INTERNATIONAL JOURNAL OF LEPROSY Volume 46, Number 1
Printed in the U.S.A.

The Association Between Age of Onset and Mortality in Lepromatous Leprosy[1]

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Complications resulting from lepromatous leprosy are known to shorten the life span of persons afflicted with the disease ([7]). The standardized death rate for those with lepromatous leprosy in Cordova, Philippines before the immediate post-war era was over five times that of the general population ([8]).

The effect of lepromatous leprosy upon mortality may not be independent of age. The extent to which mortality of those with the disease exceeds that of the general population is greatest for the middle-age range and least for those over age 50 in Cordova. Guinto *et al* ([8]) speculated that the lower death rates for older sufferers from the disease result from the attainment of higher resistance to the disease before its onset. This is consistent with the inverse correlation between age of exposure and risk of contracting leprosy, and presumably susceptibility to infection, which has been described in Cordova ([4]). If resistance to *Mycobacterium leprae* increases with age in populations in which leprosy is endemic, complications which shorten the life span might be ameliorated by a later age of onset of the disease. We attempt here to test the hypothesis that length (in years) of survival of those who contract lepromatous leprosy is inversely related to the age of onset of the disease.

MATERIALS AND METHODS

The data upon which this analysis is based was collected in the municipality of Cordova on Mactan Island near Cebu City, Philippines by the Leonard Wood Memorial Foundation. The methods of collection of this data have been described elsewhere ([2, 3, 5, 6, 8, 10]). To provide as complete a demographic history as possible for this analysis, the person-years-lived (PYL) at each single year of age, ${}_{x+1}PYL_x$, to exact age 45 were computed for those members of the population born prior to 1907 who by 1966 had never developed any form of leprosy. This sample consisted of 524 males who, to exact age 45, lived a total of 16,398 years, and 427 females with a total of 13,022 person-years of life experience to exact age 45. The expected number of years lived to exact age 45 by any individual who had already attained exact age x (${}_{45}e_x$) can be calculated ([1]) by dividing the total number of person-years-lived to exact age 45 after exact age x, $\sum_{i=1}^{45-x} {}_{45}PYL_{x+i}$, by ${}_{x+1}PYL_x$.

A total of 63 males and 29 females born prior to 1907 developed lepromatous leprosy before age 45. Sulfone drug therapy, however, can substantially reduce mortality associated with leprosy. For example, the death rate for those suffering from leprosy in the United States fell coincidentally with the introduction of sulfone treatment ([4]). Sulfone drugs were first used on a large scale in Cordova in 1951. Thus, no one in our sample benefited from sulfone therapy before attaining exact age 45.

The age of onset (x′) and number of years lived to exact age 45 after the age of onset (${}_{45}PYL_{x'}$) in these 92 individuals were recorded separately for those whose onset occurred before and after age 18. Thus, ${}_{45}PYL_{x'}$ is the number of person-years-lived between the onset of leprosy and the attainment of age 45 or until death if death occurred before age 45. An age of onset of 18 was chosen for this analysis because it subdivided the sample into two approximately equal groups. The expected years of life remaining (after onset) to exact age 45 for such persons was taken to be ${}_{45}e_{x'}$ where x′ is the age of onset of the disease in that person. Then, ${}_{45}PYL_{x'}/{}_{45}e_{x'}=SR$, the survival ratio or the proportion of the expected remaining lifetime before age 45 actually lived by an individual who developed lepromatous leprosy at age x′.

Those below and above (or at) age 18 at onset of the disease were then further sub-

[1] Received for publication 7 November 1977.

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TABLE 1. *Person-years lived at exact age x ($_{x+1}PYL_x$) and between age x and exact age 45 ($_{45}PYL_x$) and the expectation of life between age x and age 45 ($_{45}e_x$) for selected values of x (age) for the healthy population.*

Age (x)	Males			Females		
	$_{x+1}PYL_x$	$_{45}PYL_x$	$_{45}e_x$	$_{x+1}PYL_x$	$_{45}PYL_x$	$_{45}e_x$
0	524	15,874	30.29	427	12,595	29.50
5	398	13,724	34.48	323	10,831	33.53
10	374	11,825	31.62	306	9,274	30.31
15	367	9,973	27.17	296	7,776	26.27
20	357	8,165	22.87	285	6,329	22.21
25	346	6,413	18.54	276	4,936	17.88
30	339	4,709	13.89	263	3,595	13.67
35	325	3,051	9.39	251	2,316	9.23
40	308	1,477	4.80	233	1,116	4.79
45	286	0	0.00	219	0	0.00

TABLE 2. *Distribution of SR ($_{45}PYL_{x'}/\ _{45}e_{x'}$) values by age of onset of lepromatous leprosy for males and females and comparison of the distribution of SR values between males and females.*

