SEXUALLY TRANSMITTED DISEASES: AN UPDATE

JAMES P. LUBY, M.D.

DEPARTMENT OF INTERNAL MEDICINE

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER AT DALLAS

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STD EVENTS OF THE 80'S AND EARLY 90'S THAT I WOULD NOT HAVE PREDICTED IN 1979

1. AIDS
2. HPV DNA found in 85% of invasive cervical carcinomas
4. Penicillin resistance in 20% of gonococcal isolates
3. Epidemic chancroid in Dallas County peaks at 100 cases per month

Syphilis

There was a major increase in primary and secondary syphilis in the United States from 1986-1990.

Congenital Syphilis – Reported cases in infants <1 year of age and rates of primary and secondary syphilis among women: United States, 1970–1991

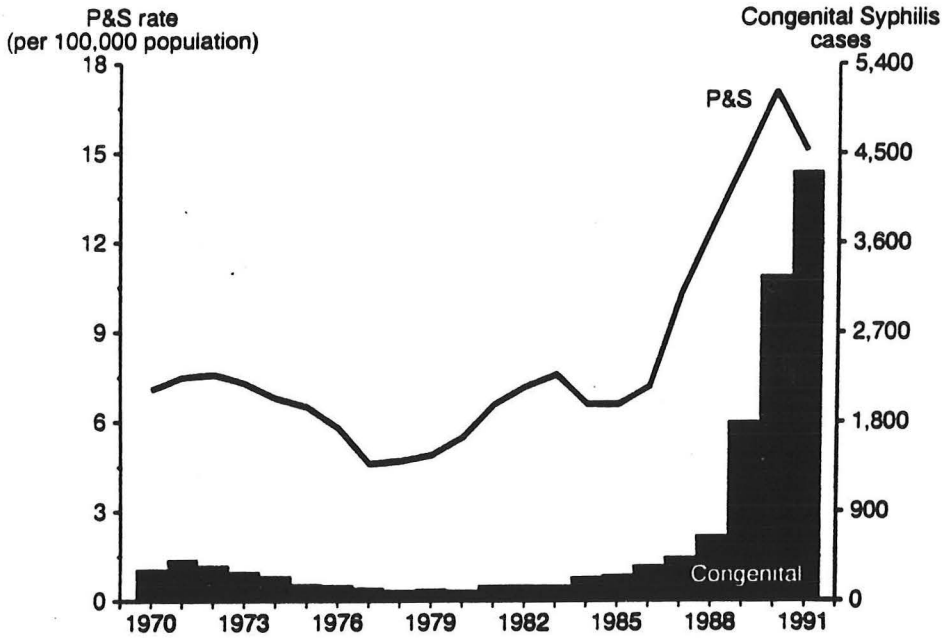


Figure 1: Division of STD/HIV Prevention, 1991

In 1991, there was a decline in the number of cases of infectious syphilis. The total number of cases of infectious syphilis reported in the United States during 1990 was 50,233 cases. Approximately 55% of those cases, 27,847, were reported from cities with populations having more than 200,000 persons. A significant proportion of the remaining cases originated in rural southern counties.

Primary and secondary syphilis – Counties with rates above and counties with rates below the year 2000 objective: United States, 1991

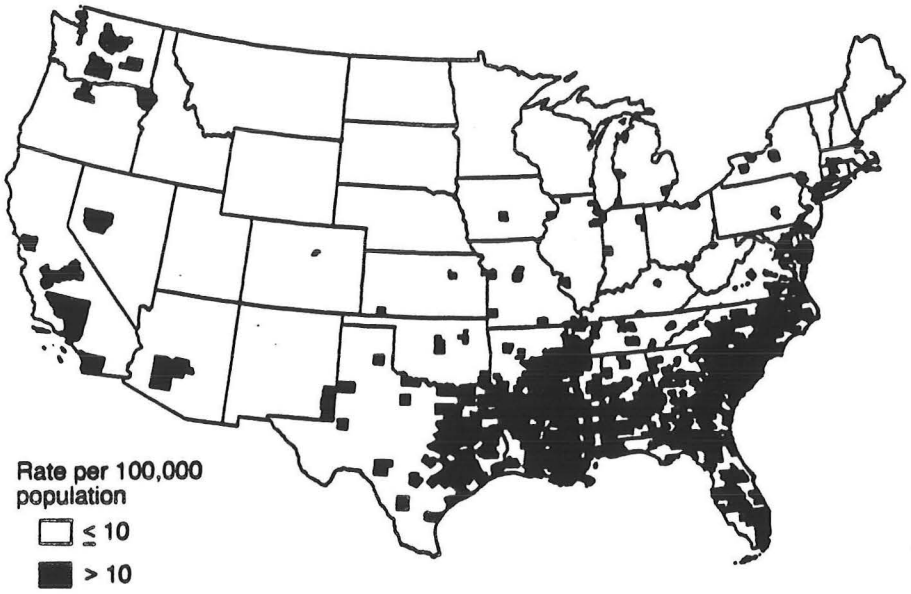


Figure 2: Division of STD/HIV Prevention, 1991

Rates for infectious syphilis in counties in the southern United States have been consistently higher than in other portions of the country. Syphilis in urban areas tended to be a disease of minority populations with the majority of cases occurring in black persons and persons with Hispanic surnames. In 1991, the primary and secondary syphilis case rate for blacks was 62 times higher than for whites; the rate for persons with Hispanic surnames was 6 times higher than that for whites. In 1990, ten cities each had more than a thousand cases. New York City has had more than 4,000 cases per year since 1987. In New York City in the late 1980's and early 1990's, syphilis was primarily a heterosexually transmitted disease mostly involving minority populations and oftentimes associated with the use of injected drugs, prostitution and crack cocaine. In association with this heterosexual epidemic of infectious syphilis, there has been an increase in congenital syphilis. Part of that increase reflected a change in the definition of congenital syphilis, but part also reflected the increase in infectious syphilis in heterosexual populations in larger cities. As of 1989, the Centers for Disease Control and the American Academy of Pediatrics recommended treating all infants whose mothers have untreated or inadequately treated syphilis at delivery, even if the infants were asymptomatic. These infants should now also be reported as congenital syphilis cases. In 1989, of the 1,747 cases of congenital syphilis reported to CDC, 1,017 were from New York City which had already adopted the newer definition. It is possible that congenital syphilis rates will continue to increase, both because of the new definition and because syphilis rates are increasing or stabilizing among women of reproductive age. There has been a decrease in male homosexual syphilis rates related to changes in sexual practices due to the advent of AIDS. In Dallas, primary and secondary syphilis cases in both men and women declined during 1992, whereas reported cases of congenital syphilis increased.

GONORRHEA

In contrast to syphilis, gonorrhea rates in the United States have fallen since 1985.

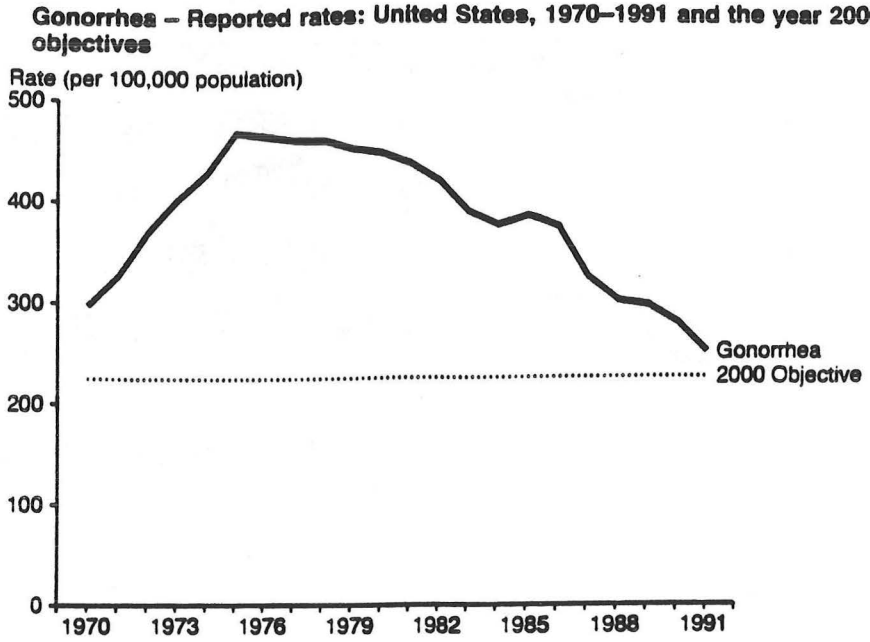
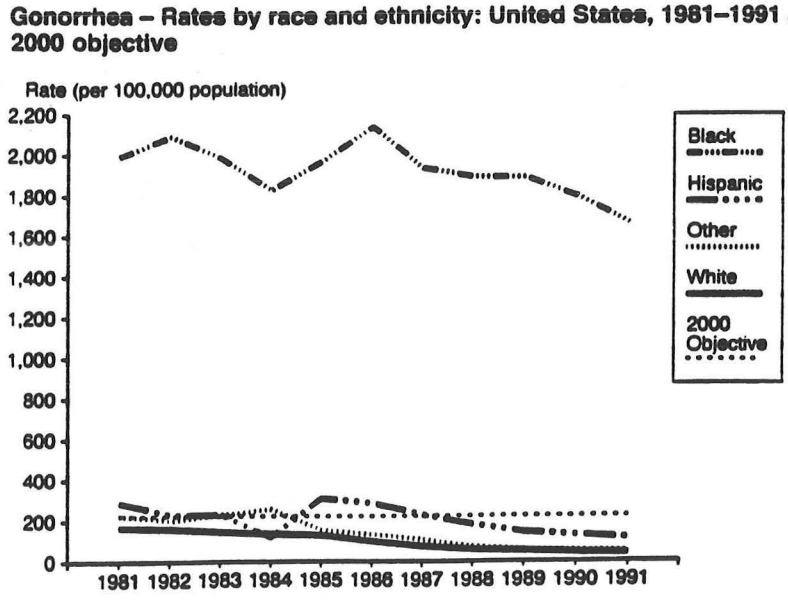


