Inf. Disease

MEDICAL GRAND ROUNDS

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SEXUALLY TRANSMITTED DISEASES

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"Of considerable importance in predicting future control is the fact that venereal disease presents a moving target. It is unrealistic to consider that solution of current problems will eliminate the impact of these diseases. New problems are constantly appearing, both from the disclosure of previously unrecognized phenomena and from real changes in venereal disease epidemiology."

Gavin Hart, M.D. (1977)

The five classic sexually transmitted diseases are gonorrhea, syphilis, chancroid, lymphogranuloma venereum and granuloma inguinale. The latter three diseases have become distinctly uncommon at the present time. In constrast, other sexually transmitted agents have begun to appear. Tables 1 and 2, respectively, list the sexually transmitted diseases seen in persons attending STD clinics in six areas of the United States as contrasted with those causes for admission to an STD clinic in Scandinavia.

TABLE 1

Sexually Transmissible Diseases (STD) in Men, STD Clinics, October 1, 1976-June 30, 1977

	Cases per 100 Visits by Men						
	New Haven	Detroit	Minneapolis	Denver	DeKalb County	Lexington	Total
Gonorrhea	22.3	44.4	20.9	20.1	22.4	36.7	24.0
Nongonococcal urethritis	29.5	25.1	24.6	27.6	24.4	4.2	24.8
Genital herpes	2.7	0.1	4.3	3.0	7.3	1.7	3.4
Venereal warts	1.0	0.1	4.6	5.5	6.5	2.2	4.3
Syphilis	2.5	2.2	1.8	1.2	1.3	3.3	1.7
Scabies	2.2	0.0	1.8	1.0	2.4	0.6	1.3
Pediculosis pubic	4.5	0.4	2.1	4.3	1.8	2.5	2.9
All other*	0.8	0.3	0.3	2.1	2.2	0.1	1.2*
Total	65.5	72.6	60.4	64.8	68.3	51.3	63.6
Total visits	1,900	2,178	6,811	8,919	2,455	1,535	23,798

*Includes (cases per 100 visits): molluscum contagiosum (1.0), chancroid (0.1), lymphogranuloma venereum (<0.1), and granuloma inguinale (0.0).

TABLE 2

Diagnoses Recorded in Per Cent at the VD Clinic, 1972

	Men (n=2,090)	Women (n=1,489)
Gonorrhoeae	23.0	33.0
Syphillis	0.5	0.3
T. vaginalis	1.0	10.0
C. albicans	4.0	20.0
Condyloma ac.	8.0	5.0
Herpes sx. gen.	2.6	1.8
Pediculosis	2.0	2.1
Scabies	0.9	0.3
Non-gon. urethritis	33.0	4.0
Non-gon. vaginitis	-	10.0
Various	6.0	3.0
Observation	26.0	23.0
Total percentages	107.0	112.5

Numerically, gonorrhea and non-specific urethritis constitute the major problems in these clinics. Other significant problems include syphilis, genital herpes, pediculosis, scabies, trichomiasis, candidiasis, non-specific vaginitis, molluscum contagiosum and condyloma acuminata. The listings do not tabulate such pathogens as cytomegalovirus which are known, in part, to be sexually transmitted. Such tabulations also do not include some of the problems encountered by the homosexual population. In gay men, for example, hepatitis B virus is a major pathogen with an attack rate that may average 5% per year. Other pathogens affecting the gay male population include enteric microorganisms such as amebiasis, giardiasis, salmonellosis and shigellosis. A broader concept of sexually transmitted diseases

is beginning to emerge. This review cannot attempt to be inclusive. We will concentrate on the major new developments occurring with relationship to gonorrhea, chlamydial infections, syphilis, genital herpes and scabies. Consideration of these varying and diverse problems should enable an enlarged perception of the total state of the art as it applies to sexually transmitted diseases today.

Neisseria Gonorrhoeae

Neisseria gonorrhoeae, the gonococcus, is a pathogen known to mankind since the beginning of recorded history. The microorganism has a particular capacity to affect columnar epithelial tissue. In uncomplicated gonorrhea in the male, the gonococcus must ascend the urethra against the normal clearing mechanisms of the downward flow of mucous and urine. The initial stage in the disease process involves attachment of the microorganism to the microvilli of the columnar epithelial cells followed by penetration into the cell, multiplication and finally entrance into the subepithelial tissue. In its attachment and passage through the columnar epithelium, the gonococcus incites an inflammatory response in which polymorphonuclear leucocytes predominate. The clinical and pathological picture of gonorrhea results from the combination of these processes culminating in an inflamed, denuded urethral epithelium along with the presence of many leucocytes. The gonococcus in the male generally causes anterior urethritis but it can cause posterior urethritis with prostatis and epididymitis. In untreated gonorrhea, there is a tendency for scar formation with urethral stricture formation as a long-known complication of the disease. In uncomplicated gonorrhea in the female, the gonococcus invades both the urethra and the endocervix. In 10-15% of gonococcal infections in the female, the microorganism finally invades the fallopian tubes destroying columnar ciliated epithelium as it passes through the opening of the tube into the area surrounding the ovary. Pelvic inflammatory disease (PID) results

somtimes followed by scar formation and infertility. In its disseminated form, the microorganism can cause perihepatitis (the Fitz-Hugh, Curtis syndrome), the dermatitis-arthritis syndrome (disseminated gonococcal infection, DGI) and in rare instances may eventuate in meningitis and endocarditis. In the neonate, gonococcal ophthalmia results but the most common form of infection in this period is orogastric colonization. Neonatal sepsis can follow and occasionally a clinical presentation resembling the dermatitis-arthritis syndrome may result.

Recent studies have made significant advances in understanding the pathogenetic mechanisms wherein the gonococcus causes disease. It has been determined that in urethral pus, the gonococcus posseses a capsule composed most probably of polysaccharide and functioning in an antiphagocytic capacity. In virulent gonococcal colony types (T_1, T_2 but not T_3, T_4, and T_5) for man, pili have been found extending from the surface of the bacterial cell. Their length approximates two microns; their composition is protein with a subunit molecular weight of 19,000 ± 2,500, varying slightly for different strains. Gonococci can be serotyped by antigenic analysis of the pilus protein. According to one typing scheme, there are six types of gonococcal pili. Other schemes accentuate the antigenic variable determinants on pili; it has also been determined that common antigens may be found on all gonococcal pili. These structures serve as the initial site of attachment of the gonococcus to the microvilli of the columnar epithelial cell. It has been found that up to 10^4 receptor sites for pili are present on each cervical-vaginal cell. The exact cell receptors which enable attachment of pili are not known but the structure may partially be composed of carbohydrate. Attachment of pili is enhanced at pH 4.5 and by the presence of the ferric ion at pH 7.4. Since non-piliated organisms also can be shown to attach to cells, although with less avidity, other attachment sites on the gonococcus must also exist. It has

been suggested that the sugar moieties on gonococcal lipopolysaccharide (LPS, endotoxin) may be able to attach to the epithelial cell directly. Gonococcal LPS was incorporated into the membrane of articially constructed liposomes with the immunodeterminants expressed at the liposomal surface. Liposomes containing gonococcal LPS were able to attach more readily to epithelial cells than control liposomes.

After attachment has been accomplished, the gonococcus is endocytosed by the epithelial cell. Multiplication of the microorganism takes place within the lumen, on the surface of the epithelial cell and within the interior of the cell. Finally, the microorganism penetrates into subepithelial tissues, initiating inflammatory changes and destroying the epithelial cells. The mechanisms wherein the cells are destroyed probably mostly involve gonococcal LPS and other toxins, incompletely characterized at present. In addition to carrying LPS, the outer cell membrane contains a mixture of proteins (1a, 1b, 2 and 3). Protein 1, the principal outer membrane protein (POMP), exists in two principal forms, 1a and 1b, but both forms are antigenically alike. Protein 2 is also expressed on the cell surface (Figure 1) (37). The original gonococcal typing scheme of Johnston and Gottschlich used an outer membrane protein complex, consisting of LPS, proteins 1 and 2, and determined that there were 16 serotypes of *Neisseria gonorrhoeae* (Figure 2) (38). Although O antigenic side-chains, originating from the core glycolipid of LPS are present, it has not been possible to arrive at a method of serotyping the microorganism by examination of the antigenic constitution of the lipopolysaccharide as has been possible with Salmonella species.

Underneath the outer cell membrane is the peptidoglycan cell wall. Changes in cell wall linking resulting in permeability differences occur on a genetic basis and account for low level resistance to multiple antibiotics. The inner cell membrane

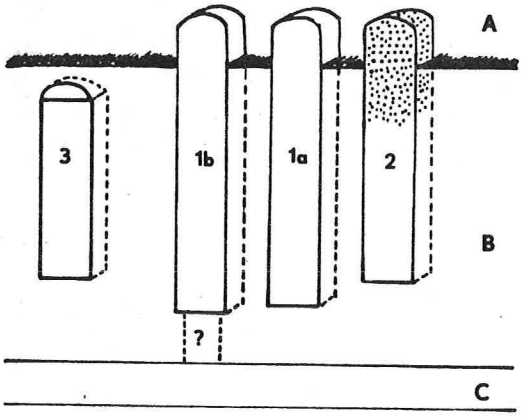

Figure 1. Proposed model depicting the relationship of proteins 1, 2, and 3 to each other and in relation to their orientation within the outer membrane of *N. Gonorrhoeae*. (A) Exterior of the gonococcal cell; (B) outer membrane matrix; (C) peptidoglycan; (1a) sodium deoxycholate-soluble polypeptide; (1b) sodium deoxycholate-insoluble polypeptide; (2) heat-modifiable polypeptide 2; (3) heat-stable polypeptide 3 which does not react with intrinsically labeled ^{3}H-dynsyl chloride-cycloheptaamylose.

