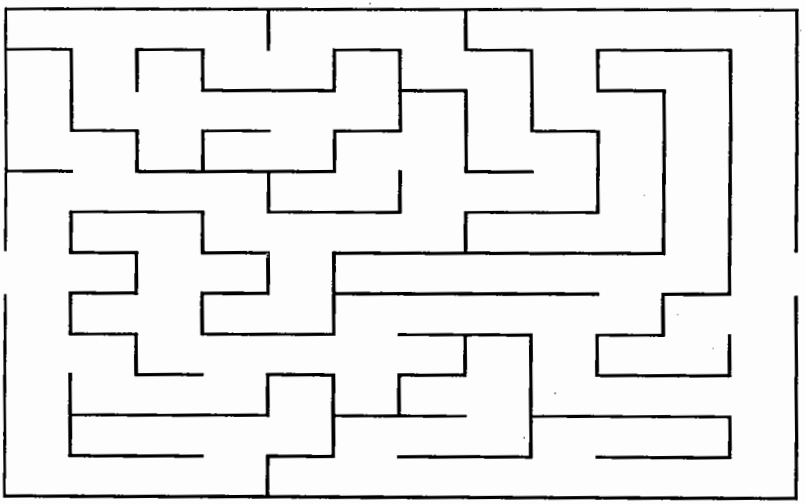
4

Time



Of all the characteristics of experience that are recorded in epidemiologic studies, those related to time are measured with the greatest accuracy. Functions of time serve as markers of biological processes and can be used as surrogates for nonbiological phenomena. The purpose of this chapter is to review ways in which time can be interpreted in observational research. The first major role for time is in the classification of exposures and their effects on humans. Here time may stand in for cumulative exposure, for latency or induction periods, or for the intensity of an exposure that has changed with calendar period. Similarly time may classify persons, by defining susceptibility or concomitant determinants of risk. Time finally may characterize our ability to observe or record events that are the objects of study.

Table 4.1 Pneumoconiosis among crocidolite miners in Western Australia

Employment duration	Heavy exposure N	x	%	Medium exposure N	x	%
<6 months	2000	12	0.6	1750	7	0.4
6mo - <1yr	529	9	1.7	330	1	0.3
1yr - <2yr	338	23	6.8	250	1	0.4
2yr - <3yr	141	23	16.3	109	5	4.6
3yr - <4yr	74	18	24.3	43	3	7.0
4yr - <5yr	84	33	39.3	47	5	10.6
≥5 years	55	36	65.4	40	16	40.0

N - Number observed x - Number with pneumoconiosis % = 100x/N

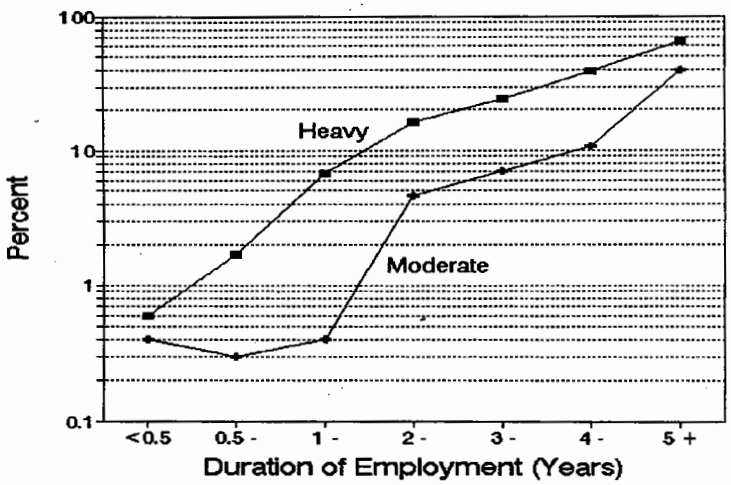


Figure 4.1 Prevalence of pneumoconiosis among crocidolite miners in Western Australia. Data from Table 4.1.

Time Characterizes Exposure and Exposure Effects

When exposure to an agent that may cause disease is continuous or nearly so over stretch of time, then the duration of exposure can stand as a proxy for the accumulated exposure dose. The situation arises commonly with occupational and environmental toxins, but can apply equally well to medicines taken regularly, or indeed to any personal habit, such as smoking or alcohol consumption, that may vary little over a period of time.