Figure 4: Division of STD/HIV Prevention, 1991

In 1991, gonorrhea rates approached the year 2000 objective of a rate of 225 cases per 100,000 population. Gonorrhea rates are highest in minority populations, particularly in blacks.

Figure 5: Division of STD/HIV Prevention, 1991



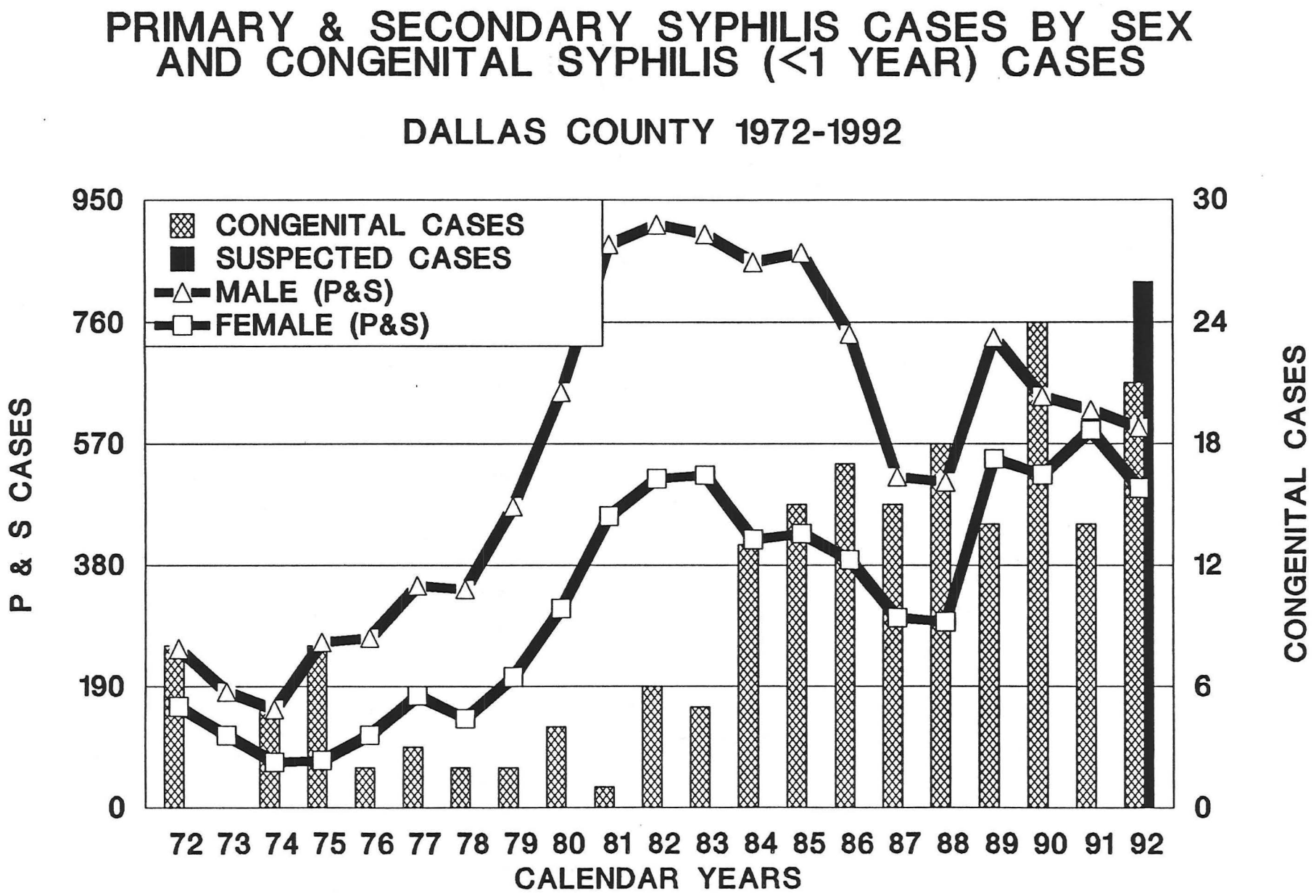


Figure 3: Dallas County Health Department, 1993

Dallas County gonorrhea cases peaked in 1976-1978 and have declined since then through 1992. Cases of gonococcal pelvic inflammatory disease in Dallas County showed a decrease from 1988 through 1992.

