# SURVIVAL-TIMES AFTER CARDIAC ALLOGRAFTS

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FROM THE CORA AND WEBB MADING DEPARTMENT OF SURGERY, BAYLOR COLLEGE OF MEDICINE, AND THE TEXAS HEART INSTITUTE OF ST. LUKE'S AND TEXAS CHILDREN'S HOSPITALS, HOUSTON, TEXAS

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***Summary*** During the period May 2, 1968, to March 1, 1969, fifteen patients underwent cardiac transplantation for end-stage heart-disease. Their survival-time is compared with that of forty-two potential recipients who did not receive allografts. Mean survival of the potential recipients was 74 days. The average for the transplant patients was 111 days (including 22 days waiting-time before operation). This difference does not justify wide clinical application of cardiac transplantation, but is an indication for its use in suitable cases where it may prolong life and relieve symptoms.

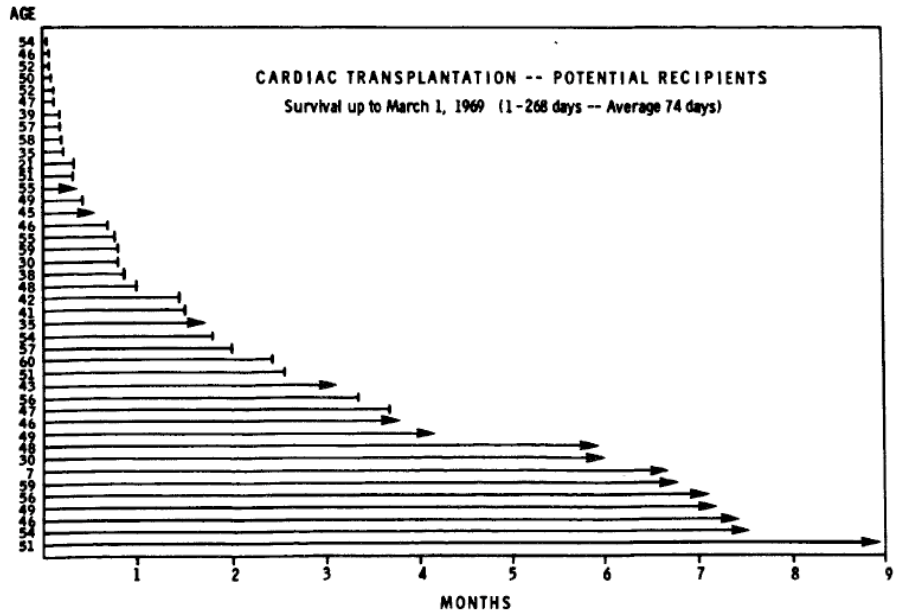


**Fig. 1—Survival of forty-two potential recipients for heart transplant.**
Arrow indicates patients still alive on March 1, 1969.

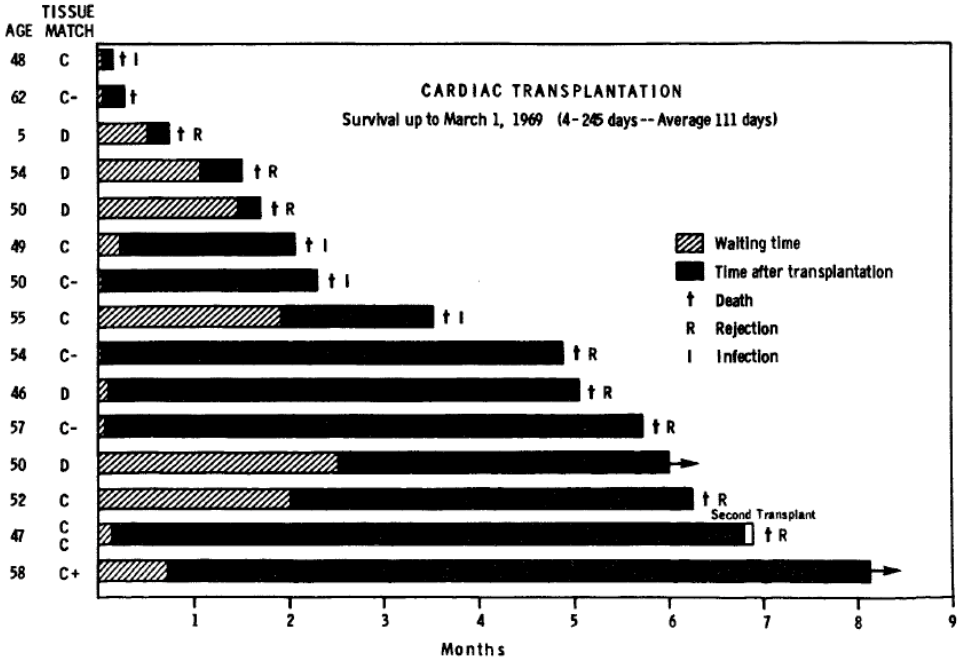


**Fig. 2—Survival of fifteen patients given a cardiac allograft.**
Arrow indicates patients still alive on March 1, 1969.

To compare the survival-times of the potential recipients with those of the transplant patients, we added the waiting-time of the transplant patients from the moment they were considered as recipients to the postoperative survival-time (fig. 2). Therefore only three (20%) transplant patients died within the first month in contrast to nineteen (45%) of the potential unoperated recipients. Eight (53%) of the transplant patients and fourteen (33%) of the unoperated potential recipients survived 3 months. Surviving 6 months were four (27%) of the transplant patients and eight (19%) of the potential recipients. The mean survival-time for the fifteen transplanted patients up to March 1, 1969, was 111 days (range 4–245 days) compared with a mean survival-time of 74 days (range 1–268 days) for the forty-two potential recipients. In the transplant patients, the mean survival-time of 111 days included 22 days waiting-time before transplantation.