Age of Onset	Males SR			Females SR			Total SR		
	<0.50	0.50-0.99	≥1.00	<0.50	0.50-0.99	≥1.00	<0.50	0.50-0.99	≥1.00
5-9	2	4	1	1	0	0	3	4	1
10-14	7	8	1	3	3	1	10	11	2
15-19	11	6	4	10	2	1	21	8	5
20-24	3	1	2	3	1	0	6	2	2
25-29	0	2	3	0	0	0	0	2	3
30-34	0	2	1	0	1	1	0	3	2
35-39	0	0	5	0	0	2	0	0	7
Total	23	23	17	17	7	5	40	30	22

	Observed Distribution of SR				Expected Distribution of SR				
	<0.50	0.50-0.99	≥1.00	Total		<0.50	0.50-0.99	≥1.00	Total
Male	23	23	17	63	Male	27.4	20.5	15.1	63.0
Female	17	7	5	29	Female	12.6	9.5	6.9	29.0
Total	40	30	22	92	Total	40.0	30.0	22.0	92.0

$$\chi^2_{(2)} = 3.98,\ p > 0.15$$

divided into those for whom SR was less than 0.50, between 0.50 and 0.99, and greater than or equal to 1.00. The survival of leprous individuals for whom SR ≥ 1.00, for example, is assumed not to have been reduced by the presence of the disease. The distributions of SR values of these two age-of-onset classes were then compared for homogeneity using a contingency chi square test. Other groupings of the data were made

TABLE 3. *Chi-square test for heterogeneity of the distribution of SR values among age of onset classes combining males and females with lepromatous leprosy.*

Observed SR

Age of Onset	< 0.50	0.50-0.99	≥ 1.00	Total
< 18	25	20	4	49
≥ 18	15	10	18	43
Total	40	30	22	92

Expected SR

Age of Onset	< 0.50	0.50-0.99	≥ 1.00	Total
< 18	21.3	16.0	11.7	49.0
≥ 18	18.7	14.0	10.3	43.0
Total	40.0	30.0	22.0	92.0

$x^2_{(2)} = 14.34, p < 0.001$

Observed SR

Age of Onset	< 1.00	≥ 1.00	Total
5-14	28	3	31
15-19	29	5	34
20+	13	14	27
	70	22	92

Expected SR

Age of Onset	< 1.00	≥ 1.00	Total
5-14	23.6	7.4	31.0
15-19	25.9	8.1	34.0
20+	20.5	6.5	27.0
	70.0	22.0	92.0

$x^2_{(2)} = 16.39, p < 0.0001$

for the chi square test to insure that the outcome of this analysis was not an artifact of our criteria for constructing classes for comparison.

RESULTS

Table 1 gives ${}_{45}e_x$ estimates for selected values of x for healthy males and females born prior to 1907. For all ages, survival to age 45 was slightly greater for males than females. The expected number of years of survival to age 45 from birth was 30.3 for males and 29.5 for females. For comparison, expectation of survival to age 45 based upon the total Philippine age-specific death rates in 1960 was 35.9 for males and 37.3 for females ([9]). If, as this suggests, survival did not change drastically throughout the entire first half of the twentieth century, changes in death rates which might have occurred during the life experience (to age 45) of those born prior to 1907 cannot have seriously affected the outcome of our analysis.

Table 2 presents the distribution of SR values for males and females by age of onset of lepromatous leprosy. The distribution of SR values of males and females who developed lepromatous leprosy combined over all ages of onset do not differ significantly, as shown in Table 2. The two distributions were

combined in the analyses to follow so as to provide a larger sample for the contrasts between the distributions of SR for different ages of onset.

As shown in Table 3, the distributions of SR values were heterogeneous among groups based upon the age of onset. The distributions of SR values for those whose age of onset occurred before and after attaining age 18 were statistically significantly different ($p < 0.001$). The greatest contribution to the total chi square was made by the difference in the number of SR values greater than or equal to 1.00 in the two age-of-onset classes. Those whose SR values were less than 0.50 and between 0.50 and 0.99 were then combined for the comparison for heterogeneity among the classes of age of onset 5-14, 15-19 and 20+. Significant heterogeneity was observed in the distributions of SR values less than 1.00 and greater than or equal to 1.00 among these three age-of-onset classes ($p < 0.0001$).

DISCUSSION

The survival (at least to age 45) of victims of lepromatous leprosy was statistically significantly lower when onset occurred before, rather than after or at, age 18. The greatest contribution (over 75%) to the total chi square for heterogeneity was contributed by the difference between the two age-of-onset classes in the proportion of lepromatous leprosy patients surviving as long or longer than the healthy population (i.e., SR $\geq$ 1.00). While only 8% of those contracting the disease before age 18 exceeded the life expectancy to age 45 in the healthy population, about 42% of those contracting leprosy after attaining age 18 did so.