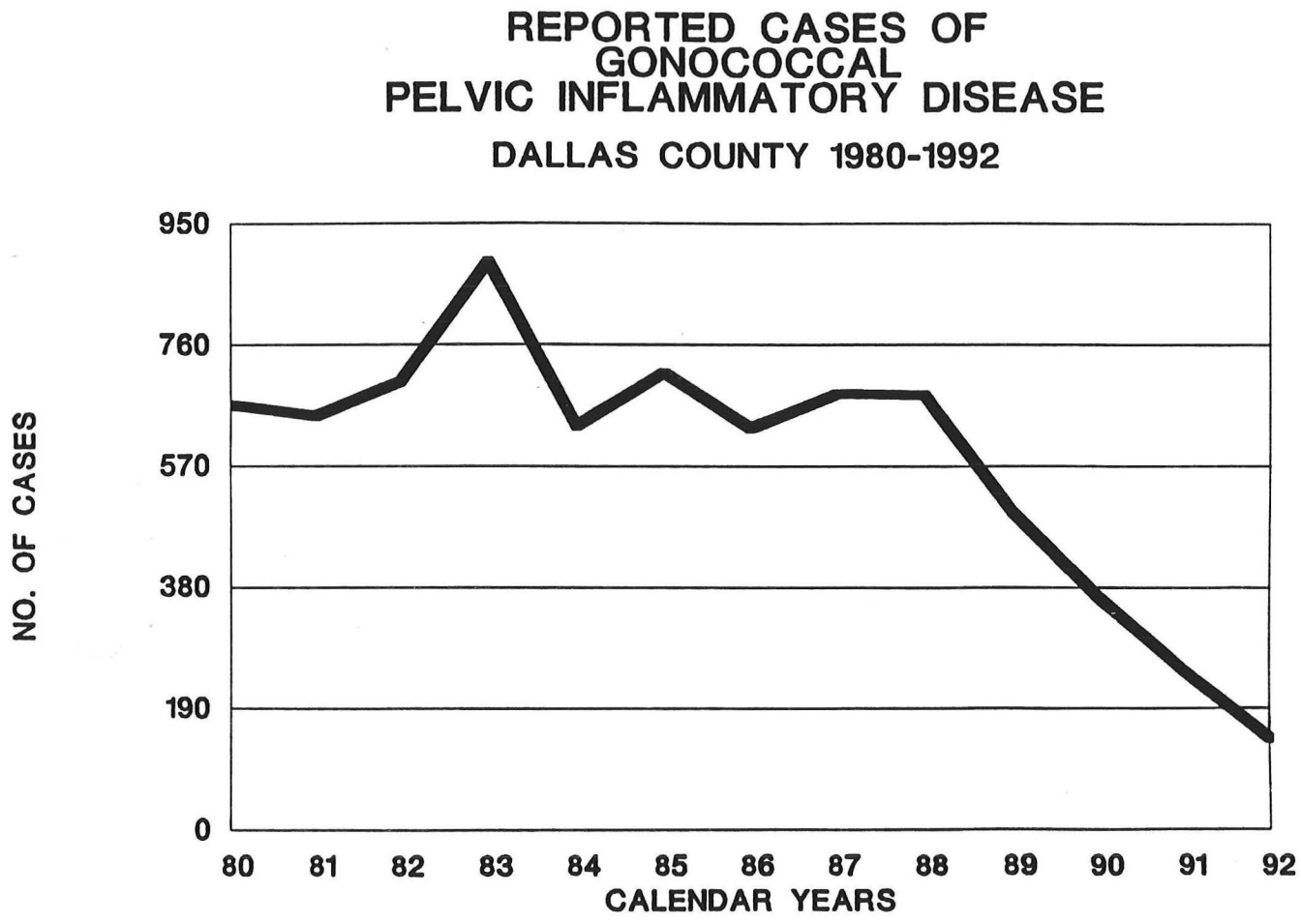


Figure 6: Dallas County Health Department, 1993

In 1989, Sexually Transmitted Disease Treatment Guidelines published by the Centers for Disease Control recommended ceftriaxone as primary therapy for gonorrhea, replacing penicillin and amoxicillin and ampicillin, taken with probenecid. Implementation of these guidelines took place during 1989-1990 throughout the country. The use of ceftriaxone was prompted by an increase in the occurrence of penicillinase producing *Neisseria gonorrhoeae* (PPNG). The Gonococcal Isolates Surveillance Project run by the Centers for Disease Control now document that 19.7% of gonococcal isolates from different portions of the country showed significant penicillin resistance.

Gonococcal Isolate Surveillance Project (GISP) – Percentage distribution of antimicrobial resistance in gonorrhea isolates, 1991

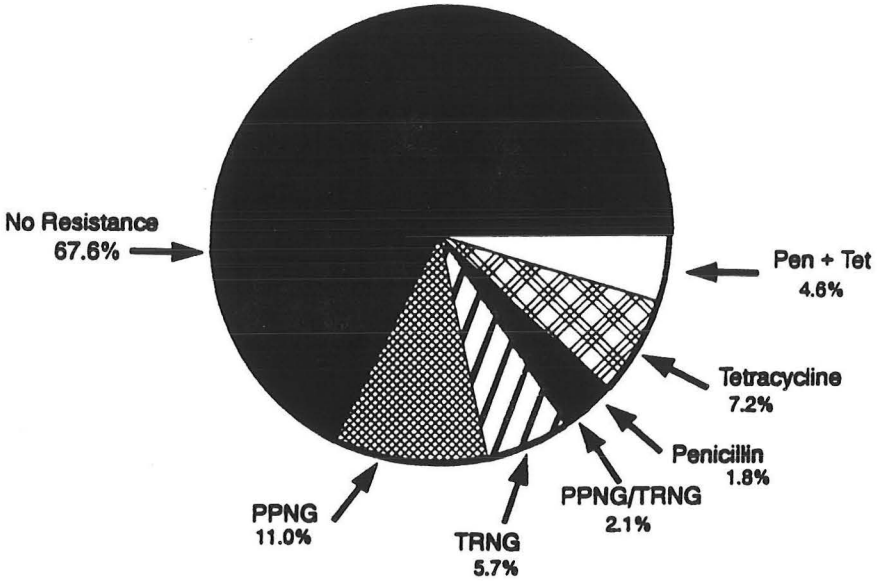


Figure 7: Division of STD/HIV Prevention, 1991

Penicillin resistance increased both because of plasmid mediated resistance (PPNG), but also because of chromosomally mediated resistance (CMR-NG). Clinically significant resistance to ceftriaxone has not been seen to the present. Cefixime, a long acting oral cephalosporin at a 400mg dose has been shown to be equivalent to 250mg ceftriaxone intramuscularly and is an alternate therapy for gonococcal infection. Other effective drugs are cefotaxime 500mg IM, ceftizoxime 500mg IM, ciprofloxacin 500mg orally, and ofloxacin 400mg orally. The rise in penicillin resistance in *Neisseria gonorrheae* most probably reflects antimicrobial pressure exerted by the widespread use of penicillin derivatives. It is also possible that penicillin-resistant isolates moved into populations like prostitutes, that led to a facilitation of transmission.

Until proven otherwise, gonococcal isolates involved in disseminated gonococcal infection and gonococcal arthritis must now be assumed to be penicillin resistant. This is not surprising, considering that the major genetic control of penicillin resistance is plasmid mediated whereas the genetic basis for strains being able to induce DGI is probably

chromosomal. DGI isolates have the capacity to survive in pooled human serum when complement is added. Strains that are incapable of producing DGI are killed when placed in pooled human serum with complement. It is now well established that DGI has been induced by penicillin resistant isolates.

In many parts of the developing world, syphilis and gonorrhea are uncontrolled. The percentage prevalence of positive serological tests for syphilis in women attending antenatal or family planning clinics in such areas of the world ranged from 0.9% to as high as 33.3%. In prostitutes from Africa, specific serological tests for syphilis are positive in 31-71% of women tested. The percentage prevalence of gonorrhea varies from 0.5% to as high as 40% for pregnant women, to a high of 17% for women attending family planning clinics and to a high of 64.8% in female prostitutes in Kenya. In contrast, in Sweden, incidence rates for both syphilis and gonorrhea have reached low points and in Scandinavia, in general, syphilis and gonorrhea are infrequent diseases. In Sweden, in 1989, the rate of gonorrhea was 14/100,000 population. The rate for syphilis was less than 5 cases per 100,000 population. Diminished numbers of cases of syphilis and gonorrhea make contact tracing possible and more efficient. In addition, major emphasis has been made to educate the population about STD's, to reduce casual sex and utilize condoms.

CHANCROID

Chancroid is caused by *Haemophilus ducreyi*. It has an incubation period varying between 3 and 10 days (usually 7-10 days). The usual clinical picture consists of multiple ulcers with soft, non-indurated bases. The ulcers are covered with a fibrinopurulent exudate and are considered "dirty" as opposed to the indurated clean based chancre of syphilis. Inguinal lymphadenopathy is present and buboes can occur in as many as 50% of cases. Buboes can reach a large size and rupture spontaneously. *Haemophilus ducreyi* is a fastidious gram negative rod that can be cultured on a variety of selected media that usually contain hemoglobin, serum, and vancomycin. At the Dallas County Health Department, 40% of chancroidal ulcers cultured were positive; cultures taken from buboes invariably were negative. Coinfection with *Treponema pallidum* is not uncommon. Chancroid is widely prevalent in the developing world. It is an endemic disease in Korea and Vietnam and is highly endemic in Africa. Since chancroid is an ulcerating disease, it predisposes the patient to HIV infection. The male to female ratio is high in chancroid and this usually infers that prostitutes are involved in transmission. Women and men are both symptomatic but it has been observed that female prostitutes with ulcers often do not seek medical attention. *Haemophilus ducreyi* has acquired the same plasmid for degrading penicillin as the gonococcus and therapy necessitates the use of ceftriaxone 250mg intramuscularly or a 7 day course of erythromycin 500mg 4 times a day for 7 days or a double-strength tablet of sulfatrimethoprim twice a day for 7 days. Alternate regimens consist of amoxicillin/clavulanate 500mg 3 times a day for 7 days or ciprofloxacin 500mg twice a day for 5 days.

Dallas has had a major epidemic of chancroid beginning in 1986 which initially involved mostly males with Hispanic surnames.