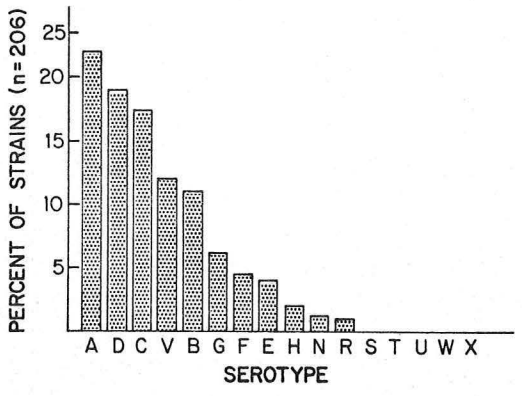

Figure 2. Histogram of the distribution of serotypes of *N. gonorrhoeae* isolated from the New York City area. Bars represent the percentage of strains having a particular serotype in a total population of 206 isolates.

encloses ribosomal elements, mitochondria and genetic information. The genetic information is in the form of chromosomal and plasmid DNA. It has been determined that there may be as many as three plasmids in the gonococcus (Table 3) (83).

TABLE 3

Two Distinct Types of Penicillinase-Producing *N. gonorrhoeae*

Geographical Distribution	R plasmid (Mdaltons)	Other Plasmids		Auxotype	Tetracycline resistance
		24.5 Mdaltons	2.6 Mdaltons		
Far East and United States	4.3	Present[a]	Present	Prototrophic proline dependent	High
West Africa and England	3.2	Absent	Present	Arginine dependent	Moderate

[a]Present in 43% of strains tested.

The largest plasmid has a molecular weight of 24.5 megadaltons; the smallest one has a molecular weight of 2.2 megadaltons. Two intermediate plasmids exist with molecular weights of 3.2 and 4.3 megadaltons. The intermediate sized plasmid has been determined to be that portion of DNA which codes for the production of penicillinase. It has been ascertained by DNA homology studies that the intermediate sized plasmid most probably was inserted into the gonococcus by conjugation with *Hemophilus parainfluenzae* under intense antibiotic pressure in several different parts of the world (Far East, West Africa). This plasmid is present only in penicillinase producing gonococci. The function of the smallest plasmid is not known and for that reason it has been termed the "cryptic" plasmid. The largest plasmid is thought to code for structures involved in the process of conjugation. Although penicillinase production is one method of antibiotic resistance, microorganisms producing this enzyme have not spread widely in the United States.

Low-level antibiotic resistance, often to multiple antibiotics including penicillin, is mediated by changes in chromosomal DNA induced by the pressure of antibiotic concentrations insufficient to kill the gonococcus. According to Sparling, in the presence of a suboptimal concentration of antibiotic, changes in chromosomal DNA occur. These changes result in increased cross-linking of the peptidoglycan cell wall and to alterations of the outer cell membrane proteins. As a consequence, there is decreased permeability of the outer surface of the gonococcus making it more difficult for multiple antibiotics including penicillin to cross into the interior of the cell. Substances such as crystal violet also are not able to penetrate into the cell; the same reasoning also applies to essential nutrients. As a consequence of these changes, the gonococcus survives in a hostile environment. The microorganism, however, is not able to compete with antibiotic sensitive gonococci when the selective pressure of inadequate antibiotic dosage is removed. Prior to the widespread use of relatively high dose penicillin usage as recommended by the USPHS, the gonococcus was becoming increasingly resistant to multiple antibiotics. After 1972, this trend was reversed with penicillin sensitive gonococci becoming more prevalent (Table 4) (83).

TABLE 4

Increasing Sensitivity of Gonococci in the United States to Penicillin

	MIC Penicillin G (μg/ml) (% Isolates)		
Year	≤0.03	0.06-0.125	≥0.25
1972	18.9	27.9	53.2
1973	32.4	30.3	37.3
1974	36.1	33.3	31.6
1975	37.2	34.6	28.2

Much also has been learned about the immunology of gonococcal infections. Polymorphonuclear leucocytes are brought to the epithelial surface by gonococcal products called chemotaxins. At the epithelial surface, both IgG and secretory IgA are formed in response to infection. The IgA most probably functions to coat gonococcal surface antigens thereby preventing attachment. Gonococci also produce a protease which is capable of splitting secretory IgA. Secretory IgA is produced by a system which has a limited immunological memory and disappears from washings of the epithelial cell surfaces relatively soon after infection has occurred (Figure 3) (89).

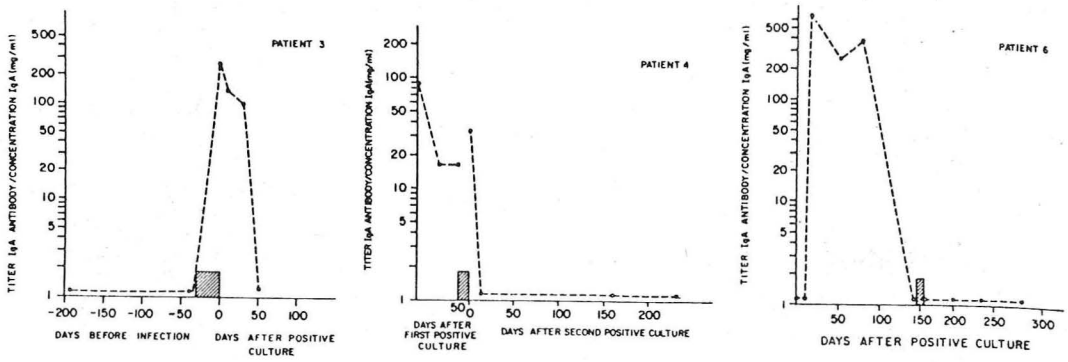

Figure 3. Secretory IgA antibody to *N. gonorrhoeae* in vaginal washings before and after infection.

In the presence of immune IgG directed against the principal outer membrane protein and complement, direct lysis of the bacterial cell can occur. In the presence of immune IgG directed against gonococcal pili, phagocytosis is enhanced (opsonic phagocytosis). It is misleading to consider that all gonococci that are encountered in urethral pus are intracellular. In phase microscopy studies, it can be seen that some of these gonococci actually rest on the surface of the cell. Once inside the phagocyte, the gonococcus is destroyed. Without specific antibiotic therapy, gonoccocal mucosal infections are limited in time. Recurrent mucosal infections are common and result from the antigenic diversity of the gonococcus aided by the

limited memory of the surface immunoglobulin secretory system. Although recurrent mucosal infections are common, a documented second episode of disseminated gonococcal infection is distinctly uncommon and should signal the physician to investigate the patient for a disorder of one of the terminal components of complement (C6 through C8).

The pathogenesis of pelvic inflammatory disease (PID) is being elucidated. It has been hypothesized that initial episodes of PID are related to infection with the gonococcus. First episodes predispose to recurrent infections by disturbing surface mucosal immunity by scar formation and disruption of the normal ciliated columnar epithelium of the endosalpynx. In cultures of women with PID taken by culdocentesis, multiple microorganisms, with and without the gonococcus can be found (Table 5, 6)(9). Even in first episodes of PID, the gonococcus may only be found in the endocervix. It appears probably that gonococcal infection predisposes to invasion of the endosalpynx by normal genital tract commensals. Secondary or tertiary episodes of PID are more completely caused by these commensals. An alternate explanation that seems less likely is that the gonococcus may initiate all episodes of PID, with the absence of that microorganism from culdocentesis cultures being a function of the time elapsed from the beginning of the infection with commensal bacteria being inhibitory for the growth of the gonococcus. Inadequate treatment may cause a prolonged course of PID or lead to complications. In Scandanavian countries, the incidence of gonorrhea is decreasing. However, the incidence of PID is not and may even be increasing. The increase in PID in those countries has been closely correlated with the increase in non-specific urethritis. Women with PID had been cultured at

TABLE 5

Results of Cultures of Peritoneal Fluid From 56 Women With Pelvic Inflammatory Disease From Whom *N. Gonorrhoeae* Was Isolated From The Lower Genital Tract

Organism		Number
Anaerobes		
Gram-positive cocci		61
Peptococcus prevotii	(14)	
Peptococcus asaccharolyticus	(7)	
Peptococcus magnus	(6)	
Peptococcus variabilis	(6)	
Peptococcus productus	(4)	
Peptococcus micros	(2)	
Peptococcus morbillorum	(1)	
Peptococcus constellatus	(1)	
Peptostreptococcus anaerobius	(11)	
Peptostreptococcus intermedius	(3)	
Peptostreptococcus parvulus	(1)	
Gaffkya anaerobius	(5)	
Bacteroids SP		18
B fragilis	(12)	
B melaninogenicus	(3)	
Other	(3)	
Clostridium SP		5
Others		5
Total anaerobes		89
Aerobes		
N. gonorrhoeae		46
Streptococci		30
S. viridans	(11)	
S. faecalis	(10)	
Group B	(5)	
Group D	(4)	
E. coli		9
Proteus SP		2
Total aerobes		71

TABLE 6

Results of Cultures of Peritoneal Fluid From Women with Pelvic Inflammatory Disease From Whom *N Gonorrhoeae* Was Not Isolated From the Lower Genital Tract

Organism		Number
Anaerobes		
Gram-positive cocci		54
Peptostreptococcus anaerobius	(15)	
Peptostreptococcus micros	(6)	
Peptostreptococcus productus	(2)	
Peptococci prevotti	(6)	
Peptococci magnus	(7)	
Peptococci asaccharolyticus	(5)	
Peptococci morbillorum	(2)	
Peptococci constellatus	(1)	
Peptococci variabilis	(1)	
Gaffkya anaerobius	(9)	
Bacteroides SP		14
Bacteroides fragilis	(11)	
Bacteroides melaninogenicus	(2)	
Bacteroides corrodens		
Clostridium SP		7
Others		4
Veillonella parvula	(2)	
Acidaminococcus sp	(2)	
Total anaerobes		79
Aerobes		
Streptococcal SP		26
S. viridans	(13)	
S. faecalis	(4)	
Group B	(4)	
Group D	(5)	
E. coli		6
Proteus SP		1
Total aerobes		33

laparoscopy and *Chlamydia trachomatis* has been found. The contribution of *Chlamydia trachomatis* to PID in the United States is not known. Women with that microorganism exclusively in the endocervix have been followed prospectively without specific therapy. Some of these patients have subsequently developed typical acute PID.