THE LANCET, DECEMBER 13, 1975

# MORTALITY STUDY OF WORKERS IN A POLYVINYL-CHLORIDE PRODUCTION PLANT

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***Summary*** Age-standardised mortality-rates for a population of 2100 male workers exposed to vinyl chloride for periods of up to 27 years do not show any excess of total or cause-specific mortality. 1 case of angiosarcoma of the liver was identified just outside the study period. There was no suggestion of an increased frequency of deaths from the more common malignant diseases.

TABLE II—TOTAL MORTALITY

| Group | O | E | S.M.R. | No. | Man-years at risk |
|---|---|---|---|---|---|
| *All exposed workers* | 136 | 142·22 | 96 | 2122 | 23 052 |
| *Occupation* | | | | | |
| Autoclave operators | 13 | 13·79 | 94 | 338 | 3745 |
| Polymer plant | 4 | 6·54 | 61 | 110 | 1282 |
| Monomer plant | 7 | 8·21 | 85 | 66 | 919 |
| Other workers | 112 | 113·68 | 98 | 1606 | 17 106 |
| *Duration of exposure* | | | | | |
| < 10 yr | 83 | 74·01 | 112 | 1538 | 13 697 |
| 10–14 yr | 28 | 26·91 | 107 | 246 | 3271 |
| 15 + yr | 25 | 41·30 | 61 | 336 | 6084 |
| *Time of first exposure* | | | | | |
| Before 1956 | 99 | 93·60 | 106 | 571 | 10 022 |
| 1956–65 | 31 | 41·04 | 76 | 757 | 9661 |
| 1966 + | 6 | 7·58 | 79 | 792 | 3368 |

O=Observed. E=Expected. No.=Number of men.

THE LANCET, JULY 24, 1976

# Letters to the Editor

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## VINYL CHLORIDE AND MORTALITY?

SIR,—Excess cancer after exposure to vinyl chloride (V.C.) was demonstrated in animals by Viola et al.[6] and Maltoni and Lefemine[7] in Italy, and subsequently suggested by Monson et al.[8] and later definitively demonstrated by several investigations in man in the United States.[9–11] However, Duck et al.[12] of British Petroleum in the U.K. found no excess of cancer mortality—indeed, the longer workers were exposed to V.C., the healthier they seemed to be, as suggested by table II of their report, which shows a decreasing risk of death with an increasing duration of exposure.

In those exposed for less than 10 years, the standardised mortality from all causes was 112, but it fell to 107 for those exposed between 10 and 14 years and to 61 for those exposed for more than 15 years. Several interpretations of these find-

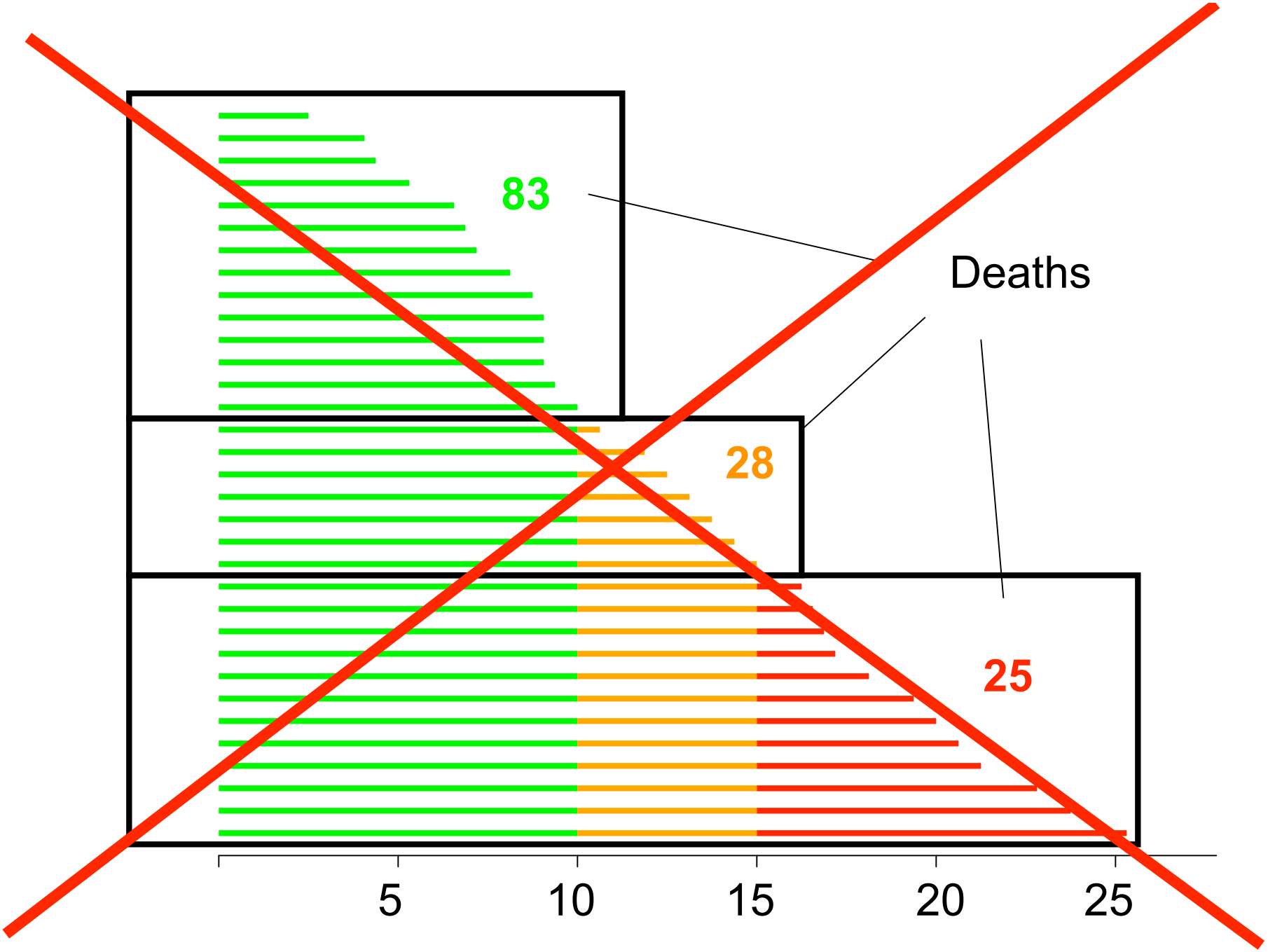
for more than 15 years. Several interpretations of these findings are possible: (1) the formulated V.C. as received by B.P. is uniquely non-toxic, (2) V.C. as polymerised or processed at B.P. is uniquely safe, (3) workers at B.P. have a particular genetic endowment which decreases their likelihood for V.C.-induced cancer, or conversely, other working populations[3–6] have a unique susceptibility to V.C., or (4) certain dietary factors unique to the workers at B.P. may scavenge free-radical V.C. (e.g., some have advocated eating lots of onions or garlic containing free sulphydryl groups.[13]) Before venturing any interpretation in biological, occupational, or technological terms, however, a closer consideration of the B.P. data seems wise, especially in view of studies[14 15] which demonstrated that the S.M.R. for total mortality increases with an increased duration of employment, due to elimination of the "healthy worker" effect. If in a follow-up study one selects, for example,