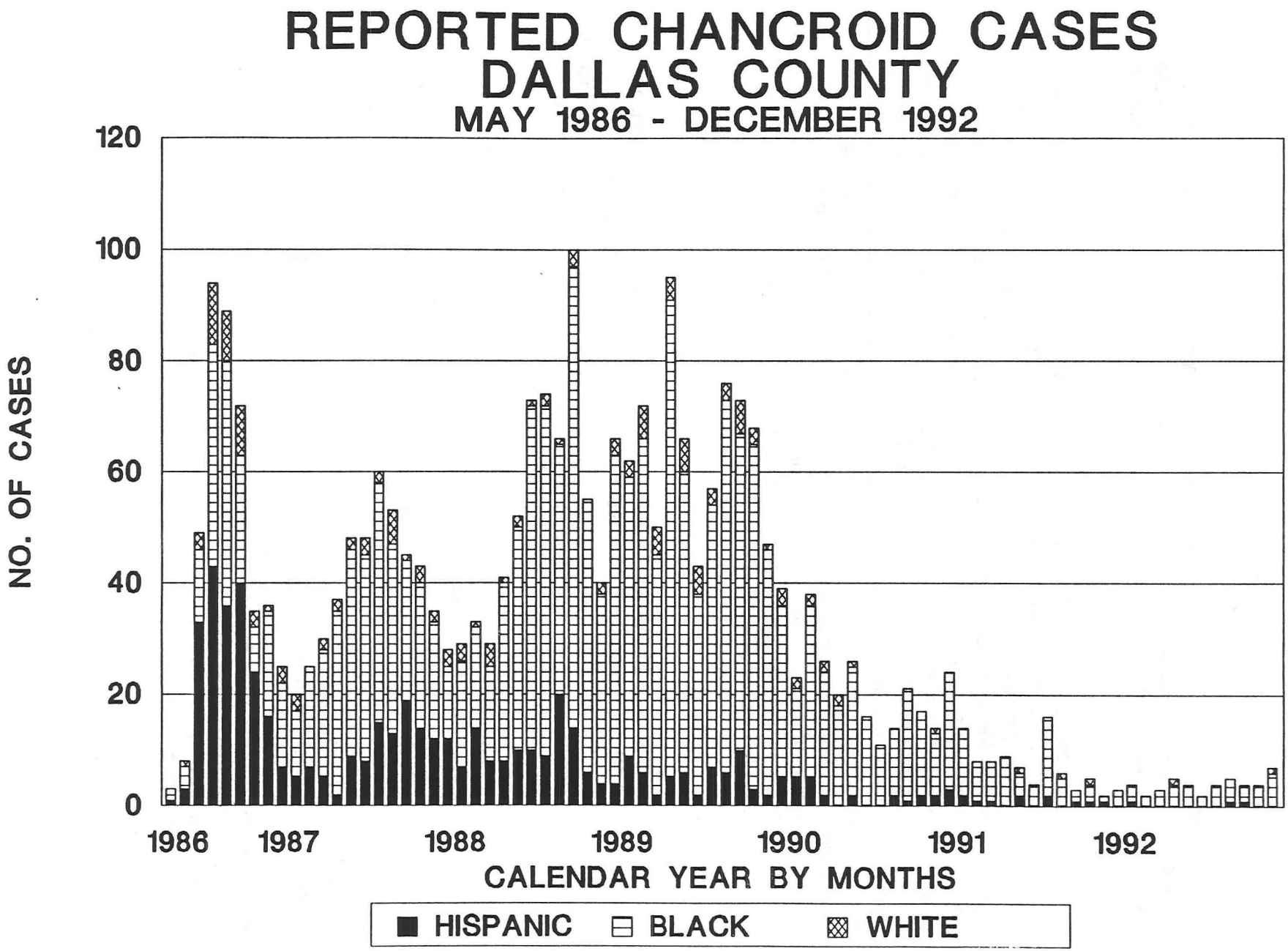


Figure 8: Dallas County Health Department, 1993

Later, men with Hispanic surnames became cases less frequently and black persons became the population group predominantly involved in the epidemic. In some months in Dallas, there were as many as 100 reported cases. Atlanta, GA, Houston, TX, New Orleans, LA, New York City, St. Petersburg and Tampa, FL also have reported epidemics in the 1980s. In Dallas, the epidemic peaked in 1989 and cases began to diminish in 1990 through 1991 and 1992. In 1991, only 31 cases were reported; the number of cases was less in 1992 and the number of cases in 1993 continues to be low. In 1989, with the publication of the STD Guidelines for the Treatment of Sexually Transmitted Diseases, ceftriaxone was instituted as primary treatment for gonorrhea. This was fully implemented in late 1989 and cases in Dallas diminished after this in a striking fashion. It has been speculated that the widespread use of ceftriaxone reduced the number of persons incubating chancroid or who may have had atypical chancroid and this diminished the pool of persons transmitting the organism in the community. Chancroid has also decreased in other areas of the country in a similar fashion, with the peak number of cases, 5,199 for the entire United States being seen in 1989, followed in 1990 by 3,099 cases and in 1991 by 2,358 cases. Conventional attempts to control chancroid through 1989 were not successful. Although *Haemophilus ducreyi* in the U.S. has shown no evidence of ceftriaxone resistance, such resistance has been reported in Nairobi, Kenya. Chancroid represents a genital ulcerative disease once common in the United States and considered one of the five classical sexually transmitted diseases that became distinctly infrequent until the 1980s where it became epidemic in a number of cities in the United States and Canada. Most probably it was spread in large part by prostitutes. Epidemics in Dallas and other North American cities are ending coincident with the widespread use of ceftriaxone for gonococcal treatment. If ceftriaxone did in fact act to abort these epidemics, it connotes the existence of numbers of persons who are effective spreaders of the microorganism who may be incubating chancroid or who may have lesions and are not coming to medical attention.

Chlamydia trachomatis

Chlamydia trachomatis is the most prevalent sexually transmitted disease in the United States today. Systematic reporting of cases has just begun in the United States. For the year 1991, 362,000 cases were reported in the U.S. with the majority being women, accounting for 265,000 of the reported cases. Present reporting practices reflect many biases, including the institution of screening surveys to detect chlamydia in the population. These surveys more completely include women than men. An average figure for the prevalence of *Chlamydia trachomatis* in a population of sexually active women might approximate 10%. A study of sexually active men in the United States Armed Forces showed that 11% had asymptomatic urethral excretion of *Chlamydia trachomatis* while the same study group had a 2% asymptomatic excretion rate of *Neisseria gonorrhoeae*.

Evaluation of factors relating to urethral infections due to *Chlamydia trachomatis* in 97 asymptomatic male U.S. military personnel.

Factors	*Chlamydia*-positive (n = 11)	*Chlamydia*-negative (n = 86)
Age	23.3 ± 3.6	23.8 ± 3.7
No. of sex partners in prior six months	1.6 ± 0.8	1.3 ± 1.1
Antibiotics in previous year	1	5
Presence of pyuria	2	8
History of urethritis	6	15

Table 1: Padgore JK, et al., 1982

Chlamydia rates will increase as more populations are surveyed. *Chlamydia trachomatis* causes nonspecific urethritis and epididymitis in the male. It can induce Reiter's syndrome.

Results of Cultures for *Chlamydia trachomatis* and *Ureaplasma urealyticum* in Men with Reiter's Syndrome

Condition	Patients (Infected/Cultured)	
	C. trachomatis	*U. urealyticum*
	← n →	
Acute, nondiarrheal Reiter's syndrome		
No antibiotic treatment	9/19	1/13
Antibiotic treated	0/16	2/6
Acute, diarrhea-associated Reiter's syndrome	0/6	0/2
Chronic Reiter's syndrome	2/10	3/9
Other forms of arthritis	0/8	3/8

Table 2: Martin, et al., 1984

Its major impact is on the female and the infant. In the female, it is a cause of the female urethral syndrome, which consists of dysuria, frequency and negative bacterial urine cultures. *Chlamydia trachomatis* also causes mucopurulent cervicitis, an asymptomatic disease, found on patient examination. Patients with mucopurulent cervicitis commonly have an everted endocervix producing an area of ectopy or an ectropion: mucopus exudes from the cervical os. Mucopus has been variously defined, but there should be at least 10 leukocytes per oil immersion field and presently many authorities think that the number should be closer to 30 leukocytes per oil immersion field to enhance specificity. Occasionally, in the area of ectopy evidence of lymphoid follicles can be seen, indicating chronicity of the infection. *Chlamydia trachomatis* can induce pelvic inflammatory disease; it is the most common cause of pelvic inflammatory disease in Scandinavia. Cases of *Chlamydia trachomatis*-induced pelvic inflammatory disease typically are not as severe as gonococcal pelvic inflammatory disease but they lead to the same sequelae, namely infertility, ectopic pregnancy, and the predisposition to future episodes of pelvic inflammatory disease that do not have to be initiated by *Chlamydia trachomatis* or the gonococcus. Pelvic inflammatory disease due to *Chlamydia trachomatis* paves the way for invasion of the endometrium and the upper genital tract with vaginal commensual microorganisms. Thus, in the fully-developed state, *Chlamydia trachomatis* has a polymicrobial etiology like gonococcal pelvic inflammatory disease.

Recommended treatment regimens for pelvic inflammatory disease include ceftriaxone 250mg IM followed by 10 days of doxycycline 100mg twice a day. If the patient needs to be hospitalized, cefoxitin 2gms q 6 h and doxycycline 100mg BID can be given and then after discharge a 10-14 day total antibiotic course can be finished with doxycycline after discharge. A third treatment regimen is with the combination of clindamycin and gentamicin to be finished with doxycycline given at home. *Chlamydia trachomatis* may ascend into the upper genital tract and cause tubal infertility by scarring. This process may be completely asymptomatic. Serological studies and isolation of the organism at laparoscopy has shown that *Chlamydia trachomatis* is an important cause of tubal infertility.