Gonococci producing DGI have been found to be distinctive. These microorganisms are exquisitively penicillin sensitive, are resistant to the normal bactericidal effect of human serum, have a distinctive auxotype (AHU^-), that is, they require arginine, hypoxanthine and uracil for growth, and 88% of strains tested have an antigenically similar principle outer membrane protein. Sites positive for gonococci by culture in DGI are shown in Table 7.

TABLE 7

Bacteriological and Serological Findings in 74 Patients With Disseminated Gonococcal Infections

	Number of Patients	
Gonococci isolated from urogenital specimens	54/63	(86%)
Gonococci isolated from blood	7/54	(13%)
Gonococci demonstrated with IFL in skin lesions	39/56	(70%)
Gonococcal antibodies in paired sera (GCFT)	48/56	(86%)

Episodes of DGI occur at or directly after menses and it has been postulated that menustration predisposes to gonococcal blood stream invasion. In the male, asymptomatic urethral and pharyngeal gonococcal colonization are often the sources of DGI. The presence of pharyngeal gonococcal colonization does not infer a homosexual preference since heterosexuals may have gonococci at this site also. To be noted in Table 8 is the absence of rectal colonization in the male population.

All the males in this series were heterosexual and the absence of rectal colonization tends to corroborate that fact.

TABLE 8

Results of Endocervical, Urethral, Rectal, and Pharyngeal Cultures for *N Gonorrhoeae* Among 95 Patients with Disseminated Gonococcal Infection

	No. cultured	Positive		Only site-positive	
		Number	%	Number	%
Males					
Urethra	37	22	59	7	19
Rectum	31	0	0	0	0
Pharynx	33	10	30	2	6
Females					
Endocervix	58	48	83	11	19
Urethra	9	7	78	0	0
Rectum	50	23	46	1	2
Pharynx	43	5	12	0	0

In an interesting approach toward explaining the incidence of DGI (1-3% of infected persons) and why the microorganism has such distinctive properties, investigators at the University of California at San Diego have recently determined that there is an antibody of the IgG class present in normal human serum that binds to the surface of DGI gonococcal strains and that subsequently prevents the binding of antibody to the gonococcus, binding of complement and bacterial cell lysis. This blocking antibody can be removed by absorption with DGI strains but not with other gonococcal isolates. The blocking antibody is considered unique because it appears to be the only known natural antibody which promotes bacteremia in humans (Figure 4) (50).

Much of the basic work done on the pathogenesis, microbiology and immunology of *Neisseria Gonorrhoeae* has direct clinical applicability. 1) No matter which antibiotic is given to the patient with gonorrhea, the dosage and duration should be sufficient to kill the microorganism. Inadequate dosages promote the low-level

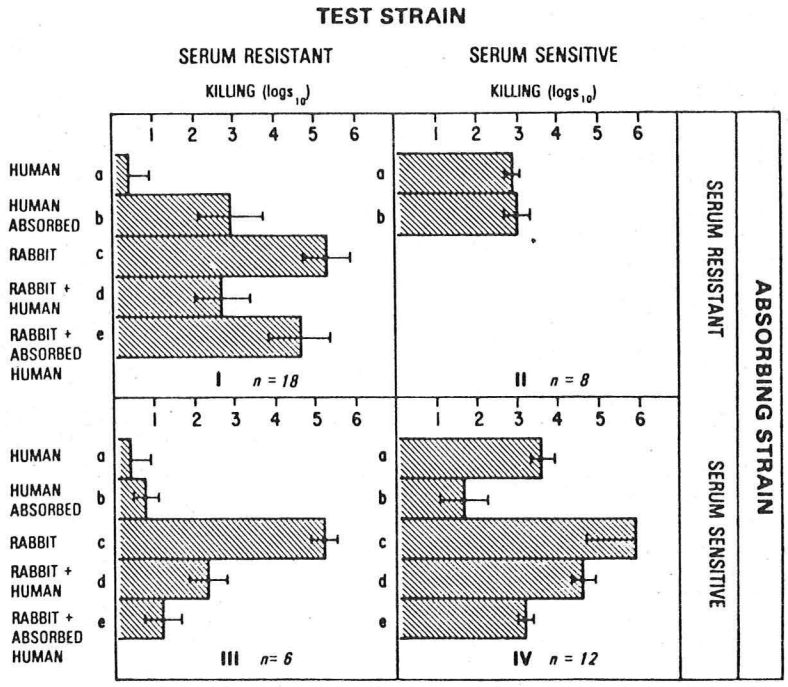

Figure 4. Human sera were absorbed at 4°C for 30 minutes three times with $3x100^9$ serum-sensitive (>1.0 $\log_{10}$ killed by human serum) or serum-resistant (<1.0 $\log_{10}$ killed by human serum) gonococci. Absorbed sera were tested for ability to kill either serum-sensitive or -resistant gonococci and to block killing by normal rabbit sera. Killing by normal human serum (a), absorbed human serum (b), normal rabbit serum (c), or mixtures (d,e) is presented by the horizontal bars, with brackets for one standard deviation. Preservation of complement in sera absorbed with sensitive strains was demonstrated by thier ability to support killing of serum-sensitive gonococci by heat-decomplemented rabbit serum. Student's t test for paired samples showed significant differences at $P<0.01$ for the following comparisons: Ia<Ib, Ic>Id, Id<Ie, IVa<IVb, IVc>IVd, IIIc>IIId, and IVd>IIId.

resistance to multiple antibiotics determined by increases in the impermeability of the cell wall. 2) Although penicillinase producing gonococci have not spread widely in the United States, the physician must be aware of their existence and a "test of cure", that is a culture of the patient after antibiotic treatment, should be performed on all patients with proven gonorrhea. 3) Patients particularly hard to treat are those with pharyngeal or anorectal gonorrhea, partly because penicillin does or may not attain adequate concentrations in oropharyngeal secretions and because of the potential presence of penicillinase producing micro-organisms (Enterobacteriacea) in the anorectal area. 4) Since microorganisms that cause disseminated gonococcal infection are exquisitively pencillin sensitive, they

have usually been easy to treat with as little as three days of a high dose penicillin regimen. Some authorities continue to recommend an additional four days of antibiotic therapy. The high dose penicillin refers to 12 million units of penicillin per day for three days. 5) It may be possible to produce a vaccine against the gonococcus. The major reasons why such a vaccine could not be produced are the antigenic diversity of the gonococcus and the limited memory of the secretory immune system at the epithelial surface where the gonococcus is most likely to be encountered first. However, a potential gonococcal vaccine might contain a mixture of the proteins which are found on pili, either multiple antigens or an antigenically broadly reactive constituent of the proteins found on pili. The vaccine might also contain representative principle outer membrane proteins so as to encompass the numerically most frequent gonococcal isolates in a given geographical area. Inclusion of multiple antigens in a vaccine preparation has a precedent in that the present pneumococcal vaccine contains fourteen different polysaccharide types. The pneumococcal vaccine also elicits some degree of surface immunity as determined by lower oropharyngeal colonization rates with the pneumococcus in persons given the vaccine. The gonococcal vaccine could be given to patients, for example, attending a clinic for sexually transmitted diseases. The known rate of repeated gonorrhea is at a high level. Such recidivism has been shown to account for a large portion of the morbidity due to the gonococcus in the population. Listed in the appendix present USPHS recommendations concerning the treatment of gonorrhea.

Chlamydia Trachomatis

Chlamydia are obligate intracellular parasites that have been divided into two groups, *Chlamydia psittaci* and *Chlamydia trachomatis*, on the basis of sensitivity to sulfonamides and the ability to form iodine staining intracytoplasmic

inclusions. *C. trachomatis* is sensitive to sulfonamides and produces inclusions which can be stained by iodine and will be the only group of microorganisms reviewed in this section. *C. Psittaci* is the cause of psittacosis. Both groups of microorganisms have a common complement fixation test antigen. The particle capable of transmitting infection is called the elementary body. It is endocytosed by columnar epithelial cells and begins to change within the endocytotic vesicle into the reticulate or intermediate body. The reticulate body is capable of multiplication by binary fission and as a consequence of multiple divisions within the vesicle an inclusion body is formed. Late in the division cycle, elementary bodies are again formed. The inclusion body can be stained with iodine, Giemsa stain or fluorescent antibody. When the inclusion body reaches a certain stage of development, lysis occurs releasing elementary bodies to initiate another cycle of infection. Chlamydial infections are noted for their persistence and for their capacity to become latent. Chlamydia can be demonstrated by direct staining of the inclusion body in cells or else they can be cultured in the yolk sac of embryonated chicken eggs or in tissue culture (Table 9) (78). It has been determined that prior irradiation of the tissue culture cells or pretreatment with idoxuridine increases the size of the intracytoplasmic inclusion and decreases the capacity of the cells to divide thus making the inclusions easier to demonstrate. McCoy cells and certain strains of HeLa cells have been found to be sensitive means for isolation of the chlamydia and tissue culture consistutes the most effective means of demonstrating the microorganism.

C. Trachomatis can be divided into serotypes by the microimmunofluorescent method of Wang and Grayston. Serotypes A through C are the cause of endemic trachoma; D through K cause oculogenital infections and L_1, L_2 and L_3 are the serotypes causing LGV (Table 10) (95).