worker'' effect. If in a follow-up study one selects, for example, a subgroup of workers by the fact that they have achieved at least 15 years' exposure, then none of these workers could have died before the 15th anniversary, so information on risk of dying can only come from the number of man-years at risk and the number of deaths after 15 years. Of course these same men, provided they are properly regrouped together with those dying or coming to the end of the follow-up between, for example, 10 and 14 years can provide similar information for this time-interval—and so on for all previous time-intervals. This

REANALYSIS OF DATA BY DUCK ET AL. SHOWING PREVIOUSLY REPORTED VERSUS ESTIMATED NUMBERS OF EXPECTED DEATHS AND S.M.R.'S BY DURATION OF EXPOSURE AND CAUSE OF DEATH

| Duration of exposure yr | Cause of death | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All causes | | | | | Total cancers | | | | |
| | O | E | | S.M.R. | | O | E | | S.M.R. | |
| | | Duck et al. | RE | Duck et al. | RE | | Duck et al | RE | Duck et al. | RE |
| <10 | 83 | 74·01 | 105·46 | 112 | 79 | 23 | 18·68 | 26·62 | 123 | 86 |
| 10–14 | 28 | 26·91 | 20·49 | 107 | 137 | 4 | 6·87 | 5·23 | 58 | 76 |
| 15+ | 25 | 41·30 | 7·09 | 61 | 353 | 8 | 10·89 | 1·87 | 73 | 428 |
| | Digestive system cancer | | | | | Lung cancer | | | | |
| <10 | 6 | 5·64 | 3·04 | 106 | 75 | 10 | 7·76 | 11·06 | 129 | 90 |
| 10–14 | 1 | 2·13 | 1·62 | 47 | 62 | 3 | 2·97 | 2·26 | 101 | 133 |
| 15+ | 4 | 3·31 | 0·57 | 121 | 702 | 3 | 4·80 | 0·82 | 62 | 366 |

O=Observed E=Expected. RE=Recalculated estimates.