Cumulative exposure. *The cumulative exposure from time t_0 to time t_1 for an individual is the summation of all exposures endured from t_0 up until t_1.*

Example 4.1. *Pneumoconiosis in crocidolite miners.*[35]

Hobbs et al. studied the prevalence of pneumoconiosis in former crocidolite miners in Western Australia. Using company and pension records they identified a cohort of 7000 men ever employed (1938-1966), with dates of employment and jobs held. The eventual appearance of disease was identified from pneumoconiosis boards (which were required to certify cases for compensation), cancer registries, master patient indices of hospitals, hospital morbidity abstracts, and death records. Workers were classed according to their total duration of employment in the mines, the typical intensity of their exposure to crocidolite dust, and their final disease status, as shown in Table 4.1 and Figure 4.1.

In effect this was a study of the risk of pneumoconiosis through a time that was considered to represent the exhaustion of the effects of mining.[36] Since there were only the coarsest data available on exposure intensity, the most accurate summary of total numbers of respired asbestos fibers is given by the duration of work. For crocidolite, cumulative exposure has a particular biologic appeal. Inhaled fibers, once lodged in the lung, appear to remain there in perpetuity. The same is true of amosite asbestos, but not of chrysotile.

35. Hobbs MST, Woodward SD, Murphy B, Musk AW, Elder JE. The incidence of pneumoconiosis , mesothelioma and other respiratory cancer in men engaged in mining and milling crocidolite in Western Australia. In Wagner JC (ed) Biological Effects of Mineral Fibres. IARC, Lyon, 1980, pp 615-25

36. If pneumoconiosis were an infectious process and crocidolite an infectious agent, the term "attack rate" would fit perfectly here. See Chapter 5.

For both heavy and medium exposure, risk appears to have increased with duration of exposure. There is also some hint of a threshold: at less than two years' exposure to the medium level jobs there appears to have been no increase in risk, while the same periods presented a tenfold increase among the heavily exposed.

If exposure does vary with time, and if the period-specific levels of exposure can be ascertained, then summed times of exposure, weighted by relative exposure intensity, still provide a measure of cumulative exposure. The use of relative exposure measures is often found in the retrospective cohort studies common in occupational health research. Exposures to possible workplace toxins may have occurred years before quantitative measurements were feasible, but historical documents and the recollections of workers may nonetheless be sufficient to provide a rough calibration of relative intensity. Example 4.3, which appears later on, incorporates observation times weighted by estimated relative exposures to derive a semiquantitative cumulative exposure.

Closed cohort studies such as that of Hobbs, above, typically encompass a follow-up time during which all the effects of exposure are expected to play themselves out. Open cohort studies, by contrast, often permit the observation of blocks of person-time that accrue before the effects of past exposure become manifest. These intervals of no evident disease comprise the time during which pathogenic mechanisms set in motion by the exposure are working toward the production of manifest disease, and the time during which disease, though present, is not yet manifest. The former interval is the *induction period*; the portion of the induction period during which disease is present but unmanifest is the time of *latency*. Both induction period and latency are properly applied only to persons destined eventually to become diseased. As a practical matter, they therefore describe only the history of persons who have become diseased.

Induction period. *The induction period is the time required for the effects of a specific exposure to become manifest.*

Table 4.2 Mortality from mesothelioma in Canadian asbestos-cement factory workers

Time since first exposure	Man years P	Mesothelioma Mortality x	R
15 - 19 years	1182	1	0.8
20 - 24 years	1061	4	3.7
25 - 29 years	555	5	9.0
30 - 34 years	104	1	9.6

P - Man years at risk x - Mesothelioma deaths R - Deaths per 1000 man years at risk

Example 4.2. *Mesothelioma among asbestos cement factory workers.*[37]

Finkelstein traced the mortality of Canadian asbestos-cement factory workers. The cohort was assembled from company files, and was confirmed as complete by cross-checking union seniority lists and radiographic surveillance lists. The cohort was restricted to men with at least one year employment who were hired before 1960 and who had passed at least 15 years since their date of hire. Vital status was obtained from the Canadian Mortality Data Base, from driver's license records, and from the U.S. Immigration and Naturalization Service. Each worker's contribution to the person time under observation was categorized according to time since first hire. The incidence of mesothelioma rose rapidly through the period from 15 to 29 years after first exposure, and then leveled off (Table 4.2).

