CHAPTER 5

MODELING GONORRHEA TRANSMISSION IN A HETEROSEXUAL POPULATION

Although sexually transmitted diseases are a major health problem among homosexuals, there is little transmission between the homosexual population and the heterosexual population (WHO, 1978; Wiesner and Thompson, 1980). Here we concentrate on a heterosexual population subdivided into women and men since the characteristics of gonorrhea are different for the two sexes. Although the groups of women and men considered here are highly active sexually, the results are more general since it was shown in Chapter 4 that changes in prevalence in the noncore group are directly related to changes in prevalence in the core group.

From the quarterly reported incidence of gonorrhea in women and men shown in figure 5.1, it is seen that gonorrhea incidence has a small but distinct seasonal oscillation. The quarterly incidence smoothed by using seasonal indices derived from the data is shown in figure 5.2. Notice that the seasonal oscillation is less than 10 percent. In this chapter we investigate the implications of the epidemiological differences between women and men and analyze the nature of the seasonality.

In the female-male model derived in section 5.1, a contact number determines whether the disease dies out or remains endemic. In section 5.2 many sources are used to estimate the parameter values and then the sensitivity of the prevalences and incidences at equilibrium to changes in parameter values is investigated. It is shown that the prevalences depend primarily on the contact number while the yearly incidences depend on the contact number and the average durations of infection. When screening programs are compared in section 5.3, it is found that because women have a longer average duration of infection, screening women is much more efficient than screening men. The effectiveness of screening women is proportional to the average duration of infection for women.

Epidemiologists have not understood why the peak incidence of gonorrhea occurs each year in August to October. In section 5.4 a model with small oscillations in the contact rates is analyzed mathematically using a perturbation analysis. The observed 6% seasonal oscillations in incidence in women and 10% oscillations in incidence in men may be due to reasonably small (5% to 7%) oscillations in the contact rate. From the analysis of the model, it appears that the

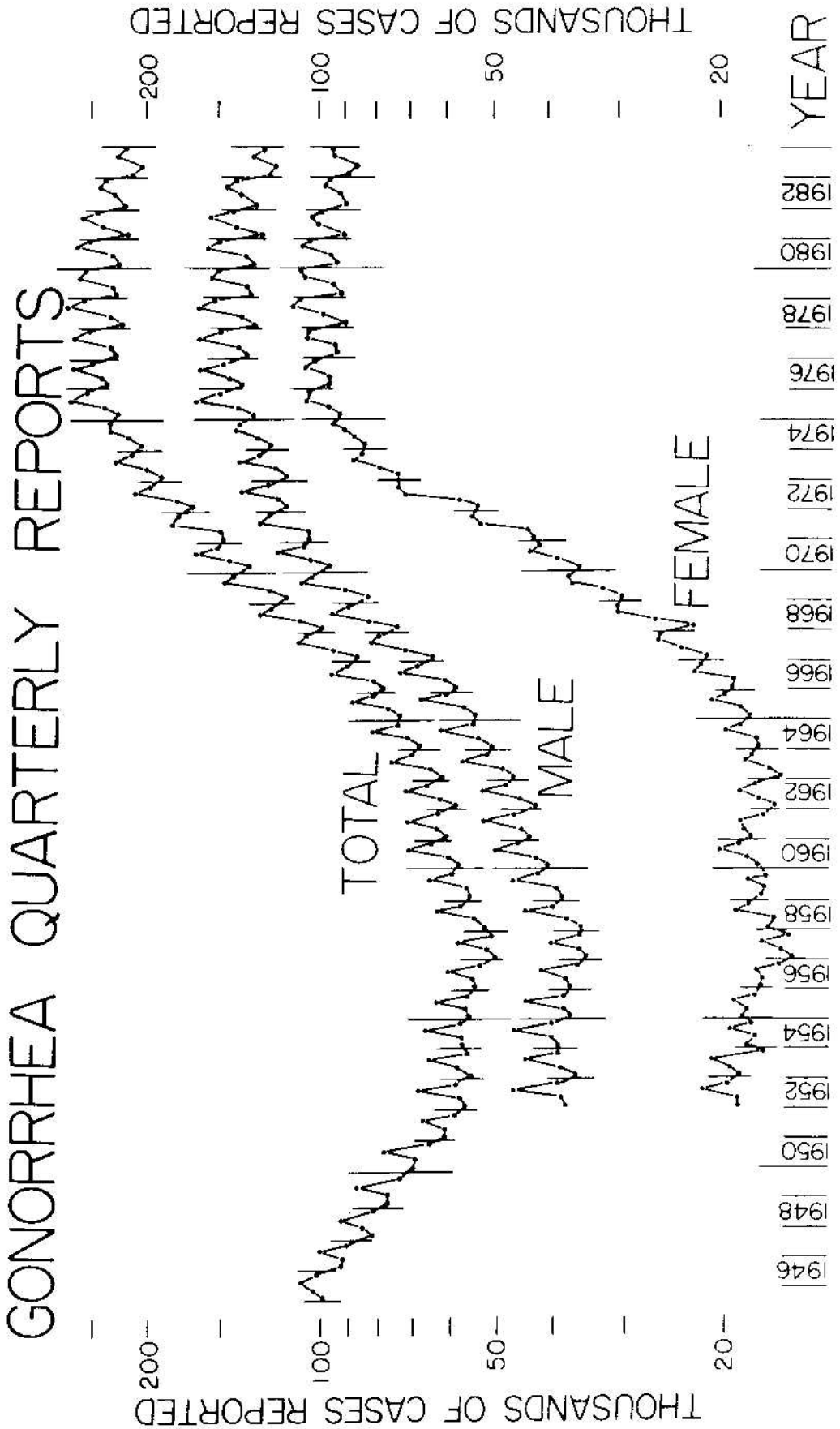

Figure 5.1. Reported cases of gonorrhea in women and men in the United States.