Occurrence of Positive Levels and Mean Levels of Serum Antibodies to *C. trachomatis*, *N. gonorrhoeae*, and *M. hominis* in Infertile Women, Stratified by the Condition of Fallopian Tubes and by Historical Data

	Patients with Damaged Tubes			
Serological Findings	History of Prior PID (n = 19)	History of Tubal Pregnancy (n = 20)	Negative History (n = 37)	Patients with Normal Tubes (n = 28)
C. trachomatis				
No. (%) positive	11 (58)	8 (40)	16 (43)	2 (7)
Mean ± SD*	59 ± 33	44 ± 39	48 ± 39	12 ± 20
N. gonorrhoeae				
No. (%) positive	5 (26)	1 (5)	5 (14)	0 (0)
Mean ± SD	28 ± 35	17 ± 36	14 ± 29	7 ± 11
M. hominis				
No. (%) positive	8 (42)	7 (35)	13 (35)	4 (14)
Mean ± SD	25 ± 21	23 ± 21	25 ± 25	13 ± 15

Table 3: Miettinen, et al., 1990

The infant is infected by passage through the infected endocervix; approximately 50% of such infants become colonized. The major disease states in the neonate that result after colonization are inclusion body conjunctivitis, an atypical pneumonia syndrome, otitis media, and nasopharyngitis.

Frequency of Illness During First 12 Weeks of Life in Uninfected and Infected Infants		
Illness	Infected Infants (n = 27), No. (%)	Uninfected Infants (n = 68), No. (%)
Conjunctivitis	20 (74)	3 (4)
Pneumonia	3 (11)	2 (3)
Other respiratory tract illnesses	10 (37)	11 (16)
No illness	4 (15)	48 (71)

Table 4: Heggie, et al., 1981

The application of erythromycin ointment to the eyes is poor prophylaxis of the infant at birth against the development of chlamydial disease.

Ocular Prophylaxis and Chlamydial Infection among 230 Infants Born to Women with Chlamydial Infection.

Prophylaxis	No. of Infants	Chlamydial Conjunctivitis	Nasopharyngeal Infection	Pneumonia
			number (percent)	
Silver nitrate	76	15 (20)	1 (1)	2 (3)
Erythromycin	92	13 (14)	4 (4)	0
Tetracycline	62	7 (11)	3 (5)	0
Total	230	35 (15)	8 (4)	2 (1)

Table 5: Hammerschlag, et al., 1989

Tetracycline ointment and silver nitrate are also relatively ineffective. Thus, prevention of disease in the neonate should be accomplished by treatment of the mother during pregnancy. This can usually be done with erythromycin base 500mg 4x a day for 7 days or 250mg 4x a day for 14 days. Chlamydial disease in the neonate is usually treated with erythromycin syrup. A new drug, azithromycin, has been found to be effective therapy in the treatment of chlamydial infections in the adult. When given as a single dose of 1gm, it effectively eliminates *Chlamydia trachomatis* and is as successful as a conventional 7 day course of doxycycline or erythromycin. The cost of a gram of azithromycin now approximates $24. Because of the cost, it should only be utilized in specific clinical circumstances, i.e., rape or the treatment of chlamydial disease in non-compliant persons.

Central to the control of *Chlamydia trachomatis* is the detection and treatment of infected persons who oftentimes are asymptomatic and yet transmit the microorganism to others. Culture has been the gold standard for diagnosis but it is expensive and relatively insensitive since an infectious unit is required for a positive culture. A micro-immunofluorescent test has been developed, which relies upon staining the specimen with a fluoresceinated monoclonal antibody directed against an outer membrane protein of the elementary body. The Chlamydia Elisa test is also in widescale use. The Chlamydia Elisa test depends upon an antibody directed against the lipopolysaccharide of the microorganism. When the Elisa test is confirmed by a subsequent test using a blocking antibody, it is very accurate but tends to be relatively insensitive, detecting only between 80-90% of persons that are carriers. Another test relies upon hybridization techniques to detect chlamydial RNA. The same specimen can also be utilized for the detection of the gonococcus. This last test needs further development because of false negative and positive results which cannot be confirmed by the same test or by alternate test methodology.

A major problem in the study of populations with a relatively low prevalence of *Chlamydia trachomatis* carriage are false positive results. Women are told that they have tests that are positive for *Chlamydia trachomatis,* a sexually transmitted disease pathogen and this is upsetting to them and their partners. One way of dealing with this problem is to require that each positive test result be confirmed by another test which detects another antigen than that detected by the first test. Thus, if the screening test is the Chlamydia Elisa, the positive report

should be confirmed by culture, microimmunofluorescence, RNA hybridization, or the use of a blocking antibody in a subsequent Chlamydia Elisa test. Attempts to screen populations with low prevalence rates have met with problems because they have not dealt with the problems posed by false positive tests. Requiring another independent test or a blocking antibody test to confirm the initial result might eliminate an important aspect of the screening problem. Screening males has previously required insertion of a swab into the distal urethra. This limits the number of men who could or would be screened. A possible approach is to test for leukocytes in the first catch urine (FCU) in the A.M.; if positive than the urine sample can be processed for chlamydial antigen.

Frequencies of *N. gonorrhoeae* and *C. trachomatis* Infection in Adolescent Males with Pyuria

	n	(%)
Urethral CT only	17	(34)
Urethral NG only	17	(34)
CT and NG	8	(16)
FCU CT only	7	(14)
FCU NG only	23	(46)
FCU CT and NG	2	(4)
Urethral and/or FCU CT and/or NG	43	(86)

Table 6: Woods, et al., 1991

—Performance of the Urinary Leukocyte Esterase Strip by Clinic Site

	Culture Results*					
	Schools (n = 35)		Teen Clinics (n = 116)		Detention Clinics (n = 284)	
	+	−	+	−	+	−
Esterase activity						
Positive	6	4	11	2	21	22
Negative	2	23	3	100	10	231
Sensitivity, %	75		79		68	
Specificity, %	85		98		91	
Predictive value, %						
Positive	60		85		49	
Negative	92		97		96	
Prevalence rates among subjects, No. (%)						
Culture positive	8 (23)		14 (12)		31 (11)	
Esterase positive	10 (29)		13 (11)		43 (15)	
Chlamydia trachomatis	7 (20)		12 (10)		20 (7)	
Neisseria gonorrhoeae	1 (3)		2 (2)		11 (4)	

Table 7: Schafer, et al., 1989

Ways of improving the sensitivity of the antigen assay for urine are currently being investigated.

Herpes Simplex Virus

There have been major advances in our knowledge of genital herpes. Specific tests are now available to measure antibody to HSV-1 and HSV-2 in serum. These tests are available on a research basis only; conventional commercial tests do not now differentiate between antibodies that are specific to HSV-1 or HSV-2. Patients infected primarily with HSV-2 will have antibody responses to both HSV-1 and HSV-2 and IgM antibody responses to both viruses in conventional assays. By constructing an Elisa test with a protein that is unique to HSV-1 or HSV-2 or by performing Western blot tests, one can now make a reliable determination about whether persons have been exposed to either one of the viruses or both. Glycoprotein G is different between the two herpes simplex viruses and is the basis of one Elisa test. Serological tests have demonstrated that HSV-2 antibody prevalence rates in adult populations in the U.S. may vary between 20 and 65%. It has been ascertained that the majority of persons who have antibody to HSV-2 do not realize that they have genital herpes.

Past History and Current Physical Signs of Genital Herpes Among HSV-2 Seropositive Women

	STD Clinic	University Clinic
Findings	*n* (%)	*n* (%)
No history or physical signs of genital herpes	222 (66)	40 (71)
History, but no current physical signs of genital herpes	64 (19)	14 (25)
No history, but current physical signs of genital herpes	14 (4)	1 (2)
History and signs of genital herpes	37 (11)	1 (2)
Total	337	56

Table 8: Koutsky, et al., 1989

Similarly, as many as 50% of persons infected by HSV-1 do not realize that they are infected. It is now established that prior infection with HSV-1 may influence the severity and clinical course of disease caused by primary infection with HSV-2. The disease may be atypical or it may be less severe. A differentiation between first episode true primary disease (the patient has his first episode of genital disease but does not have antibody either to HSV-1 or HSV-2 at the time of first visit) and first episode nonprimary disease (the patient has neutralizing antibody to either virus on initial presentation) can be made. Recurrent disease is characterized by recurring episodes of genital disease. First episode, true primary disease may be severe and cause systemic symptomatology; it may be also asymptomatic or not recognized. First episode, non-primary disease tends to be less severe and recurrent disease is the least severe and lasts for 6-8 days. If only first episode, true primary genital herpes is considered 70% of the isolates are HSV-2 and 30% are HSV-1. In recurrent disease in the genital area, 95% of the isolates are HSV-2. Although prior infection with one herpesvirus alters the severity and course of genital disease caused by the other herpesvirus, it does not

prevent neonatal disease initiated by primary genital infection of the mother in the latter stages of pregnancy.