83
28
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Deaths
5
10
15
20
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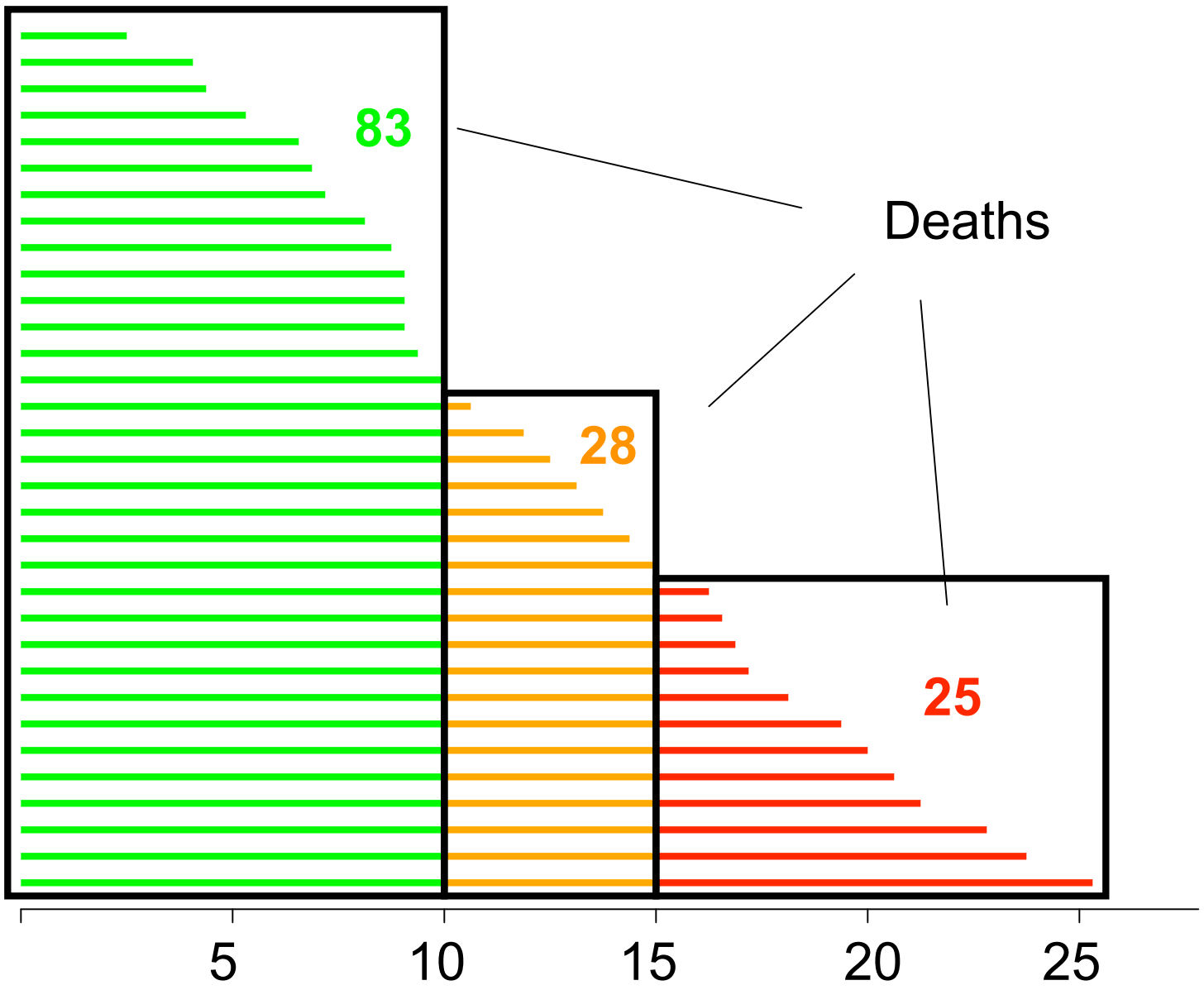
83
28
25
Deaths
5
10
15
20
25

# Allocation of person-time to time-dependent exposure categories

The correct assignment of each increment in person-time-years of follow-up is to…

**THAT SAME EXPOSURE CATEGORY TO WHICH A DEATH WOULD BE ASSIGNED SHOULD IT OCCUR AT THAT TIME**

Breslow & Day, Vol II, page 83

**William Farr** (1807 - 1883)
British epidemiologist
one of founders of medical statistics

# VITAL STATISTICS:

## *A Memorial Volume of Selections from the Reports and Writings of WILLIAM FARR*

With an Introduction by
Mervyn Susser
and
Abraham Adelstein

Published under the auspices of the Library
of The New York Academy of Medicine

The Scarecrow Press, Inc.
Metuchen, N.J. 1975

certain professions, stations, and ranks are only attained by persons advanced in years; and some occupations are only followed in youth; hence it requires no great amount of sagacity to perceive that "the mean age at death," or the age at which the greatest number of deaths occurs, cannot be depended upon in investigating the influence of occupation, rank, and profession upon health and longevity.

If it were found, upon an inquiry into the health of the officers of the army on full pay, that "the mean age at death" of "Cornets, Ensigns, and Second Lieutenants" was 22 years; of "Lieu-"tenants" 29 years; of "Captains" 37 years; of "Majors" 44 years; of "Lieutenant-Colonels" 48 years; of general Officers, ages still further advanced—

—and that the ages of Curates, Rectors, and Bishops;

of Barristers of seven years' standing, leading Counsel and venerable Judges—differed to an equal or greater extent, a strong case may no doubt be made out on behalf of those young, but early-dying Cornets, Curates, and Juvenile Barristers, whose "mean age at death" was under 30! It would be almost necessary to make them Generals, Bishops, and Judges—for the sake of their health.