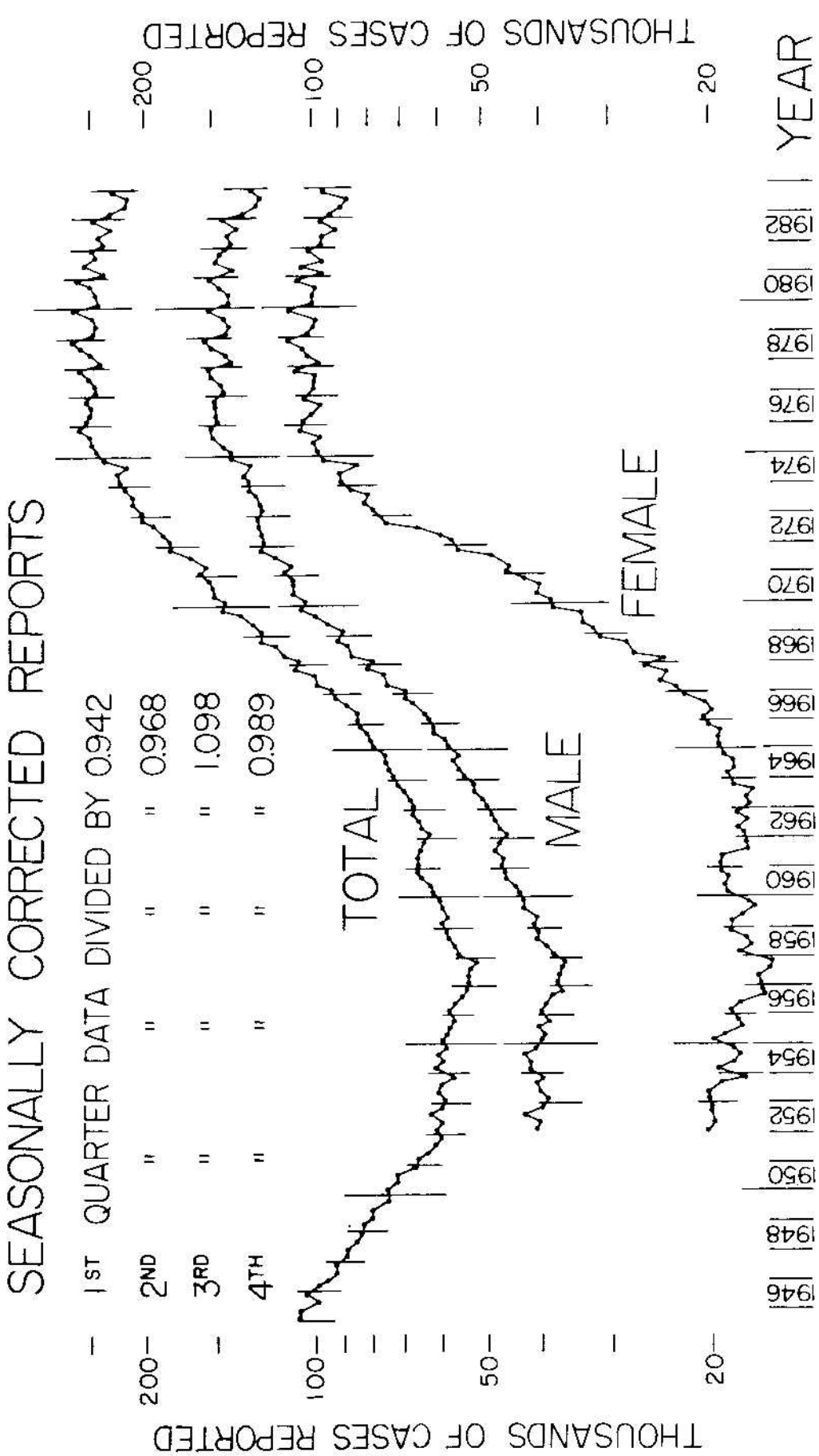

Figure 5.2. Seasonally corrected quarterly reported cases of gonorrhea in the United States.

observed peaks in August to October may be due to a peak contact rate about two months earlier. This prediction that the peak contact rate is probably in the summer months agrees with the data and the intuition of epidemiologists.

5.1 The Female-Male Model

Consider the model 3.1 with two groups where group 1 consists of women and group 2 consists of men. Since it is assumed that there is only heterosexual transmission of gonococcal infection, the contact rates λ_{11} and λ_{22} are zero. Thus this is <u>not</u> a proportionate mixing model. Indeed, the model is formally the same as a host-vector model (Hethcote, 1976). The differential equations for the model are:

$$\frac{dI_1}{dt} = (\frac{\lambda_{12}}{r})(1-I_1)I_2 - \frac{I_1}{d_1}$$
$$\frac{dI_2}{dt} = (\lambda_{21} r)(1-I_2)I_1 - \frac{I_2}{d_2} \qquad [5.1]$$

where $r = N_1/N_2$ is the ratio of the female to male population sizes. A flow diagram is given in figure 5.3.

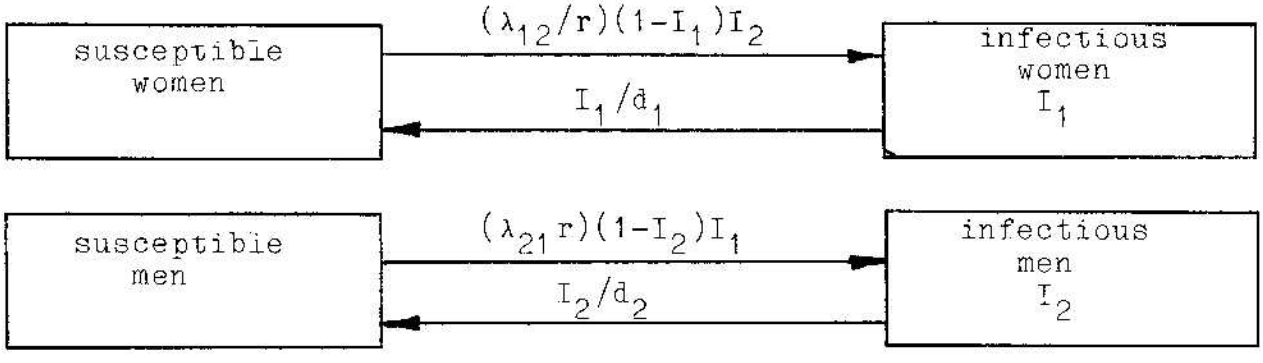

Figure 5.3 Flow diagram for the female-male model.

Let a_1 and a_2 be the activity levels of women and men, which are the average daily rates of new encounters by women and men, respectively. Let q_1 be the probability that there is an adequate contact by an infectious woman during a new encounter and q_2 be the analogous probability for an infectious man. Using these definitions, the contact rates are $\lambda_{12} = q_2 a_2$ and $\lambda_{21} = q_1 a_1$. The contact number k_1 for women, which is the average number of adequate contacts by an infectious woman during her infectious period, satisfies $k_1 = \lambda_{21} d_1 = q_1 a_1 d_1$. The contact number k_2 for men satisfies

$k_2 = \lambda_{12} d_2 = q_2 a_2 d_2$.

The second generation contact number $K = k_1 k_2$ in the theorem below determines whether the disease fades out. Since K is the product of the female contact rate and the male contact rate, it has the following interpretation: K is the average number of women (second generation) adequately contacted by men (first generation) who were adequately contacted by an average infectious woman during her infectious period. It also has a symmetric interpretation by switching the roles of women and men. See Hethcote (1974) or Lajmanovich and Yorke (1976) for a proof of the following threshold theorem.

