# Survival Among Leprosy Patients With Special Consideration of Cancer as a Cause of Death[1]

**Arthur Oleinick**[2]

Leprosy persists as a major medical problem in many countries of the world. Estimates of worldwide prevalence place the number of cases at between 5 and 15 million ([42, 43]). Despite the magnitude of the problem, comparatively little is known about the exact effect of the sulfone drugs upon the excess mortality associated with lepromatous leprosy in the presulfone era. The present study provides information concerning the mortality risk of leprosy patients in the United States during the sulfone era. Demographic characteristics of the study population are compared with data from other areas of the world as a background for evaluating the mortality experience.

The study was also undertaken to evaluate the effect of chronic antigenic stimulation of the lymphoid system by *M. leprae* upon the risk of lymphoid malignancy. In addition, the relationship between a chronic illness characterized by a defect in cellular immunity, such as leprosy, and susceptibility to all forms of cancer was investigated. Hopefully, studies of this type will provide insights into the role of host factors in the development of cancer.

## METHODS

**The sample.** The study group consists of 953 patients whose first admission to the U.S. Public Health Service Leprosarium in Carville, Louisiana, occurred during the period 1939 through 1963. Follow-up through 1 January 1964 is complete for 90 per cent of all patients in the study group. In the group of 279 patients originally classified as "lost to follow-up" (Table 1-A), intensive follow-up efforts provided mortality status on 64 per cent. Forty-two of the 100 patients who remain in the "lost to follow-up" category are known to have emigrated. Nonwhites were more difficult to locate than were whites (Table 1-B), and, among the former, Orientals were more difficult (20.2%) than were Negroes (14.2%). The heterogeneous national origins of the Oriental cases, as well as skewed distributions on other demographic variables, led to the exclusion of this group of 99 patients from the analysis.

Death certificates were requested from State Vital Records Offices for the 236 deceased individuals. For 11 of the 236 patients only a date of death was available.

**Definitions.** The terminology of the Madrid Congress classification of leprosy was employed ([9]). This classification subdivides leprosy into two major types, lepromatous and tuberculoid, and two intermediate groups, borderline (dimorphous), and indeterminate. Borderline and lepromatous leprosy were considered together in accordance with the recommendations of the WHO Expert Committee on Leprosy ([44]). The six cases of indeterminate leprosy were omitted from the analysis since they constituted such a small fraction of the study group. Initial diagnoses were utilized in classifying patients, since shifts in type were rarely found.

**Analysis.** Demographic characteristics of the study group are presented first. The effects of sex, race, age at first admission, and type of disease upon the composition of the study group were analyzed by means of the Mantel-Haenszel chi-square ([28]).

Life table methods were used to compute survival ([14]). The cumulative observed survival rates reflect the actual mor-

1 Received for publication 25 January 1968.

2 A. Oleinick, M.D., M.P.H., Medical Officer, Ecology Studies Section, Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014.

TABLE 1. *Follow-up status of patients with leprosy admitted to the U. S. Public Health Service Hospital, Carville, Louisiana, during the period 1939–1963.*

A. Summary

| Survival status | Before follow-up 1 July 1965 | After follow-up 1 March 1966 |
|---|---|---|
| Alive as of 1 Jan. 1964 | 451[a] | 617 |
| Known dead as of 1 Jan. 1964 | 223 | 236 |
| Lost to follow-up | 279 | 100 |
| Total | 953 | 953 |

B. Percentage lost to follow-up by race, sex, and age at admission

| | Age (yrs.) | | | | | | |
|---|---|---|---|---|---|---|---|
| | <30 | | 30–59 | | 60+ | | |
| Race | Male | Female | Male | Female | Male | Female | Total |
| White | 12.2 (139)[b] | 14.3 (77) | 9.6 (281) | 4.8 (145) | 3.0 (67) | 0.0 (32) | 8.6 (741) |
| Negro | 15.0 ( 20) | 18.2 (11) | 14.6 ( 41) | 21.7 ( 23) | 0.0 ( 7) | 0.0 (11) | 14.2 (113) |
| Oriental | 20.0 ( 35) | 14.3 ( 7) | 23.3 (43) | 12.5 ( 8) | 16.7 ( 6) | — — | 20.2 ( 99) |
| | 14.2 (289) | | 10.4 (541) | | 2.4 (123) | | 10.5 (953) |

