Title
An Investigation of the Follow-up of the *Livermore Lipoprotein Follow-up Study* Cohort

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An Investigation of the Follow-up of the
***Livermore Lipoprotein Follow-up Study* Cohort**

By

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THESIS

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This Thesis is dedicated to Ellen
and baby Daria.
May their patience and encouragement
enlighten these pages.

I would like to thank my committee, Chairman Don Heyneman, PhD., Steve Selvin, PhD., and Paul Williams, PhD., for their support of this work.

I would like especially to thank Paul Williams, Principal Investigator of the Livermore Lipoprotein Follow-up Study, for his encouragement, advice, and enthusiasm for the gumshoe's craft.

"But in the end the truth gave the past back to me."

-Robert Penn Warren
All the King's Men

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Part I. <u>Introduction</u>

Longitudinal cohort studies have proven quite productive in establishing the nature of various biological, behavioral, and social risk factors for many types of disease. Despite the expense and the long period of time required from the start of a trial to the point at which meaningful data analysis can be undertaken, the long-term study may be the only means for establishing the existence of causal factors that contribute to the development of disease or asymptomatic conditions like atherosclerosis, which manifest themselves only after years if at all. Unlike the acutely pathogenic infectious diseases, chronic conditions require assessment of cohorts over many years both to observe the progression of the condition and to attribute causality to factors associated with it.

One may imagine the pathogenic mechanisms that lead to clinical disease, but establishing in the laboratory the causal pathways of a hypothetical pathogenic mechanism is best attempted only after epidemiologic data lights the way. Contributors to atherogenesis such as high cholesterol levels, hypertension, cigarette smoking, inadequate control of blood glucose in diabetes, and genetic heritage have been studied in detail because of earlier epidemiologic work suggesting their importance in the culminating event of heart disease. It would be impossible on the basis of observation of the acute event, myocardial infarct, or of the observed pathology, atherosclerotic plaque, to understand what action could be taken at what stage of life to prevent the development of atherogenesis and thereby prevent coronary thrombosis and infarction.

Because we do not usually perform experiments on our fellow humans, epidemiologists must rely on observational studies in which nature designs the experiment and the investigator attempts to analyze it. Medical research in general may increasingly rely on observational studies because of various complications inherent in controlled placebo trials (Greenfield, 1989). Two observational study designs have served the quest to identify and even quantify the effects of adverse exposures: prospective cohort and retrospective cohort designs (Monson, 1980). Prospective designs define a cohort of disease-free individuals and then gather as much data related to study hypotheses as is feasible. With time's passage the cohort members develop disease and suffer fatal events. The design is experimental to the extent that

1) random or non-systematic variability (noise) within the cohort can be removed statistically given adequate numbers of cohort members and

2) observation of systematic variability (hopefully of the relationship of interest) within the cohort is permitted by segregation of the cohort into subgroups that are relatively homogeneous with respect to a given determinant, but vary randomly with respect to other "non-determinants" (potential confounders). In theory then, differences in the outcome of

interest between those exposed to the determinant and those not exposed to it are due (to a degree and with a quantifiable probability) to the differential exposure to the determinant.

What separates a prospective study from a controlled experiment is the fact that exposures are not entirely defined by the investigator and that selection as well as complete randomization of study subjects to be placed in exposed or non-exposed groups may not be accomplished. The prospective study may be prone to external influences and therefore is not as controllable as studies done in the laboratory. Nevertheless, careful and successful selection of a study population permits useful generalizations suitable both for theoretical validity and to the population at large.

In a retrospective study, the cohort has been at least partially defined by some event in the past. Frequently, an occupational group serves as the population base because administrative records provide useful identifying information, making it possible to establish past exposure levels and to locate individuals in the present for follow-up. Unlike the prospective design, initial selection of a retrospective study cohort is limited by whatever selection processes occurred naturally prior to the investigator's arrival on the scene. If employees comprise the base population then the process which leads to hiring necessarily becomes part of the investigator's selection criteria. If administrative records are lost for any reason, then the factors that permit a record to survive become part of the selection criteria. Thus the investigator yields some degree of control of the selection process to "natural" forces that may not be apparent to him (Miettinen, 1985).

A problem for both prospective and retrospective cohort studies is completeness of follow-up. In prospective studies, loss to follow-up, usually referred to as attrition, primarily results from subjects becoming disenchanted with the investigation, its goals, or its investigators, becoming exhausted or unable because of life circumstances to continue to participate. In a retrospective study, loss to follow-up generally represents the inability of investigators to gather data from a subject at the end of the follow-up period either because of a subject's refusal to participate (technically, a subject must be alive to refuse, thus, vital status can be determined without subtler aspects of the subject's health history being obtainable) or because the investigator is unable to locate the individual.

The loss of study subjects may bias analysis of results in unpredictable ways. Loss to follow-up is also significant in that combatting it may represent one of the largest time and money expenses in a cohort study's budget. Achieving 99% follow-up may require years of labor-intensive searching, persuasion, and expense.

Ethical problems may limit the ability to follow a given cohort to completion. Because of a combination of consumer awareness of the growing number of databases maintained on individuals and the strong public reaction concerning confidentiality of medical and death records in the wake of AIDS discrimination, investigators are increasingly challenged by both lack of access and resistance to access to data. Human subjects committees appropriately place the burden of proof on the investigator that complete follow-up can be attained without resorting to means that might compromise privacy or cause psychological or social harm to subjects. However, because there are no strict guidelines concerning what the "benefits" of complete follow-up may be and since there is a murky area of potential "costs" to subjects as an investigator applies more assiduous means of follow-up, the follow-up process itself may be the one aspect of a retrospective study that generates the most uncertainty and potential for conflict between human subjects committees and investigators (Carter, 1981). For instance, follow-up methods used by one investigation in the 1960's would probably not be permitted today (Modan, 1966). A discussion of the ethical implications of observational studies is beyond the scope of this paper, but some passing comments will be made in the section dealing with specific techniques of follow-up.

Ideally, it would be possible to determine whether complete follow-up is necessary without expending the resources that are frequently required when a retrospective search has entered a stage of rapidly diminishing returns (fewer subjects located per dollar spent). Although there is evidence in published studies demonstrating a correlation between achieving greater than 99% follow-up and producing a significant positive result (Swaen, 1988), the causal nature of that relationship is not entirely apparent. It is possible that such studies may have been better designed and implemented from the outset. In effect, the degree of completeness of follow-up would be an independent correlate of design skillfulness, which would in itself be related to the greater probability of a positive outcome.

In this study of a study in progress, I propose to analyze the follow-up process for a particular cohort, the Livermore Lipoprotein Follow-up Study (LLFS) cohort. Goals of the analysis are 1) to assess the degree of potential bias eliminated by greater degrees of follow-up, 2) to assess the degree to which the follow-up process itself may introduce biases by unintentionally selecting certain types of individuals, thereby altering the composition of the study population, 3) to examine the determinants that increase the likelihood of locating an individual and 4) to examine strategies that could be used to fulfill objectives related to follow-up, such as efficiency, control of expense, and the use of ethically sound procedures.

The LLFS cohort is ideally suited for this study because the base population was prospectively defined by data collection in 1954-57, but determined follow-up was not implemented prior to 1986 when the original data were recovered from various attics and basements. The study was prospective in intent, but because of the 25-year time lapse between last contact with subjects and the initiation of follow-up, the process of locating all members of the original cohort required a decidedly retrospective approach.

Also unique to this cohort is the fact that data collection in 1956 which defined the study population base (the medical database) was kept separately from employment administrative data (personnel records). Data collection preceded employment in many instances and as a consequence the medical database includes individuals who were never hired by the laboratory but only applied for work. This cohort therefore offers an opportunity to appraise the quality and completeness of administrative data of the kind generally used to select a population base for retrospective cohort studies.

Additionally, the hypothesis that the Healthy Worker Effect, described later, results from differential selection of healthy job applicants can be tested through a comparison of the group of LLFS subjects who had personnel records with the group of subjects who were not employed and therefore did not have such records.

Part II. Theory of Follow-up

Background

In both prospective and retrospective studies the possibility of selection bias has been recognized at least since the controversy surrounding smoking and its health effects (Greenland, 1977). It is difficult in an analysis of cohort follow-up and potential follow-up biases to examine the literature without a clear definition of what constitutes loss at the time of cohort selection and what is strictly loss to follow-up. Some investigators refer to all losses except refusal to participate as selection losses, reserving "loss to follow-up" for those who refuse to take part in the study. Others prefer to define any loss that occurs after initial selection and randomization as loss to follow-up. The latter scheme seems preferable because selection bias then refers to problems the investigator encountered in selecting a cohort that is truly randomized. Follow-up bias is distinct from selection bias insofar as baseline or screening measurements may be available for subjects not later contacted. The significance of making a distinction is twofold. First, the non-respondents to initial selection are likely to differ from those who respond initially but then drop out (Criqui, 1978). Separating subjects lost into two categories allows exploration of their baseline characteristics. In the data analysis phase, the meaning of the loss of the two groups and the direction in which they could bias results may be more readily assessed. Secondly, there is value in designing an observational study such that it mimics a controlled experiment, i.e. the investigator has completed the selection process at time zero and cannot further influence membership of the initially selected cohort except by failure to contact subjects. If this is done, then the possibility of further follow-up of the cohort remains open. In the future when subjects may change their attitude and want to participate in the study or they may become traceable again by moving back to the investigator's area. A study burdened by selection bias may lose generalizability to larger populations, but maintains internal validity if loss to follow-up is slight. The findings produced by a study plagued by follow-up losses may be without internal validity as well as being rigidly limited to comparison with specific sub-populations within the general population.