THEOREM 5.1 If $K<1$, then the solutions $I_1(t)$ and $I_2(t)$ of [5.1] approach 0 as t approaches ∞ (i.e., fade out case). If $K>1$, then for positive values of $I_1(0)$ or $I_2(0)$, the solutions $I_1(t)$ and $I_2(t)$ of [5.1] approach E_1 and E_2, respectively as t approaches ∞ (i.e., endemic case) where the female and male prevalences at the endemic equilibrium are

$$E_1 = \frac{K-1}{K+(\lambda_{21}/r)d_2} , \qquad E_2 = \frac{K-1}{K+(\lambda_{12}/r)d_1} . \qquad [5.2]$$

This theorem has an intuitive interpretation. If the average infectious woman infects less than one other second generation woman even at low prevalence levels, then gonorrhea dies out. If she infects more than one, then gonorrhea remains endemic and the prevalences approach equilibrium levels. It can be verified algebraically that at the endemic equilibrium, the infectee number $KS_1S_2 = k_1k_2(1-E_1)(1-E_2)$ is 1 as predicted in section 1.5. The female cases per woman per year at equilibrium Y_1 is equal to the prevalence E_1 times the population size N_1 divided by the duration d_1 given in years. The definition of Y_2 is analogous.

Since the number of encounters of women must equal the number of encounters by men, $a_1N_1 = a_2N_2$. This relationship can be used to reduce the number of parameters appearing in the four coefficients in [5.1] from five (λ_{12}, λ_{21}, r, d_1, d_2) down to four. Define the contact effectiveness ratio e to be q_1/q_2. Then

$$\frac{\lambda_{21} r}{\lambda_{12}/r} = \frac{q_1 a_1 N_1 r}{q_2 a_2 N_2} = er$$

so that

$$K = (\lambda_{12}/r)(\lambda_{21}r)d_1d_2 = (\lambda_{12}/r)^2(er)d_1d_2 = [(\lambda_{21}r)^2/er]d_1d_2$$

and

$$\lambda_{21}r = \left[\frac{K(er)}{d_1d_2}\right]^{1/2} \qquad \lambda_{12}/r = \left[\frac{K}{(er)d_1d_2}\right]^{1/2} \qquad [5.3]$$

Thus the four coefficients in [5.1] now depend on the four convenient parameters d_1, d_2, K and er. Since K, e, and r have a more direct epidemiologic interpretation than λ_{12} and λ_{21}, better estimates of them can be made from available data.

5.2 Parameter Estimation and Sensitivity Analysis

Since it is not possible to estimate the ratio of the population sizes N_1 and N_2 of the women and men at risk, we simply assume that $r = N_1/N_2$ is 1. As described in section 1.2 the probability of transmission of gonococcal infection during one sexual intercourse by an infectious woman is about 0.2 to 0.3 while the corresponding probability of transmission by an infectious man is 0.5 to 0.7 (Wiesner and Thompson, 1980; Rein, 1977). Thus the probability of transmission in n sexual intercourses increases as n increases and can be estimated to be $1-(0.75)^n$ for an infectious woman and $1-(0.4)^n$ for an infectious man though in fact the n events are not truly independent. If encounters consisted of exactly one, two or three sexual intercourses, then the contact effectiveness ratio $e = q_1/q_2$ would be approximately 0.42, 0.52, 0.62, respectively. Since some encounters involve only one sexual intercourse and some involve several, the value used for er is 0.5.

The average durations of infection can be calculated as a weighted average of the average durations of symptomatics and asymptomatics. Estimates of periods of infection are 3-45 days for symptomatic women, 3-12 months for asymptomatic women, 3-30 days for symptomatic men and 3-6 months for asymptomatic men. Moreover, approximately 60% of cases in women are asymptomatic and 10% of cases in men are asymptomatic (Wiesner and Thompson, 1980; Kramer and Reynolds, 1981). Realistically, there is no way to obtain highly reliable estimates of these values. Using average durations of infection of 8 days for symptomatic women and 128 days for asymptomatic women, the weighted average duration for women is 80 days. Using an average duration of 8 days for symptomatic men and 128 for asymptomatic men, the weighted average duration for men is 20

days.

The contact number K is greater than 1 since gonorrhea is endemic. It cannot be close to 1 since small changes in sexual behavior or in health care delivery would then cause large changes in incidence and large changes have not been observed (Yorke, Hethcote and Nold, 1978). Here the contact number K is taken to be 1.4 as in section 2.3.

The ratios of reported female cases to reported male cases in the United States for the calender years from 1964 through 1980 were: .33, .33, .32, .33, .33, .35, .37, .42, .52, .65, .68, .68, .68 , .68, .70, .70, and .69 (Blount, 1979). The increase in this ratio in the early seventies is obvious and coincides with the increase in nationwide screening and with the awareness of the importance of finding infected woman. Epidemiologists believe that the increase is due to the increased searching out and identification of infective women by the screening program. Studies involving contact investigation have been used to estimate the ratio of actual female to actual male cases, but the estimates are not consistent so that the ratio of actual incidences is unknown (Rein, 1977). Consequently, for a model to be satisfactory, we require the ratio (using equilibrium values) to lie between 0.6 and 1.0. The current ratio of reported cases is 0.69. In fact this ratio may vary from population to population. Our best estimate of the parameters of the model is parameter set number 1 in Table 5.1. The uncertainty in this "baseline" parameter set requires the examination of the other sets in that table.

The sensitivity of the prevalences and yearly incidences in the model in section 5.1 to changes in parameter values is now investigated. Table 5.1 shows the prevalences and incidences for the baseline parameter set (number 1) and for modified parameter sets. At the endemic equilibrium for the baseline parameter set 1, 22% of the women and 8.4% of the men have gonorrhea at a given time so that the susceptible fractions are .78 for women and .916 for men. For the baseline parameter set 1 the contact numbers are $k_1 = 1.67$ for women and $k_2 = 0.84$ for men. The average number of transmissions at the endemic equilibrium by an infectious woman is 1.53 and by an infectious man is .65 so that the infectee number is 1. For the baseline parameter set 1 the prevalence in women is above 0.20 but the prevalence in men is not so that according to the criterion in section 4.1, the women form the core group in this model. For the baseline parameter set 1 the yearly incidence in women is 0.65 times the yearly incidence in men which is consistent with the ratio 0.69 of reported

incidences.