[a] 199 of these patients were hospitalized in Carville as of 1 July 1965.
[b] Number in parentheses refers to the size of the group.

tality experience of the study group, while the cumulative relative survival rates (CRSR) provide an estimate of the effect of leprosy on mortality risk. The relative survival rate is defined as ([14]):

> "the ratio of the observed survival rate in a group of patients, during a specified interval, to the expected survival rate. The expected survival rate is that of a group similar to the patient group in such characteristics as age, sex, and race, but free of the specific disease under study. A relative survival rate of less than one indicates that, during the specific interval, mortality in the patient group exceeded that of persons in the general population free of the disease under study."

To avoid possible artefacts produced by small groups and heavy withdrawal during observation, only those survival rates that satisfy the following criteria were used: (1) No fewer than 10 persons were observed during the last year of any five year interval, and, (2) No more than 20 per cent of patients were in the "withdrawn alive," i.e., lost to follow-up, category during any single year's observation.

Different time intervals were utilized in reporting the observed and relative survival rates. The observed survival rates are cumulated from the time of admission and represent the per cent of the original patient group surviving. The relative survival rates, in contrast, are cumulated in five year periods, and the per cent surviving refers to the number of patients alive at the beginning of the particular period. The use of consecutive cumulative relative survival rates is particularly helpful in portraying early and late mortality effects.

The survival of patients who entered the leprosarium during the first five years of the

TABLE 2. *Survival rates of leprosy patients admitted to the U. S. Public Health Service Hospital, Carville, Louisiana, 1939–1958, by sex, age at admission, calendar period of admission, race, and type of leprosy.*

| Type of Leprosy | No. in group | Survival rates | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cumulative observed survival rate (yrs.) | | | | Cumulative relative survival rate (yrs.) | | | |
| | | 0–5 | 0–10 | 0–15 | 0–20 | 0–5 | 6–10 | 11–15 | 16–20 |
| A. Lepromatous (incl. borderline) | | | | | | | | | |
| *White* | | | | | | | | | |
| 1939–1943 | | | | | | | | | |
| Male | 98 | .88 | .77 | .69 | .63 | .94 ± .04[a] | .93 ± .04 | .97 ± .04 | .99 ± .04 |
| Female | 48 | .77 | .77 | .65 | .50 | .81 ± .06 | 1.04 ± .06[b] | .88 ± .06 | .83 ± .08 |
| 1944–58 | | | | | | | | | |
| Male | 243 | .88 | .77 | .64 | — | .93 ± .02 | .94 ± .03 | .92 ± .05 | — |
| Female | 123 | .90 | .83 | .80 | — | .93 ± .03 | .96 ± .03 | 1.00 ± .03 | — |
| Age (yrs) | | | | | | | | | |
| under 30 | | | | | | | | | |
| Male | 75 | .96 | .88 | .85 | — | .97 ± .02 | .92 ± .04 | .98 ± .03 | — |
| Female | 38 | .97 | .97 | .97 | — | .98 ± .03 | 1.00 ± .03[b] | 1.01 ± .03[b] | — |
| 30–59 | | | | | | | | | |
| Male | 135 | .87 | .82 | .66 | — | .91 ± .03 | 1.00 ± .03 | .90 ± .06 | — |
| Female | 69 | .96 | .87 | .83 | — | .98 ± .03 | .94 ± .04 | 1.00 ± .04 | — |
| 60+ | | | | | | | | | |
| Male | 33 | .72 | .34 | — | — | .96 ± .10 | .70 ± .17 | — | — |
| Female | 16 | .50 | .36 | — | — | .60 ± .15 | .91 ± .21 | — | — |
| *Negro* | | | | | | | | | |
| 1944–1958 | | | | | | | | | |
| Male | 27 | .92 | .73 | — | — | .96 ± .06 | .82 ± .10 | — | — |
| Female | 20 | .90 | .80 | — | — | 1.01 ± .08 | 1.04 ± .12 | — | — |
| B. Tuberculoid | | | | | | | | | |
| White | | | | | | | | | |
| 1944–1958 | | | | | | | | | |
| Male | 37 | .97 | .90 | — | — | 1.02 ± .03 | 1.01 ± .05 | — | — |
| Female | 23 | .95 | .90 | — | — | .98 ± .05 | .99 ± .05 | — | — |