The Framingham Study is probably the best example of the frustrations that may arise when prospectively defining a cohort, and then defining who has been lost because of selection problems and who has been lost to follow-up (Gordon et al, 1959). Using town rosters, a random sample of 6,507 men and women were selected to participate. However, only 4,494 or 68% of the selected population underwent the screening examination. Since the others did not officially enter the study, it was clear that their absence presented a potential selection bias. For instance, the requirement that subjects travel to the clinic excluded those who were bedridden or ill. Beyond this type of limited conjecture, too little could be directly known about the non-respondents to estimate how their absence might affect the study. Indirect surveillance established that the non-respondents had double the mortality rate in the initial year, suggesting that there were indeed important differences between the groups (Gordon, 1959).

Because of difficulty entering sufficient numbers of subjects, the initial randomly selected cohort was modified by the addition of a group of volunteers from a prior pilot study and the first two biennial examinations were considered "screening examinations" so that persons lost during that period were also placed in the category of lost at time of selection rather than follow-up. One result was that although 9 percent of those who had the first examination refused to take the second and the net loss to clinical follow-up at 6 years was 12 percent of the sample (not counting the volunteers), it could later be written that there was "an overall loss to follow-up of only 2%" over a thirty year period (Dawber, 1980). The discrepancy in those estimates is accounted for because indirect surveillance of the selected population allowed determination of vital status as well as medical information from hospital records even for subjects who had not returned for a biennial examination. Also, some of those who did not originally respond were brought back into the study at later stages.

The Framingham Study provides the best example of the intensive methods of both direct and indirect surveillance required to obtain complete follow-up (Friedman, 1967). Biennial examinations at a study clinic and frequent communications with both community doctors and the hospital were required. Is claimed that a single ten year follow-up would have failed to identify 17% of all of the cases of CHD described. However, losses could have been higher if good rapport with subjects and the community had not been established. Other authors have speculated that less frequent examinations may improve completeness of follow-up by demanding less time and effort from the subjects (Sharma, 1986). As investigators have more contact with study subjects, the risk of Hawthorne bias increases. Hawthorne bias refers to the influence investigators have over study variables merely by virtue of the subjects' awareness of their presence. In considering whether to employ a retrospective design or a prospective design and determining how frequently subjects will have contact with investigators, there will remain an inevitable tradeoff between bias due to less complete follow-up and the Hawthorne bias that may appear in a population that investigators enthusiastically recruit and exhort in order to maintain high levels of participation. It has been suggested that "camouflage" of the study's true intent may avoid this influence on subjects (Mantel, 1985). Minimization of the Hawthorne effect is one of the benefits of a retrospectively-designed study. Subjects experience a long period of time during which they are not aware that they are someday to be part of an epidemiologic study.

The investigator conducting a retrospective study faces a tremendous challenge to complete follow-up when undertaking the contacting of a cohort for whom the best records may be twenty to thirty years old. Although the methodology of retrospective studies is frequently used in epidemiology there are relatively few guides to the effective tracing of a large group of people. This may be because the methods employed are thought to be self-evident, or there may be a belief that each follow-up cohort requires a unique approach. However, the absence of guides should not be taken as proof of the simplicity of the task. Tracing subjects after a period of time without contact may require the knowledge, experience, and patience of a detective. Some epidemiologists have even resorted to the use of private detective agencies to trace isolated participants (Modan, 1965). Tracing large numbers of people must be approached with careful planning, otherwise time is wasted and an incomplete follow-up process may itself ruin what would otherwise have been a meaningful result.

Although there have been studies to validate statistical models, survey instruments, and use of medical records as sources of bias, there are few evaluations of the bias introduced by using combinations of particular methods to trace subjects. Investigators do not routinely follow a standardized approach to locating subjects as follow-up continues. Although authors generally believe that a larger percentage of subjects located is more representative of the whole study population, this is not necessarily the case. (Modan, 1965; Greenland, 1977; Boice, 1978) Partial use of available follow-up methods that are more likely to trace certain types of individuals will most certainly introduce some kind of bias into the final database.

In a study comparable to the present investigation, Boice (1978) examined the follow-up process for a retrospectively defined cohort of former female Massachussetts TB sanatorium patients exposed to multiple chest fluoroscopies. The cohort was selected to determine if increased chest irradiation subsequently increased the risk of developing breast cancer. The treatments had occurred between 1930 and 1954. The group was especially challenging to trace because young women can change their names many times through marriage or divorce. At that time, they were less likely to enter the work force than men and therefore less likely to have a social security number. Women tended to have fewer public records. For instance, a woman may have appeared in the telephone book only under her husband's name. Also, the Veteran's Administration, so useful in tracing men, is virtually useless for locating women.

Despite a great deal of information from medical records of the sanatoria, the relatively lower mobility of

Massachussetts residents, the existence of complete city directories, and access to federal records which are now inaccessible because of the 1974 Privacy Act, only 93.6% of the 1,764 women could be located in a four year period. The last 9.7% of the cohort that was located (more difficult to trace) was found to have approximately the same proportion of breast cancer cases, but fewer of them had died. Of the 6.4% lost to follow-up, a higher proportion were younger, non-white, and had been exposed to less radiation at their original hospitalization. It must also be mentioned that 130 subjects (7.3%) who were included in the analysis as alive at the end of the study had actually refused to participate. Epidemiologists of the future may have better luck tracing women if current trends toward increased employment and the retention of maiden names continue.

The Healthy Worker Effect

In an occupational cohort mortality usually appears to be lower among members of the employed cohort when they are statistically compared with the general population. This is the so-called Healthy Worker Effect (HWE). Although the HWE always decreases standardized mortality ratios (SMRs) by definition, the contribution of Loss-to-Follow-up (LTF) bias may either add to or not modify this effect depending on whether there were more or fewer deaths in the LTF group. If more deaths were distributed in the LTF group and thus invisible to the investigator who treats all members of the

LTF group as living, then LTF bias will add to the HWE and depress SMRs even further. If the opposite is the case, meaning fewer deaths were in the LTF group, then downwardly biased SMRs will be due almost entirely to the HWE. In most studies, any difference between observed and expected numbers of deaths is simply attributed to the HWE without accounting for the potential number of deaths in the LTF group.

The causal origins of the HWE itself are not well understood. In part it seems to be a function of the process described by Ogle nearly one hundred years ago by which employers initially select healthier employees and those who are ill are more likely to drop out of the workplace if hired (Howe, 1988). Howe proposes four components of the HWE:

1) Initial selection by either employee or employer as to whether a hire occurs.

2) Employees may differ from the non-employed population according to health-relevant risk factors such as smoking rates, frequency of physician visits, etc.

3) Employees who remain healthy are employed for longer periods. This confounder should not affect a study where initial hire defines entry into the study cohort.

4) Differential attribution of cause of death or medical diagnosis because of employment status. Physicians frequently use work-related exposures as evidence to support a particular diagnosis.

The difficulty separating HWE bias from LTF bias arises from the fact that components two and three above may influence the traceability of a subject during follow-up as well as playing a role in selection bias. Component two is relevant in that subsets of employed persons with unique health risk factor profiles may be less likely to be found than those who do not share such risks. As an example, someone who smoked more heavily and had a higher blood pressure might have a stroke of enough severity that he has no driver's license and lives in a nursing home. Such a person will be almost impossible to trace except through relatives or neighbors. Component three directly affects traceability. Longer employment ensures that more data conducive to tracing will be available, there will be more likelihood of references from co-workers, and the last known address will not be as old. The cumulation of these sources promotes an easier trace.

Statistical Treatment of Subjects Lost to Follow-up

The absence from a data set of subjects lost to follow-up, long recognized as a problem, has recently engendered studies of the effect of different statistical methods for treating such persons as well as the degree of confounding they represent in mortality studies (Swaen, 1987). In the belief that complete follow-up is not attainable or is too costly, some authors have focused on determining a general method to be applied to subjects lost to follow-up--

specifically in the calculation of standardized mortality ratios (SMRs) (Vena, 1987; Johnson, 1988).

The direction in which LTF bias per se will influence occupational mortality study results cannot be predicted. If methods of follow-up fail to detect deaths then SMRs will be artificially low. However there is no good method for disentangling this effect from the HWE (see above) which is invoked to explain the apparently lower morbidity and mortality among employed cohorts when they are compared to the general population. On the other hand, follow-up which selectively identifies decedents will counteract the HWE and tend to raise SMRs.

In general, studies of industrial populations are undertaken to detect excess mortality caused by an adverse workplace exposure. For this reason, it has become the commonly practiced recommendation of the National Institute for Occupational Safety and Health of the United States to treat all subjects lost to follow-up as alive at the end of a study. For political as well as scientific reasons it is preferable to underestimate the true mortality in such studies. Before accepting the study's findings as a scientific "truth" and taking costly action to change a workplace to decrease the observed excess mortality, the "true" excess mortality must be strong enough to statistically overcome the HWE, to overcome any tendency for the living to be more easily traced than the dead, and to overcome the relative excess of living individuals in an LTF group which is treated as alive in its entirety. This practice is meant to guarantee that an observed higher mortality is not due to confounding, since the presumed direction of the above confounders is against a positive outcome.

Although it may be desirable to underestimate the true mortality in an occupational cohort this practice limits the usefulness of quantitative data that might otherwise be available. For instance, dose-response relationships could be calculated if data were complete enough, but the magnitude of a risk attributable to a given exposure dose cannot be accurately stated unless that risk can be shown to far exceed the degree of potential confounding.

On the other hand, if ascertainment of deaths is relatively complete, as it may be expected to be once the National Death Index has had a long enough history (Stampfer, 1984), then treating subjects as alive to the end of the study period will confound results less than treating them as dead or censored at the time of last contact because it more accurately reflects the true cohort experience.

It is frequently believed, in the statistical analysis of long-term studies, that if missed observations can be shown to be randomly distributed with respect to the study parameters defined at the outset of the study, then the missing follow-up measurements represent simply another expression of random variation and cannot significantly bias the result. For instance, suppose 100 subjects entered into a study of cholesterol and heart disease 30 years ago. By chance 50 had low serum cholesterol and 50 had high serum cholesterol. At the time of follow-up twenty subjects cannot be located but it is found that of the twenty missing, 10 were in the high cholesterol group and 10 were in the low cholesterol group. Under the "randomly distributed loss" assumption, the loss to follow-up would not seem able to significantly bias the results. However, as Greenland has eloquently argued, this is not the case (Greenland, 1978).