From parameter sets 1-7 we see that the prevalences E_1 and E_2 depend primarily on the contact number K and only slightly on d_1, d_2 and er. On the other hand, the yearly incidences are strongly dependent on the durations. Doubling both durations d_1 and d_2 as in parameter set 2 does not change the prevalences, but it does halve the yearly incidences. At first glance it may seem strange that the prevalences are not changed. This is because the contact number remains unchanged. In effect, increasing the duration automatically decreases the number of contacts per day for both men and women. As seen in parameter set 7, the value of the parameter er influences the distribution of the prevalence between women and men. Some of the qualitative observations above can be deduced from equation [5.2] and [5.3] and hold for all parameter values.

Although the estimates in this section of the parameters are subject to uncertainty and the model in section 5.1 involves simplifications, the model and baseline parameter set 1 are accurate enough to obtain comparisons and estimates in subsequent sections.

TABLE 5.1

Equilibrium Prevalences and Yearly Incidences
for Various Parameter Sets

Parameter set	1	2	3	4	5	6	7
Duration d_1	80	**160**	**160**	80	80	80	80
Duration d_2	20	**40**	20	**40**	20	20	20
Contact number K	1.4	1.4	1.4	1.4	**2.**	**1.2**	1.4
Parameter er	.5	.5	.5	.5	.5	.5	**1.**
λ_{21} r	.021	.010	.015	.015	.025	.019	.030
λ_{12}/r	.042	.021	.030	.030	.050	.039	.030
Equilibrium							
Prevalence E_1	.220	.220	.236	.201	.400	.126	.201
Prevalence E_2	.084	.084	.065	.106	.167	.047	.106
Y_1=yearly cases per woman	1.004	.502	.538	.916	1.825	.575	.916
Y_2=yearly cases per man	1.538	.769	1.190	.969	3.042	.849	1.938

5.3 Screening Women and Men

We consider the effect of screening as a gonorrhea control procedure by modifying the female-male model in section 5.1 to include screening. Let C_1 and C_2 be the fraction of the women and men that are screened for gonorrhea per day. Assume that the screened fraction is a random sample so that its mixture of susceptibles and infectives is typical of the populations being considered. Thus we assume that the fractions $C_1 I_1$ and $C_2 I_2$ are treated and removed per day from the respective infective classes.

When the differential equation model [5.1] is modified to include screening, it becomes

$$\frac{dI_1}{dt} = \left(\frac{\lambda_{12}}{r}\right)(1-I_1)I_2 - \frac{I_1}{d_1} - C_1 I_1$$

$$\frac{dI_2}{dt} = (\lambda_{21} r)(1-I_2)I_1 - \frac{I_2}{d_2} - C_2 I_2 \qquad [5.4]$$

A flow diagram is given in figure 5.4.

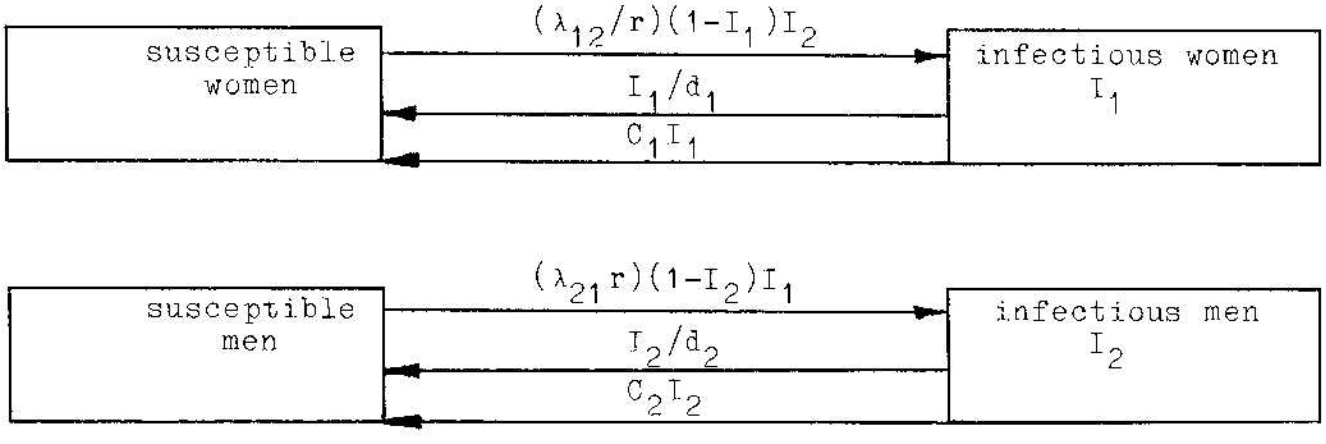

Figure 5.4. Flow diagram for the female-male model with screening.

Thus the net effect of screening is to decrease the average duration of infection and, consequently, the contact number. If d_1^s and d_2^s denote the average female and male durations in the presence of screening, then

$$d_i^s = [1/d_i + C_i]^{-1}.$$

Screening women is much more effective in reducing average

duration than screening men at the same rate because the average duration of infection is longer for women. For example, assume that 25% of the women and men are screened per year so that $C_1 = C_2 = .25/365$. If $d_1 = 80$ days and $d_2 = 20$ days, then $d_1^s = 75.8$ which is a 5.2% decrease and $d_2^s = 19.73$ which is a 1.4% decrease. In this case the percentage decrease in average duration is about 4 times greater for women than for men. The average duration of women is larger than for men since more women are asymptomatic. Indeed, the national screening program in the United States screens only women in an attempt to identify asymptomatic women. In the remainder of this section we will only consider screening of women.

Table 5.2 shows some calculated values of prevalences at equilibrium and yearly incidences for various yearly screened fractions $365\ C_1$ of women. Parameter sets 1 and 3 from Table 5.1 were used as baseline parameter sets in computing the percentage changes. For parameter set 2 in Table 5.2 interception and cure of 5.5% of the female infectives in each 80 day period (the average duration in women) shortens the average duration in women by 5.2% so that the prevalence in women is reduced by 14.8% and the prevalence in men is reduced by 13.7%. Since both the prevalence and durations are decreased in women, the female cases per woman per year is reduced by only 10.2%. Since the average duration in men is unchanged, the male case per man per year is reduced by 13.7%. In parameter set 5, screening women an average of 2 times per year causes gonorrhea to die out. It is clear in Table 5.2 that screening a given fraction of women is more effective in reducing prevalences and incidences when the original average duration for women is 160 days than when it is 80 days.

As described in section 5.2 the ratio of female to male reported cases increased from .33 to about .69 when the screening program was started. We now investigate possible causes of this increase.