[a] ± 1 standard error. [b] Standard error estimated.

study, 1939 through 1943, was analyzed separately. Survival rates for this group possibly reflect the effect of delayed initiation of sulfone therapy and/or mortality due to unrelated infections, since neither sulfones ([17]) nor penicillin ([41]) was widely available during the interval.

The expected number of cancer deaths was calculated by multiplying the person years at risk of the leprosy patients by the age, sex, race, and calendar-year specific United States mortality rates for all cancers, leukemia, and lymphoma ([16]). The observed cancer cases were ascertained from death certificates. The ratio of the observed to the expected number of cancer deaths was tested for significance by use of the Poisson distribution ([2]).

## RESULTS

**Descriptive.** Males comprised 64.9 per cent of leprosarium admissions. Excluding Orientals (see above), 86.7 per cent of the patients were white. Of the patients 28.5 per cent were less than 30 years of age at admission, 57.7 per cent from 30 through 59 years, and 13.8 per cent, 60 years or older. Lepromatous leprosy accounted for 85.8 per cent of the cases among whites and 74.3 per cent among Negroes. The sex, race, age at admission, and type distributions did not vary significantly when the study group was cross-classified by these variables, with the single exception of type distribution by race.

**Survival.** Cumulative observed and relative survival rates for leprosy patients by sex, age at admission, calendar period of admission, race, and type of leprosy are shown in Table 2. Although the cumulative relative survival rates indicate that most leprosy patients experience a normal mortality risk (CRSR + 2 S.E. $\geqq$ 1) there appear to be significant exceptions among patients with lepromatous leprosy. Females admitted between 1939 and 1943 had an increased mortality risk during the five years following admission, followed by ten years of normal survival, and then demonstrated a late excess in mortality. Males admitted during the same period experienced normal survival during all follow-up periods. Among patients of all ages admitted subsequently, 1944-1958, there was a slight excess of mortality among both sexes during the first five years following admission. Analysis of survival by age at admission indicates that males aged 30-59 at admission accounted for the early excess mortality among males. The early female excess mortality is the product of an increased mortality among older females, a rather small group.

**Cancer.** The expected and observed cancer mortality among various subgroups of leprosy patients, 1939-1963, is shown in Table 3. Three cases were excluded from tabulation because necropsy failed to confirm the death certificate diagnosis of cancer. Two patients whose diagnosis of cancer antedated their first admission and one patient whose admission symptomatology was probably attributable to a lymphosarcoma, were excluded to avoid the possibility of selection bias for cancer patients in the study group. Among the remaining 21 patients who died with cancer, 17 cases were confirmed histologically. There was no significant excess in cancer mortality for patients with either type of leprosy.

Two cases of leukemia/lymphoma were observed, as against 1.66 cases expected.

## DISCUSSION

**Descriptive.** Among the variables characterizing the Carville population the sex and type of leprosy distributions invite comparison with previous reports. The sex ratio (male/female 2:1) among Carville patients is comparable to the sex ratios reported from all areas of the world ([19, 20, 26, 27, 30, 31, 35, 37]) except Africa ([5, 45]). The type of leprosy distribution is similar to that reported from other western hemisphere countries ([27, 32, 37]) and differs from the distribution in African and Asian countries, where there is a considerably lower proportion of lepromatous and borderline (dimorphous) cases ([3, 5, 19, 20, 31, 35, 45]). The similarity between the sexes in type distribution is at variance with the results of previous studies ([26, 31]).