Uniform loss with respect to the exposure alone is not sufficient to determine what the proportion of loss will be with respect to disease outcome. In other words, the distributions of individual exposure variables cannot determine the joint distributions of outcome variables. The significance of this is that even if study losses are perfectly random with respect to exposures, the potential for bias invisible to the investigator is still present if loss to follow-up is great enough. Furthermore, since study losses are virtually never randomly distributed, losses are even more likely to confound the result obtained. The investigator is likely to be unaware of all potential confounding factors since measurement at the outset is limited to a finite number of variables and the relationship of those variables to later loss of a subject may be complex indeed.

Reasons for Loss to Follow-up

The political and practical limits to how intensively follow-up should be pursued should not be confused with limits imposed by inadequate or poorly conducted attempts at follow-up. Recognizing the imperative to minimize loss to follow-up, it may be useful to understand who is likely to be lost to follow-up in order to generate new approaches to tracing all missing subjects. If a standardized method for conducting follow-up existed (allowing for the different distribution of demographic aspects for given cohorts) then greater percentages of subjects might be identified and investigation of the yields of these follow-up processes would allow a better characterization of which subjects will be untraceable and for what reasons. This would also promote comparability among studies.

Loss generally will occur either because of refusal to participate or inability of the investigator to trace an individual. Traceability will act as a confounder in any study designed to measure a health variable that may alter a subject's likelihood of moving, of taking or maintaining employment, of dying, of driving, of engaging in financial transactions such as loans or mortgages, of having children, of having a telephone, or of being able to read. Needless to say, most health conditions of interest are also likely to influence any one of these variables as well. To the extent that the investigator can overcome the effect of these confounders, traceability is less likely to bias the final analysis of a study. For example, the investigator or his surrogates may have to visit a subject in person if he or she is without a telephone and unable or unwilling to read mail.

Loss to follow-up secondary to subject refusal to participate is more likely to be a function of the study design and the investigator's expectations of the subject. Although there are some populations that are generally less likely to respond than others (i.v. drug users, for example), the quality of the investigator's contacts with subjects may be a the primary determinant of the likelihood of participation (Carter, 1981). This is not to say that there will never be refusal to participate or to place the onus of complete follow-up entirely on the investigator's shoulders, but rather to observe that the amount of such loss can be controlled to a great extent by the investigator.

Prospective studies, designed with long follow-up periods in mind ensure a low percentage lost-to-follow-up by frequent (annual or biennial) contacts with subjects (Hansen et al, 1985; Sharma et al, 1986). Frequent contact, while effective in terms of keeping up with an individual's location may contribute to attrition. Factors that influence attrition can be classified as demographic characteristics, psychological attributes, and physical health measures. Those at highest risk of dropping out of a prospective longitudinal health-related study tend to be:

(1) older, (2) not married, (3) less educated, (4) in stressful or high demand occupations, (5) financially less well off, and (6) in poor health relative to those who remain in a study (Sharma et al, 1986). Additionally, subjects less than 30 years of age appear to have an increased risk of dropping out of a longitudinal study. Because of the less rigorous definition, loss to clinical follow-up in the Framingham Study appeared to be related to migration or refusal. Older men and women were more likely to refuse. Younger men and to a lesser extent younger women were more likely to move from the Framingham area (Gordon, 1959).

Retrospective studies may produce greater percentages of follow-up with less investment simply because they require less effort on the part of subjects. Studies that rely on self-reported data from survey questionnaires, but do not require medical exams, or on-site visits from subjects are likely to have a higher positive response rate. However, such studies also harvest considerably less data in general (Colditz, 1986). For instance, a mortality study which determines only whether a person is dead or alive at a certain date will not be liable to as many subjects' refusals to participate.

Minimal demand of subjects' time explains in part the high percentage (99.8%) of follow-up obtained in a large 20-year retrospective study (59,072 subjects) of steelworkers (Redmond, 1969). Also critical to the success of that follow-up effort was the gender of study subjects. As mentioned above, women are notoriously more difficult to trace than men.

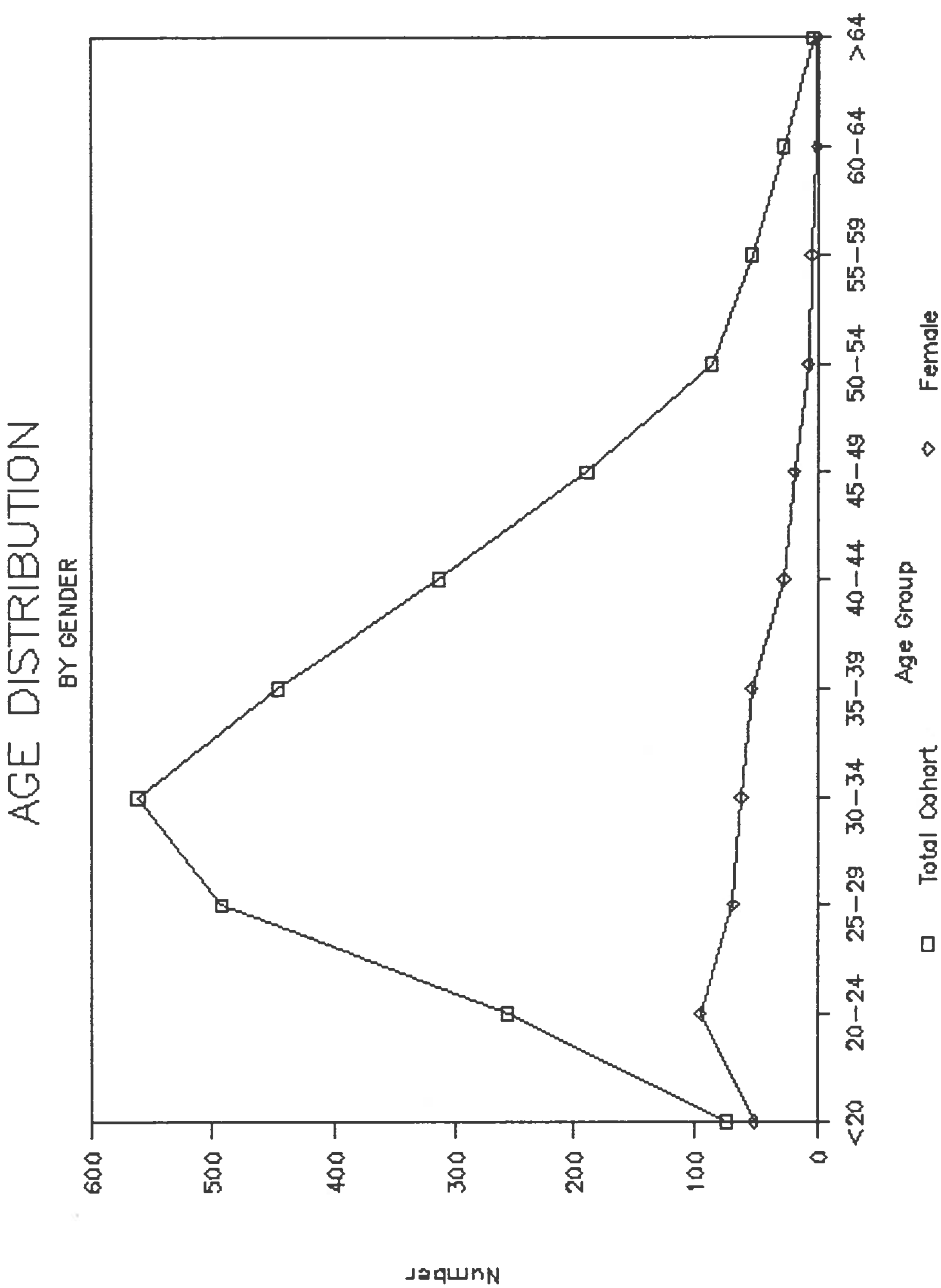
Members of a study population remaining to be located after initial methods of follow-up are attempted will be untraced for a variety of reasons which can be placed into three categories: 1) subject mobility; 2) search database errors; and 3) subject resistance. The definitions and significance of these categories will be discussed below with examples drawn from the Livermore Lipoprotein Follow-up Study experience.

Part III. <u>The LLFS Cohort</u>

The LLFS cohort was prospectively defined by data collected in the years 1954-57 by Dr. John Gofman of the Donner Laboratory, University of California. Serum lipoprotein concentrations including subfractions of HDL, LDL, and VLDL were measured using the flotation rate technique still in use today. Other data such as blood pressure, tobacco use, total serum cholesterol, height and weight, and a complete blood count were also collected.

Data were collected and available for 2121 men and 397 women. The data had been coded and preserved on batch cards and computer tape. The original log books used to record the processing of all incoming blood samples were available as a check on the completeness of the data taken from batch cards and computer tape. Thus every member of the medically defined cohort was identifiable.

The age distribution of this complete cohort at the time of entry into the study was as seen in figure 1 (pg. 24a). It can be seen in Table 1 that women were generally younger at the time of hire with a mean age of 30.26 years (S.D.=9.86) compared to the mean age of 35.81 (S.D.= 9.27) years for the men. The great majority of the study population was white. In 1987, at the start of the contact process, the entire cohort would have been greater than 45 years of age. Assuming that all members of the cohort were still living, 48.2% of the cohort would be older than 65,


AGE DISTRIBUTION
BY GENDER
Number
600
500
400
300
200
100
0
<20
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
>64
Age Group
Total Cohort
Female

15.9% of the cohort would be older than 75, and 3.9% would exceed 85 years of age (Table 2).

Table 1. Average Age at Entry for the LLFS Cohort

	mean	(S.D.)
men	35.81	(9.27)
women	30.26	(9.86)
all	34.94	(9.58)

Table 2. Projected 1987 age distribution*

Age	CHRT I	CHRT II	CHRT III	total
<45	2	0	0	2
46-55	186	49	43	278
56-65	847	108	62	1017
66-75	674	94	42	810
76-85	243	51	11	305
86-95	61	19	10	90
96-100	3	0	1	4
Total	2016	321	169	2506

*Excludes 12 individuals lacking a date of birth. Cohorts are described below.