It is estimated that 7 out of the 8 million culture tests each year are screening tests and the balance are diagnostic tests (Yorke, Hethcote, and Nold, 1978). The number of women in the United States between ages 19 and 29 is about 28 million so that the female population at risk is probably less than 28 million. It could be something like 7 million or 14 million. Thus the fraction of the female population at risk screened each year might be about 25% or 50% or 100%. In the calculations for parameter sets 1-4 in Table 5.2, the ratio of Y_1 to Y_2 increases from 0.65 with no screening to 0.68 with 25% screening to 0.71 with 50% screening to 0.76 with 100%

screening. These calculations suggest that a screening program for women could cause a slight increase in the ratio of incidences in women to men, but could not cause this ratio to double. Hence, the explanation of the observed doubling of this ratio is probably that given by most epidemiologists; namely, that the doubling of the ratio of incidences in women to men is due to increased case finding in women.

TABLE 5.2

Equilibrium Prevalences and Yearly Incidences for Various Yearly Screened Fractions $365C_1$ of Women.

Parameter set	1	2	3	4	5	6	7	8
duration d_1	80	80	80	80	80	**160**	**160**	**160**
duration d_2	20	20	20	20	20	20	20	20
contact number K	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
parameter er	.5	.5	.5	.5	.5	.5	.5	.5
$365C_1$	0	.25	.5	1	2	0	.25	.5
prevalence E_1	.220	.187	.156	.095	0	.236	.168	.103
prevalence E_2	.084	.073	.061	.038	0	.065	.047	.029
Y_1=yearly cases per woman	1.004	.902	.780	.527	0	.538	.425	.286
Y_2=yearly cases per man	1.538	1.327	1.117	.695	0	1.190	.864	.538
% change in Y_1	0	-10.2%	-21.4%	-47.5%	-100%	0	-21.0%	-46.8%
% change in Y_2	0	-13.7%	-27.4%	-54.8%	-100%	0	-27.4%	-54.8%

5.4 Seasonal Oscillations in Gonorrhea Incidence

The reported incidence of gonorrhea in the United States has oscillated seasonally ever since data collection was started in 1919 (Cornelius, 1971; Jones, 1978). Seasonality of reported incidence has also been observed in Austria, Sweden and Bulgaria (Rein, 1977). The maximum incidence in the United States, which has always occurred in August to October, is at least 20% higher than the minimum incidence, which has always occurred in February to May (Wiesner and Thompson, 1980). Cornelius (1971) used quarterly data from 1950 through 1968 to calculate seasonal indices for gonorrhea incidence. The seasonality of reported incidence using quarterly data from 1946 to 1977 is shown in figure 5.1. The smoothness of the quarterly incidence data

corrected by seasonal indices in figure 5.2 shows the regularity of the seasonal variation of gonorrhea incidence. The median of the weekly reported cases for 1966-1980 are shown in figure 5.5. Even though the median is very erratic the low point seems to be in the winter or spring and the peak is between August and October.

The reason for the seasonality of reported gonorrhea is unknown. It does not seem to be due to variations in reporting (Cornelius, 1971; Rein, 1977). Legitimate and illegitimate conceptions show the opposite seasonal pattern as gonorrhea. Although syphilis incidence does not seem to vary seasonally, incidence of nonspecific urethritis has the same seasonal pattern as gonorrhea (Rein, 1977). Similar seasonal case patterns have been observed for both sexes, for public and private cases, for large and small cities, for rural areas, and for cities with temperate and severe winters (Cornelius, 1971). The seasonality could reflect seasonality in susceptibility to gonorrhea or in the virulence of the gonococcus or increased use of antibiotics in winter months (Wiesner and Thompson, 1980). W. W. Darrow at the Centers for Disease Control predicted that the peak contact rate for gonorrhea should occur in the summer when students and other people often move and change sex partners. Why the peak incidence of gonorrhea occurs in August to October has baffled epidemiologists. This late peak is explainable by this model.

A perturbation analysis is now used to determine an approximate solution for a small oscillation in the contact rates. Some readers may wish to skip the detailed mathematical analysis and go directly to the conclusions at the end of the section. Note that Aronsson and Mellander (1980) showed that if the general model [3.1] is modified so that the contact rates and removal rates are periodic, then above the threshold there is a unique nontrivial periodic solution, which is globally asymptotically stable. Our analysis below yields estimates and further information regarding the unique periodic solution of the female-male model.

Seasonality is introduced into the model [5.1] by assuming that the contact rates vary seasonally so that λ_{12} and λ_{21} are both multipled by $1 + \varepsilon \sin wt$ where ε is the relative amplitude of the perturbation and the frequency w corresponds to a period of one year. The model [5.1] becomes

$$\frac{dI_1}{dt} = \left(\frac{\lambda_{12}}{r}\right)(1 + \varepsilon \sin wt)(1-I_1)I_2 - \frac{I_1}{d_1}$$

$$\frac{dI_2}{dt} = (\lambda_{21} r)(1 + \varepsilon \sin wt)(1-I_2)I_1 - \frac{I_2}{d_2} \qquad [5.5]$$

