] According to a research news article in *Science* (August 1989),[23] similar studies tend to confirm these findings in Africa. The results in the United States are conflicting.

COMPLICATIONS OF CIRCUMCISION

The possible benefits of an intervention (circumcision) have been considered. Now to address the price that some individuals pay if this intervention is undertaken. One universal complication of circumcision is pain.[24,25] Dixon and others[26] performed blinded Brazelton assessments on babies repeatedly before and after circumcision and uncircumcision and reported that circumcision results in disruptions in the children's behavior and recovery reactions for 24 hours or more.

In Table 2 the common and more serious early and late complications of circumcision are portrayed. The complications have been grouped into three categories: hemorrhage, infection, and surgical trauma. Surgical trauma includes removal of too much or too little skin, injury to the urethra or glans, wound dehiscence, circumcision of a child with hypospadias, and the like. The data are based mainly on recent reports on circumcisions performed in

the neonatal period. Gee and Ansell[27] reported the experience at the University of Washington nurseries for 5521 newborns circumcised at that institution from 1963 to 1972. The total rate of complications in this series was 1.9%. Fourteen of the complications (0.2%) were gravely serious: 1 life-threatening hemorrhage, 4 systemic infections, 8 circumcisions of infants with hypospadias, and 1 complete denudation of the penile shaft. Metcalf et al,[28] at the University of Utah, using interviews, questionnaires, and chart reviews on an outpatient population, got a total rate for hemorrhage, infection, and trauma of about 4%. Harkavy[29] reported on 4000 circumcisions with an incidence of 0.6% for "notifiable complications, mostly bleeding." It is not totally clear from his report what "notifiable" means, but the impression is that the physician had been notified about the particular complication. Wiswell and Geschke[30] reported on over 100,000 newborns from all army hospitals for the years 1980 through 1985. They sought only complications specifically recorded as such in the first month of life. Their total rate for the three groups of complication is about 0.19%, probably reflecting the stringency of the criteria and recording practices of the physicians involved. Late complications tend to divide themselves into three groups: the need for surgical revision; the presence of adhesions, skin bridges, and the like; and the occurrence of meatitis. Later surgical revision, usually requiring general anesthesia, is required approximately 1% of the time,[28,31] as was shown in two studies, one in the United States,[28] with a sample size of 230 outpatients, the other in England,[31] with a random population-based sample of 2428 boys.

The articles cited in Table 2 give a general sense of what one may expect in the way of common and moderately severe to severe early complications of circumcision. Extensive reviews[25,32,33] list many more potential complications, but these seem to be quite rare. Death as a complication from newborn circumcision has been estimated to occur in from 1 in 24,000 to 1 in approximately 500,000.[30,33] Some investigators have actively sought out complications by interview and have recorded rates of 55%.[34]

HOW SHOULD PRACTICING PHYSICIANS INTERPRET THE PUBLISHED DATA FOR PATIENTS?

In Table 3 the above question is approached by considering a hypothetical cohort of 2000 newborn male infants, 1000 of whom are circumcised and 1000 of whom are not circumcised. If one accepts the suggestive evidence presented by Wiswell and others as reviewed earlier, one can estimate that the relative differences for these two subcohorts will be a possible 10-fold relative increase in urinary tract infections in the uncircumcised male infants in the first year of life.[1-4] From the perspective of absolute differences, there will be 9 more urinary tract infections per 1000 newborns not circumcised. From the perspective of those without the morbid event (UTI), these data mean that 99.9% of circumcised infants would not experience the morbid event, while for the uncircumcised group the figure would be 99.0%. As noted in Table 3, the absolute benefit (possibly 9 infants will have urinary tract infection prevented) is weighed against the price paid by those experiencing the intervention (990 individuals circumcised who do not get urinary tract infections plus 1 who was circumcised and experiences a urinary tract infection in the first year of life) without any benefit to them. The price

TABLE 3. EXAMINATION OF POSSIBLE ASSOCIATION BETWEEN URINARY TRACT INFECTION (UTI) AND NONCIRCUMCISION IN A HYPOTHETICAL COHORT OF 2000 NEWBORN IN THE FIRST YEAR OF LIFE, WITH 1000 CIRCUMCISED, 1000 UNCIRCUMCISED