The Follow-up Process Selects Three Cohorts

For the purposes of examining follow-up, the LLFS study population was divided into three cohorts so as to permit comparison of the efforts required to find each group of subjects and the characteristics of the subjects found. Cohort I included those people located between January, 1987 and May, 1988. Cohort II was located between June, 1988 and April, 1989. Cohort III represented all the individuals remaining to be followed up after April, 1989. A summary of this cohort membership is given in Table 3. Prior to June 1, 1988, the phase 1 methods of follow-up had located 2018 (80.14%) people (Cohort I) leaving 500 (19.86%) unfound (Cohort II + III). During phase 2, 321 (12.7%) additional people were located (Cohort II), leaving 179 (7.1%) people still unfound (Cohort III).

Table 3. Summary of Cohort Membership (% of grand total)

COHORT	I	II	III	Total
Dates	1/87-5/88	6/88-4/89	5/89-?	--
Male	1757 (69.7)	261 (10.4)	103 (4.1)	2121 (84.2)
Female	261 (10.4)	60 (2.4)	76 (3.0)	397 (15.8)
Total	2018 (80.1)	321 (12.7)	179 (7.1)	2518 (100.0)

Once the cohort of 2518 individuals had been defined the first phase of search methods focused on the simplest and most direct means of locating individuals. An individual was considered located if they returned a 2-page survey questionnaire, or if they were interviewed, or if a death certificate was obtained. Personnel records contained last known addresses for retirees, current assignments for those still employed by the Laboratory, and some death records. The original medical intake records were surveyed to obtain accurate dates of birth for all individuals. A mailing was sent to all last known addresses for both current and former employees. A list of names and birth dates was sent to the California Automated Mortality Linkage

System (CAMLIS) which produced approximately 448 high probability matches later confirmed by death certificates. Some death certificates and addresses were available from the Laboratory's ongoing study of the melanoma incidence among all employees. Lists of the names and birthdates of those not found by these methods were submitted to the California Department of Motor Vehicles (DMV) to update addresses. At about the same time a mailing was sent to all those already identified inquiring about the whereabouts of those not yet located. Tracing of social security numbers through a credit bureau identified additional addresses and was helpful for locating some subjects who had moved to other states and would not therefore be found by the California DMV. Follow-up of unreturned mail by second mailings and telephone contact identified the remainder of the subjects in Cohort I.

An approximate summary of the yields of these various methods is given in Table 4. Of the 2018 people contacted prior to June 1, 1988 only 17 refused to participate in the study implying that careful explanation of the study purpose and the design of the questionnaire both were agreeable to the overwhelming majority of subjects.

Table 4. Distribution of Cohort I Subjects According to Method Used to Obtain Last Address

Method	# found	(% total)	alive	dead
LLNL Personnel	1335	(66.15)	891	444
CA DMV	402	(19.92)	381	21
Credit Trace	256	(12.69)	242	14
Tel Direct	4	(0.20)	2	2
Reference	8	(0.40)	8	0
*CAMLIS only	13	(0.64)	0	13
TOTALS	2018	(100.0)	1524	494

*CAMLIS identified 448 decedents. For 435 a last address was obtainable by other means

Initial follow-up methods required approximately 18 months and were relatively inexpensive. The major expenses were labor, mail, telephone costs, Credit Company, DMV, and CAMLIS expenses. Thus 80.14% of the cohort was located over a period of 17 months.

The members of the study population remaining to be located after June 1, 1988 (Cohorts II and III) could have been lost to follow-up for a variety of reasons that can be categorized as stated above:
1) subject mobility; 2) search database errors; and 3) subject resistance.

Subject mobility refers broadly to migration: any change of residence, name, vital status (death in a state other than the investigator's) or health status (confinement in a hospital or other institution) which could make a person difficult to trace. The United States is a high mobility society and California represents the extreme of that mobility. As many as thirty years may have passed since last contact with a person, there was exceptional opportunity for changes of residence, name, vital and health status.

Search database errors could occur for multiple reasons but primarily because of difficulty matching original medical data with personnel records. Those with common names may be difficult to distinguish from one another, especially if the date of birth is equivocal (the medical database provided a numeric age rather than a date of birth). About six hundred of the individuals in the study were never hired by the laboratory or changed names while employed and lacked adequate personnel cross-reference. Some temporarily hired individuals may have had little more than a motel address listed in personnel records. The social security number, so ubiquitous today, was not required by the laboratory and was therefore absent from records. Computer linkage provided social security numbers for only 55% of the men and 24% of the women. Data entry errors and unreadable personnel records may have contributed to a misspelled name or a birthdate which was off by one or two digits.

The etiology of subject resistance is difficult to characterize, but it was found that some subjects would only reply after four to five mailings and one or two phone calls. Subjects occasionally wanted something in return for participation such as information we could provide. A special group of subjects were different from the refusal-to-participate group in the degree of their ambivalence. They expressed interest in responding, but would not answer questions. When offered the chance to refuse to participate they were not eager to drop out. This psychological confluence, at once fascinating and frustrating, will be left to other investigators to ponder.

Accounting for methods already used to locate Cohort I, a missing subject had not been contacted by June 1, 1988 because:

1) The individual had not yet responded to the mailed questionnaire and had not been contacted by telephone, but the address was correct.

2) The individual had moved, the California state DMV had not been informed of the new residence, and a postal forwarding order expired (the post office only forwards mail for one year).

3) The individual had changed names. This is particularly a problem in locating women who do not retain their maiden name.

4) The individual had died outside of California.

5) The search database contained erroneous information not permitting a match with conventional databases (for example, the California DMV must have the exact spelling and date of birth in order to generate a match).

6) The individual did not have a credit record with the particular credit company used to trace social security numbers.

The task at this stage was to extend the follow-up both by using new methods to expand the scope of the search beyond California, and to recheck records and correct errors in the search database. Many methods were employed, frequently in combination to achieve this end. In the next section each method is discussed separately. Its advantages, disadvantages, and ultimate yield are examined.

Part IV. <u>Methods of Follow-up</u>

The chronological approach to continuing follow-up after 80% of the LLFS cohort had been located was complex. A balance had to be established between the use of methods which would produce more immediate and direct location of subjects in fewer numbers, and techniques which would require a longer turn around time and might be more expensive, but could produce larger numbers of subjects once completed. As a hypothetical example, it might cost less in the long run to submit the names of all 500 missing subjects to all fifty of the state Departments of Motor Vehicles and then contact those for whom an address was returned. This would cost roughly 68,000 dollars not counting the additional costs of mailing and phoning subjects once the addresses were returned. However, if the death rate for Cohort I is extrapolated to Cohort II (potentially an underestimate of Cohort I's true mortality), 122 subjects are expected to have died. Policy varies, but driver's records are normally not updated to reflect a death and usually are erased after 3-7 years. Anyone who has left the country or does not drive will not be found. Computerized driver databases may not reflect previous names therefore a large proportion of the 136 women may not be identifiable. A date of birth, required by most states, may not available for some subjects and misspelled names (a problem in at least 20 subjects of Cohort II) will produce either no match or an incorrect match. Therefore as many as half of the subjects may be untraceable by this single method. Worse yet, a state may return all matches for a given name and given date of birth, so that every John Smith born on 3/25/21 in the United States would be returned as a match leaving the investigator to sort out which one is the one involved in the study. One state does not use the date of birth, but returns all matches to a particular name. Two other states will not divulge driver information at all.

Clearly, a single method approach will end up being more expensive and potentially more time consuming than a mixed method approach. The question remaining is how best to mix the methods. Table 5 provides a breakdown of the productiveness of methods used to locate Cohort II. Not all methods were applied to locating all subjects therefore methods cannot be directly compared, however the method recorded for each subject was that method which produced the earliest "find" of that individual and the method without which contact would not have been possible.

Table 5. Method of Find for Cohort II

Method	All	(%)	Living	(%)	Deceased	(%)
MOTOR VEHICLE	73	(22.7)	70	(33.8)	3	(2.6)
PERSONNEL RECORD	39	(12.1)	25	(12.1)	14	(12.3)
CREDIT COMPANY	39	(12.1)	36	(17.4)	3	(2.6)
COHORT REFERENCE	31	(9.7)	19	(9.2)	12	(10.5)
NATIONAL DEATH INDEX	29	(9.0)	0	(0.0)	29	(25.4)
VETERANS ADMINISTRATION	29	(9.0)	2	(1.0)	27	(23.7)
TELEPHONE DIRECTORY	28	(8.7)	27	(13.0)	1	(0.9)
NEIGHBOR TRACING	24	(7.5)	21	(10.1)	3	(2.6)
AGE SEARCH	7	(2.2)	0	(0.0)	7	(6.1)
DMV RELATIVE	6	(1.9)	2	(1.0)	4	(3.5)
NDI GRID	5	(1.6)	0	(0.0)	5	(4.4)
CAMLIS REVIEW	4	(1.2)	0	(0.0)	4	(3.5)
IN-PERSON VISIT	3	(0.9)	3	(1.4)	0	(0.0)
PROPERTY RECORDS	2	(0.6)	1	(0.5)	1	(0.9)
MARRIAGE CERTIFICATE	1	(0.3)	1	(0.5)	0	(0.0)
UNKNOWN	1	(0.3)	0	(0.0)	1	(0.9)
TOTALS	321	(100.0)	207	(100.0)	114	(100.0)

Personnel and Medical Records

Despite the fact that a personnel record may not contain complete information leading to immediate location of a subject, personnel records are the best source of information to enable matching of people located with people in the medical database. For purposes of tracing the LLFS cohort, medical records were more complete for obtaining a date of birth. Only 29 males (1.1%) and 20 females (5.0%) could not be matched with dates of birth. Personnel records provided much more information, but on initial linkage 603 (23.9%) subjects could not be matched presumably because they were either not hired or their records were lost or archived elsewhere. Other paper records filled such gaps and should always be sought. For instance, the discovery of index card files used to keep medical appointment dates with names and dates of birth contributed more matches. Exhaustive collection of personnel record information was only done as needed after mailing and phoning had screened out those easier to locate. This minimized the tedious task of going through records. However, once the list narrowed, it was very useful to gather all information and to have it checked independently for accuracy before attempting wider search methods. Accuracy is vital because hours and dollars may be spent looking for someone who does not even exist. The search may require extra months of resubmitting lists to state agencies when an extra hour spent earlier could have corrected an error.