TABLE 9

Application of Diagnostic Tests for Chlamydial Infections

	Psitta-cosis	LGV	Trachoma	Inclusion Conjunctivitis Adult	Inclusion Conjunctivitis Newborn	Urethritis	Cervi-citis
Diagnostic Test							
A Cytology							
Iodine	-	-	±	±	+	-	-
FA	-	-	++	++	++	+	+
Giesma	-	-	++	+	++	±	+
B Serology							
CF	++	+	-	±	-	-	±
Micro-IF	?	+	+	+	+	+	+
C Isolation							
Yolk sac	++	++	+	+	++	+	+
Mice	++	+	-	-	-	-	-
Tissue Culture	++	++	++	++	++	++	++

Note: This emphasizes diagnostic tests. Some tests, particulary the micro-IF, are extremely useful in epidemiologic surveys - less so for diagnosis.
+ = often successful
++ = a most useful technique
± = rarley successful, usually not worth performing
- = not useful

TABLE 10

Distribution of 563 Trachoma-LGV Strains (Derived From 514 Patients) According To Immunotype and Origin

	Trachoma Types										LGV Types		
Origin	A	B	Ba	C	D/E	F/G	H	I	J[a]	K	L_1	L_2	L_3
Ocular Trachoma-endemic area[b]	10	34	13	104	4[c]								
Trachoma-non-endemic area		2	4	2	40	13	1	4	2	1			
Genital		17			134	91	23	16	10	16		4	1
LGV-bubo											3	11	3

[a]Two "CJ" strains are included. [b]American Indian reservations are included.

[c]All are type D.

One of the most common sexually transmitted diseases in the world today is non-specific urethritis. Symptoms include dysuria and urethral discharge but that discharge is mucopurulent and generally not frankly purulent as in gonorrhea. A smear taken from within the urethra reveals at least five leucocytes per high power field and the absence of intracellular Gram negative diplococci. Usually *C. trachomatis* causes anterior urethritis but is capable of invading the posterior urethra where it can cause epididymitis. In males below the age of 35 years, *C. trachomatis*, serotypes D-K, have been shown to be a definite cause of epididymitis by direct puncture and culture of the inflamed epididymis. Follicular conjunctivitis with inclusion bodies can occur in sexually active adults. The conjunctivitis is characterized by the presence of follicles (collections of mononuclear cells) on the conjunctival surfaces and for its chronicity. Pannus formation, consisting of neovascularization and corneal scarring, and which is characteristic of trachoma usually does not occur in these infections. It is to be noted that pannus formation in endemic trachoma areas usually occurs with the second or third infection. In experimental infections with non-human primates, pannus formation occurs only with repeated infections. Thus, one thesis of the pathogenesis of trachoma is that it occurs from repeated infections with the same or different serotype, often in a family setting and where the predominant mode of transmission is eye-finger-eye. In the female, asymptomatic carriage in the endocervix may occur as well as mucopurulent cervicitis. In the latter condition, the cervix becomes edematous resulting in the endocervix becoming apparent to external observation (ectropion). Mucopus can be seen extending through the os. The microorganism is also capable of ascending into the endosalpynx and it has been shown in Scandanavia that *C. trachomatis* can cause PID. The microorganism in females also is capable of ascending into the urethra

and it is a prime candidate for a potential role as a cause of the urethral syndrome (dysuria, frequency, negative bacterial cultures with or without pyuria). Antibody studies performed at the Hooper Foundation in San Francisco illustrate the prevalence of chlamydia infections and indicate that low-level complement fixation antibody titers with the group specific antigen are common with urethral, endocervical and conjunctival infections (Tables 11, 12) (78).

TABLE 11

Antichlamydial Antibodies in Selected Populations
Tested at the Hooper Foundation

	CF ≥1:16 (%)	Micro-IF ≥ 1:8 (%)
Screening studies		
Normal adults, all ages	2-3	25-45
Pediatric sera	<1	10
Trachoma-endemic population	5-15	>80
Males, venereal disease study, young adults without disease	5-10	20-25
Males, symptomatic attending VD clinic	10	60
Females, venereal disease study, young adults	15-20	50-70
Prostitutes	30-60	Up to 85
Proven chlamydial infections (isolation)		
Lymphogranuloma venereum	100	100
Psittacosis	100	ND*
Adult inclusion conjunctivitis	50	100
Male, urethritis	15	90
Female, cervical infection	45	99

*Not determined

TABLE 12

Distribution of Chlamydial CF Titers in Patients with Proven Infections

Disease	No. Tested	No. with CF Titer				
		≤1:16	1:16	1:32	1:64	≥1:128
Lymphogranuloma venereum	15	0	1	2	0	12
Psittacosis	30	0	2	5	5	18
Adult Inclusion conjunctivitis	93	46	28	11	6	2
Cervicitis, females	55	30	9	6	4	6
Urethritis, males	60	51	8	1	0	0

The neonate is an important cause of concern. An infant born to a mother with endocervical carriable of *C. trachomatis* may develop neonatal inclusion body conjunctivitis. The incubation period is 7-12 days and differs from the two to three day incubation period of gonococcal ophthalmia neonatorum. The course is chronic and parents of the affected child may have or develop non-specific urethritis, conjunctivitis or PID. A new disease syndrome has recently been described by Beem and Saxon. They found that *C. trachomatis* was the cause of a distinctive form of pneumonia in children. The onset of the pneumonia was gradual and generally began at one to three months of life. It was characterized by a staccato cough, interstitial infiltrates, eosinophilia and a tendency to chronicity. *C. trachomatis* could be grown from the nasopharynx, trachea and conjunctivae of these infants. Interestingly, cytomegalovirus could sometimes be grown concomitantly from these infants. Since cytomegalovirus is a human cervical pathogen, the infant may come into contact with both microorganisms by aspiration of cervical mucus during the delivery process (Tables 13, 14) (1).

TABLE 13

Prospective Studies of 12 Infants with Distinctive Pneumonia Syndrome[a]

Pt.	Sex	Age at Admission (weeks)	Conjunctivitis	Chlamydiae			Viruses		
				Conj	NP	Trach	Conj	NP	Trach
Saw	F	12	+	+	+		0	CMV	
Bark	M	10	0	+	+	+	0	0	0
Har	F	10	0	0	+		0	CMV	
Han	M	9	0	+	+		0	RS	
Barn	F	7	0	0	+	+	0	Rhino	Rhino
Stub	M	7	+	+	+	+	0	0	0
Bog	M	7	0	0	+	+	0	0	0
Port	F	7	+	0	+	+	0	CMV	CMV
Chat	M	6	+	+	+	+	0	CMV	CMV
Shi	M	6	+	+	+	+	0	0	0
Ruw	M	6	0	0	+	+	0	0	0
Wash	M	6	+	+	+	+	0	0	0
Summary:									
	F = 4	$\bar{x}$ = 8	6/12	7/12	12/12	9/9	0/12	6/12	3/9
	M = 8								

[a]Conj, conjunctiva; NP, nasopharyngeal aspirate; Trach, tracheal aspirate; +, present or isolated; 0, absent or not isolated; CMV, cytomegalovirus; RS, respiratory syncytial virus; Rhino, rhinovirus.

Therapy of urethritis and mucopurulent cervicitis due to *C. trachomatis* consists of two grams of tetracycline for seven to ten days. Erythromycin at the same dosage level is an alternate therapeutic regimen. *C. trachomatis* is the cause for more than 40% of the non-specific urethritis seen. This includes 70% of post-gonococcal urethritis. Since non-specific urethritis may be caused by other agents, it has been debated whether the female contact of the male with non-specific urethritis should be treated. Since the microorganism can produce mucopurulent cervicitis and PID and can be transmitted to the infant, it is

TABLE 14

"Distinctive" Pneumonia Syndrome of Infants

Age	1-3 months
Onset	Gradual, over many days
Systemic manifestations	Absent; fever = 0, malaise = ±
Respiratory	Distinctive cough Tachypnea X-ray: Interstitial infiltrates Hyperexpansion Pleural thickening Auscultation: Good breath sounds Inspiratory crepitant rales Absent or minimal expiratory wheezing
Laboratory	Eosinophilia Low PaO_2, normal $PaCO_2$ High immunoglobulins G and M; sometimes A
Course	Protracted Clinical illness lasts weeks X-ray and physical signs last months

recommended at the present time that sexual contacts secure epidemiological treatment in a similar manner as with gonorrhea. *Ureaplasma urealyticum*, a strain of mycoplasma producing small (T) colonies and able to split urea, probably constitutes the cause of approximately 30% of the cases of non-specific urethritis. Although *Trichomonas vaginalis* and herpes simplex virus can rarely cause non-specific urethritis, the remaining causes of about 30% of the cases do not have a known etiology at the present time.

Lymphogranuloma venereum is one of the traditional venereal diseases and can be considered to represent the generalized form of chlamydial genital infections similar to DGI in gonorrhea. LGV is characterized by a painless evanescent

papule appearing three to five weeks after the time of inoculation. The papule lasts three to four days and the patient rarely seeks medical attention because of its presence. Inguinal lymphadenopathy then follows. The adenopathy can be bilateral or predominantly unilateral, involving both the femoral and the inguinal lymph nodes. The characteristic groove sign may be produced in which the inguinal ligament separates enlarged lymph nodes and causes a groove between the nodes. The lymph nodes can suppurate and form buboes. LGV in its acute form can also produce typical clinical manifestations of arthritis, generalized lymphadenopathy, pericarditis, hepatitis and aseptic menigitis. In homosexual males, anoproctitis can occur with involvement of the colon to the extent that the diagnosis of ulcerative colitis may be made. In homosexual men and in women where inoculation has been on the posterior vaginal wall, one characteristic late complication of the disease is formation of a tubular rectal stricture. The infection is a classic example of persistence; the microorganism can be recovered from retroperitoneal nodes late in its course and hyperglobulinemia may be present. Treatment is with tetracycline for a four week period of time. The diagnosis of LGV can be made by the complement fixation test, usually requiring a four-fold rise in titer to a level of at least 1:128.