Relative Differences	**UTI Rate**	**Comment**
Circumcised	0.1	Possible 10-fold relative increase in uncircumcised boys
Uncircumcised	1.0	
Absolute Differences	**UTI, (No./%)**	Possible absolute difference of 0.9% (9/1000) between circumcised and uncircumcised boys
Circumcised	1 0.1	
Noncircumcised	10 1.0	
	9 0.9	
Perspective of Those without the Morbid Event (UTI)	**Nonevent Probability (no UTI)**	Possible boost in chances of no UTI in first year from 99% to 99.9%
Circumcised	999/1000	
Noncircumcised	990/1000	

Weighing absolute benefit against absolute price paid by those experiencing the intervention without benefit to them for a cohort of 1000 circumcised male infants.

Possible absolute benefit		9 UTIs possibly averted		
"Price" in circumcision complications* for 991 with no benefit:				
		If % incidence is:		
Early: hemorrhage, infection, surgical trauma	Number	0.2% 2	2% 20	4% 40
Late: surgical revision	Number	1% 10	— 10	— 10
Balance of benefits to complications. (Number of individuals)		−3†	−21	−41

Complications: hemorrhage, infection, or "surgical trauma." (See footnote Table 2 for definition of "surgical trauma.")
†+9 possible benefit, −2 early complications, −10 late complications = −3.

paid by the 991 receiving no benefit depends on the rates of complication. Three possible rates for early (0.2% from Wiswell and Geschke,[30] 2% from Gee and Ansell,[27] 4% from Metcalf et al[28]) and 1% for late complications have been examined.[28,31] At the lowest rate for early complications (0.2%) three more individuals on balance will have moderately severe to very severe complications from circumcision than will benefit from circumcision. At the other extreme (4% early complications), the result will be 41 more individuals moderately or seriously adversely affected by circumcision than the 9 who may benefit.

It can be argued that the gravity of urinary tract infection in infancy (≤1 year of age), and the neonatal period (≤30 days) in particular, is so significant as to outweigh numerical comparisons such as those in Table 3. Two questions seem relevant. How common are neonatal urinary tract infections in uncircumcised male infants? From the work by Bergstrom and colleagues,[35] Wiswell and Geschke,[30] and Ring and Zobel,[36] the incidence can be estimated at from 1.6 to 2.4/1000. This range is comparable to the yearly incidence rate of breast cancer or colon cancer in middle-aged adults and is more common than neonatal hypothyroidism. The second question is, how serious is a neonatal urinary tract infection? The answer to this question is less clear. From the data of Wiswell and Geschke,[30] the population-based mortality rate for uncircumcised male infants is 5.5 in 100,000 or about 1 in 18,000. The case fatality rate for their series was 1.9% (2/108). Other recent population-based data were not found in the literature. Case fatality rates for case series are available, however. In the pre-antibiotic era Craig[37] reported a case fatality rate of 15%; Littlewood[38] reported a rate of 7.6% in a series from 1950 to 1968. Davies and Gothefors,[39] in their review of newborn infections, concluded that the immediate prognosis should be uniformly favorable except in children with serious malformations or other underlying conditions. In summary, neonatal urinary tract infection is not a common event; the prognosis in the modern era is potentially serious, but not easily quantifiable.

CONCLUSIONS

Unequivocal proof that lack of circumcision is a risk factor for increased urinary tract infection is currently unavailable. "Intervention based on risk factors differs qualitatively from the treatment of already manifest disease."[6] The standard to be met is higher; it has not been met. The behavior change suggested (circumcision) is not harmless and therefore cannot be recommended without unequivocal proof of benefit. The rate of nonevent (no urinary tract infection) may be increased from 99.0% to 99.9% by circumcision. The price of a potential benefit to 9 in 1000 will be numerically overbalanced by the moderately severe to severe complications (early and late) even if the rate for early complication is as low as 0.2%.

Specific information on circumcision to be offered to parents should include the following:

1. An assessment of the potential benefits and risks as outlined
2. The suggestion that a strict rooming-in approach in hospital and early discharge have much to recommend them
3. The suggestion that the prepuce is not a mistake of nature

Sir James Spence's pithy observation from Newcastle-on-Tyne seems to capture the message best: "Nature is a possessive mistress and whatever mistakes she makes about the structure of the less essential organs such as the brain and stomach, and in which she is not much interested, you can be sure that she knows best about the genital organs."[40]

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