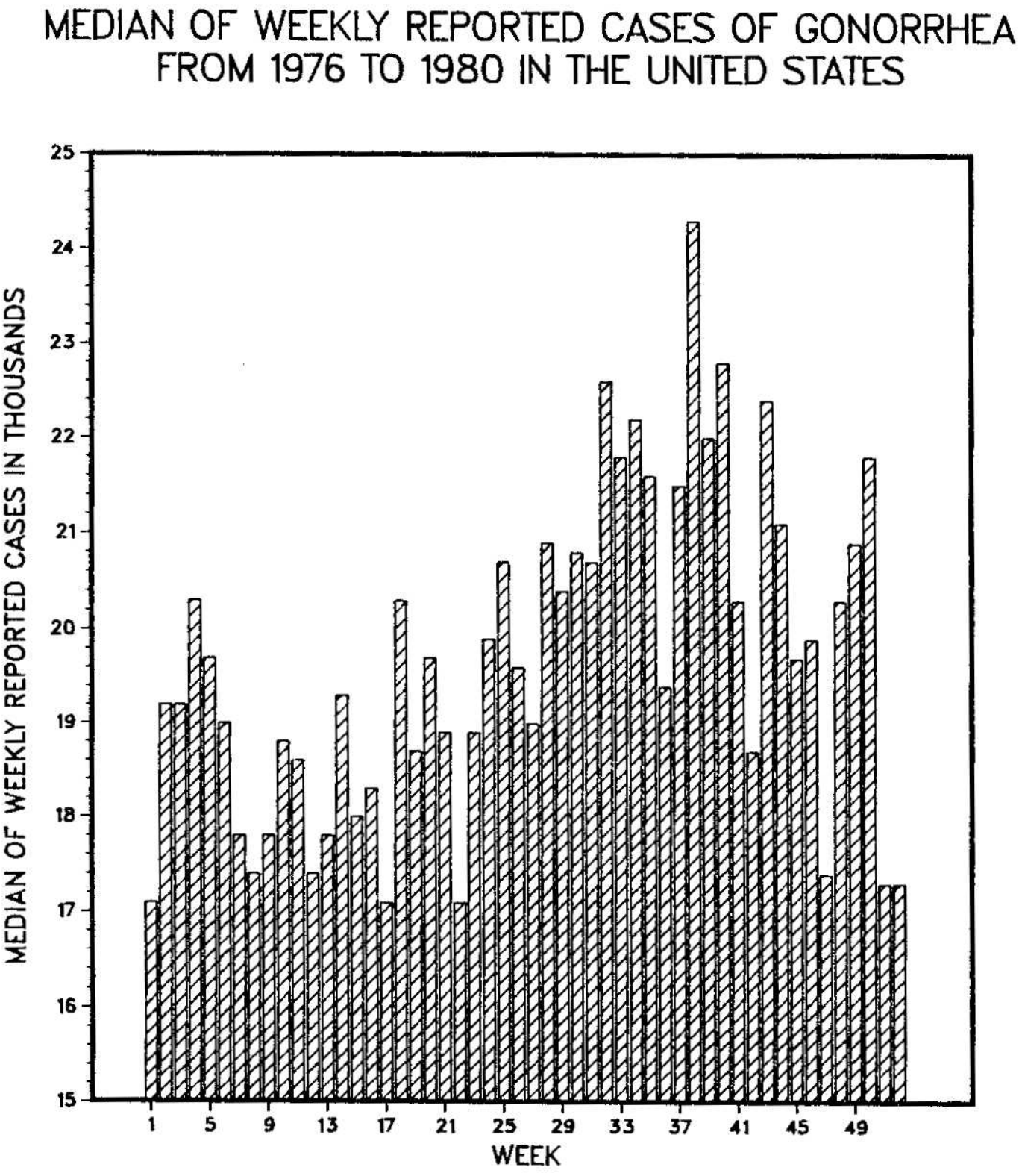

Figure 5.5. Median of weekly reported cases of gonorrhea from 1976 to 1980 in the United States.

The dimensionless and scaled form of this model is

$$\frac{dI_1}{d\tau} = \mu(1 + \varepsilon \sin \psi\tau)(1-I_1)I_2 - I_1$$

$$\frac{dI_2}{d\tau} = \zeta\nu(1 + \varepsilon \sin \psi\tau)(1 - I_2)I_1 - \zeta I_2 \qquad [5.6]$$

where the dimensionless time is $\tau = t/d_1$ and the dimensionless parameters are $\mu = \lambda_{12}d_1/r$, $\psi = wd_1$, $\nu = \lambda_{21}d_2r$ and $\zeta = d_1/d_2$.

When the equilibrium point [5.2] is translated to the origin by letting $I_1 = E_1 + U$ and $I_2 = E_2 + V$, the model [5.6] becomes

$$\frac{dU}{d\tau} = -(\mu/R)U + RV - \mu UV + \mu\,\varepsilon \sin \psi\tau\,[R/\mu-U][E_2+V]$$

$$\frac{dV}{d\tau} = (\zeta/R)U - \zeta\nu RV - \zeta\nu UV + \zeta\nu\varepsilon \sin \psi\tau\,[1/\nu R-V][E_1+U] \qquad [5.7]$$

where $E_1 = (\mu\nu-1)/\nu(1+\mu)$, $E_2 = (\mu\nu-1)/\mu(1+\nu)$ and $R = E_1/E_2$. Note that $\mu\nu > 1$ since $K > 1$. It is reasonable to expect that the small periodic forcing in system [5.7] leads to a small periodic solution around the equilibrium point. In fact we show that there is a unique periodic solution which is uniformly asymptotically stable and then we analyze the asymptotic behavior of the first two terms in the power series expansion in ε .

System [5.7] is of the form $x' = f(\tau,x,\varepsilon)$ where x is a vector function of dimension 2 and f is periodic in τ with period $2\pi/\psi$. The system [5.7] with $\varepsilon = 0$ has no nonzero $2\pi/\psi$ periodic solution. By a theorem based on the implicit function theorem (Miller and Michel, 1982, p. 313), for sufficiently small ε , system [5.7] has a unique solution $\phi(\tau,\varepsilon)$ which is $2\pi/\psi$ periodic and continuous, and such that $\phi(\tau,0)$ is the trivial solution. Since the characteristic roots of the linearization of [5.7] with $\varepsilon = 0$ are negative real numbers, the solution $\phi(\tau,\varepsilon)$ is uniformly asymptotically stable.

The preceding paragraph shows that a regular perturbation analysis for small ε can be used and that there is no danger of parametric resonance or secular terms. In contrast, Dietz (1976) showed numerically that in a measles model with a spiral equilibrium point, seasonal oscillations in the contact rate lead to biennial oscillations in incidence because of subharmonic resonance.

We expand an arbitrary solution in powers of ε with the form

$$U(\tau,\varepsilon) = U_o(\tau) + \varepsilon U_1(\tau) + \varepsilon^2 U_2(\tau) + \ldots$$
$$V(\tau,\varepsilon) = V_o(\tau) + \varepsilon V_1(\tau) + \varepsilon^2 V_2(\tau) + \ldots \qquad [5.8]$$

The terms $U_o(\tau)$ and $V_o(\tau)$ satisfy [5.7] with $\varepsilon = 0$ so that they are bounded. Since the eigenvalues of the linearization of [5.7] with $\varepsilon = 0$ are negative real numbers, $U_o(t)$ and $V_o(t)$ approach the origin exponentially (Miller and Michel, 1982, p. 261).