Vital information for use in other search methods consisted of a correctly spelled name, date and place of birth, social security number, a termination address and the date of termination, the names and ages of all relatives and references, military service numbers and years of military service, and professional organizations. Alternate names or maiden names were critical for locating women. The occasional record contained inquiries from later employers, permitting an estimate of where the person lived at a later date. All other information such as height, weight, hair and eye color, previous employers and addresses was held in reserve and only used if it was necessary to confirm the identity of someone who did not remember participating in the study or if a death certificate was incomplete in some way.

The most rapid use of personnel records to find someone was to attempt contact with the subject in the area code of the termination address, then to attempt to contact any male relatives or references at their addresses, and then to attempt to contact female relatives or references. Often there was one relative still living at an address given or within the area code who could promptly inform the investigation of the subject's vital status and whereabouts if living. Attempting to find a subject near their place of birth sometimes worked, presumably because people tend to return to their place of birth. Table 5 reveals that 12.1% of Cohort II was located by this method and that it worked best for locating women and deceased men, but was also useful for locating living men.

Vital Records

Death certificates, birth certificates and marriage certificates played a role in locating subjects. Death certificates were required to confirm any death, but were also occasionally the first source of information to locate a subject. Veteran's administration records were included as vital records because they were a source of vital status information as well as copies of death certificates for deceased veterans.

The National Death Index (Curb, 1985; Edlavitch, 1988) located 9.0% of Cohort II. Its usefulness was limited because a majority of decedents had died prior to 1979 or after 1986. Some deaths identified by NDI had already been confirmed by other methods. The application process required time because of extensive review of the study protocol, however it was relatively time efficient because NDI approval could often be used to obtain permission to retrieve death certificates from other states, eliminating the need to separately apply to each state. Some states, unfortunately, do not accept an NDI approval.

Another approach to retrieving death certificates was to make request directly to a state in which the subject was believed to have died giving only an approximate time period. The greater the evidence that the subject last lived in that state and the narrower the time period searched, the more likely the result would be positive. For instance, in the belief that some records were missed by CAMLIS, a list of all men greater than 70 years of age was submitted for the thirty year time period 1956-1986 to the state of California death records office. This simple effort retrieved 7 death certificates or 2.2% of all of Cohort II. If a person's driver's license had expired without renewal in a state, a death certificate was requested for the time since last issuance of a license. Without other information hinting at a death in a particular state, blind submission of requests to states was not usually effective (Modan, 1969). It was difficult at times to establish the particular state of death even if a subject was known to be deceased. If a body was not recovered a subject could be legally declared dead without a death certificate. The decedent's last address was not always useful since death certificates are filed within the state where the event occurred. Thus deaths in motor vehicle accidents, or deaths in hospitals in the same metropolitan area as the decedents last address, but located across state lines may frustrate the investigator's best attempts. The veteran's administration provided a very good way of circumventing these difficulties because copies of death certificates or legal records are available no matter where the death occurred. Death certificates which cannot definitively be said to belong to the study subject may require the additional information on relatives, previous addresses, and place of birth mentioned in personnel files to establish their veracity.

Birth and marriage certificates were used in limited ways to revise birth dates or gain leads for other methods. For example, names of the children of subjects taken from 1957 personnel records could be submitted to the state for birth certificates to establish a date of birth which could then be submitted to a department of motor vehicles to locate the grown child. This lengthy technique (listed under the rubric "DMV RELATIVE" in Table 5) provided 1.9% of successful traces. Marriage certificates could provide spouse names, later addresses, and revised dates of birth. Because of the long period required to search for marriage certificates, this method was not extensively used to trace Cohort II, but will be used to trace the remaining subjects in Cohort III.

Veteran's Administration records were most useful to identify deceased veterans, but the V.A. could also forward mail if they had a more current address for a veteran. As mentioned above, the national character of V.A. records makes them useful to trace migrants, however, the time required to retrieve results was on the order of 6 months or more. Living subjects had frequently already been identified by the time the V.A. confirmed that they had a record and would be willing to forward mail.

Current Location Techniques

Departments of motor vehicles, credit bureaus, and telephone directory searches helped to locate 43.5% of all the Cohort II subjects. A complete list of all Cohort II men with dates of birth was sent to the departments of motor vehicles for twelve of the states most likely to yield subjects. Additionally, any mention of a state in a subjects' personnel file prompted a request to that state (especially the state of birth). A list of all remaining subjects was resubmitted to California later in the ten month period to update addresses or catch any subjects moving back into the state from elsewhere. The time required for replies was minimal (frequently less than one month) and the information obtained almost always aided the establishment of contact with a subject either by mail or phone. By targeting some of the record requests and submitting complete lists to selected states a balance was struck between the expense of blanket submissions, and the excessive time requirement of waiting for better information before making a DMV request.

Available social security numbers (SSNs) were submitted to one credit bureau company (different from the one used to locate Cohort I). Of the 245 SSNs (49% of those remaining) submitted initially, 38.8% were successfully matched, 54.3% went unmatched, and 6.9% were either for the wrong person or not legitimate numbers (meaning usually that they had to be rechecked for accuracy). The matched numbers provided addresses and date of last address. The same company was employed a second time when 21 new or corrected SSNs were submitted yielding 61.9% correct matches. Four numbers were incorrect (19.0%) and four were unmatched (19.0%). The use of this simple and highly cost effective method was the primary method of contact for 12.1% of Cohort II. The time for reply was reasonable.

It has been suggested that use of only this method would introduce a "company" bias (Page, 1987). The regionalization of credit bureau databases will select against migrants if only one such bureau is used. However, this effect can be overcome by submitting lists of subjects remaining after a given trace to other regional credit companies as the number of subjects lost-to-follow-up dwindles. This is currently being done to attempt to trace Cohort III. It was unfortunate for the LLFS that at the outset social security numbers were available for only 54.9% of the men and 23.7% of the women. For the women particularly, the SSN is an excellent tool. It bypasses all name changes over any period of time.

The Social Security Administration, formerly used to identify addresses for missing subjects (Redmond, 1969), now can only confirm whether a death claim has been filed or not for a given SSN. The underascertainment of deaths by SSA records is well established (Wentworth, 1983; Tonascia, 1983). Therefore the SSA was not used during phase II of follow-up, but will be reserved to attempt to identify deaths when no other information can be gathered.

Telephone Directory Searches

The local area code was searched for matches to subject names. A special contract arrangement made it possible to search the entire area code and retrieve more than three numbers. If a name was common, all possibilities with the correct initial were attempted. We accepted all last name matches for rare names on the presumption that persons with a rare last name were likely to be relatives. Aside from the time and expense of collecting the numbers, one of the staff had to dial all of them, briefly explain the study purpose and inquire as to whether the person sought was at the number or a member of the extended family. 8.7% of Cohort II could be located by this method which was relatively fast at first. Many of the contacts were with relatives who could tell us where the subject had gone. However, as the local area list was exhausted, the yield dropped off dramatically. It occasionally became difficult to determine whether someone was the subject or not, since a name and approximate age match could generate two or three persons. In all cases it was possible with a brief history to rule someone out on the basis of their whereabouts in 1956. This technique was used whenever a subject was said to have moved to a given city or state.

<u>Complex Tracing</u>

<u>Cohort Follow-back</u>

As subjects in an occupational cohort are identified and interviewed, they become a resource for information about the whereabouts of their former colleagues. Therefore, initial interviews were followed by mail describing the project of locating all members of the cohort and inviting the subject to identify names from a list of subjects still missing. Additionally, all current and former employees of the laboratory were sent the same inquiry. This method, requiring a large (approximately 8,000 piece) mailing, was in terms of yield (9.7%) comparable to the National Death Index, the Veteran's

Administration, and the telephone directory search. It selected against non-hires however, and thus became less useful as more non-hires remained to be located.

<u>Neighbors</u>

A reverse directory permitted contact with the people living in the immediate vicinity of a subject's last address. Long a staple of collection agencies, this technique was surprisingly effective even when the address was as many as thirty years old. Initially, a list of subjects was drawn up with last known addresses. The reverse directory provided the listed phone numbers for all residences on a given street. Five to ten numbers were collected prioritized according to proximity to the last address, and side of the street (even or odd). The absence of many residence numbers, originally discouraging was not a handicap because a person telephoned on a block who did not know the subject or had not been at the address for very long could frequently provide the phone number or name of the person who had lived in the neighborhood the longest, or who was most likely to know the subject. After the prioritized list was drawn up, telephoning evenings and Saturdays eliminated the useless leads very quickly. In the best case, a neighbor could provide the address and phone number of someone who had moved to another state. In the worst case, the street or residence no longer existed, having been bulldozed to make way for a freeway or shopping mall.

This method, inexpensive when conducted locally, could be quite expensive if done long distance, therefore it tended to select people who had remained in the local area for some time and discriminated against transients.

Tracking Relatives

Where a spouse name or the names of children were available these could be submitted to the department of motor vehicles. Marriage and birth certificate records were required to recover an exact date of birth since medical records contained a numeric age. This method was best reserved until the list of subjects had dwindled because it effectively multiplied the number of people sought by at least two. With less information available for these secondaries, it was much more difficult to rule out someone who was an apparent match unless contact was sufficient enough to permit the putative relative to deny knowing the subject. However, when the search returns diminished, locating one of a number of children increased the odds of finding the subject. In the most typical scenario, mail sent to the child or other relative would be forwarded to the relevant subject. Direct contact with relatives might also expedite the determination that a subject had died, the state and date of death.