The induction periods for the 11 cases of mesothelioma cannot be ascertained exactly from Table 4.2, which presents the data only in intervals. Approximately, the induction periods ranged from 15 to 34 years. Note that there is no single induction period that characterizes mesothelioma in asbestos cement workers; there is rather a collection of intervals, whose relative frequency will be determined both by the pathophysiology of human response to the exposure and by the durations of follow-up of the men in the cohort.

37. Finkelstein MM. Mortality among long-term employees of an Ontario asbestos-cement factory. Br J Ind Med 1983;40:138-44

Finkelstein's work is an example of an open cohort study. Workers contributed person time of follow-up to each of the interval categories of Table 4.2 for so long as they were under observation in each category. The persons contributing time to successive categories of time since first exposure were largely the same individuals.[38] Contrast this to Table 4.1, in which the categories of exposure were mutually exclusive insofar as individuals are concerned. In Table 4.2 the mutual exclusivity pertains to the classification of person time.

The interval from first exposure to time of observation is often called *latency* in the literature of occupational epidemiology; the "latency" of disease onset is the term used to denote the induction period. "Latency" in its ordinary English usage implies that disease is present but unobserved. The implication is at odds with the technical meaning in occupational studies during most of the interval between first exposure and onset for diseased persons, and during all of the time of observation for persons who never develop disease. Since the ordinary usage is a valuable and reasonably precise method of denoting a disease state with no observable manifestations, "latency" should be used in its common sense in epidemiology as well. However, because there is an entrenched history of the nonintuitive usage in studies of occupational health, authors and readers should be clear which meaning of latency is intended.

Latent. *A disease that is present but not symptomatic is latent.*[39]

Latency. *The time interval during which a disease is latent. Also, in occupational epidemiology, the interval from first exposure to observation.*

When an induction period is present, incidence rates rise only after a time lag following the onset of exposure. This phenomen of delayed manifestation of causally attributable events is sometimes called the *residual effect* of an exposure.

Residual effect. *The subsequent changes in disease incidence that are attributable to an exposure are said to be the residual effect of that exposure.*

38. See Tables 3.5, 4.5, and 5.2 for other examples of this characteristic property of open cohorts: the divisibility of persons.

39. The theory of screening tests employs a related concept, the "detectable preclinical phase" of disease. Whether or not a latent disease is in its detectable preclinical phase depends on the available means of detection.

Cumulative exposure, induction period, and residual effect all derive from a central concept of the influence of exposure on disease occurrence. Imagine each increment of time as characterized by an isolated element of exposure whose effect on incidence is cast into the future, typically as a function that rises, plateaus, and then falls. Let the effect of each one of these exposure increments be superimposed on the effects of all other exposure increments in a simple additive way. The hazard[40] at any moment is then the sum of the hazards attributable to all past exposures. If the hazard function attributable to a particular past exposure quantum has fallen to zero at a given moment, then the particular past exposure is without residual effect.

Cumulative exposure is a linear predictor of hazard for as long as the residual effects of past exposures are not changing with the passage of time and can be summed onto one another. During such a period the hazard will rise in direct proportion to the total prior exposure. The minimum induction period is not a well-defined interval, but corresponds rather to the time elapsed until the summed residual effects from all prior exposures become high enough to result in observable disease. The residual effect of the cumulative exposure and the observed induction periods are the playing out of the summed residual effects of past exposures over the duration of follow-up.

Example 4.3. *Colon cancer and the production of acrylic sheet.*[41]

> Jobs in a factory engaged in the production of acrylic sheet prior to 1945 were classified according to the estimated vapor phase exposure to acrylate monomers. Exposure was scored on a scale running from 1 to 5, and was based on the recollections, some 40 years later, of workers who had been familiar with the plant. Exposure essentially ceased after 1945 because of changes in the manufacturing process. Cumulative exposure to acrylate monomers up to any point in time was calculated for each man by multiplying the exposure score in each of his jobs by the duration of that job, and summing the result over all jobs up to the time in question. The highest cumulative exposure was 20

40. The hazard is the expected value of the incidence rate; it is the unobservable parameter of which the observed incidence rate provides an estimate. See Chapter 7 for more on hazard and on the relation between parameters and estimates.