A straight-forward calculation shows that $U_1(\tau)$ and $V_1(\tau)$ satisfy

$$\frac{dU_1}{d\tau} = -(\mu/R)U_1 + RV_1 - \mu(U_oV_1 + V_oU_1) + \mu \sin \psi\tau\,[R/\mu - U_o][E_2 + V_o]$$
$$\frac{dV_1}{d\tau} = (\zeta/R)U_1 - \xi\nu RV_1 - \zeta\nu(U_oV_1 + V_oU_1) + \zeta\nu \sin \psi\tau[1/\nu R - V_o][E_1 + U_o] \qquad [5.9]$$

The matrix form of [5.9] is

$$x'(\tau) = [A + B(\tau)]x + f(\tau) + g(\tau) \qquad [5.10]$$

where

$$x(\tau) = \begin{bmatrix} U_1(\tau) \\ V_1(\tau) \end{bmatrix} \qquad A = \begin{bmatrix} -\mu/R & R \\ \zeta/R & -\zeta\nu R \end{bmatrix}$$

$$B(\tau) = \begin{bmatrix} -\mu V_o & -\mu U_o \\ -\zeta\nu V_o & -\zeta\nu U_o \end{bmatrix} \qquad f(\tau) = \begin{bmatrix} E_1 \sin \psi\tau \\ \zeta E_2 \sin \psi\tau \end{bmatrix}$$

$$g(\tau) = \begin{bmatrix} (RV_o - \mu E_2 U_o - \mu U_o V_o) \sin \psi\tau \\ (U_o/R - \nu E_1 V_o - \nu U_o V_o)\,\zeta \sin \psi\tau \end{bmatrix}$$

Since $B(\tau)$ and $g(\tau)$ in [5.10] approach zero as τ approaches infinity and the solution of the homogeneous equation is zero, the solution of [5.10] for large time should be determined primarily by $f(\tau)$.

THEOREM 5.2 If all eigenvalues of the real constant matrix A have real parts less than $-\sigma$ which is less than 0, $B(t)$ is a real continuous matrix on $[0,\infty)$, $f(t)$ and $g(t)$ are real continuous vector functions on $[0,\infty)$, $f(t)$ is bounded on $[0,\infty)$, $\int_0^\infty B(s)\,ds < \infty$, and $\int_0^\infty g(s)\,ds < \infty$, then solutions of $x'(t) = [A + B(t)]x + f(t) + g(t)$ approach $u(t) = \int_0^t e^{A(t-s)}f(s)ds$ as t approaches ∞.

PROOF. Let $y(t) = x(t) - u(t)$. Then

$$y'(t) = [A + B(t)]y + h(t) \qquad (P)$$

where $h(t) = B(t)u(t) + g(t)$. Since $u(t)$ is bounded, the finite integral of $B(t)$ implies $\int_0^\infty h(t) < \infty$. To prove the theorem we need only show that **all solutions y(t) of (P) tend to 0 as $t \to \infty$.** This will follow from Strauss and Yorke (1968), Theorem A part ii, in three steps.

First we view the linear system

$$w'(t) = Aw(t) + B(t)w(t) \qquad (L)$$

as a perturbed form of $x'(t) = Ax(t)$. Since 0 is (uniform) asymptotically stable, we may apply Theorem A part ii and conclude 0 is "eventually uniform asymptotically stable" (EvUAS) for (L). We refer the reader to the source for a detailed definition, but **all solutions w(t) of (L) tend to 0 as $t \to \infty$.**

Next we view (P) as a perturbed form of (L) and again apply Theorem A part ii to conclude 0 is EvUAS for (P). This implies that **(P) has some solution y_1 satisfying $y_1(t) \to 0$ as $t \to \infty$.**

Finally let $y_2(t)$ be any other solution of (P). Then $w(t) = y_2(t) - y_1(t)$ satisfies (L) and so tends to 0 as $t \to \infty$. Since $y_1(t) \to 0$, we have $y_2(t) \to 0$ as $t \to \infty$. The proof is complete.

All of the assumptions in Theorem 5.1 are satisfied by the $A, B(\tau)$, $f(\tau)$ and $g(\tau)$ in [5.10] since $U_0(\tau)$ and $V_0(\tau)$ are bounded and approach the origin exponentially. The particular solution corresponding to the forcing term $f(\tau)$ can be found by converting the system [5.9] to a second order differential equation. As $\tau \to \infty$ we obtain

$$x(\tau) \to \int_0^\tau e^{A(\tau-s)}f(s)ds \longrightarrow \begin{bmatrix} C_1 \cos\psi\tau + C_2 \sin\psi\tau \\ C_3 \cos\psi\tau + C_4 \sin\psi\tau \end{bmatrix} \qquad [5.11]$$

where

$$D = [\zeta(\mu\nu-1) - \psi^2]^2 + (\mu/R + \zeta\nu R)^2\psi^2$$

$$DC_1 = -\psi[\zeta + (\zeta\lambda R)^2 + \zeta(\mu/R + \zeta\nu R) + \psi^2]E_1$$

$$DC_2 = [(1 + \nu R)(\zeta^2)(\mu\nu - 1) + (\mu/R - \zeta)\psi^2]E_1$$

$$DC_3 = -\zeta\psi[\zeta + (\mu/R)^2 + (\mu/R + \zeta\nu R) + \psi^2]E_2$$

$$DC_4 = \zeta[(\mu/R + 1)\zeta(\mu\nu - 1) + (\zeta\nu R - 1)\psi^2]E_2$$

Thus if the relative seasonal change ε in the contact rates is small, then solutions of [5.7] approach ε times the periodic solution in [5.11] for large time. Solutions (I_1, I_2) of [5.5] approach the equilibrium point (E_1, E_2) plus ε times the periodic solution in [5.11] for large time.

We are interested in the size of the oscillations in the prevalences in women and men and in the relationships between the time when the peak contact rate occurs and the times when the peak infective fractions occur. Now $U_1(t)$ has a maximum of $(C_1^2 + C_2^2)^{1/2}$ and a minimum of $-(C_1^2 + C_2^2)^{1/2}$ at times $t = \arctan(C_2/C_1)/w$. The maximum fractional change in the prevalence in women is

$$\frac{\varepsilon(C_1^2 + C_2^2)^{1/2}}{E_1} = \varepsilon\left(\frac{w^2 + \zeta^2(1+\nu R)^2}{D}\right)^{1/2} \qquad [5.12]$$

The results for men are analogous with the maximum fractional change given by

$$\frac{\varepsilon(C_3^2 + C_4^2)^{1/2}}{E_2} = \varepsilon\rho\left(\frac{w^2 + (1 + \mu/R)^2}{D}\right)^{1/2} \qquad [5.13]$$

Table 5.3 shows the calculation results for the same sets of parameter values as in Table 5.1. The maximum fractional changes are given by [5.12] and [5.13]. The phase shifts are the number of days that peak prevalence lags behind the peak contact rate. For example, using parameter set 1 a 1% oscillation in the contact rate causes a 1.09% oscillation in the prevalence for women and a 1.37% oscillation in the prevalence for men. The peak prevalence for men occurs 62 days