Since names of children were not generally available, birth certificates could be found by using the parents' names and searching state birth indexes. The father's last name served as the child's last name and the mother's maiden name provided the means of narrowing the search. County of residence during childbearing years could also narrow the list of possible children considerably, even for common last names.

<u>Other</u>

As the numbers lost to follow-up decrease, the search for those remaining necessarily becomes more individualized and more reminiscent of the clue-gathering of a Raymond Chandler novel. Techniques described above can be applied in a blanket fashion and subjects can be pursued en masse or methods can be mixed and recombined to follow a given subject's trail. As an example, a neighbor of thirty years ago remembers that a subject moved to another area to be closer to family. A telephone area code search unearths a relative who remembers the subject moving to another state twenty years ago and supplies the number of yet another relative. The next relative gives an address from 15 years ago, but has lost contact. The DMV of that state may be tried or another reverse directory search may be attempted. Other methods that may add to this type of tracing involve using unique kinds of information such as from what school someone graduated (attempt to use alumni associations), of what professional or other organizations someone was a member, voter registration records, and property records.

Unfortunately, the more varied the kinds of information are for someone the greater the likelihood that they will be traced by easier means. The art of follow-up must be used when other methods fail, and it involves seeing the relevance of seemingly insignificant information, a fruitful imagination, and the confidence to pursue apparent long shots. This aspect of follow-up, while most difficult, is most gratifying when a subject answers the phone or the questionnaire appears in the morning mail.

Part V. <u>Effects of Follow-up</u> (Quantitative Analysis)

In this part, a statistical comparison of Cohorts I, II, and III is described with the aim of providing insight into how the process of follow-up succeeds or fails at selecting a final sample representative of the entire cohort. Cohort I (2018 individuals), as described above was located during phase 1 (17 months). Cohort II (321 individuals) was identified over a ten month period (phase 2). Cohort III (179 individuals) remained lost to follow-up at the time of this analysis (although approximately 30 subjects had been traced to recent or known addresses and had not yet responded to mailings and another 15 were known to be deceased, but no death certificate had been obtained as of April 21, 1989). The chi-square test was used to compare proportions with the Mantel-Haenzel procedure used to compare age stratified proportions. T-tests were done to compare age means.

The results are presented in order of potential relevance to selection bias. The null hypothesis is that there is no statistically significant difference between the three cohorts on the following measured parameters. Demographic variables-- gender, age, and migration status (residence or death outside of California) may estimate the extent of selection biases introduced by follow-up among the three cohorts. Male mortality rates and self-reported morbidity rates for the living male population (as ascertained by the study questionnaire) permit examination of variables more directly related to the specific purpose of the Livermore Lipoprotein Follow-up Study.

This comparison is necessarily observational in that efforts made to control the methods used were motivated only by the desire to find the greatest number of people in the shortest time at a reasonable cost. Not all methods were applied to all subjects. Such an experiment would require the enormous expense of reduplicating all trace methods for all subjects regardless of whether a contact was made or not and then determining what proportions of the subject group would have been found if each method had been used alone. Thus it was not possible to separate any observed bias into a component caused by the unintentional self-selection of subjects and a component caused by the investigator's best attempt to locate the cohort. However, to the extent that this follow-up was conducted as any "real-world" follow-up would be, the observation of trends in the data serve to answer the question, 'What would the bias have been had follow-up not been attempted?'. In the section titled "HWE and LTF Bias", the influence of personnel record information on follow-up is considered with a preliminary attempt to observe the extent of HWE due to employer selection, and to distinguish LTF bias from the Healthy Worker Effect in this study.

Gender

A summary of the gender distribution was given in Table 3 (pg. 26). In that table it can be seen that although women represent only 15.8% of the entire cohort, they represent 18.7% of Cohort II and 42.5% of Cohort III. Thus it is apparent that methods used to locate Cohorts I and II (and indirectly III) disproportionately selected men. The addition of the 261 Cohort II males to the Cohort I group raised the male follow-up percentage from 82.8% in June, 1988 to 95.1% of all men ten months later. By contrast, the percentage of women accounted for rose from 65.7% to only 80.9%

Preferential selection of women is partially due to "investigator-generated bias". The primary goal of the LLFS is to ascertain the relationship between lipoprotein subfractions and coronary heart disease in men. Thus tracing women was a secondary goal. During the search for Cohort II lists of all of the women's names were not submitted to state DMVs other than California's because of concern that name changes would make them untraceable. It seemed more cost effective to reduce the list of women's names by means more likely to locate them such as relatives and neighbors. It was also thought that the experience gained from locating the men would make the task of tracing the women more straightforward by revealing geographic areas more likely to yield results. The search for women's death certificates was also less intensive because of their younger age. In retrospect, their overall mortality was somewhat less ($p<.10$) than that of the men in Cohort I (Table 6a). Inspection of Table 7b (pg. 52) shows that even for methods used to trace both men and women such as telephone directory searching and neighbor contact, men were more likely to be traced. Only laboratory references, such as personnel records (usually providing the names of relatives) and references from other members of the cohort providing "leads" to women were more effective at locating women. Use of the Veterans' Administration as the sole contact method obviously would have discriminated against women. That 60 women were located in spite of these barriers was encouraging.

Table 6a. Cohort I: Vital Status vs. Gender

	male	female	Total
alive	1315 (74.8)	209 (80.0)	1524 (75.5)
dead	442 (25.2)	52 (19.9)	494 (24.5)
Total	1757 (87.1)	261 (12.9)	2018 (100.0)

Table 6b. Cohort II: Vital Status vs. Gender

	male	female	Total
alive	162 (62.1)	45 (75.0)	207 (64.5)
dead	99 (37.9)	15 (25.0)	114 (35.5)
Total	261 (81.3)	60 (18.7)	321 (100.0)

Investigator preference is not the only factor in the lower identification rate for women. The fact that a selective bias against locating women will exist even if equal effort is applied to tracing them can be seen in the lower percentage of women identified in Cohort I (12.9% as against a 15.8 percent representation in the total group, $p<.005$) despite the use of all available methods to trace women as well as men. Tables 7a and 7b show that in contrast to the relatively poor yield from motor vehicle records for the women in Cohort II, the California DMV located significantly more of the Cohort I women than Cohort I men (25.7% vs. 19.1%, $p<.02$). Significantly fewer (57.9% vs. 67.4%, $p<.01$) of the Cohort I women than Cohort I men were identified by personnel records. There was no difference in the ability of credit records to trace men or women in Cohort I and Cohort II, reflecting the specificity and immutability of the social security number for women as well as men.

Table 7a. Cohort I: Location Method vs. Gender

Method	male (%)	female (%)
LLNL Personnel	1184 (67.39)	151 (57.85)
CA DMV	335 (19.07)	67 (25.67)
Credit Trace	218 (12.41)	38 (14.56)
Tel Direct	2 (0.11)	2 (0.77)
Reference	6 (0.34)	2 (0.77)
CAMLIS only	12 (0.68)	1 (0.38)
TOTALS	1757(100.00)	261(100.00)

Table 7b. Cohort II: Method of Find vs. Gender

Method	All (%)	Males (%)	Females(%)
MOTOR VEHICLE	73 (22.7)	66 (40.7)	7 (11.6)
PERSONNEL RECORD	39 (12.1)	32 (19.8)	7 (11.6)
CREDIT COMPANY	39 (12.1)	31 (19.1)	8 (13.3)
COHORT REFERENCE	31 (9.7)	15 (9.3)	16 (26.7)
NATIONAL DEATH INDEX	29 (9.0)	23 (14.2)	6 (10.0)
VETERANS ADMINISTRATION	29 (9.0)	29 (17.9)	0 (0.0)
TELEPHONE DIRECTORY	28 (8.7)	25 (15.4)	3 (3.0)
NEIGHBOR TRACING	24 (7.5)	17 (10.5)	7 (11.6)
AGE SEARCH	7 (2.2)	7 (4.3)	0 (0.0)
DMV RELATIVE	6 (1.9)	4 (2.5)	2 (3.3)
NDI GRID	5 (1.6)	5 (3.1)	0 (0.0)
CAMLIS REVIEW	4 (1.2)	2 (1.2)	2 (3.3)
IN-PERSON VISIT	3 (0.9)	2 (1.2)	1 (1.7)
PROPERTY RECORDS	2 (0.6)	1 (0.6)	1 (1.7)
MARRIAGE CERTIFICATE	1 (0.3)	1 (0.6)	0 (0.0)
UNKNOWN	1 (0.3)	1 (0.0)	0 (0.0)
TOTALS	321(100.0)	261(100.0)	60(100.0)

Because of the smaller numbers of women in the study, as well as less complete data for them, they were excluded from the mortality and morbidity analyses.