41. Walker AM, Cohen A, Loughlin J, DeFonso L, Rothman KR. Mortality from cancers of the colon and rectum in workers exposed to ethylacrylate and methylmethacrylate. Scand J Work Environ Hlth 1991;

Table 4.3 Deaths from colon cancer in relation to the time since accumulation of 15 units of exposure to acrylates

	Not exposed to acrylates	Exposed to less than 15 units	Years since achieving 15 units of exposure <5	5-14	15+
Incidence[1]	40	62	0	11	89
Deaths observed	11	26	0	1	11
Deaths expected[2]	11.48	19.81	0.11	0.88	4.58
Ratio obs/exp	0.96	1.3	0	1.1	2.4
Person years	23,487	51,552	1,812	5,040	5,531

[1] Deaths per 100,000 person years among men aged 30-84 years, standardized to the age distribution of person time in the full cohort

[2] Expectations were calculated on the basis of contemporaneous local mortality rates for cancer of the colon.

units. All men who achieved 15 units of exposure did so by working three or more years in a single high-exposure aspect of production, the "boil out" process. Men who had worked in the plant for at least 10 months were traced, and deaths from colon cancer were identified from a variety of sources. For the results presented in Table 4.3, person time was accumulated in categories defined by age, calendar year, and the time since achievement of a cumulative exposure of at least 15 units. Because colon cancer was not expected to (and did not) lead to any deaths under the age of 30 years, and because there was essentially no experience to summarize from the age of 85 years on, the data in Table 4.3 concern only person years from age 30 to 84.

The partitioning of person time in Table 4.3 was chosen so as to examine the possible existence of an induction period for colon cancer following a cumulative exposure of 15 units. The data indicate that the age-standardized colon cancer rates did rise with the passage of time since the accumulation of 15 units of exposure. If the association is causal, then in Table 4.3 there is evidence for the

existence of a residual effect of acrylates on colon cancer mortality, with induction periods from the completion of 15 units of exposure to death typically exceeding 15 years.

Historical Intensity of Exposure

In most retrospective cohort studies (and essentially all case-control studies), there is a tight relation between "time since first exposure" and "era of first exposure." It is very often the case that the nature and intensity of exposure has changed in poorly documented ways with the evolution of time. Finkelstein (Example 4.2), for example, assigned the following asbestos fiber exposures to mixing operators:

1949 40.0 f/ml
1969 20.0 f/ml
1979 0.2 f/ml

The meaning of the term "mixing operator" changed with the passage of time. As a result, any portrayal of the rate of asbestos-related disease in mixing operators at a fixed time, say 1985, could give the appearance of a dependence of disease on time since entry into the field, and on age, that was entirely an artifact of variations in asbestos exposure history. Proper analysis of the effect of age or time since entry into the trade would have to be done within blocks of human experience defined by exposure intensity, that is to say, defined by calendar period of entry into the trade. Necessarily such studies would have to be carried out over an extended period.

The change in the meaning of exposure with the passage of time is the origin of a *cohort effect* among the exposed. In the analysis of vital statistics data, cohort effects are variations in disease incidence, seen at all ages, that are characteristic of persons born in a particular era. The characteristics that drive cohort effects are usually in place in childhood or young adult life, but in any case, prior to the regular onset of disease occurrence in the population.

Cohort effect. *Changes in disease frequency that are shared by all members of a group who entered follow-up at common time constitute a cohort effect.*

Cohort effects are typically produce by shared characteristics of subgroups of the the persons under observaton.

Changes in Cohort Composition

The deceleration in the rise of mesothelioma mortality recorded in Table 4.2 may have been due to chance. It may also have been the result of biological phenomena, such as a declining residual effect of asbestos exposure. It may also occur because the exposure categories contain different proportions of persons at high risk of death.