# Evaluation of Response-Time Data Involving Transient States: An Illustration Using Heart-Transplant Data

NATHAN MANTEL and DAVID P. BYAR*
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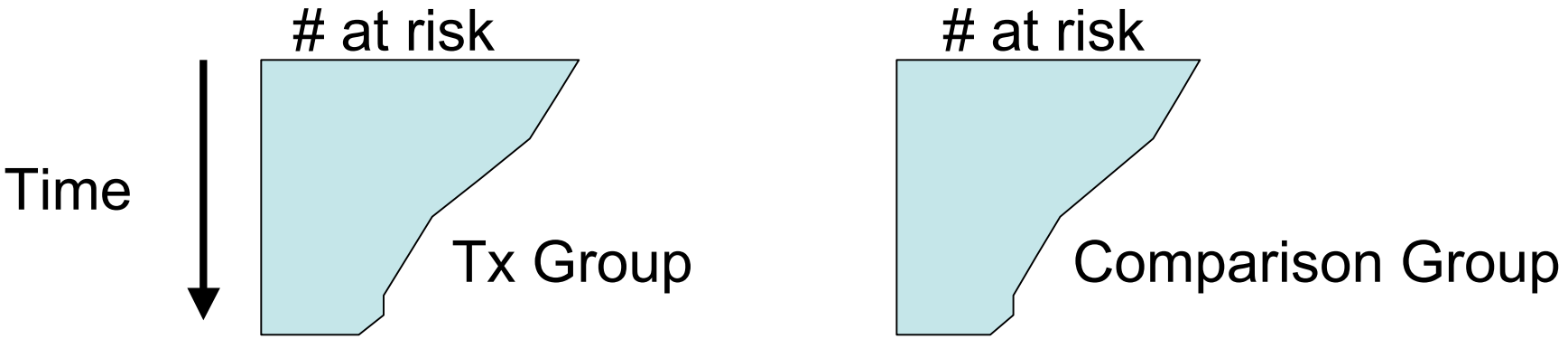
situation. A particularly common bias when the survival of treated patients is compared with that of untreated controls results from a failure to make allowance for the fact that the treated patients must have at least survived from time of diagnosis to time of treatment, while no such requirement obtained for their untreated controls.

Alternative statistical methodologies for avoiding the "time-to-treatment" bias indicated by Gail have been proposed by Turnbull, Brown, and Hu [9]. In these methodologies, a patient selected for heart transplant is nevertheless considered to be a control patient until he actually receives his transplant and to be a treated patient thereafter. This possibility of a patient trans-

## 2. MODIFICATION OF COMPARATIVE LIFE TABLES TO COVER TRANSIENT STATES

In the customary presentation of life-table data, one begins a time interval with a certain number of individuals at risk, observes the number of responses during the interval and the number of losses to observation for the interval (which it would be desirable to arrange to have occur at the end of the interval, see [5, Appendix Discussion 1]). The number at risk at the beginning of the next interval is simply the preceding number less both the preceding interval losses and responses (for responses like death which remove the individuals from further risk.)



In principle there is no reason why the number of individuals at risk may not be *increased* by accessions of survivors from some other comparable study group, a point noted in [5]. In the transient-state problem just such accessions do occur. Thus when a heart-transplant candidate receives his heart transplant, he becomes an accession into the transplanted group, though a loss from the untransplanted group. The usual life-table procedure is adapted simply to cover this case by adding a column for accessions into a group. Losses remain as before, but it may be desirable to distinguish between losses to observation and losses through transfer. With this concept we may actually have any number of different groups, keeping track of responses, accessions, losses to observation, and losses through transfer for each group. We illustrate this later with the heart-transplant data, although in this case only one kind of transfer arises, from untransplanted to transplanted.

| Day of death | Transplants | | | | | | |
|---|---|---|---|---|---|---|---|
| | $N_1$ | Deaths (A) | Accessions | Losses | | $N_2$ | Deaths (C) |
| | | | | From observation | By transfer | | |
| 0 | 0 | | II | | | 68 | I |
| 1 | 2 | | II | | | 65 | II |
| 2 | 4 | | IIII | | | 61 | III |
| 5 | 8 | I | | I | | 54 | II |
| 7 | 6 | | I | | | 52 | I |
| 8 | 7 | | I | | | 50 | I |
| 11 | 8 | | III | | | 48 | I |
| 15 | 11 | I | III | | | 44 | I |
| 17 | 13 | | IIII IIII | | | 40 | I |
| 27 | 22 | I | III | | | 28 | |

*CALCULATION OF CHI SQUARE*

$$\sum A = 26; \quad \sum \text{Exp (A)} = \sum \frac{N_1 M_1}{T} = \sum \frac{N_1(A + C)}{N_1 + N_2} = 26.575$$

$$\sum \text{Var (A)} = \sum \frac{N_1 N_2 M_1 M_2}{T^2(T-1)} = \sum \frac{N_1 N_2 (A + C)(N_1 + N_2 - A - C)}{(N_1 + N_2)^2 (N_1 + N_2 - 1)} = 7.349$$

$$\text{Chi Square} = \frac{(|\Sigma A - \Sigma \text{Exp (A)}| - 0.5)^2}{\Sigma \text{ Var (A)}} = \frac{(0.075)^2}{7.349} = 0.001$$