**Survival.** Life table analyses of mortality in leprosy have been reported infrequently.

TABLE 3. *Expected and observed cancer deaths among leprosy patients, United States, 1939–1963, by leprosy type, race, and interval of follow-up.*

| Race (both sexes) | Lepromatous (incl. borderline) | | | | | | Tuberculoid | Lepromatous & tuberculoid combined |
|---|---|---|---|---|---|---|---|---|
| | Years of survival or follow-up | | | | | | | |
| | <5 | 5–9.9 | 10–14.9 | 15–19.9 | 20+ | Total | Total | Total |
| *White* | | | | | | | | |
| Expected | 4.6 | 3.98 | 2.96 | 1.84 | 0.80 | 14.18 | 2.92 | 17.10 |
| Observed | 6 | 6 | 2 | 2 | 1 | 17 | 3 | 20 |
| Observed/expected | 1.30 | 1.51 | 0.68 | 1.09 | 1.25 | 1.20 | 1.03 | 1.17 |
| *Negro* | | | | | | | | |
| Expected | 0.60 | 0.48 | 0.28 | 0.19 | 0.05 | 1.60 | 1.01 | 2.61 |
| Observed | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 |
| Observed/expected | 0 | 2.08 | 0 | 0 | 0 | 0.62 | 0 | 0.38 |
| *Both races combined* | | | | | | | | |
| Expected | 5.20 | 4.46 | 3.24 | 2.03 | 0.85 | 15.78 | 3.93 | 19.71 |
| Observed | 6 | 7 | 2 | 2 | 1 | 18 | 3 | 21 |
| Observed/expected | 1.15 | 1.57 | 0.62 | 0.99 | 1.18 | 1.14 | 0.76 | 1.07 |

Guinto *et al.* ([18]) compared the survival in the presulfone era of 272 lepromatous and 346 tuberculoid leprosy patients with that of unaffected members of the same villages. They demonstrated an increased mortality risk among the lepromatous patients, which was most marked in the group aged 30 to 49 at diagnosis or onset of their disease. There was no unequivocal sex differential in mortality, although the male mortality rates were higher. Gray and Bancroft ([17]), in a study based upon the population resident at Carville between 1942 and 1950, concluded that sulfone-treated leprosy patients had no excess in mortality over that expected from 1940 Louisiana mortality rates. Their study probably confounded host resistance and sulfone efficacy, since long-term residents and recent admissions were analyzed together. Patients who survived to the sulfone era might reasonably be considered to have demonstrated a superior host response. The present study excluded patients who were resident at Carville, or who had their first admission to the Hospital, prior to 1 January 1939.

Potential deficiencies of the present study include the use of life tables derived from the mortality experience of the entire United States and the failure to adjust for variables other than race and sex. The former deficiency is of little import, since life expectancy varies little in the United States between regions ([14]). The latter deficiency is more serious, but not presently correctable because life tables by socio-economic class covering the entire study period are unavailable. However, an analysis of 1950 mortality data indicates that lower socio-economic groups have a higher mortality risk ([32]). Therefore, such a correction would have increased the cumulative relative survival rates because most of the Carville patients come from lower socio-economic groups.

The early mortality risk of patients with lepromatous leprosy admitted after the advent of sulfone therapy is comparable to that of an unaffected population, except among older females and middle-aged males. The late fall in relative survival among females admitted in the presulfone era who survived to the sulfone era, could be explained in several ways. First, the late excess in mortality may reflect the natural outcome for patients with a consistently poor response to therapy. Second, the excess mortality may occur in individuals who fail to resume therapy following relapse after discharge. Third, the excess mortality may reflect the relentless progression of a process such as amyloid disease ([36]), which is initiated during active disease and continues following apparent bacteriologic and clinical improvement. A future study will compile the data necessary to examine the relationships between the extent of disease at time of diagnosis, clinical course, and mortality risk.

The current study also provides fragmentary data suggesting that even the delayed onset of therapy may reverse an excess mortality trend. This appears to have been the case for females admitted between 1939 and 1943 in the presulfone era.