If the workers within each category of follow-up actually have an undocumented variety of exposure histories, and if exposure is related to continuation under follow-up for any reason, then the exposure composition of the surviving cohort change will change over time. In the present instance, particularly high levels of exposure to asbestos would lead to elevated mortality. With the passage of time, a group of workers comprising individuals with both high and low levels of exposure will selectively lose those cohort members with the higher exposures. The average intensity of exposure in the surviving portion of the cohort will be lower than that of the cohort at its inception. The change in disease patterns with time will then be that truly related to the lapse of time mixed with (that is, confounded by) changes due to the changing exposure profile of the persons who continue to be observed.

Because the cohort composition with respect to unmeasured determinants of disease does commonly evolve with the passage of time, it is useful to distinguish a cohort as it exists at some initial point of observation from one that is far removed from an initial membership-determining event.

Inception cohort. *The persons who are under observation at the beginning of an exposure that defines cohort membership are termed an inception cohort.*

Survivor cohort. *The persons who remain under observation at some point after the beginning of an exposure that defines cohort membership are a survivor cohort.*

All cohorts defined later than at birth are in some sense survivor cohorts,[42] and studies of multiple causes of disease almost necessarily identify persons who are members of survivor cohorts for some of the causes under study.

42. A reproductive epidemiologist might extend the definition to cohorts defined after conception.

Susceptibility

Identical exposures may have different effects when administered to the same person at different times. The prototypical example of this phenomenon is teratogenesis.

Example 4.4. *Prenatal DES exposure and vaginal epithelial changes.*[43]

The DESAD (Diethylstilbestérol Adenosis) project obtained follow-up gynecologic examinations on 1340 young women identified through reviews of obstetricians' notes as having been exposed to DES (diethylstilbesterol) prenatally. At examination, the presence of macro- or microscopic changes in vaginal mucosa were noted. The project found the relation shown in Figure 4.2 between prevalence of VEC (vaginal epithelial changes) and the timing of first maternal DES exposure.

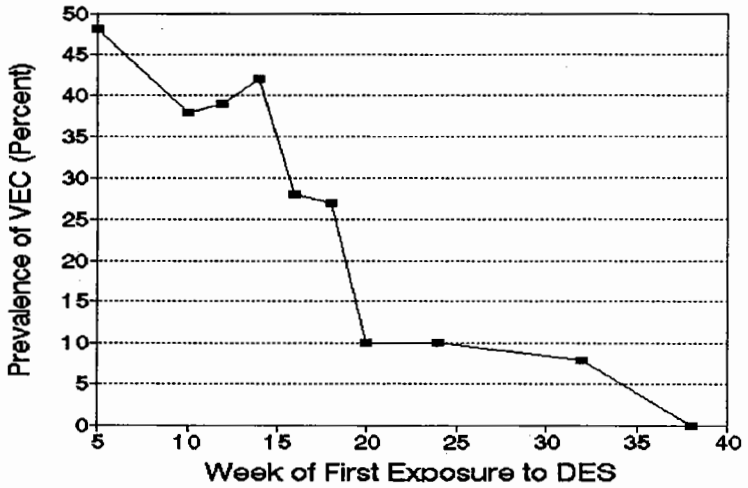


Figure 4.2 Prevalence of VEC in relation to the timing of in utero exposure to DES

43. O'Brien PC, Noller KL, Robboy SJ, et al. Vaginal epithelial changes in young women enrolled in the National Cooperative Diethylstilbesterol Adenosis (DESAD) project. Obstet Gynecol 1979;53:300-8

It appears that exposure prior to the twentieth week of pregnancy posed a much greater risk for eventual VEC in the offspring than did exposure at a later date. The most crucial period was probably early in pregnancy, when the vaginal epithelium is being formed. The gradual diminution in risk after week 20 may represent either a decline in sensitivity of the fetal vagina to the effects of DES, or it may be an artifact of error in the ascertainment of onset of DES use, superimposed on an abrupt disappearance of susceptibility.

Concomitant Determinants of Risk or Diagnosis

Time, measured by age, can stand as a proxy for individual characteristics that determine risk. Although many diseases occur more frequently in elderly people than in younger persons, the relation between age and incidence is entirely disease-specific, as Example 4.5 will show.

In the form of calendar year of observation, time may stand as a determinant of the risk of diagnosis among persons with a given disease status. For diseases with long induction periods, changes in the definition of disease, in the technology for diagnosing disease, or in the *a priori* expectation that a disease is present are the most important determinants of calendar-year specific changes in the risk of diagnosis.