*CALCULATION OF RELATIVE ODDS*

$$\sum \frac{AD}{T} = \sum \frac{A(N_2 - C)}{N_1 + N_2} = 7.263$$

$$\sum \frac{BC}{T} = \sum \frac{(N_1 - A)C}{N_1 + N_2} = 7.838$$

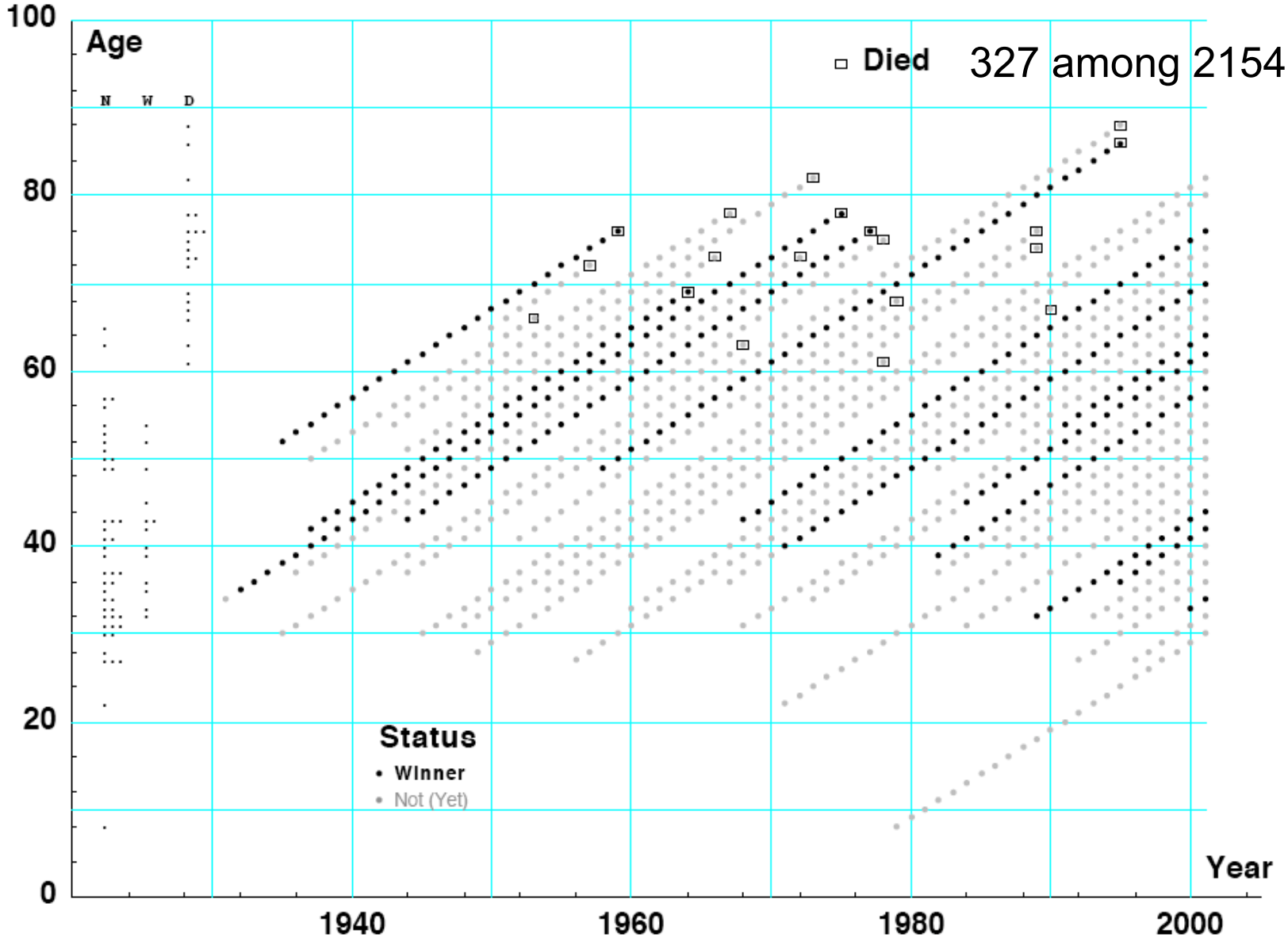
$$R = \left(\sum \frac{AD}{T}\right) \Big/ \left(\sum \frac{BC}{T}\right) = \frac{7.263}{7.838} = 0.927$$

# Transient States: Beyond the Hazard Ratio

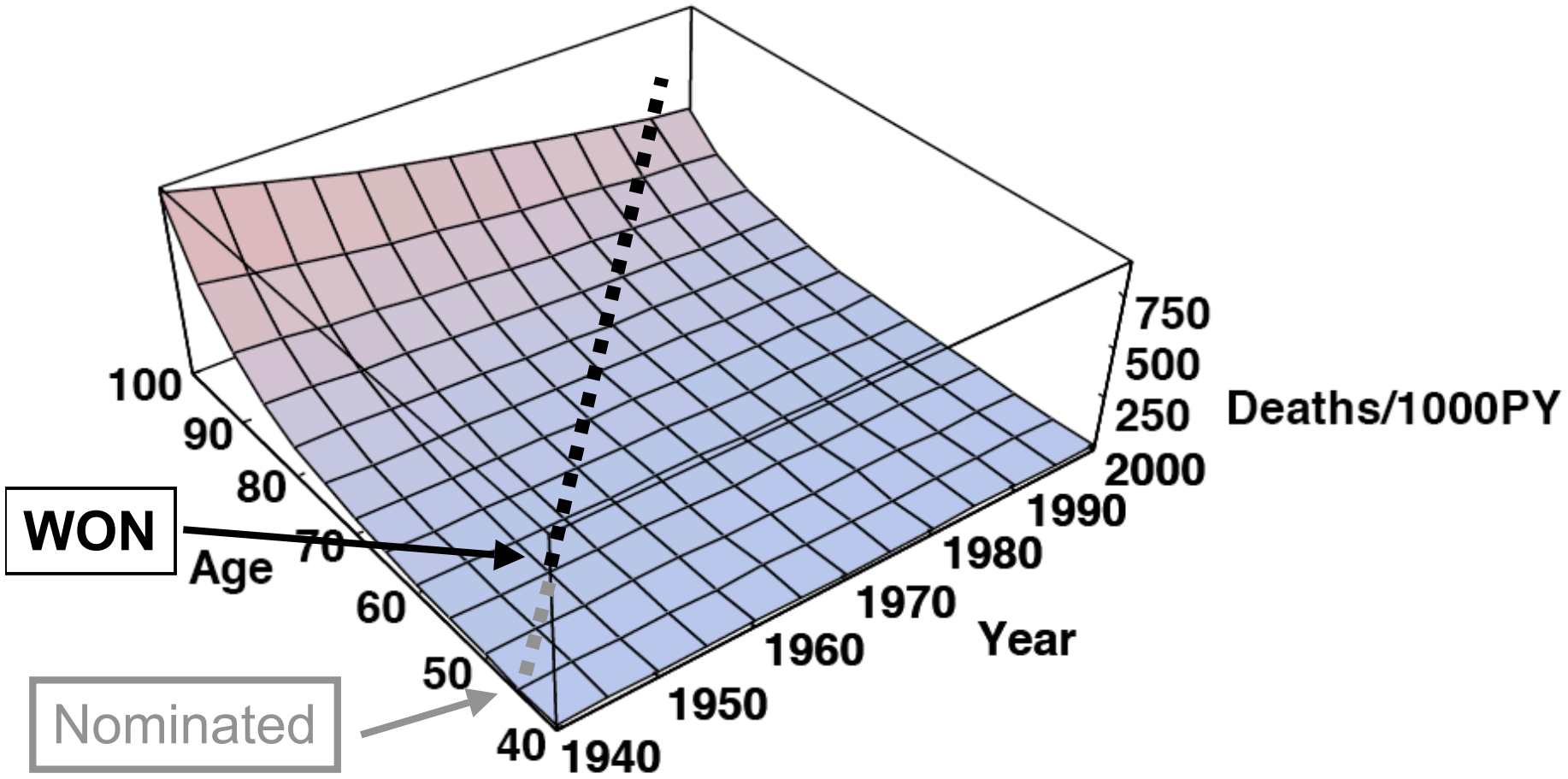
?? Cumulative Incidence CI[t] (Risk)
or
?? “t-year survival” S[t] = 1 - CI[t]