SYPHILIS

The following represent some of the major recent developments concerning syphilis. 1) To the present date, attempts to culture *Treponema pallidum* on an artificially defined medium have been unsuccessful. 2) A new serological test using treponemal antigen has been developed and promises to replace the FTA-ABS because of its simplicity, potential quantification and the possibility that it may be performed by automated procedures. The test is called the micro-

hemagglutination test for *T. pallidum* (MHA-TP). It is less sensitive than the FTA-ABS in primary syphilis but should have the same specificity since it uses treponemal antigen which has been attached to erythrocytes. 3) The percentage of men contracting syphilis who are homosexual or bisexual is increasing and may approach 40% of the total male cases in some areas (Figure 5) (102).

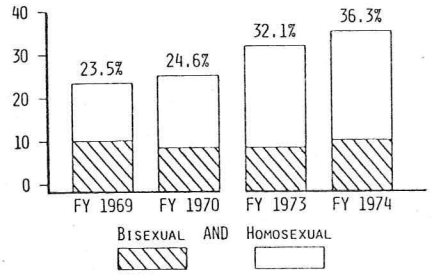

Figure 5. Proportion of men with primary or secondary syphilis who name at least one other man as a sex partner 1969-1974.

4). The most consistently successful method of containing the spread of syphilis is the adequate treatment of the patient and his/her sexual contacts. This necessitates reporting the case to the public health department and epidemiological investigation. The patient should be assured that confidentiality will be maintained. 5) From the standpoint of therapy, simplifications have been made. Syphilis is either defined as being less than one year in duration or of being more than one year in duration or indeterminate in duration. Syphilis of less than one year in duration can be treated with 2.4 million units of benzathine penicillin or alternately 30 grams of tetracycline or erythromycin given over a fifteen day interval. When syphilis is greater than one year in

duration or of indeterminate duration and neurosyphilis is not present, the patient can be treated with 2.4 million units of benzathine penicillin once a week for three weeks or for 30 days with either tetracycline or erythromycin at a daily dosage level of two grams. Since benzathine penicillin does not cross into the cerebrospinal fluid, it is necessary to know if neurosyphilis is present. This necessitates performance of a lumbar puncture. If asymptomatic or active neurosyphilis is diagnosed, a different penicillin regimen is necessary. There is no evidence that any regimen is more efficacious than 1 million units or procaine penicillin per day for ten days. However, in active neurosyphilis, many experienced clinicians advocate hospitalization and therapy with high dose penicillin (20 million units per day for ten days). Adequate follow-up of patients with active neurosyphilis is essential. It is not necessary to perform a lumbar puncture in patients with syphilis of less than one year in duration since it has been demonstrated that appropriate therapy for that stage prevents the occurrence of neurosyphilis. Syphilis in pregnancy should be treated with benzathine penicillin or erythromycin at a dosage level consistent with the duration of the disease. Specific USPHS recommendations for the treatment of syphilis are listed in the appendix.

GENITAL HERPES

Case Presentation

This 15 year old married white woman gave birth to a male infant weighing 4100 grams on August 15, 1979. Delivery was by C-section for fetal distress; the membranes had ruptured 3.5 hours prior to the C-section. The mother was a primigravida and had had adquate prenatal care without any complications noted by her or the physicians caring for her. The mother's post-delivery

course was complicated by the development of endometritis, parametritis and possible septic pelvic thrombophlebitis. On August 21, the infant developed a fever of 102°. Two vesicles with erythematous bases were observed at the site of placement of scalp monitors. The vesicles were cultured and grew hepes simplex virus. At the same time the mother was examined. The perineum and cervix were normal to inspection. Cervical culture, however, grew herpes simplex virus. The infant was begun on adenine arabinoside, 25 mg/kg every day for ten days. New vesicles continued to appear through August 26. On August 25, the liver was felt 5 cm below the rib margin and the liver edge became palpable. At this time the SGOT was 1860 with a total bilirubin of 1.6. Since the liver continued to be palpable after the Ara-A had been discontinued and the infant appeared to be doing well, the urine was cultured for virus. Cytomegalovirus was grown from this urine specimen. The infant left the hospital for home on September 10.

Genital herpes simplex viral infection is increasing in frequency. It has been determined that in certain STD clinics the virus can be recovered by culture from 40% of genital ulcers. During the initial infection, the virus ascends to sacral root ganglion cells where it presumably remains for the lifetime of the individual. Primary infection lasts three to four weeks, is accompanied by painful vesicles and ulcers and by regional lymphadenopathy. Occasionally during the primary infection, aseptic meningitis may result. A peripheral neuropathy

corresponding to involvement of the nerves in the caudae equina has also been described. In a rare patient, generalization of the virus has occurred with hepatic dysfunction and ultimately death. The patient may be subjected to recurrent infection, which generally lasts about seven to ten days with the episodes usually tending to become less frequent with time. There is no proven therapeutic modality effective at present in ameliorating the disease process. The critical question to be answered is why so much difficulty is encountered in the therapy of genital herpes when effective agents have been found to treat herpetic keratitis, viz., ointments containing idoxuridine, adenine arabinoside, adenine arabinoside monophosphate and trifluorothymidine. The therapeutic dilemma can be divided into two components: 1) Shortening the duration of the initial or recurrent episode and 2) preventing recurrent episodes. With regard to shortening the duration of the episode itself. To date, too little attention may have been paid to the pharmaceutical formulation of the drug. The antiviral drug must penetrate the epithelial tissue and its solubility in the tissue must exceed its solubility in the vehicle, i.e., the partition coefficient of the drug in the ointment should favor entrance into the skin. British workers have reported success with idoxuridine in dimethylsulfoxide and this formulation is being tested now by investigators in Seattle. A new drug, acyclovir, is presently being tested in three centers in the U.S.; Seattle, Salt Lake City and Atlanta. The drug is selectively changed to its active phophorylated derivative by the viral coded enzyme, thymidine kinase, and accumulates in infected cells where it functions in an antiviral capacity by blocking the action of viral DNA polymerase. This new drug appears to have the greatest promise in shortening the duration of the primary or recurrent episode. It should be noted that in recurrent disease, new vesicles appear

over a finite period, sometimes for as long a period as five days. This may infer continued "firing" of the virus into the area of the lesions from its source in the dorsal root ganglion. If topical therapy is effective in recurrent disease, it seems difficult to imagine that it might prevent further episodes since the virus has already been implanted in the ganglion during the primary infection. A report claiming efficacy of 2-deoxy-D-glucose needs to be watched with caution and should be repeated by other investigators with quantitative virological techniques before any potential clinical application.

Preventing recurrent episodes appears to be a more difficult problem. To date, most efforts have been directed toward an augmentation of the immune response (inactivated vaccine, BCG vaccine, transfer factor, levamisole, inosiplex). There is no evidence that such therapies are effective and no solid information that patients troubled by frequent recurrences have a demonstrable immunological defect.

One of the feared complications of genital herpes infection is transmission of the virus to the neonate. The case-fatality ratio in this disease has approximated 90% in some series (PMH, CMC, Dallas, Texas). Although obstetricians are cognizant of the problem and perform C-sections in pregnant women with active lesions at delivery, the disease continues to occur, generally in women with inadequate prenatal care and counseling and to women who give no history of the disease and who have no demonstrable lesions at the time of delivery. It has been possible to culture the virus from the cervix of such women in certain instances after neonatal infection has been recognized and directs attention to its possible source. In a NIAID sponsored multi-institutional study, parenterally administered adenine-arabinoside (15 mg/kg/day for 10 days) has been shown to have a significant therapeutic effect on the course of neonatal herpes. Although the effect

was significant and in the right direction, it most probably should be considered marginal. A new study is planned using adenine arabinoside (25 mg/kg/day for ten days) and acyclovir.

In dealing with patients with genital herpes, effective counseling is essential. The diagnosis should be established by culture or a Tzanck preparation. Therapeutic limitations should be explained to the patient as well as the fact that present research may eventually yield a successful treatment. The patient should be told that he/she is most infectious when active lesions are present and intercourse should be avoided at that time. If the patient is not sure of his/her infectivity, a condom should be worn. The women should have a Pap smear once a year to detect early dysplastic changes. The couple planning a family should advise their obstetrician of the problem so that necessary precautions can be taken at delivery. Self-help organizations are in existence and can help the patient become more comfortable with his/her disease. One such organization is called HELP, Herpetics Engaged in Living Productively. Chapters exist in San Francisco, Los Angeles and Washington, D.C.

SCABIES

Infestations by *Sarcoptes scabiei* result from close human contact and are being increasingly recognized as one of the sexually transmitted diseases. Important investigations into the nature of scabies were undertaken by Mellanby at the beginning of World War II. It was expected that scabies would become epidemic during the war. Using conscientious objectors as volunteers, it was found difficult if not impossible to infect them if they wore clothes or slept in the bedding of proven scabetic patients. The female mite, however, could be extracted from the end of the serpiginous burrow created during egg laying and then implanted into the skin of the volunteers. No changes could be noticed

for one month when pruritus developed. In primary infections, the number of adult female parasites increased dramatically through 100-150 days when a downturn in female mite burden occurred spontaneously (Figure 6) (76). The experiments then had to be terminated because of symptomatology. When the female mite was implanted on persons previously infected but cured of their infection, the total mite burden over the same period of time was dramatically reduced. Symptoms, however, began at the onset of infection and often overshadowed those seen with primary infections (Figure 7) (76). The frequency with which various body sites were actually infested with the female mite is shown in Figure 8 (76). To be noted, however, is the nonconcordance of the scabetic rash shown in Figure 9 (76). It has been reasoned that the follicular, papular eruption that is widely distributed over areas where mite burrows are absent results from sensitization to the presence of the mite and its products. Secondary infection may occur. If nephritogenic Group A streptococci are present in the population such as in Trinidad, West Indies, scabetic infections may be a major factor predisposing such patients to the development of acute glomerulonephritis. Diagnosis is usually made by the clinical presentation of the patient, with a pruritic rash particularly worse at night in a characteristic distribution and clinical appearance. Some authorities suggest the necessary demonstration of the female mite to sophisticate the clinical impression and avoid overdiagnosis. Treatment is with gamma-benzene hexachloride ointment (Kwell) applied to the body below the face after a complete bath. After twelve hours of application, the ointment should be removed by another bath. Partners should also be treated; clothes and bedding should be washed. Since many of the symptoms result from sensitization to the parasite and its products, the patient should be instructed not to expect immediate relief. Repeated administration of the ointment should be avoided because of the possible development of skin sensitization to the drug.