Example 4.5. *Replacement estrogens and fibrocystic disease of the breast.*[44]

Jick et al examined the incidence of biopsy diagnosis of fibrocystic breast disease (FBD) in an HMO for whose members it was possible to identify use of prescription drugs. Among nonusers of replacement estrogens, they found the incidence rates graphed in Figure 4.3.

The incidence of biopsy-proven FBD declined both with age and with calendar time. The decline with age had been seen in previous studies, and may reflect a diminution in circulating estrogen levels after menopause. The decline is an example of an *age effect.*

Age effect. *A change in disease incidence that is due to a biological concomitant of aging is an age effect.*

44. Jick SS, Walker AM, Jick H. Conjugated estrogens and fibrocystic breast disease. Am J Epidemiol 1986;124:746-51

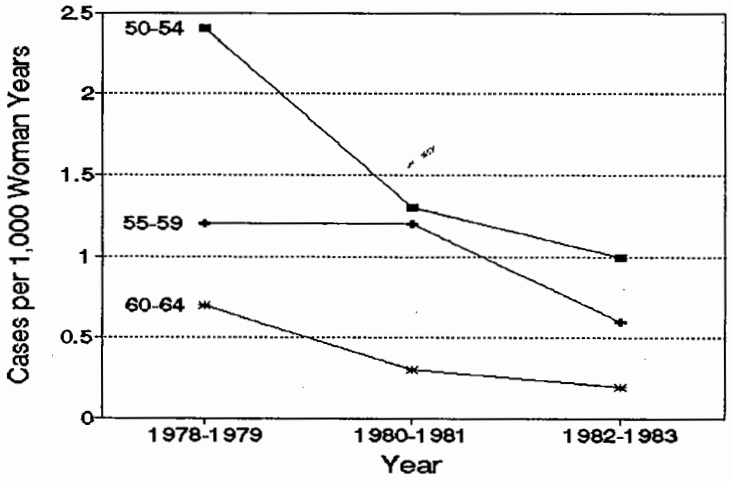


Figure 4.3 Incidence of biopsy-proven FBD in non-users of replacement estrogens aged 50-54, 55-59, and 60-64 years

The notable in incidence of FBD decline over the six calendar years of observation in all age groups also suggests a changed definition of pathology in the female breast. Late in the 1970s, there was a campaign against what was conceived to be a misguided practice of labeling as fibrocystic "disease" a normal condition found in many women. Particularly because of the psychological burden on patients who were left with the impression that they harbored a premalignant condition, biopsies became less frequent, and a diagnosis of FBD became less frequent among biopsied women. The decline in the apparent incidence of FBD with time is an example of a *period effect.*

Period effect. *Changes in disease frequency that are specific to a calendar time are collectively termed a period effect.*

Period effects are most commonly the result of secular changes in the deifinition of disease or in diagnostic practice. Period effects can also result from secular changes in the prevalence of exposures that produce disease with short induction periods.

Look again at Table 4.3. A secular trend in the diagnosis of colon cancer might confound the comaprison of the incidence rates listed in the last three columns. One purpose of calculating the "Deaths expected" on the basis of calendar-year specific mortality data was to compensate for period effects.

Diagnostic Suspicion

The proclivity to carry out a diagnostic maneuver or to make a diagnosis often varies with time in a way that is closely related to duration of exposure. For current users of replacement estrogens, Jick et al (Example 4.4) found the following crude data shown in Table 4.4.

Table 4.4 Duration of replacement estrogen use and the incidence of fibrocystic breast disease

Year of Use	Woman Years	FBD	Incidence
First	1383	4	2.9
Second	1833	1	0.6
Third	1930	1	0.5
Fourth	1339	2	1.5
Fifth & up	5033	11	2.2

Incidence = FBD / 1000 woman years

The elevated incidence in the first year of replacement estrogen use may have resulted from increased surveillance. Women who begin use of replacement estrogens necessarily have had recent physician contact, and may be particularly willing to report breast symptoms. Replacement estrogens themselves increase breast tenderness in some women and may lead to consultation with physicians. Either mechanism can set off a chain of events that leads to a biopsy for a suspicious breast mass in a very small percentage of women. Although the motivating concern is the early detection of a possible breast cancer, the result is a final diagnosis of a benign condition (FBD) and a blip in the FBD incidence rates in the first year of replacement estrogen therapy.