**Cancer.** Earlier reports concerning the relationship between leprosy and cancer are contradictory. Some observers reported a diminished cancer mortality or prevalence among leprosy patients ([4, 38]), and others a cancer mortality similar to that of unaffected individuals ([12]), while at least one observer suggested that cancer may occur with unusual frequency during the course of leprosy ([24]). However, serious methodologic deficiencies in these earlier reports preclude useful conclusions regarding the cancer mortality among leprosy patients.

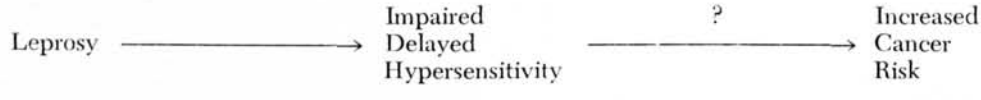
In the present study the absence of a cancer excess could reflect a methodologic artefact rather than the true biologic condition. If a methodologic artefact were responsible, it would operate either by means of an overestimate of expected cancer mortality or an underenumeration of observed cancer. The expected cancer mortality appears well estimated, although adjustment for region of origin and socio-economic class of the leprosy patients was not possible. There would have been little net change in expected values with adjustment for these variables, since survey data indicate that cancer mortality is lower in the leprosy-endemic states than in the whole

United States ([16]), while cancer mortality is higher in the socio-economic class of origin of the leprosy patients ([13]).

Errors in enumeration of observed deaths arise as a result of lack of accuracy (confirmation) and/or completeness (detection) in the ascertainment of cause of death. Previous studies have demonstrated that detection and confirmation errors occur at the rate of 10 per cent of the cancer mortality rates ([23]). Since the errors are of the same magnitude, but in the opposite direction, they tend to cancel each other. In the present study the excluded cancer cases were undoubtedly partially balanced by the increased cancer detection in a chronically hospitalized patient population.

Figure 1 illustrates a possible sequence of events linking leprosy with cancer. Two recent reports have delineated an impairment of delayed hypersensitivity among patients with leprosy that tends to return to normal following prolonged chemotherapy ([7, 40]). The second step in the sequence is speculative and was suggested by data obtained on cancer patients and on patients with ataxia-telangiectasia. An impairment of delayed hypersensitivity has been correlated with a poor host response among cancer patients ([6,21]). The immune system has been more directly implicated as a factor in host susceptibility to cancer by the eleven case reports of lymphoma and two cases of leukemia among patients with ataxia-telangiectasia ([15]), an immunologic deficiency disease associated with a defect in delayed hypersensitivity. The normal cancer risk among leprosy patients provides preliminary evidence against this hypothesis.

FIG. 1




**Leukemia-lymphoma.** The absence of a disproportionate risk of leukemia or lymphoma among leprosy patients provides a possible insight into the pathogenesis of these malignancies. Several observers ([10, 11, 34, 39]) have suggested that the chronic lymphoid stimulation associated with the autoimmune diseases is attended by an increased risk of lymphoid malignancy. An analysis of the mortality experience of published series of patients with rheumatoid arthritis and systemic lupus erythematosus did not confirm this hypothesis ([33]).

Leprosy patients provide additional data relevant to this hypothesis. First, lepromatous leprosy is characterized by chronic lymphoid stimulation manifested both clinically and serologically in the form of hyperglobulinemia and numerous autoantibodies ([8, 29]). Second, the duration of the lymphoid stimulation is remarkably long, even with treatment ([25]). This provides data particularly amenable to person-years-at-risk analyses. Third, the infectious etiology of leprosy, in contrast to the unknown etiology of autoimmune disease, provides a means of segregating the risk attributable directly to lymphoid hyperplasia from any possible risks associated with susceptibility to autoimmune diseases.

The present study demonstrates that the risk of leukemia or lymphoma in leprosy patients is not increased. It would appear that chronic lymphoid stimulation plays a negligible role in the etiology of lymphoid malignancies. However, special circumstances could alter the malignancy potential of chronic lymphoid stimulation. Thus, lymphoid stimulation has been implicated in the etiology of the sporadic cases of leukemia that occur during the course of tuberculosis ([1]) as well as in the etiology of childhood leukemia ([22]). Neither hypothesis has been well substantiated and definitive studies in these latter circumstances remain to be done.