Age

Table 8 reveals average ages and standard deviations by cohort and gender. The total age distribution at time of entry into the study, as graphed in figure 1 (pg. 24a) reveals the preponderance of females in the younger age groups. Table 9 provides the age distributions of subjects in the three cohorts. Figure 2 (pg. 53) graphs this age distribution. Follow-up is not as uniform as inspection of figure 2 suggests. Figure 3 (pg. 53a), expressing the proportion of subjects from Cohorts II and III in each age group relative to the total number of subjects for that age

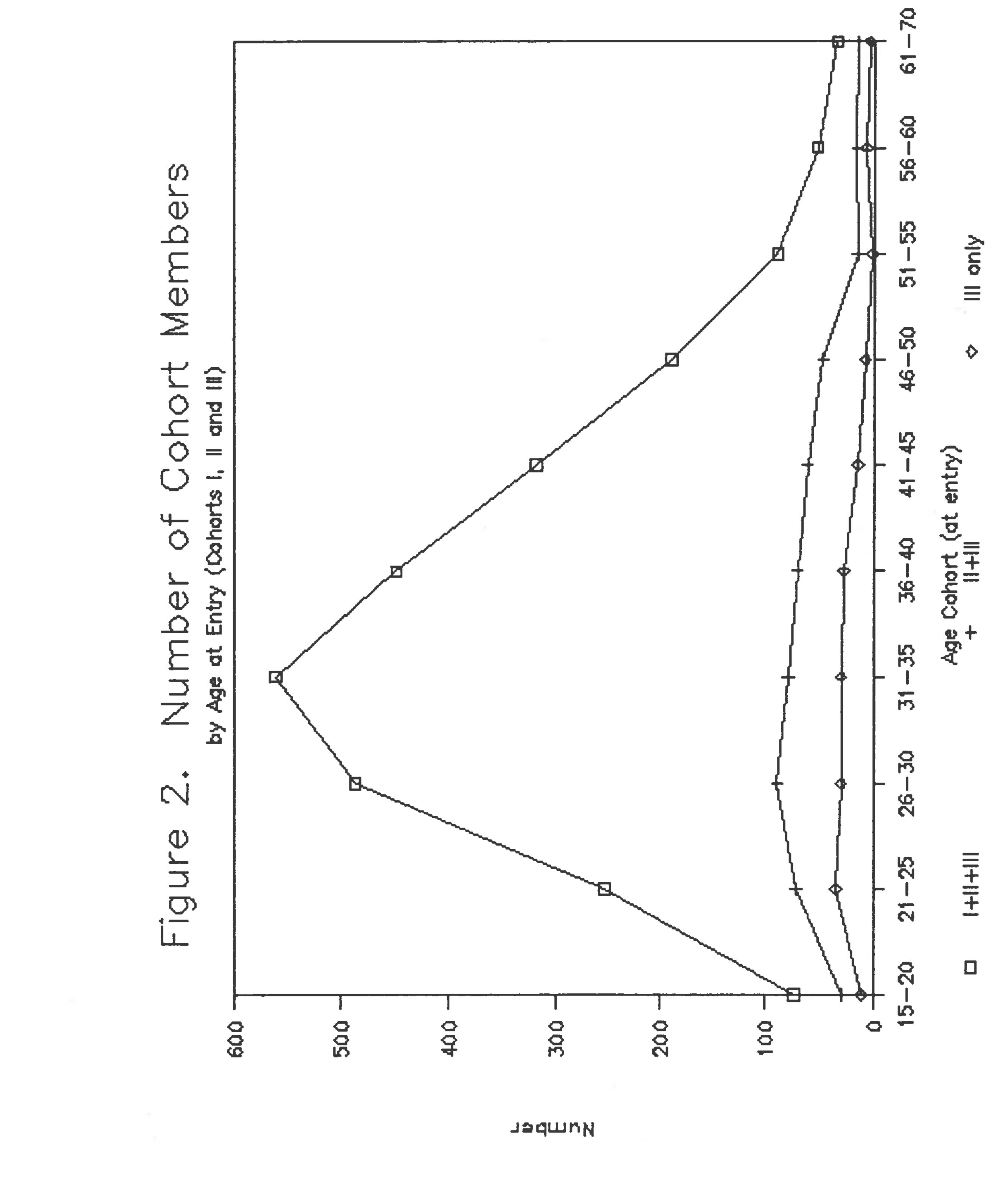
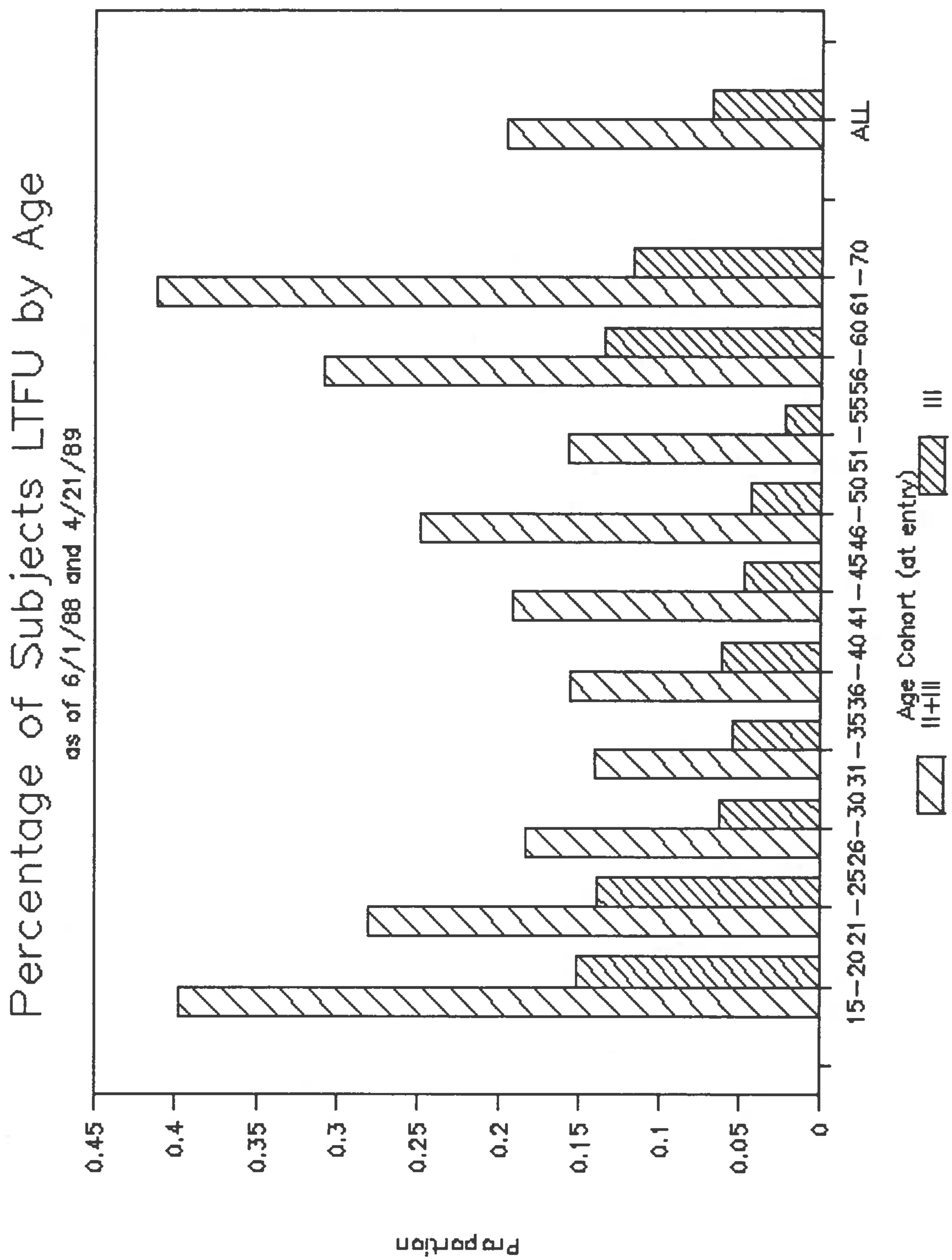


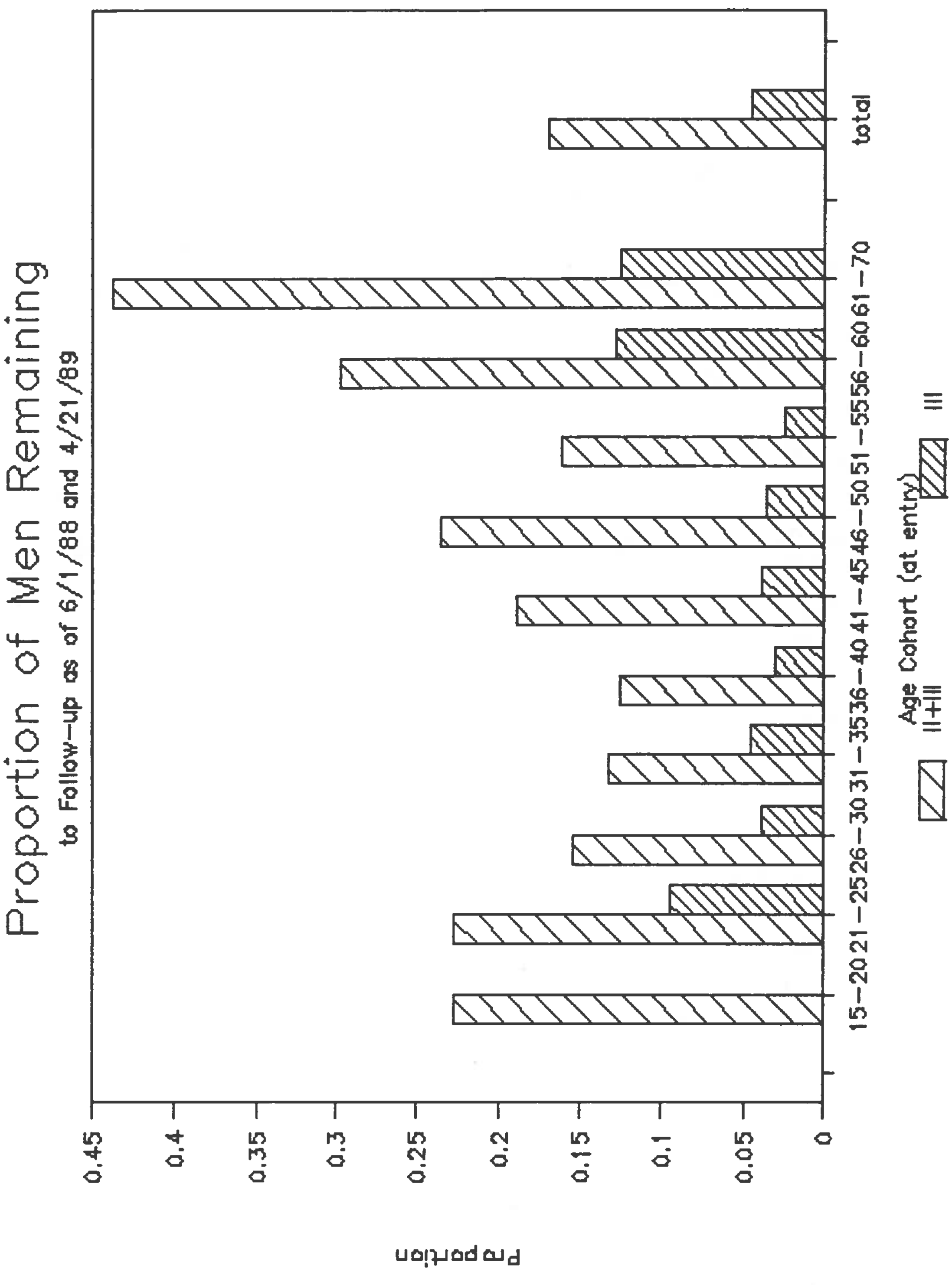
Figure 2. Number of Cohort Members
by Age at Entry (Cohorts I, II and III)