The later rise in the FBD rates of Table 4.4 may also be related to an increased surveillance for possible breast cancer. In the latter part of the 1970s, there were a number of reports of an association between replacement estrogen use of long duration and breast cancer. One of those reports had been based on observations at the HMO where the FBD study was carried out. If you were a treating physician and were faced with very slightly suspicious change in the texture of the breast tissue in one of your patients, for whom would your inclination to order a biopsy be greatest? Given equal symptoms, women who were long-term users of replacement estrogens were at the highest risk for biopsy. Nonmalignant changes in lumpy breasts tended to receive the diagnosis FBD, and women who were long-term users of replacement estrogens tended to receive the diagnosis with greater frequency than others.

Time that is Event-Free by Definition

Members of a survivor cohort have accumulated experience prior to the time at which the formal period of their observation begins. Similarly, any cohort whose defining characteristic occurs later than birth has members who have experienced risk of disease before they joined the cohort. Person time prior to becoming eligible for a study is an example of what is called *immortal person-time.* The term derives from the logical impossibility of death having occurred prior to the study for anybody included in the study. Immortal person-time should never be counted as part of the denominator of a rate calculation.

Immortal person-time. *The experience of study subjects that is event-free by definition is immortal person-time.*

When the Mt. Sinai researchers established a cohort of insulation workers who were union members on January 2, 1967 (Example 5.2), all prior experience of those men was immortal person-time, immortal because their presence in the cohort meant that they had not died earlier. Correctly, the researchers did not incorporate that past time into the person years recorded in Table 5.2.

Be aware that there is a distinction between the passage of time that must be accounted for in order to categorize an exposure correctly, and the passage of time that constitutes observed experience. The 15 years that had to elapse after first exposure to asbestos before a worker's person-time could appear in Table 4.2 were immortal

person-time. Nonetheless, the time interval had to be accounted for in order to classify the observed person time. The first ten months of employment of the workers in Example 4.3 comprised immortal person-time.

When the observable person-time lies entirely outside the bounds of cohort membership, as in the insulation workers example, then it is easy to ignore the immortal person-time: it is inaccessible to direct observation. Similarly, when accessible person-time has been excluded from an analysis, as were the very young and very old person-years of Table 4.3, the person time is effectively rendered immortal, but in an innocuous way. The threat posed by immortal person time arises only when it is included in the analysis.

Occasionally, a circumstance that defines exposure and cohort membership occurs in persons already under observation. For a study of the relation between replacement estrogen use and myocardial infarction in an HMO that had records of drug use and hospitalization, one might define a cohort of estrogen users who had not suffered a past MI. Women who were members of the HMO and who had not suffered an MI would enter the cohort at the time of first estrogen use, and their rate of occurrence of MI would be compared to a selected group of nonusers who had not suffered an MI at the beginning of the observation period. How should we allocate the person time at risk that the users accrued prior to their first prescription for replacement estrogens?

If the time were assigned to the "user" category, the effect would be to dilute the true person-time at risk among users with time during which no estrogens had been consumed. The result would evidently distort any apparent estrogen effect. Yet if the time were assigned to the nonuser category, there would also be a dilution: it is known *a priori* that no MI occurred during this time; women who had suffered an MI would never have entered the exposed cohort, and would not have come into our ken.

Segregate the time into a "pre-use" category and the correct analysis becomes obvious. The rate of MI prior to estrogen use in women chosen as being MI-free at the time of onset of estrogen use is necessarily zero. The time is immortal person-time and should be excluded from analysis.

A common feature of immortal person-time is that it occurs in study subjects prior to the events that designate them as being eligible for the study. Consider a variation on the example above. If the person time of all female members of the HMO who had not suffered an MI were being monitored and a woman who was a nonuser of replacement estrogens suffered an MI, and then subsequently used replacement estrogens, her person time prior to use (prior to the MI) would be legitimately counted in the category of "nonuser." The difference between this and the preceding example is that observation of the woman in this case is not contingent on her use of replacement estrogens. Note also that a nonfatal MI in this case marks the beginning of another sort of immortal person-time: we can never again observe a first time myocardial infarction.