## SUMMARY

This report analyzes the mortality experience of the 953 leprosy patients admitted to the U.S. Public Health Service Leprosarium, Carville, Louisiana, between 1939 and 1963. Follow-up is complete for 90 per cent of the study group. Demogra-

phic characteristics of the study group were analyzed and compared with results reported from other areas of the world. In general, the mortality risk of patients with both types of leprosy has been normal. A diminished survival was observed early and late in follow-up among females whose first admission occurred in the presulfone era. Middle-aged males and older females admitted during the sulfone era showed a slight excess in mortality during the five years following admission. Additional studies are planned to elucidate the relationships between the extent of disease at time of diagnosis, clinical course, and relative survival.

No significant excess of cancer mortality among leprosy patients was demonstrated. More specifically, the risk of lymphoid malignancy is also not significantly elevated. An attempt is made to interpret these findings in terms of current theories of carcinogenesis.


## RESUMEN

Este informe analiza le experiencia de un estudio sobre la mortalidad en 953 enfermos de lepra admitidos en el Leprosarium del Servicio de Salud Pública de los Estados Unidos, en Carville, Louisiana, entre los años 1939 y 1963. La observación ulterior está completa en el 90% del grupo estudiado. Las características demograficas en el grupo estudiado se analizaron y compararon con los resultados comunicados en otras regiones del mundo. En general, el riesgo de morir de los enfermos con ambos tipos de lepra fué el normal. La observación ulterior señaló una disminución de la sobrevida, temprana y tardía, en las mujeres cuya primera admisión tuvo lugar en la era presulfónica. Los hombres de edad media y las mujeres de edad mayor admitidas durante la era sulfónica tuvieron un ligero aumento en la mortalidad en los cinco años que siguieron a la admisión. Nuevos estudios se planean para aclarar las relaciones que hay entre el grado de extensión de la enfermedad en el momento del diagnóstico, el curso clínico y la sobrevida relativa.

No se demostró un aumento significativo de la mortalidad por cáncer en los pacientes de lepra. Más específicamente, el riesgo de la malignidad linfoide no está significativamente elevado. Se hace un ensayo de interpretación de estos hallazgos a la luz de las teorías corrientes sobre carcinogénesis.

## RÉSUMÉ

Cet article analyse la mortalité de 953 malades de la lèpre admis au U. S. Public Health Service Leprosarium de Carville, en Louisiane, entre 1939 et 1963. L'observation est complète pour 90 pour cent du groupe étudié. Les caractéristiques démographiques du groupe étudié ont été analysées et comparées aux résultats rapportés dans d'autres régions du monde. En général, le risque de mortalité des malades, atteints de l'une ou l'autre forme de lèpre, a été normal. Une diminution de la survie, a été observée au debut et á la fin de la période d'observation, chez les femmes qui avaient été hospitalisées pour la première fois avant la période des sulfones. Les hommes d'âge moyen, et les femmes plus âgées, admis à la léproserie au cours de la période des sulfones, ont présenté un léger excès de mortalité au cours de cinq premières années suivant l'admission. On se propose de mener des études complémentaires, afin d'élucider les relations entre l'étendue de la maladie au moment du diagnostic, son évolution clinique, et la survie relative.

On n'a mis en évidence aucun excès significatif de mortalité par cancer chez les malades de la lèpre. Plus particulièrement, le risque de cancer lymphoïde n'était pas non plus significativement plus élevé. On a essayé d'interpréter ces observations, à la lumière des théories actuelles de la carcinogenèse.


**Acknowledgments.** I wish to thank Dr. John R. Trautman for his advice on clinical problems; Drs. Edgar B. Johnwick (deceased) and Merlin L. Brubaker for making available the facilities of the USPHS leprosarium; and Mrs. Zelda Janus and Mr. Max H. Myers for their assistance in the statistical analysis. Special thanks are due the Leonard Wood Memorial and the Bureau of Disease Control of the Philippine Government for their help in providing follow-up information for the patients whose last address was the Philippines.