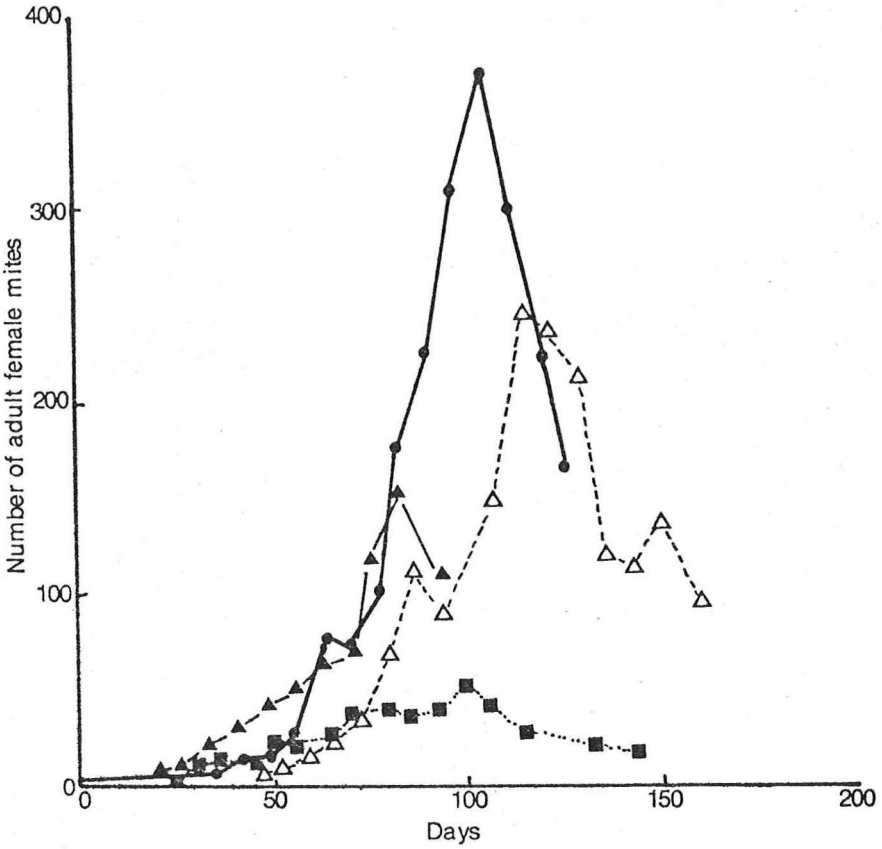

Figure 6. Changes in the number of adult female parasites in four individuals infected for the first time with scabies.

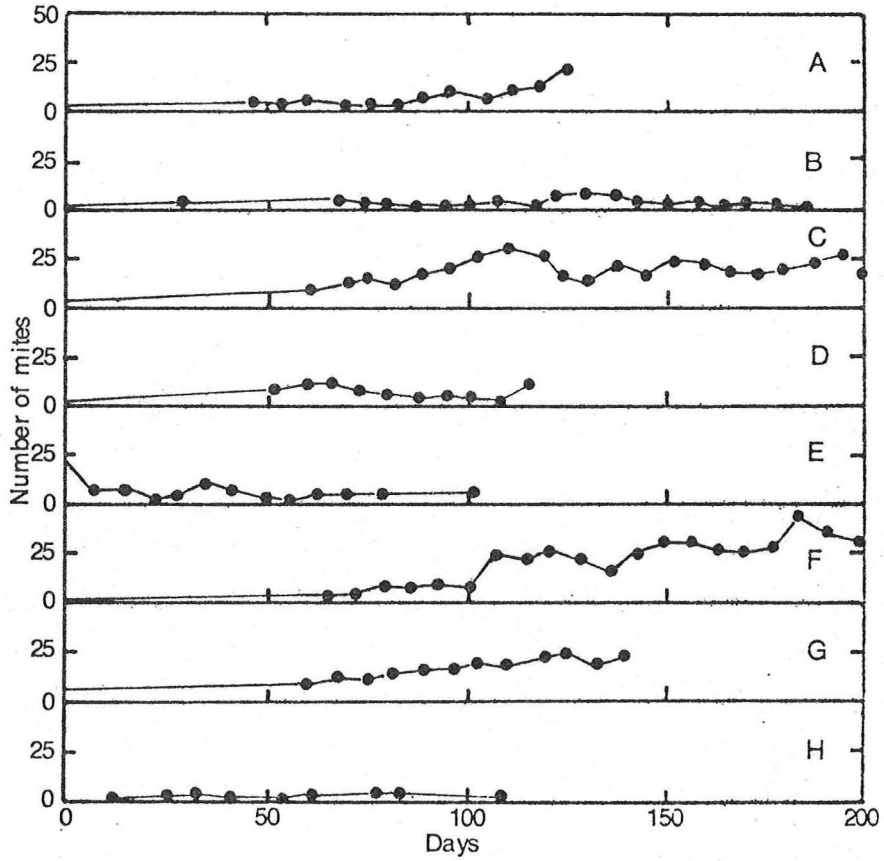

Figure 7. Changes in the number of adult female parasites of eight cases of scabies in individuals who had suffered from previous infections.

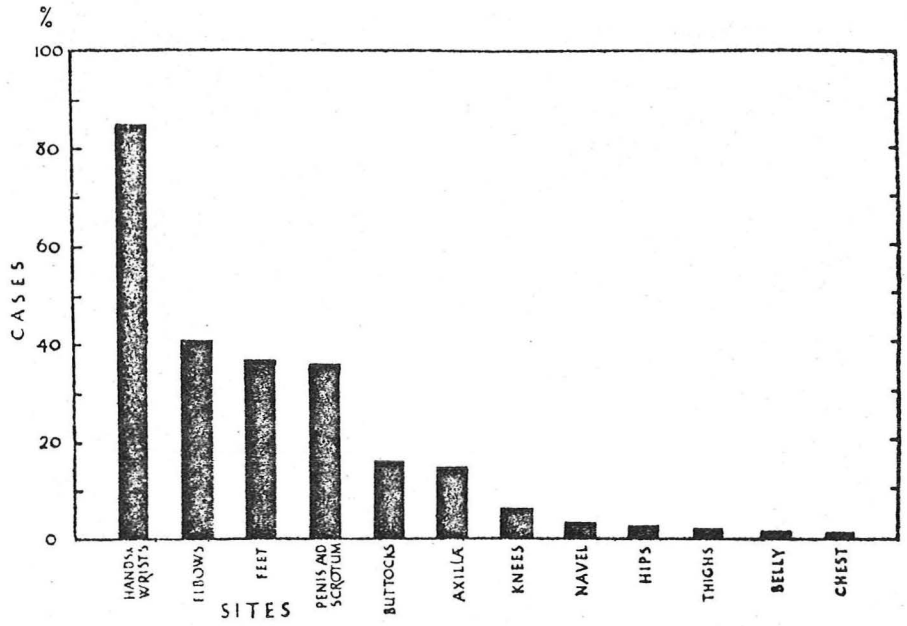

Figure 8. The frequency with which various sites are infested with *Sarcoptes*.

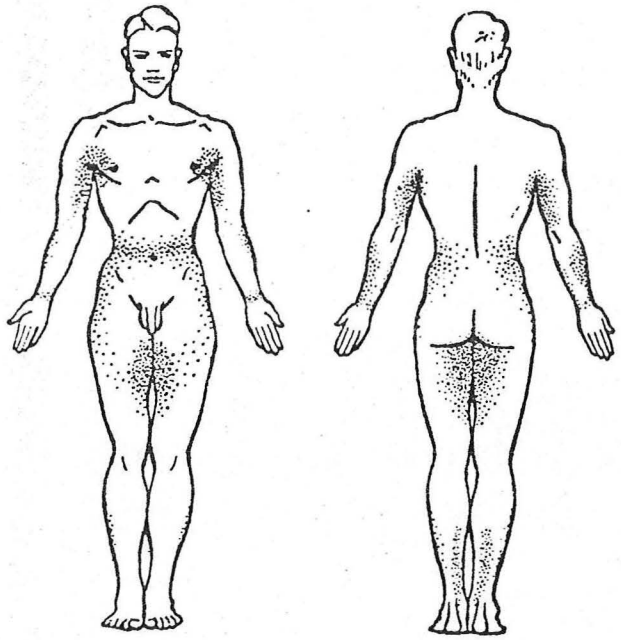

Figure 9. Scabies "rash". (Note: the rash does not correspond with the sites of election of the acari.)

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EARLY SYPHILIS

EARLY SYPHILIS (primary, secondary, latent syphilis of less than one year's duration)

Rx: (1) Benzathine penicillin G – 2.4 million units total by intramuscular injection at a single session.

Benzathine penicillin G is the drug of choice, because it provides effective treatment in a single visit.

OR

(2) Aqueous procaine penicillin G – 4.8 million units total: 600,000 units by intramuscular injection daily for 8 days.

OR

(3) Procaine penicillin G in oil with 2 percent aluminum monostearate (PAM) – 4.8 million units total by intramuscular injection: 2.4 million units at first visit, and 1.2 million units at each of two subsequent visits 3 days apart.

Although PAM is used in other countries, it is no longer available in the United States.

Patients who are allergic to penicillin:

Rx: (1) Tetracycline hydrochloride* – 500 mg four times a day by mouth for 15 days.

OR

(2) Erythromycin (stearate, ethylsuccinate or base) – 500 mg four times a day by mouth for 15 days.

These antibiotics appear to be effective, but have been evaluated less extensively than penicillin.