The discovery of specific serological tests, the ready availability of isolate typing and fingerprinting of viral isolates by DNA restriction fragment mapping have led to a further elucidation of how transmission may occur between partners. If first episode cases of genital disease can be collected, the infecting partner can be delineated and his/her identifying attributes determined. In such a study, it has been found that virus isolated from the infected patient is the same type or has an identical DNA restriction fragment pattern as the source contact or the source contact has type specific antibody that is the same as the isolated virus. Source contacts usually are asymptomatic or do not recognize their symptoms as being due to herpes at the time of transmission and many do not know that they have genital herpes.

First Episode Genital HSV Infections
Source Contact Characteristics

41/66 (62%) were unaware of the fact that they had genital herpes at the time of transmission

47/66 (71%) were asymptomatic or did not attribute their symptoms to genital herpes at the time of transmission

Table 9: Mertz, et al., 1989

First Episode Genital HSV Infections
Source Contact Characteristics

Source Contact HSV Infection History	No. Source Contacts with Lesions at Transmission		
	Present	Absent	Total
First Episode genital herpes	8	0	8
Recurrent genital herpes			
Aware	8	14	22
Unaware	10	0	10
Recurrent oral-labial herpes	3	0	3
Negative	0	23	23
Total	29	37	66

Table 10: Mertz, et al., 1989

Numerous case reports exist where asymptomatic persons have transmitted the virus to patients and they do not know that they have genital herpes. If couples are studied in which one is infected with genital herpes and the other not, the rate of transmission of the virus to the uninfected partner is about 12% per year. Many of these transmissions are asymptomatic and are found only by performing serial antibody assays. The couples participating in this study were informed about the potential transmission of the virus to the uninfected partner. Persons with genital herpes may have no or an occasional recurrent episode or may have as many as 8-12 recurrent episodes per year. In persons with genital herpes who have been studied, they have been found to be infectious prior to knowing that the episode was occurring and may be infectious during asymptomatic intervals. By culturing numbers of such persons on multiple occasions, it has been found that on average patients with genital herpes are excreting the virus asymptomatically about 1% of the time. In the female, as deduced by self-culture, the virus is excreted either at the cervix or in the vagina or can be present asymptomatically on the perineum equally as frequently. In the male, self culture of the external genitalia reveals the virus to be present asymptomatically about 1% of the time. Evidently, there are microscopic breaks in the skin in which virus is present. Asymptomatic transmission of the virus makes control difficult.

The neonatal herpes simplex problem is becoming better defined. Previously, most attempts to prevent neonatal herpes centered on the woman with recurrent genital herpes. It is now known that such women even when shedding virus at the time of delivery and when the infant is delivered vaginally have an approximate risk of 10% that they will transmit the infection to the infant. It is probable that women with recurrent disease pass only a small amount of virus but significant immunity to the infant. Studies now show that the woman who is most at danger of having a child with neonatal herpes is one that is experiencing primary genital infection with either HSV type at or near the end of the pregnancy and is asymptomatic. In a series of 140 women, assessed retrospectively after they had given birth to a child who developed neonatal herpes, 77% could not recall having genital herpes before the pregnancy, during the pregnancy, or at the time of delivery.

Maternal Evidence of Genital Herpes Infection N = 140*

	Before Pregnancy	During Pregnancy	Genital Sores at Delivery	Number
	+	+	+	6 (4%)
	−	+	+	5 (4%)
	+	−	+	0 (0%)
	−	−	+	1 (1%)
	+	+	−	9 (6%)
	−	+	−	5 (4%)
	+	−	−	6 (4%)
	−	−	−	108 (77%)
Column Total (+)	21 (15%)	25 (18%)	12 (9%)	
Column Total (−)	119 (85%)	115 (82%)	128 (91%)	

* 43 case reports with missing information were excluded from analysis.

Table 11: Stone, et al., 1989

Their obstetricians did not recognize the presence of genital herpes at the time of delivery. In another study, women who were asymptomatically excreting the virus and who had reactivated infection passed the virus on to less than 10% of their infants even though delivered vaginally.

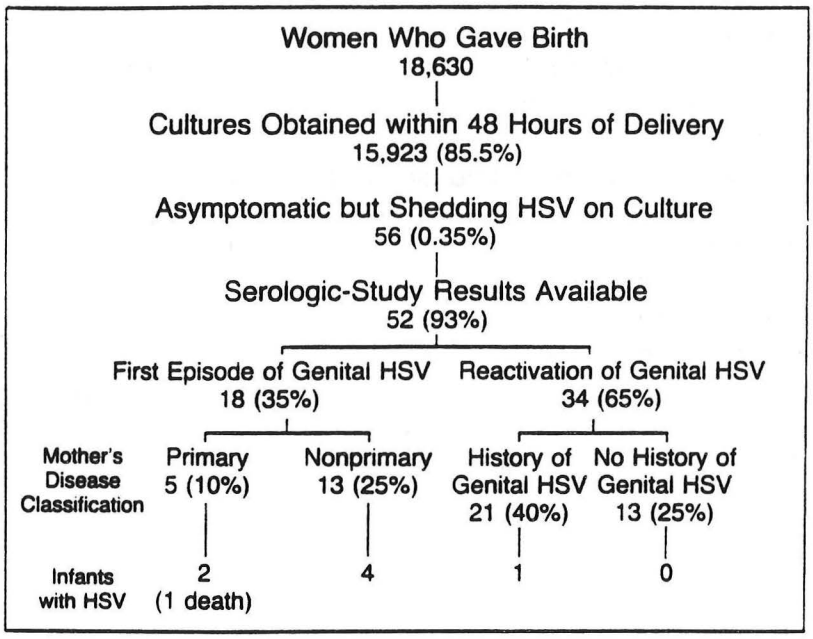


Figure 9: Brown, et al., 1991

Women who were experiencing primary genital infections, either having had prior oral-labial or no HSV infection were much more likely to pass the virus on to their offspring, even though they were asymptomatic. In about a third of women whose primary genital infection occurred at or around the time of delivery, infected infants resulted. Thus the challenge now in preventing cases of neonatal herpes lies in finding women who are experiencing asymptomatic primary genital infection in the latter stages of pregnancy. Such women might just be in the process of forming antibody and they would have virus in the genital tract. Detection of viral antigen might be a way to find these patients but in a population with a low incidence of primary HSV infection, if the test were not sufficiently specific, it might lead to finding false positives and unnecessarily high Cesarean section rates.

Incidence of Neonatal HSV in the Infants of 56 Infected Mothers, According to Viral Type and Anatomical Site of Asymptomatic Viral Shedding in Early Labor.

Site	HSV-1	HSV-2
	no. of women (no. of infants with HSV)	
Labia	3 (0)	31 (1)
Cervix	2 (2)	8 (0)
Both	—	12 (4)
All sites	5 (2)	51 (5)

Table 12: Brown, et al., 1991

Acyclovir has been shown to effective treatment for first episode true primary genital disease. It is less efficacious in first episode non-primary infections and it is marginally effective in recurrent disease. Acyclovir treats immunosuppressed patients with herpes effectively. When given as a prophylactic agent at 400mg twice a day, it prevents manifest recurrences of genital herpes. The use of prophylactic acyclovir, however, does not prevent asymptomatic shedding. If infection is to be prevented in people taking acyclovir, protected sex needs to be practiced. Resistant isolates of herpes simplex virus to acyclovir have been reported. These occur mainly in highly immunosuppressed patients, particularly in those with AIDS. The viruses are usually thymidine kinase negative or thymidine kinase deficient (TK^-, TK^d). They are less commonly due to a mutation in viral DNA polymerase. These viruses can cause severe disease in immunosuppressed persons and have to be treated with sodium phosphonoformate given intravenously. Patients may have acyclovir susceptible virus on subsequent recurrences but the majority of experience is that they recur with resistant viruses and have to be treated with additional courses of sodium phosphonoformate. Ganciclovir is also effective against herpes simplex virus infections but is not effective against acyclovir resistant mutants. A vaccine is in the process of being developed. It will probably consist of some complex of envelope glycoproteins. A prior vaccine was insufficiently antigenic to protect patients against infection.

Human papillomaviruses

Human papillomaviruses are DNA viruses which have not yet been grown in tissue culture. There are approximately 65 human papillomavirus types based upon DNA homology studies. At least twenty of these human papillomaviruses cause disease (condyloma acuminata) in the genital and perianal areas and are common infections.