## REFERENCES

1. Andre, J., Schwartz, R. and Dameshek, W. Tuberculosis and myelosclerosis with myeloid metaplasia: report of three cases. J. American Med. Assoc. **178** (1961) 1169-1174.
2. Bailar, J. C. and Ederer, F. Significance factors for the ratio of a Poisson variable to its expectation. Biometrics **20** (1964) 639-643.

3. Bechelli, L. M., Martinez Dominguez, V. M. and Patwary, K. M. WHO epidemiologic random sample survey of leprosy in Northern Nigeria (Katsina), Cameroon and Thailand (Khon Kaen). Internat. J. Leprosy **34** (1966) 223-243.
4. Bjarnhjedinsson, S. Lepra og carcinom. Med. Rev. (Bergen) **28** (1911) 336-338.
5. Brown, J. A. K. The incidence and epidemiology of leprosy in Uganda. Trans. Roy. Soc. Trop. Med. & Hyg. **49** (1955) 241-252.
6. Brunschwig, A., Southam, C. M. and Levin, A. G. Host resistance to cancer: clinical experiments by homotransplants, autotransplants and a mixture of autologus leukocytes. Ann. Surg. **162** (1965) 416-423.
7. Bullock, W. E. Immunity mechanisms in leprosy: I. Depression of delayed allergic response. New England J. Med. **278** (1968) 298-304.
8. Cathcart, E. S., Williams, R. C., Ross, Sr. H. and Calkins, E. The relationship of the latex fixation test to the clinical and serologic manifestations of leprosy. American J. Med. **31** (1961) 758-765.
9. [Congress, Madrid] Classification. Technical Resolutions. Internat. J. Leprosy **21** (1953) 504-516.
10. Cornes, J. S., Smith, J. C. and Southwood, F. W. Lymphosarcoma in chronic ulcerative colitis with report of two cases. British J. Surg. **49** (1961) 50-53.
11. Dameshek, W. and Schwartz, R. S. Leukemia and auto-immunization. Some possible relationships. Acta Haemat. (Basel) **24** (1960) 41-52.
12. De Martins, A. M. and De Martins, A. M., Jr. Lepra e tumores malignos (contribuiçao ao seu estudo anatomo-clinico). Rev. brasileira Leprol. **5** (1937) 179-222.
13. Dorn, H. F. and Cutler, S. J. Morbidity from cancer in the United States. Publ. Hlth. Mono. No. 56, Publ. Hlth. Serv. Publ. No. 590, 1959, p. 117.
14. Ederer, F., Axtell, L. M. and Cutler, S. J. The relative survival rate: a statistical methodology. Natl. Cancer Inst. Mono. **6** (1961) 101-121.
15. Fraumeni, J. F., Jr. and Miller, R. W. Epidemiology of human leukemia: recent observations. J. Natl. Cancer Inst. **38** (1967) 593-605.
16. Gordon, T., Crittenden, M. and Haenszel, W. Cancer mortality trends in the United States, 1930-1955. Natl. Cancer Inst. Mono. **6** (1961) 142-146; 324; 326.
17. Gray, H. H. and Bancroft, H. Tuberculosis at the United States Public Health Service Hospital, Carville, Louisiana, 1922-1950. Internat. J. Leprosy **20** (1952) 467-478.
18. Guinto, R. S., Doull, J. A., De Guia, L. and Rodriguez, J. N. Mortality of persons with leprosy prior to sulfone therapy, Cordova and Talisay, Cebu, Philippines. Internat. J. Leprosy **22** (1954) 273-284.
19. Guinto, R. S., Rodriguez, J. N., Doull, J. A. and De Guia, L. The trend of leprosy in Cordova and Talisay, Cebu Province, Philippines. Internat. J. Leprosy **22** (1954) 409-430.
20. Harter, P. and Bang, T. V. Haute endemicite et particularites cliniques de la lepre dans les regions montagneuses dy Sud Vietnam. Internat. J. Leprosy **29** (1961) 265-278.
21. Hughes, L. E. and Mackay, W. D. Suppression of the tuberculin response in malignant disease. British Med. J. **2** (1965) 1346-1348.
22. Innes, M. D. Immunization and childhood leukemia. Lancet **1** (1965) 605.
23. James, G., Patton, R. E., and Heslen, A. S. Accuracy of cause-of-death statements on death certificates. Publ. Hlth. Rept. **70** (1955) 39-51.
24. Keil, E. Zusammentreffen von Karzinom und Lepra. Krebsarzt **20** (1965) 269-274.
25. [Leprosy] Veterans Administration Med. Bull. No. 10, 1965, p. 36.
26. Lewis, R. A. and Edwards, R. A statistical study of 1,000 cases of leprosy observed in Rangoon for approximately two years. Internat. J. Leprosy **26** (1958) 236-251.
27. Luviano, A. A. El problem de la lepra en Mexico. Bol. Epidem. (Mexico) **25** (1961) 24-32.
28. Mantel, N. and Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. **22** (1959) 719-748.
29. Matthews, L. J. and Trautman, J. R. Clinical and serological profiles in leprosy. Lancet **2** (1965) 915-918.
30. [Ministerio de Salud Publica] La lepra en Cuba. Estado actual y programa de control. Dept. de Dermatologia y Venerologia. Rev. Cubana Med. **3** (1964) 334-347.
31. Mohamed Ali, P. An epidemiological leprosy survey in Chingleput District of Madras State. Leprosy in India **35** (1963) 176-187.