?? Additional years of life

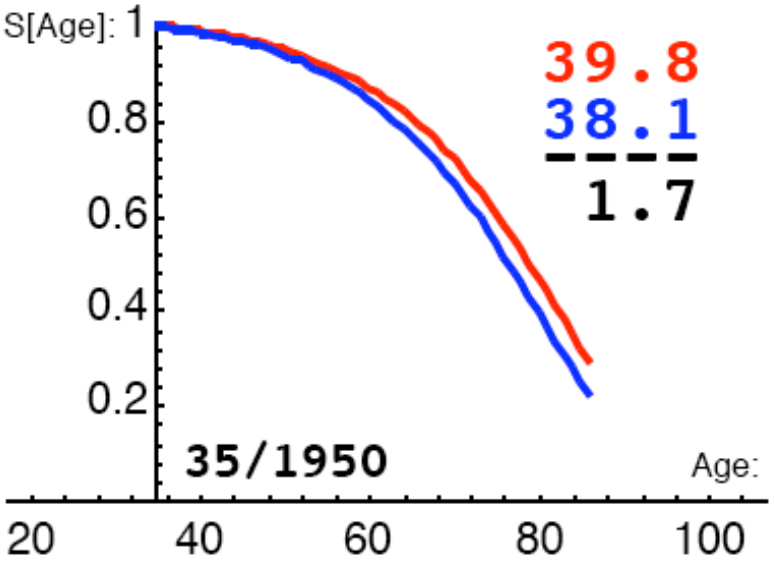
**Estimates available from ph-model only if subjects remain in their initial “groups”**