**Food and some dairy products interfere with absorption. Oral forms of tetracycline should be given one hour before or two hours after meals.*

SYPHILIS OF MORE THAN ONE YEAR'S DURATION

SYPHILIS OF MORE THAN ONE YEAR'S DURATION (latent syphilis of indeterminate or more than one year's duration, cardiovascular, late benign, neurosyphilis)

Rx: (1) Benzathine penicillin G – 7.2 million units total: 2.4 million units by intramuscular injection weekly for three successive weeks.

OR

(2) Aqueous procaine penicillin G – 9.0 million units total: 600,000 units by intramuscular injection daily for 15 days.

The optimal treatment schedules for syphilis of greater than one year's duration have been less well established than schedules for early syphilis. In general, syphilis of longer duration requires higher-dose therapy. Although therapy is recommended for established cardiovascular syphilis, there is little evidence that antibiotics reverse the pathology associated with this disease.

Cerebrospinal fluid (CSF) examination is mandatory in patients with suspected, symptomatic neurosyphilis. This examination is also desirable in other patients with syphilis of greater than one year's duration to exclude asymptomatic neurosyphilis.

Published studies show that a total dose of 6.0-9.0 million units of penicillin G results in a satisfactory clinical response in approximately 90 percent of patients with neurosyphilis. There is more published clinical experience with short-acting penicillin preparations than with benzathine penicillin G. Some clinicians prefer to hospitalize patients with neurosyphilis, particularly if the patient is symptomatic or has not responded to initial therapy. In these instances they treat patients with 12-24 million units of aqueous crystalline penicillin G given intravenously each day (2-4 million units every 4 hours) for 10 days.

Patients who are allergic to penicillin:

Rx: (1) Tetracycline hydrochloride – 500 mg four times a day by mouth for 30 days.

OR

(2) Erythromycin (stearate, ethylsuccinate or base) – 500 mg four times a day by mouth for 30 days.

There are **NO** *published clinical data which adequately document the efficacy of drugs other than penicillin for syphilis of more than one year's duration. Cerebrospinal fluid examinations are highly recommended before therapy with these regimens.*

SYPHILIS IN PREGNANCY

Evaluation of Pregnant Women

All pregnant women should have a nontreponemal serologic test for syphilis, such as the VDRL or RPR test, at the time of the first prenatal visit. The treponemal tests such as the FTA-ABS test should not be used for routine screening. In women suspected of being at high risk for syphilis, a second nontreponemal test should be performed during the third trimester.

Seroreactive patients should be expeditiously evaluated. This evaluation should include a history and physical examination, as well as a quantitative nontreponemal test and a confirmatory treponemal test.

If the FTA-ABS test is nonreactive and there is no clinical evidence of syphilis, treatment may be withheld. Both the quantitative nontreponemal test and the confirmatory test should be repeated within 4 weeks. If there is clinical or serologic evidence of syphilis or if the diagnosis of syphilis cannot be excluded with reasonable certainty, the patient should be treated as outlined below.

Patients for whom there is documentation of adequate treatment for syphilis in the past need not be retreated unless there is clinical or serologic evidence of reinfection such as darkfield-positive lesions or a fourfold titer rise of a quantitative nontreponemal test.

Rx: (1) **For patients at all stages of pregnancy who are not allergic to penicillin**: Penicillin in dosage schedules appropriate for the stage of syphilis as recommended for the treatment of nonpregnant patients.

(2) **For patients of all stages of pregnancy who are allergic to penicillin**: Erythromycin (stearate, ethylsuccinate or base) in dosage schedules appropriate for the stage of syphilis, as recommended for the treatment of nonpregnant patients. Although these erythromycin schedules appear safe for mother and fetus, their efficacy is not well established. Therefore, the documentation of penicillin allergy is particularly important before treating a pregnant woman with erythromycin.

Erythromycin estolate and tetracycline are not recommended for syphilitic infections in pregnant women because of potential adverse effects on mother and fetus.

FOLLOW UP

Pregnant women who have been treated for syphilis should have monthly quantitative nontreponemal serologic tests for the remainder of the current pregnancy. Women who show a fourfold rise in titer should be retreated. After delivery, follow up is as outlined for nonpregnant patients.

CONGENITAL SYPHILIS

Congenital syphilis may occur if the mother has syphilis during pregnancy. If the mother has received adequate penicillin treatment during pregnancy, the risk to the infant is minimal. However, all infants should be examined carefully at birth and at frequent intervals thereafter until nontreponemal serologic tests are negative.

Infected infants are frequently asymptomatic at birth and may be seronegative if the maternal infection occurred late in gestation. Infants should be treated at birth if maternal treatment was inadequate, unknown, with drugs other than penicillin, or if adequate follow up of the infant cannot be ensured.

Infants with congenital syphilis should have a CSF examination before treatment.

Infants with abnormal CSF:

Rx: (1) Aqueous crystalline penicillin G, 50,000 units/kg intramuscularly or intravenously daily in two divided doses for a minimum of 10 days.

OR

(2) Aqueous procaine penicillin G, 50,000 units/kg intramuscularly daily for a minimum of 10 days.

Infants with normal CSF:

Rx: Benzathine penicillin G, 50,000 units/kg intramuscularly in a single dose.

Although benzathine penicillin has been previously recommended and widely used, published clinical data on its efficacy in congenital neurosyphilis are lacking. If neurosyphilis cannot be excluded, the procaine or aqueous penicillin regimens are recommended. Since cerebrospinal fluid concentrations of penicillin achieved after benzathine penicillin are minimal to nonexistent, these revised recommendations seem more conservative and appropriate until clinical data on the efficacy of benzathine penicillin can be accumulated. Other antibiotics are not recommended for neonatal congenital syphilis.

Penicillin therapy for congenital syphilis after the neonatal period should be with the same dosages used for neonatal congenital syphilis. For larger children, the total dose of penicillin need not exceed the dosage used in adult syphilis of more than one year's duration. After the neonatal period, the dosage of erythromycin and tetracycline for congenital syphilitics who are allergic to penicillin should be individualized but need not exceed dosages used in adult syphilis of more than one year's duration. Tetracycline should not be given to children less than 8 years of age.

FOLLOW UP AND RETREATMENT

All patients with early syphilis and congenital syphilis should be encouraged to return for repeat quantitative nontreponemal tests 3, 6, and 12 months after treatment. Patients with syphilis of more than one year's duration should also have a repeat serologic test 24 months after treatment. Careful follow up serologic testing is particularly important in patients treated with antibiotics other than penicillin. Examination of CSF should be planned as part of the last follow up visit after treatment with alternative antibiotics.

All patients with neurosyphilis must be carefully followed with serologic testing for at least 3 years. In addition, follow up of these patients should include clinical reevaluation at 6-month intervals and repeat CSF examinations, particularly in patients treated with alternative antibiotics.

The possibility of reinfection should always be considered when retreating patients with early syphilis. A CSF examination should be performed before retreatment unless reinfection and a diagnosis of early syphilis can be established.

Retreatment should be considered when:

(1) Clinical signs or symptoms of syphilis persist or recur;
(2) There is a sustained fourfold increase in the titer of a nontreponemal test;
(3) An initially high-titer nontreponemal test fails to decrease fourfold within a year.

Patients should be retreated with the schedules recommended for syphilis of more than one year's duration. In general, only one retreatment course is indicated because patients may maintain stable, low titers of nontreponemal tests or have irreversible anatomical damage.

EPIDEMIOLOGIC TREATMENT

Patients who have been exposed to infectious syphilis within the preceding 3 months and other patients who on epidemiologic grounds are at high risk for syphilis should be treated as for early syphilis. Every effort should be made to establish a diagnosis in these cases.

Uncomplicated Gonococcal Infections in Men and Women

DRUG REGIMENS OF CHOICE

Aqueous procaine penicillin G (APPG): 4.8 million units injected intramuscularly at 2 sites, with 1.0 g of probenecid by mouth; **OR**

Tetracycline hydrochloride†: 0.5 g by mouth 4 times a day for 5 days (total dosage 10.0 g). Other tetracyclines are not more effective than tetracycline hydrochloride. All tetracyclines are ineffective as a single-dose therapy; **OR**

Ampicillin or amoxicillin: Ampicillin, 3.5 g, or amoxicillin, 3.0 g, either with 1 g probenecid by mouth. Evidence shows that these regimens are slightly less effective than the other recommended regimens.

Patients who are allergic to the penicillins or probenecid should be treated with oral tetracycline as above. Patients who cannot tolerate tetracycline may be treated with spectinomycin hydrochloride, 2.0 g, in 1 intramuscular injection.

SPECIAL CONSIDERATIONS

Single-dose treatment is preferred in patients who are unlikely to complete the multiple-dose tetracycline regimen. The APPG regimen is preferred in men with anorectal infection.

Pharyngeal infection is difficult to treat. High failure rates have been reported with ampicillin and spectinomycin.

Tetracycline treatment results in fewer cases of postgonococcal urethritis in men. It may eliminate coexisting chlamydial infections in men and women.

Patients with incubating syphilis (seronegative, without clinical signs of syphilis) are likely to be cured by all the above regimens except spectinomycin. All patients should have a serologic test for syphilis at the time of diagnosis.

Patients with gonorrhea who also have syphilis or are established contacts of syphilis patients should be given additional treatment appropriate to the stage of syphilis.

TREATMENT OF SEXUAL PARTNERS

Men and women exposed to gonorrhea should be examined, cultured, and treated at once with one of the regimens above.

FOLLOW-UP

Follow-up cultures should be obtained from the infected site(s) 3-7 days after completion of treatment. Cultures should be obtained from the anal canal of all women who have been treated for gonorrhea.

TREATMENT FAILURES

The patient who fails therapy with penicillin, ampicillin, amoxicillin, or tetracycline should be treated with 2.0 g of spectinomycin intramuscularly.