32. [National Vital Statistics Division] Mortality by occupation and industry among men 20-64 years of age: United States, 1950. (Lilian Guralnick). Vital Statist. Spec. Rep. 53, No. 2, 1962, pp. 58-61.
33. Oleinick, A. Leukemia or lymphoma occurring subsequent to an autoimmune disease: analytical review. Blood **29** (1967) 144-153.
34. Peterson, R. D. A., Cooper, M. D. and Good, R. A. Disorders of the thymus and other lymphoid tissues. Progr. Med. Genet. **4** (1965) 1-31.
35. Sharma, V. K. and Prasad, B. G. An epidemiological study of leprosy in the Masuli Block of Barabanki District, Uttar Pradesh. Indian J. Med. Res. **52** (1964) 1293-1312.
36. Shuttleworth, J. S. and Ross, Sr. H. Secondary amyloidosis in leprosy. Ann. Int. Med. **45** (1956) 23-28.
37. Sisiruca Q., C. and Convit, J. La epidemiologia de la lepra en Venezuela. Rev. Venezol. Sanid. **29** (1964) 31-44.
38. Söegaard, M. Lepra og cancer. Med. Rev. (Bergen) **27** (1910) 635-640.
39. Talal, N., Sokoloff, L. and Barth, W. F. Extra-salivary lymphoid abnormalities in Sjogren's syndrome (reticulum cell sarcoma, "pseudo-lymphoma," macroglobulinemia). American J. Med. **43** (1967) 50-65.
40. Waldorf, D. S., Sheagren, J. N., Trautman, J. R. and Block, J. B. Impaired delayed hypersensitivity in patients with lepromatous leprosy. Lancet **2** (1966) 773-776.
41. Weinstein, L. Antibiotics. II. Penicillin. *In* The Pharmacological Basis of Therapeutics. L. S. Goodman and A. Gilman, Eds. New York, MacMillan & Co., 1965, p. 1194.
42. [World Health Organization] Report on the World Health situation. Third Report, 1961-1964. Off. Rec. WHO No. 155, 1967, p. 18.
43. [World Health Organization] Scientific Meeting on Rehabilitation in Leprosy, Vellore, India, November 1960. Tech. Rept. Ser. WHO No. 221, 1961, p. 5.
44. [World Health Organization] WHO Expert Committee on Leprosy. Third Report. Tech. Rept. Ser. No. 319, 1966, p. 6-7.
45. Worsfold, J. T. A survey of leprosy amongst the Lovale tribe in the Upper Zambesi Basin Northern Rhodesia. Central African J. Med. **3** (1957) 359-363; 401-406.