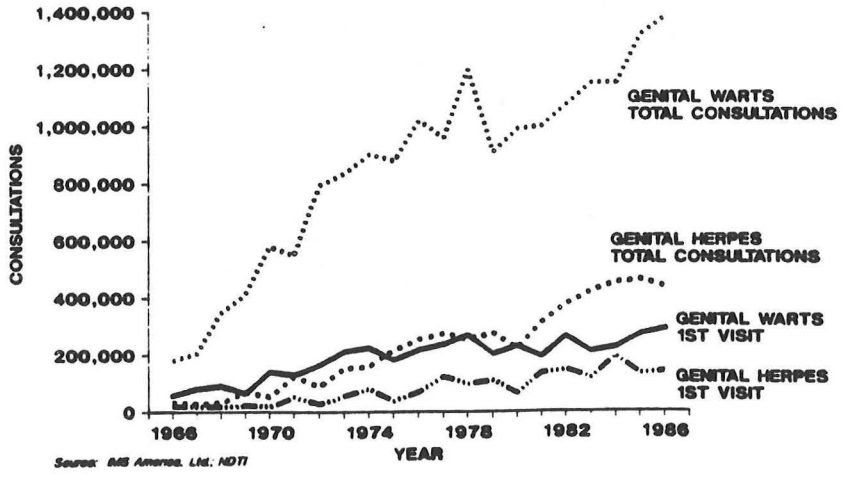


Figure 10: Shah, et al., 1990

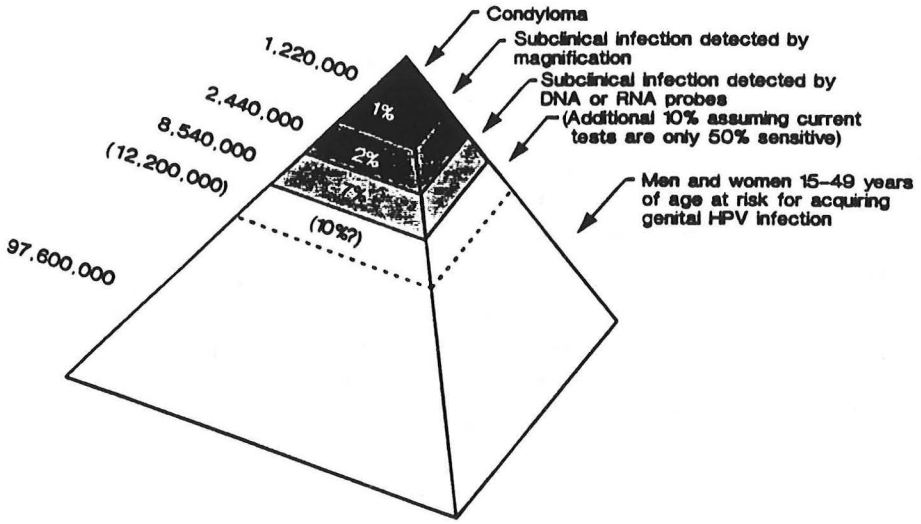


Figure 11: Koutsky, et al., 1988

Occasionally human papillomaviruses also cause disease in the rectum, mouth, larynx, trachea, breasts, and belt line but they are rarely found on the extremities. In contrast, human papillomaviruses causing the common wart produce disease on the extremities and the viruses usually cannot be transferred to the genital tract. Studies pioneered by zur Hausen and associates and also performed by others have shown that the majority of human cervical carcinomas, approximating 85%, contained HPV genomic DNA. Human papillomavirus genomic DNA has also been found in penile, anal/rectal, vulvar, and vaginal cancers. It has been determined that types 16 and 18 have a high potential of being associated with cervical and other cancers; 6 and 11 have a low association, while types 31, 33, and 35 have intermediate associations.

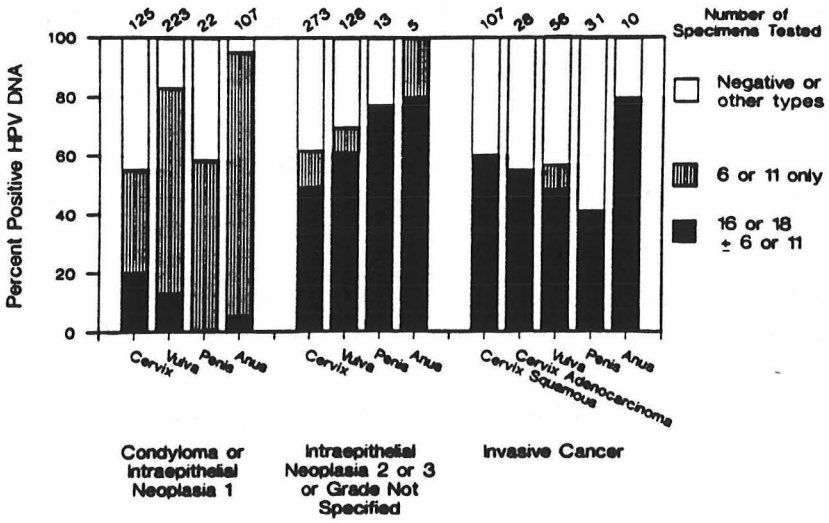


Figure 12: Koutsky, et al., 1988

Infection with HPV occurs through breaks in the skin which expose the basal layer and it is this portion of the epithelium which primarily becomes infected. The infected epithelial cell differentiates as it moves to the surface of the squamous epithelium. As the cell becomes more differentiated, mature infectious virions are produced. The cell containing these mature virions is known as a koilocyte. It is a squamous cell that has a nucleus that is slightly enlarged and hyperchromatic. There is a clear zone or halo around the nucleus and then a condensed rim of cytoplasm. These cells are sufficiently distinctive to be recognized as such by the experienced cytologist. In infection with papillomavirus, the viral DNA exists initially in an episomal form. Later, in association with transformation, viral DNA integrates itself randomly into host cell chromosomal DNA. The viral DNA that integrates usually does so along the stretch of the genome coding for the E1 and E2 gene products.

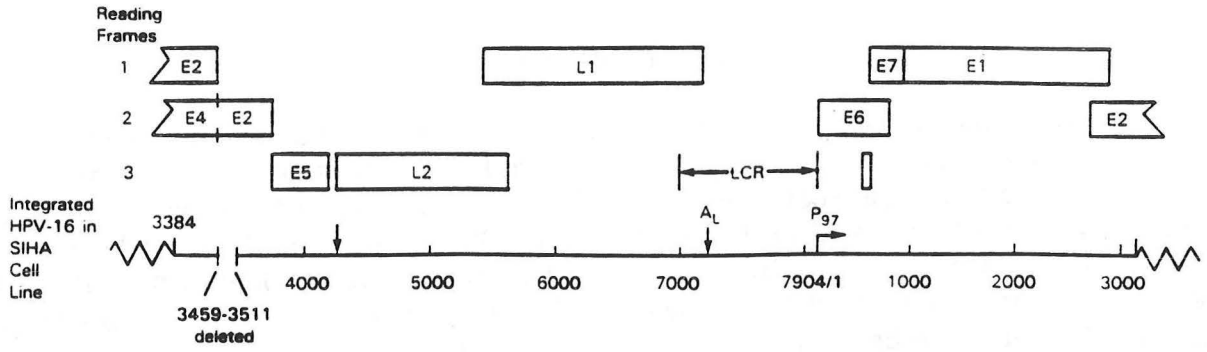


Figure 13: Shah, et al., 1990

E refers to proteins produced early in the course of infection. The E2 gene product regulates the transcription of the E6 and E7 gene products. If integration at the E2 DNA coding region occurs, it may interfere with formation of the product encoded by E2, and unregulated transcription and translation of E6 and E7 take place. It has been ascertained that the proteins coded for by E6 and E7 combine with tumor suppressor proteins, namely p53 and pRB or the retinoblastoma suppressor protein. The combination of E6 and E7 with these tumor suppressor proteins allows for unregulated transcription and eventually transformation of the cell. Viral DNA has been found in about 85% of invasive cervical cancers. In the remaining cervical cancers, it has been postulated that there are either unknown HPV viral types present or that spontaneous mutations have occurred in p53 or pRB. Although the events leading to cancer have been thought to occur over a relatively long interval, there is now suggestive evidence that infection, particularly with human papillomavirus 16 can lead to a more rapid appearance of cervical intraepithelial neoplasia (CIN) than previously considered possible.