Most recurrent infections after treatment with the recommended schedules are due to *reinfection* and indicate a need for improved contact tracing and patient education. Since infection by penicillinase (β-lactamase)-producing *Neisseria gonorrhoeae* is a cause of treatment failure, posttreatment isolates should be tested for penicillinase production.

NOT RECOMMENDED

Although long-acting forms of penicillin (such as benzathine penicillin G) are effective in syphilotherapy, they have NO place in the treatment of gonorrhea. Oral penicillin preparations such as penicillin V are not recommended for the treatment of gonococcal infection.

Penicillinase-Producing *Neisseria Gonorrhoeae* (PPNG)

Patients with uncomplicated PPNG infections and their sexual contacts should receive spectinomycin, 2.0 g, intramuscularly in a single injection. Because gonococci are very rarely resistant to spectinomycin and reinfection is the most common cause of treatment failure, patients with positive cultures after spectinomycin therapy should be re-treated with the same dose.

A PPNG isolate that is resistant to spectinomycin may be treated with cefoxitin, 2.0 g, in a single intramuscular injection, with probenecid, 1.0 g, by mouth.

†Food and some dairy products interfere with absorption. Oral forms of tetracycline should be given 1 hour before or 2 hours after meals.

Treatment in Pregnancy

All pregnant women should have endocervical cultures for gonococci as an integral part of the prenatal care at the time of the first visit. A second culture late in the third trimester should be obtained from women at high risk of gonococcal infection.

Drug regimens of choice are APPG, ampicillin, or amoxicillin, each with probenecid as described above.

Women who are allergic to penicillin or probenecid should be treated with spectinomycin.

Refer to the sections on acute salpingitis and disseminated gonococcal infections for the treatment of these conditions during pregnancy. Tetracycline should not be used in pregnant women because of potential toxic effects for mother and fetus.

Acute Salpingitis (Pelvic Inflammatory Disease)

There are no reliable clinical criteria to distinguish gonococcal from nongonococcal salpingitis. Endocervical cultures for *N. gonorrhoeae* are essential. Therapy should be initiated immediately.

HOSPITALIZATION

In the following situations, hospitalization should be strongly considered: uncertain diagnosis, in which surgical emergencies such as appendicitis and ectopic pregnancy must be excluded; suspicion of pelvic abscess; severe illness; pregnancy; inability of patient to follow or tolerate an outpatient regimen; or failure of patient to respond to outpatient therapy.

ANTIMICROBIAL AGENTS

Outpatients: *Tetracycline**: 0.5 g, taken orally 4 times a day for 10 days. This regimen should not be used for pregnant patients; **OR**

APPG: 4.8 million units intramuscularly, ampicillin, 3.5 g, or amoxicillin, 3.0 g, each with probenecid, 1.0 g. Either regimen is followed by ampicillin, 0.5 g, or amoxicillin, 0.5 g, orally 4 times a day for 10 days.

Hospitalized patients: *Aqueous crystalline penicillin G*: 20 million units given intravenously each day until improvement occurs, followed by ampicillin, 0.5 g, orally 4 times a day to complete 10 days of therapy; **OR**

*Tetracycline**: 0.25 g, given intravenously 4 times a day until improvement occurs, followed by 0.5 g orally 4 times a day to complete 10 days of therapy. This regimen should not be used for pregnant women. The dosage may have to be adjusted if renal function is depressed.

Since optimal therapy for hospitalized patients has not been established, other antibiotics in addition to penicillin are frequently used.

SPECIAL CONSIDERATIONS

Failure of the patient to improve on the recommended regimens does not indicate the need for stepwise additional antibiotics, but requires clinical reassessment.

The intrauterine device is a risk factor for the development of pelvic inflammatory disease. The effect of removing an intrauterine device on the response of acute salpingitis to antimicrobial therapy and on the risk of recurrent salpingitis is unknown.

Adequate treatment of women with acute salpingitis must include examination and appropriate treatment of their sex partners because of their high prevalence of nonsymptomatic urethral infection. Failure to treat sex partners is a major cause of recurrent gonococcal salpingitis.

Follow-up of patients with acute salpingitis is essential during and after treatment. All patients should be recultured for *N. gonorrhoeae* after treatment.

Acute Epididymitis

Acute epididymitis can be caused by *N. gonorrhoeae, Chlamydia*, or other organisms. If gonococci are demonstrated by Gram stain or culture of urethral secretions, treatment should be APPG, 4.8 million units, ampicillin, 3.5 g, or amoxicillin, 3.0 g, each with probenecid, 1.0 g. Either regimen is followed by ampicillin, 0.5 g, or amoxicillin, 0.5 g, orally 4 times a day for 10 days; **OR**

Tetracycline*: 0.5 g, orally 4 times a day for 10 days.

If gonococci are not demonstrated, the above tetracycline regimen should be used.

Disseminated Gonococcal Infection

TREATMENT SCHEDULES

There are several, equally effective treatment schedules in the arthritis-dermatitis syndrome. These include the following.

Ampicillin/amoxicillin: ampicillin, 3.5 g, or amoxicillin, 3.0 g, orally, each with probenecid, 1.0 g, followed by ampicillin 0.5 g, or amoxicillin, 0.5 g, 4 times a day orally for 7 days; **OR**

Tetracycline*: 0.5 g, orally 4 times a day for 7 days. Tetracycline should not be used for complicated gonococcal infection in pregnant women; **OR**

Spectinomycin: 2.0 g, intramuscularly twice a day for 3 days (treatment of choice for disseminated infections caused by PPNG); **OR**

Erythromycin: 0.5 g, orally 4 times a day for 7 days; **OR**

Aqueous crystalline penicillin G: 10 million units intravenously per day until improvement occurs followed by ampicillin, 0.5 g, 4 times a day, to complete 7 days of antibiotic treatment.

SPECIAL CONSIDERATIONS

Hospitalization is indicated in patients who may be unreliable, have uncertain diagnosis, or have purulent joint effusions or other complications.

Open drainage of joints other than the hip is not indicated. Intra-articular injection of antibiotics is unnecessary.

MENINGITIS AND ENDOCARDITIS

Meningitis and endocarditis caused by the gonococcus require high-dose intravenous penicillin therapy. In penicillin-allergic patients with endocarditis, desensitization and administration of penicillin are indicated. Chloramphenicol may be used in penicillin-allergic patients with meningitis.

Gonococcal Infections in Pediatric Patients

With gonococcal infections in children beyond the newborn period, the possibility of sexual abuse must be considered. Genital, anal, and pharyngeal cultures should be obtained from all patients before antibiotic treatment. Appropriate cultures should be obtained from individuals who have had contact with the child.

*Food and some dairy products interfere with absorption. Oral forms of tetracycline should be given 1 hour before or 2 hours after meals.

Prevention of Gonococcal Ophthalmia

When required by state legislation or indicated by local epidemiologic considerations, effective and acceptable regimens for prophylaxis of neonatal gonococcal ophthalmia include ophthalmic ointment or drops containing tetracycline or erythromycin OR a 1% silver nitrate solution.

SPECIAL CONSIDERATIONS

Bacitracin is not recommended. The value of irrigation after application of silver nitrate is unknown.

Management of Infants Born to Mothers with Gonococcal Infection

The infant born to a mother with gonorrhea is at high risk of infection and requires treatment with a single intravenous or intramuscular injection of aqueous crystalline penicillin G, 50,000 units to full-term infants or 20,000 units to low-birth-rate infants. Topical prophylaxis for neonatal ophthalmia is not adequate treatment. Clinical illness requires additional treatment.

Neonatal Disease

GONOCOCCAL OPHTHALMIA

Patients should be hospitalized and isolated for 24 hours after initiation of treatment. Untreated gonococcal ophthalmia is highly contagious. Aqueous crystalline penicillin G, 50,000 units/kg/day, in 2 doses intravenously should be administered for 7 days. Saline irrigation of the eyes should be performed as needed. Topical antibiotic preparations alone are not sufficient or required when appropriate systemic antibiotic therapy is given.

COMPLICATED INFECTION

Patients with arthritis and septicemia should be hospitalized and treated with aqueous crystalline penicillin G, 75,000 to 100,000 units/kg/day, intravenously in 2 or 3 divided doses for 7 days. Meningitis should be treated with aqueous crystalline penicillin G, 100,000 units/kg/day, divided into 3 or 4 intravenous doses, and continued for at least 10 days.

Childhood Disease

Children who weigh 100 lbs. (45 kg) or more should receive adult regimens. Children who weigh less than 100 lbs. should be treated as follows.

UNCOMPLICATED DISEASE

Uncomplicated vulvovaginitis, urethritis, proctitis, or pharyngitis can be treated at 1 visit with amoxicillin, 50 mg/kg, orally with probenecid, 25 mg/kg (maximum 1.0 g), OR with aqueous procaine penicillin G, 100,000 units/kg, intramuscularly plus probenecid, 25 mg/kg (maximum 1.0 g).

SPECIAL CONSIDERATIONS

Topical and/or systemic estrogen therapy are of no benefit in vulvovaginitis. Long-acting penicillins, such as benzathine penicillin G, are not effective. All patients should have follow-up cultures, and the source of infection should be identified, examined, and treated.

GONOCOCCAL OPHTHALMIA

Ophthalmia in children is treated as in neonates, but the dose of penicillin is increased to 100,000 units/kg/day intravenously.

COMPLICATED INFECTIONS

Patients with peritonitis or arthritis require hospitalization and treatment with aqueous crystalline penicillin G, 100,000 units/kg/day, intravenously for 7 days. Aqueous crystalline penicillin G, 250,000 units/kg/day, intravenously in 6 divided doses for at least 10 days, is recommended for meningitis.

ALLERGY TO PENICILLINS

Children who are allergic to penicillins should be treated with spectinomycin, 40 mg/kg, intramuscularly. Children older than 8 years may be treated with tetracycline, 40 mg/kg/day, orally in 4 divided doses for 5 days. For treatment of complicated disease, the alternative regimens recommended for adults may be used in appropriate pediatric dosages.