When the distributions of SR values below and above 1.00 were compared among three new age-of-onset classes, constructed to provide an approximately equal number of observations on each of the three classes, the effect of age of onset of lepromatous leprosy upon survival was even more striking. The proportion of observations with SR values exceeding 1.00 whose age of onset occurred between 5 and 14, 15 and 19, and after 20 were, respectively, 0.10, 0.15 and 0.52. Choosing still different arbitrary values of SR and age of onset as criteria for constructing the classes for comparison did not change the outcome of this analysis.

The decrease in survival following the onset of lepromatous leprosy is an inverse function of the age at which onset of the disease occurred. The low number of cases whose onset occurred after age 20 prevented a more detailed analysis of this relationship at greater ages of onset, but the association does not appear to be strictly linear. Survival, relative to that of the healthy population, increases slowly with advancing age of onset until age 20 after which it increases much more rapidly. Of those whose onset occurred after age 20, approximately equal numbers lived less than and more than the average years of survival to age 45 experienced by healthy members of the same population.

It appears, then, that lepromatous leprosy in Cordova decreases survival, at least to age 45, only when its onset occurs before age 20. It will be of interest to determine whether this finding can be generalized to other populations and to survival beyond age 45 as well. The attainment of greater resistance to invasion with *M. leprae* by age of maturity might minimize complications which result after the onset of lepromatous leprosy and prevent the decrease in survival in the presence of the disease. The results of our analyses are consistent with this explanation for variation in mortality for different age groups of leprosy patients. These results also raise interesting questions regarding the possibility of an effect of age of onset of lepromatous leprosy upon communicability of the disease.

SUMMARY

A life-table approach was employed to estimate expectation of survival of the nonleprous members of a population in which leprosy is endemic. The observed survival of members who developed lepromatous leprosy at different ages was compared with that expected after having attained the age at which onset occurred. Those whose onset occurred at later, as opposed to earlier, ages more frequently lived their expected remaining years of life. Survival was not decreased in those whose onset occurred after age 20. It is hypothesized that those whose onset occurs after maturity are more resistant to complications arising from infection with *M. leprae* which can lead prematurely to death.

RESUMEN

Se utilizó una tabla de vida para calcular el promedio de sobrevida de los miembros no leprosos de una población donde la lepra es endémica. En cuanto a los enfermos, la sobrevida observada en aquellos cuyas edades de aparición de la enfermedad fueron tardías, vivieron sus años esperados de sobrevida con más frecuencia que los individuos donde la aparición de la enfermedad ocurrió a una edad temprana. La sobrevida esperada no disminuyó en los individuos donde la enfermedad apareció después de los 20 años de edad. Se establece la hipótesis de que aquellos individuos en donde la enfermedad aparece después de la madurez, son más resistentes a las complicaciones originadas por la infección con *M. leprae*, las cuales pueden conducir a muerte prematura.

RÉSUMÉ

On a utilisé une méthode de table de survie pour estimer l'espérance de vie des individus sains dans une population où la lèpre est endémique. La survie des membres de cette population qui développent la lèpre lépromateuse à différents âges a été comparée avec la survie attendue chez les individus sains d'un âge identique à celui auquel la maladie était apparue chez les sujets malades. Les malades chez lesquels l'apparition de l'affection est survenue à des âges plus tardifs vivent plus fréquemment leur espérance de vie entière, à partir de cet âge, que les malades chez lesquels la maladie est apparue plus tôt. La survie n'était pas diminuée chez les malades ayant manifesté l'apparition de la maladie après l'age de 20 ans. On fait l'hypothèse que les malades chez lesquels l'apparition de la maladie survient après la maturité sont plus résistants aux complications survenant à la suite de l'infection par *M. leprae* et qui peuvent mener à un décès prématuré.

Acknowledgments. This work was supported by USPHS grants CA-06551, RR-05539 and CA-06927 from the National Institutes of Health and by an appropriation from the Commonwealth of Pennsylvania. We are indebted to the staff members of the Philippine Division of the Leonard Wood Memorial, the Cebu Skin Clinic and the Eversley Childs Sanitarium Cebu, Philippines all of whom directed, helped in, or facilitated the collection of the data used in this analysis. We express our appreciation to Drs. Baruch S. Blumberg and Edward Lustbader of the Institute for Cancer Research, Philadelphia, Pennsylvania and to Dr. Thomas Farver of the Department of Epidemiology and Preventive Medicine, University of California for their critical comments on earlier drafts of this manuscript.

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