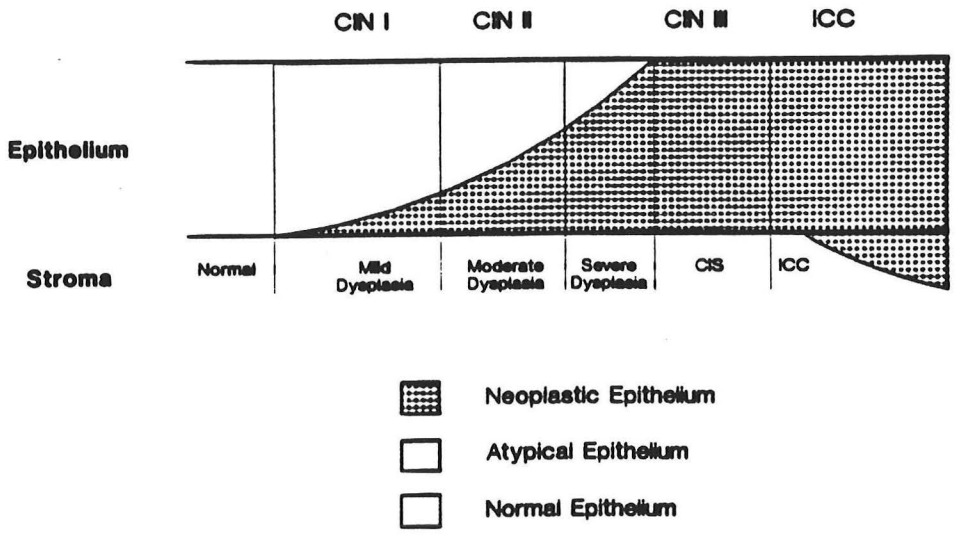


Figure 14: Paavonen, et al., 1990

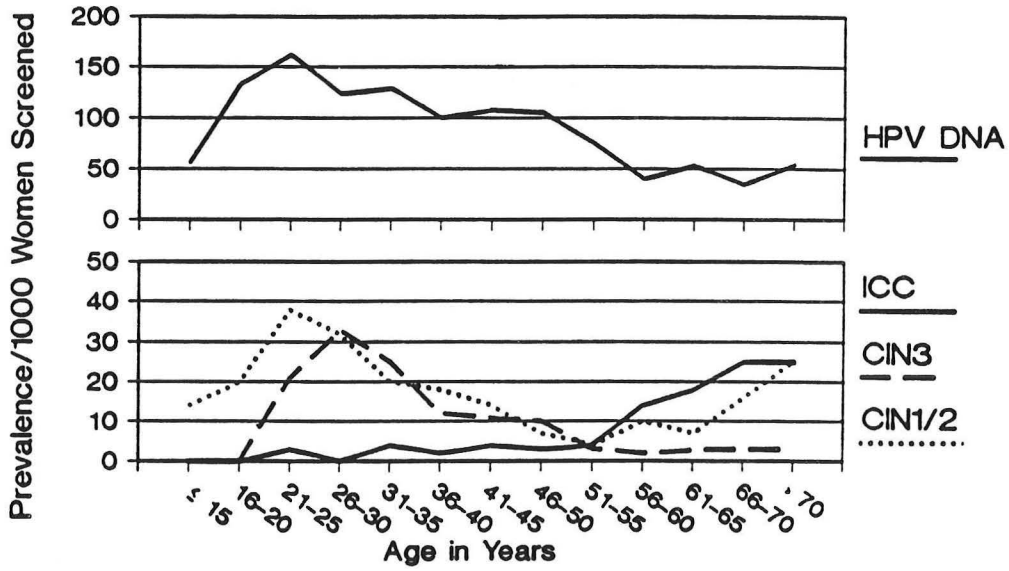


Figure 15: DeVilliers E-M, et al., 1987

Prior studies have been cross-sectional rather than prospective. In a recent prospective study of women that had just acquired human papillomavirus infection, it was shown that as many as 50% of those with HPV types 16 or 18 went on to develop CIN grades 2 or 3 in a two year period of time. Infection with human papillomavirus types 6 and 11 are associated with a low transformation potential of producing high grades of cervical intraepithelial neoplasia.

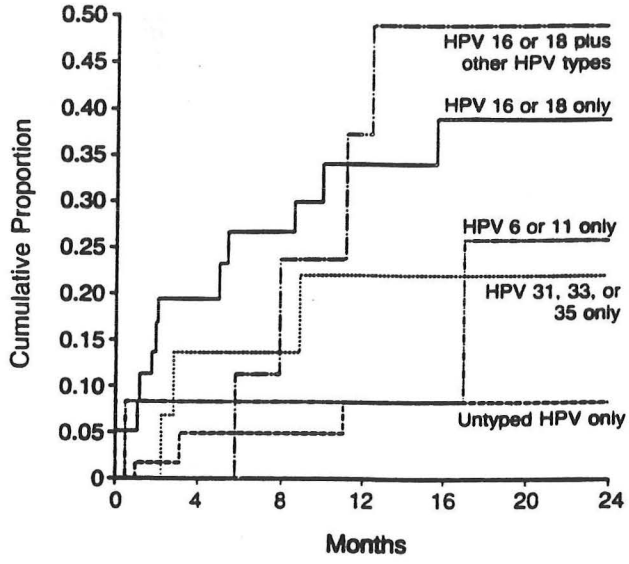


Figure 16: Koutsky, et al., 1992

Infection with HIV also been shown to be associated with an acceleration of transformation induced by human papillomaviruses. Since the mid-1980's, there has been a revolution in our concepts of the induction of genital tract malignancy. The association of malignancy with papillomaviruses has made the management of condyloma acuminata or venereal warts exceptionally important and more difficult.

In the male, genital warts can be removed by cryotherapy, by the application of podophyllin or the active principle of podophyllin, by electrocautery or by the use of certain chemicals such as 5-fluorouracil, bichloroacetic acid, or trichloroacetic acid. Since men with penile condylomas may have associated urethral condylomas, many doctors treating these patients will also perform urethroscopy and attempt to remove the urethral condylomas. Condylomas can be made more apparent by acetowhitening, i.e., an application of a 3-5% solution of acetic acid. This dehydrates the epithelial surface. Since cell nuclei in the papilloma are hyperchromatic, dehydration accentuates the nucleus so that the condyloma appears white in relationship to the normal epithelium. Acetowhitening can be used on the external surface of the genitalia, in the urethra, the vagina, and on the cervix. Urethral condylomas are usually removed by either cryosurgery or the application of 5-fluorouracil.

Female condylomas are more difficult to manage. In the presence of perineal condylomas, Pap smears should be prepared to determine the presence of koilocytes or atypical cells suggestive of higher grades of CIN. If the pap smear is positive, colposcopy, inspection of the vagina and the uterine cervix with a microscope, is performed. The examination is aided by acetowhitening of apparent lesions. Cervical cancer usually starts at the transformation zone, the area between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix. Clinically apparent lesions can be seen and removed. Cryosurgery is applicable to the perineum and vagina. If the zone of transformation is involved or if the cells that are seen by Pap smear suggest higher grades of CIN, a biopsy may be

necessary to determine the actual grade of CIN present. Management of higher grades of CIN necessitates consultation with an expert. Since there may be islands of tissue which may contain viral DNA that are separate from clinically apparent disease, it is generally thought that the emphasis of treatment should be made to remove the disease and not try to eradicate the infection completely. There is probably an element of spontaneous cure of HPV infections but recurrences are the rule. The inability to eradicate infection completely demonstrates the need for recurrent examinations by Pap smear or by colposcopy and biopsy techniques. Since infection may not be eliminated by therapy, transmission of these viruses may continue to occur.

It is now possible to type the HPV present in clinical specimens by several techniques. Cells or biopsied tissue can be used. In situ hybridization with cells and tissue can be performed or the DNA can be extracted and subjected to analysis by dot-blotting or by Southern blotting. Using radiolabelled or biotinylated probes and hybridization under varying stringency conditions, human papillomaviruses, in general, can be detected and the specific viruses present can be typed. Commercial kits are available to type exfoliated cells or biopsy specimens. The critical question is whether knowledge that a patient had infection with HPV types 16 or 18 would lead to a different course of therapy than if one were infected with types 6 or 11 is presently being studied. The decrease in rates of cervical cancer and deaths from that disease in Europe and North America during the last two decades have been accomplished without viral typing. Virus typing would be expensive and might not give enough additional information to be worthwhile doing. Since most HPV types may have some malignant transformation potential, typing might lead to a false sense of security. Furthermore, additional types may be acquired after typing and the presence of one virus type in abundance may obscure the presence of another type which could cause progression to malignancy. The area is one under active study at the present time; it is impossible now to make firm recommendations as to whether viral typing could be useful in managing these patients.
Human papillomaviruses can be transmitted from the mother to the infant where they can cause laryngeal nodules or tracheopapillomatosis. Such transmission can also cause genital warts in infancy. Most authorities agree, however, that condyloma acuminata occurring after the first two years of life in young children should lead to a suspicion that child abuse may have occurred.

Since many women infected with human papillomaviruses never progress to malignancy, there are probably cofactors that also need to be present. These cofactors are presently being elucidated and might include infection with human immunodeficiency virus, herpes simplex virus, type 2, cytomegalovirus, or *Chlamydia trachomatis*. Cigarette smoking might be another cofactor. Other diagnostic approaches to detect HPV infection might be utilized in the future. By cloning certain HPV proteins, it may be possible to assess infectivity rates in humans by serological methods. This has been done for type 11 virus; the studies as of present are of interest but the specificity of the antibody assays has yet to be ascertained.

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