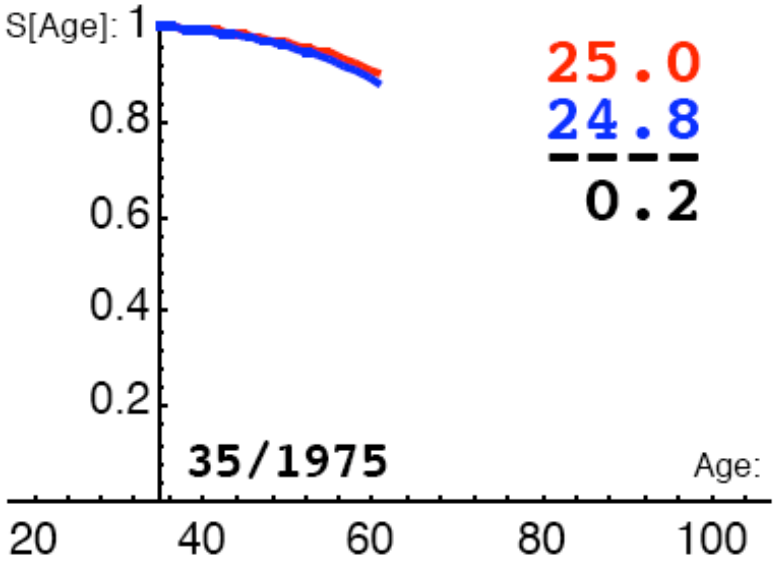


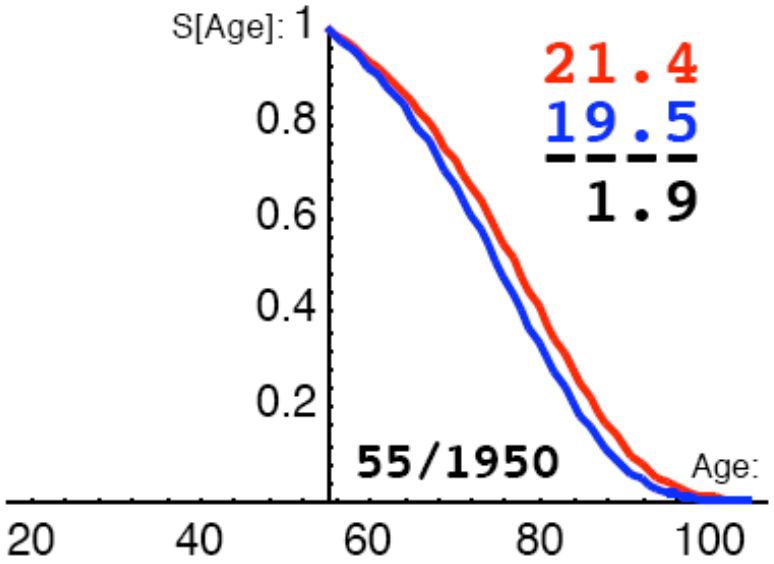

$$\text{logit}\,[\text{Prob}[\square] = B_0 + B_1\text{Age} + B_2\text{Year} + B_3\text{Male} + B_4\text{Winner}$$

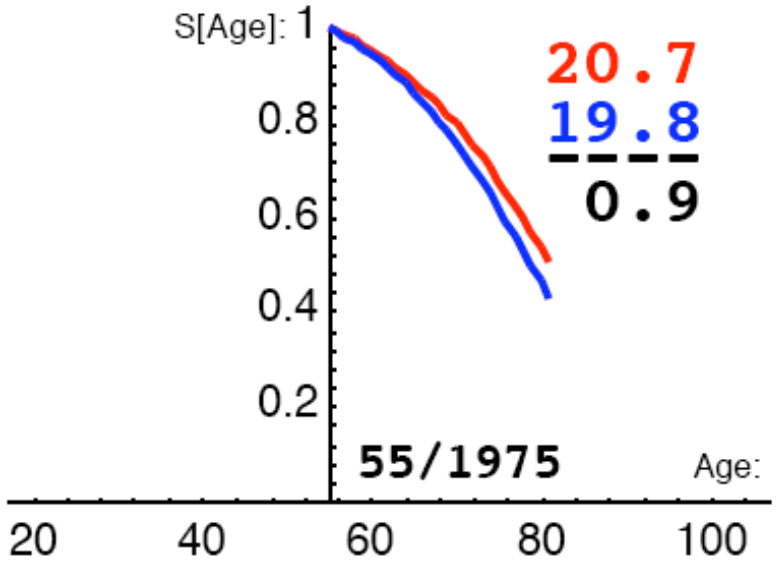



$$\text{Log}\left(\frac{\text{Deaths}}{1000\text{PY}}\right) = \log[h] = 9.2 + 0.08\text{Age} - 0.01\text{Year} + 0.4\text{Male} - 0.21\text{Winner}$$




$$CI\,[\ age_{WHEN\ WON} - age_{\ IN\ 2001}\ ] = 1 - \exp[\ -\int h[a]\ da\ ]$$

# FITTED VALUES (logistic model)

Years lived/gained by 238 Winners if (Hazard Ratio, HR) Mortality Rate Reduction were …

| HR<br>% Reduction | 1.04<br>-4%<br>LIMIT | 1<br>0%<br>NULL | 0.82<br>18%<br>Obs'd | 0.64<br>36%<br>LIMIT |
|---|---|---|---|---|
| Years Lived** | 5923 | 5968 | 6194* | 6451 |
| Years Gained | -45 | 0 | +226 | 483 |
| Average Gain | -0.2 | 0 | 1.0 | 2.0 |

** from year/age won until 2001 or age 105

* Actual years lived: 6223

# FITTED VALUES
# from 'Baseline Survival' (Cox model)

Years lived/gained by 238 Winners if (Hazard Ratio, HR) Mortality Rate Reduction were …

| HR<br>% Reduction | 1.04<br>-4%<br>LIMIT | 1<br>0%<br>NULL | 0.82<br>18%<br>Obs'd | 0.64<br>36%<br>LIMIT |
|---|---|---|---|---|
| Years Lived** | 5923 | 5992 | 6217* | 6451 |
| Years Gained | -45 | 0 | +225 | 483 |
| Average Gain | -0.2 | 0 | 1.0 | 2.0 |

** from year/age won until 2001 or age 105

* Actual years lived: 6223

# extras

When the first evidence of liver angiosarcoma in workers exposed to vinyl chloride became available in February, 1974,[1] we began to look for similar cases among workers at the Penarth plant. All workers who had been exposed to vinyl chloride at any time since 1948 were identified from company records. Details of their exposure histories were taken, and they were traced to see if they were still alive.

All men still working on the plant or elsewhere on site were identified, and local electoral rolls for 1973 and 1974 were searched for retired and other former employees. All men known to have died were listed, and a list of untraced individuals was submitted to the Department of Health and Social Security for identification of those shown as dead on National Insurance records. Individuals who emigrated were not identified separately.

Death certificates were obtained for all known deaths, and the causes of death were coded according to the International Classification of Diseases (8th revision) and

152 deaths were found in 2120 male workers. 136 of these were at less than 75 years of age and fell within the study period. 3 men could not be traced as they were known to have emigrated and 4 other

TABLE I—AGE-DISTRIBUTION OF MAN-YEARS AT RISK

| Age | Man-years |
|---|---|
| 20- | 1994·3 |
| 25- | 3013·5 |
| 30- | 3381·9 |
| 35- | 3317·8 |
| 40- | 3140·8 |
| 45- | 2750·3 |
| 50- | 2266·3 |
| 55- | 1628·4 |
| 60- | 937·7 |
| 65- | 439·3 |
| 70-74 | 181·5 |
| 20-74 | 23 051·7 |