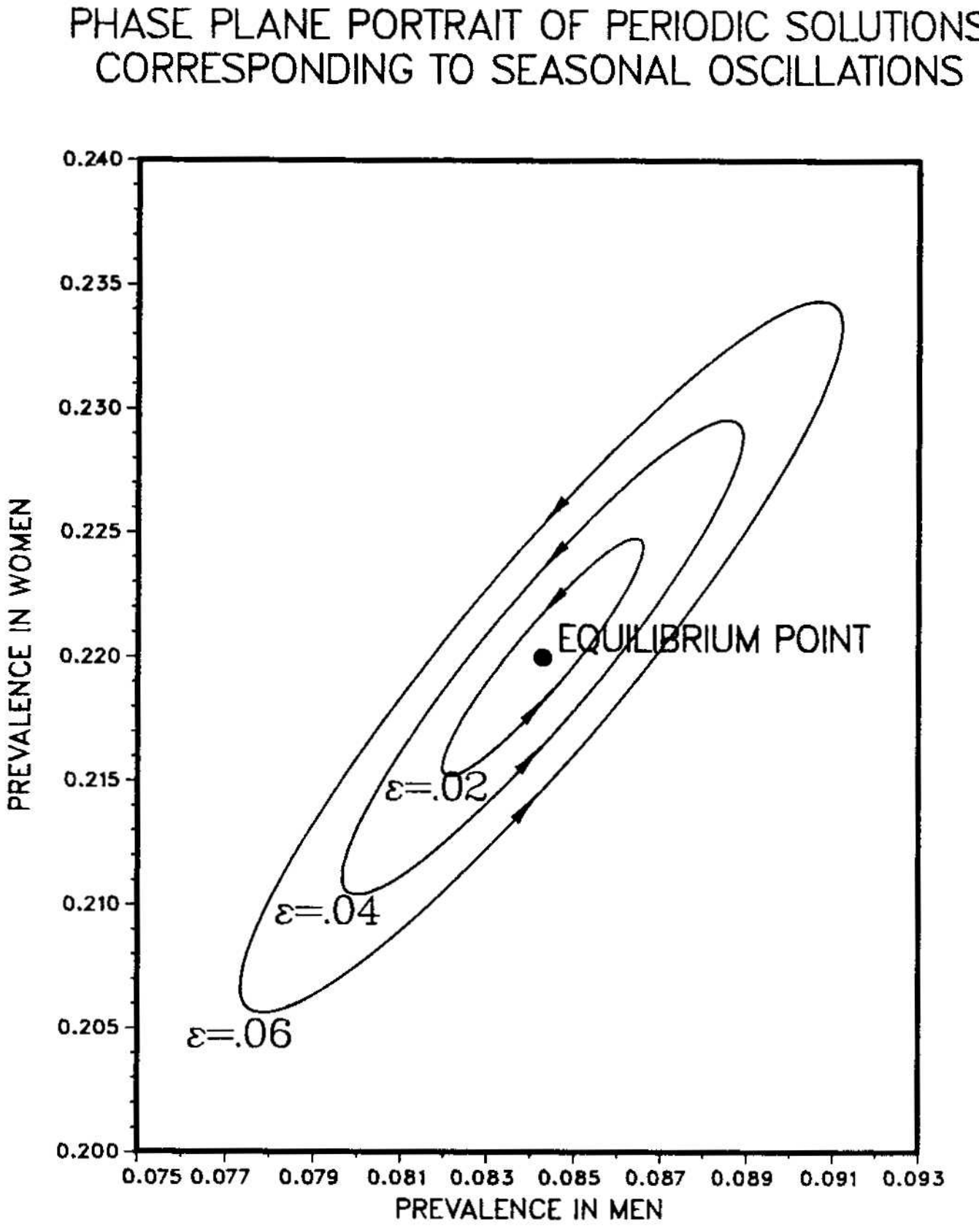

Figure 5.6. Approximate periodic solutions when the contact rate varies seasonally. For a given ε and parameter set 1, solutions of (5.5) approach these periodic solutions.

after the peak in the contact rates and the peak prevalence for women occurs another 22 days later. The pattern is similar for the other parameter sets.

Using parameter set 7, the approximate periodic solution of [5.5] found from [5.8] and [5.11] is

$$I_1(t) = .220 + \varepsilon(-.238 \cos wt + .030 \sin wt)$$
$$I_2(t) = .084 + \varepsilon(-.101 \cos wt + .056 \sin wt). \qquad [5.14]$$

Figure 5.6 shows approximate periodic solutions around the equilibrium point for small values of ε. The global asymptotic stability mentioned earlier means that for a given ε, all solutions of [5.5] starting with nonzero initial prevalences approach a periodic solution which is closely approximated by the periodic solutions given by [5.14] and shown in figure 5.6.

TABLE 5.3

Amplitude and phase shifts of the forced oscillations for various parameter sets.

parameter set		1	2	3	4	5	6	7
duration d_1		80	**160**	**160**	80	80	80	80
duration d_2		20	**40**	20	**40**	20	20	20
contact number K		1.4	1.4	1.4	1.4	**2.0**	**1.2**	1.4
parameter er		.5	.5	.5	.5	.5	.5	**1.0**
ε		.01	.01	.01	.01	.01	.01	.01
oscillation amplitude	women	1.09%	0.53%	0.61%	0.90%	0.97%	1.12%	1.09%
	men	1.37%	0.86%	1.04%	1.07%	1.31%	1.37%	1.34%
phase shift (days)	women	84	94	91	86	67	90	84
	men	62	62	50	72	50	67	62

The maximum fractional change in reported incidences is the difference between the maximum and minimum incidences divided by the sum of the maximum and minimum incidences. Seasonal indices (0.942, 0.968, 1.098, 0.989) for all reported cases are given in figure 5.2. Using the seasonal indices for women and men for the years 1964 to 1975 the maximum fractional change in reported incidences are (1.064 - .955)/(1.064 + .954) = .054 for women and (1.107 - .923)/(1.107 +

.923) = .091 for men. These estimates are crude since they are based on quarterly data. The actual oscillations in incidence are probably around 6% in women and 10% in men. It is not possible to estimate the actual phase shifts; however, the quarterly data shows that the peak incidence in women probably occurs about 2 to 3 weeks after the peak incidence in men.

Using parameter set 1 in Table 5.3 it seems that the actual seasonal oscillations in incidence would be caused by a 5% to 7% seasonal oscillation in the contact rate (ε = .05 to .07). Moreover, the actual phase shifts may be about 9 weeks for men and 12 weeks for women. Thus the model suggests that the observed peaks in gonorrhea incidence which occur in August to October are probably due to peak contact rates in June or July.

Thus the first important conclusion is that the observed seasonal oscillations in incidence may be due to reasonably small (5% to 7%) oscillations in the contact rate. The second conclusion is that the observed peak incidences in August to October may be due to a peak contact rate in the summer months. These results were surprising to the epidemiologists in the VD Control Division of the Center for Disease Control when we first announced them.