Percentage of Subjects LTFU by Age
as of 6/1/88 and 4/21/89
Proportion
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
15–20
21–25
26–30
31–35
36–40
41–45
46–50
51–55
56–60
61–70
ALL
Age Cohort (at entry)
II+III
III

group, demonstrates the discriminatory nature of phase I and phase II tracing methods. The tracing of Cohort I tended to exclude those who were either young at entry (less than 25 years old) or older at entry (greater than 56 years of age). This differential age selection persists even after Cohort II has been located. Figures 4a and 4b (pp. 55, 56), separating subjects by gender, reveal that loss at the ends of the age spectrum is due disproportionately to men at older ages and due to women at the younger ages. This impression is supported by the younger mean age of women (not significant at $p<.10$) and the greater mean age of men ($p<.02$) in Cohort II (Table 8). Although the lower overall mean age of Cohort III is partly due to the higher proportion of women, Cohort III men also have a lower mean age than their counterparts in the other two cohorts ($p<.01$).

Table 8. Average age at entry by Cohort (S.D.)

	CHRT I	CHRT II	CHRT III
men	35.75 (8.68)	37.33 (10.24)	33.02 (14.27)
women	31.25 (9.82)	28.85 (10.09)	28.00 (9.31)
all	35.17 (8.97)	35.75 (10.74)	30.89 (12.66)


Proportion of Men Remaining
to Follow-up as of 6/1/88 and 4/21/89
Proportion
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
15-20
21-25
26-30
31-35
36-40
41-45
46-50
51-55
56-60
61-70
total
Age Cohort (at entry)
II+III
III

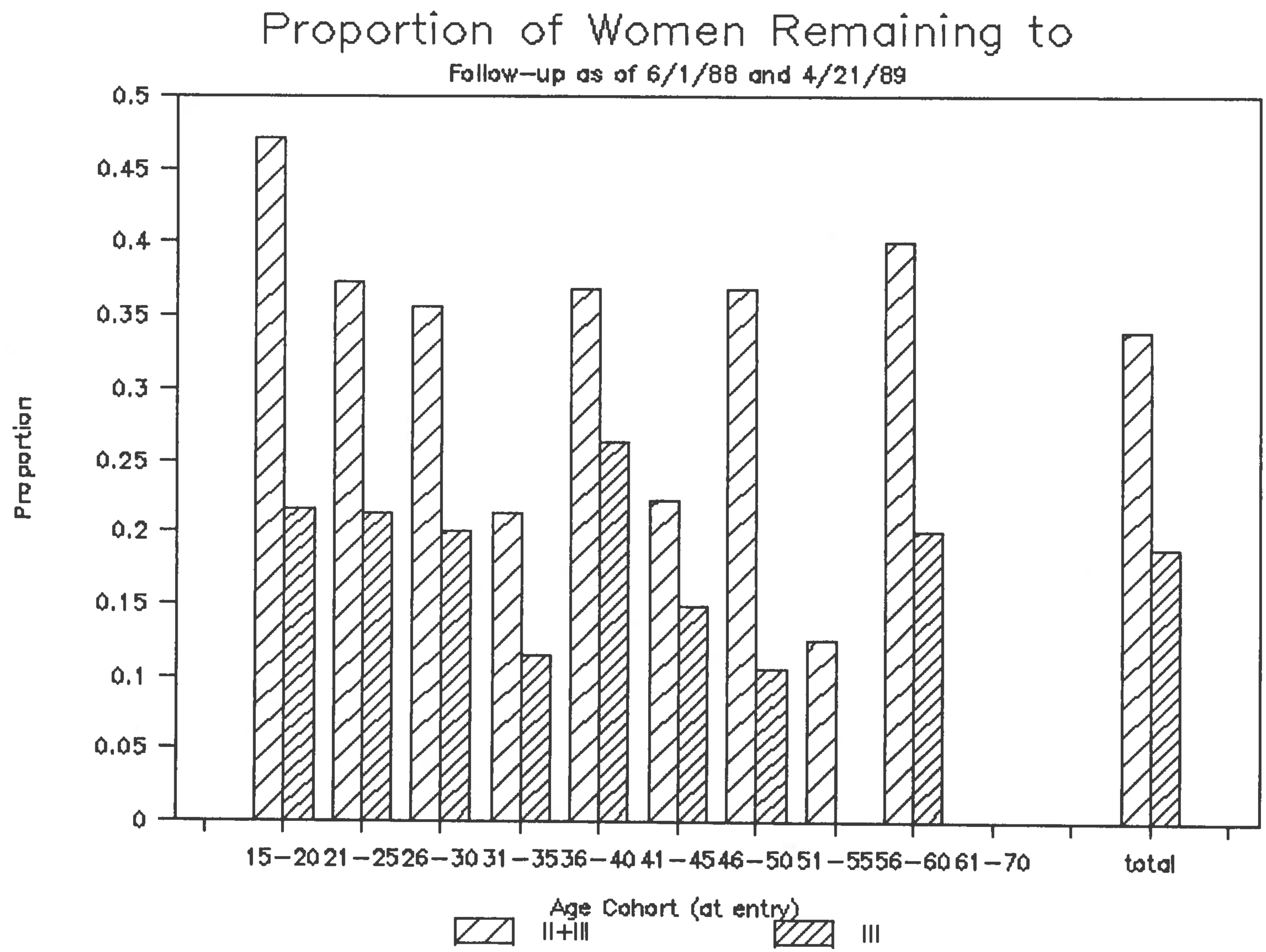

Proportion of Women Remaining to
Follow-up as of 6/1/88 and 4/21/89
Proportion
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
15-20
21-25
26-30
31-35
36-40
41-45
46-50
51-55
56-60
61-70
total
Age Cohort (at entry)
II+III
III

Table 9. Age distribution by Cohort (age at entry)*

Age	CHRT I	CHRT II	CHRT III	ALL
15-20	44 (2.2)	18 (5.6)	11 (6.5)	73 (2.9)
21-25	182 (9.0)	36 (11.2)	35 (20.7)	253 (10.1)
26-30	398 (19.7)	59 (18.4)	30 (17.8)	487 (19.4)
31-35	483 (24.0)	49 (15.3)	30 (17.8)	562 (22.4)
36-40	379 (18.8)	43 (13.4)	27 (16.0)	449 (17.9)
41-45	257 (12.7)	46 (14.3)	15 (8.9)	318 (12.7)
46-50	142 (7.0)	39 (12.1)	8 (4.7)	189 (7.5)
51-55	75 (3.7)	12 (3.7)	2 (1.2)	89 (3.6)
56-60	36 (1.8)	9 (2.8)	7 (4.1)	52 (2.1)
61-70	20 (1.0)	10 (3.1)	4 (2.4)	34 (1.4)
ALL	2016(100.0)	321(100.0)	169(100.0)	2506(100.0)

*Excludes 12 individuals without birthdates.

Migration

Strictly speaking, a confounding effect of migration or "migration bias" should be due to a health or risk factor that influences a subject's mobility (classic confounding). However, migration also contributes to LTF bias because of the greater difficulty posed to the investigator trying to locate a subject who has moved. In this study, subjects who moved out of the country were the most difficult to trace unless a reference could be found. The State Department maintains copies of the death certificates of all U.S. Nationals who die overseas, however they required the exact year of death before they would search their files. People who moved to another state and died there were also more difficult to find, particularly if the subject had died prior to 1979 when the National Death Index first began compiling its records.

The two components of migration bias, differential health and differential traceability will express their effect in the same direction if poorer health is associated with greater mobility (unlikely), but in opposite directions if poorer health is associated with reduced mobility. Complicating this analysis is the fact that the location of subjects in the LLFS cohort at time zero, application for a job, was not necessarily their primary residence. Thus there was likely to be greater variability in primary residence than would be found under the assumption that everyone "lived" in the Livermore, CA area in 1956. Nevertheless it may be instructive to see how Cohort II differs from Cohort I in terms of mortality and morbidity with respect to migration using the address at contact or state of death as the endpoint.

Figure 5a (pg. 60) shows the proportions of living people located in each cohort by geographic region using the final zip code as the defining factor. Figure 5b (pg. 60a) similarly graphs proportions of deaths outside of California. It can be seen that the tracing of subjects to other states became more important in phase II. On the other hand, the largest share of subjects were still located in California despite the fact that exhaustive DMV, personnel, and credit company checks had been done. This surprising outcome indicates that coverage of a given geographic area such as the state of California even by three extensive databases may fail to exhaust all the possible "finds" in that area. For example, local telephone area code searching turned up individuals who should have been found by these other means, but were not. The mortality experience by geographic region (figure 5b) shows a comparably higher proportion of deaths outside of California during phase 2 of follow-up.

Mortality

The mortality experience of the males of Cohort I and Cohort II was compared using the Mantel-Haenzel procedure. Given the significantly older mean age at entry of the men in Cohort II, (37.3 years vs. 35.8 years, $p<.02$) it is expected that they will bear a greater crude mortality burden. From tables 6a and 6b (p. 50), it can be seen that this is the case: Cohort II has a 37.9% mortality while Cohort I has only a 25.2% mortality. Surprisingly, even when age stratified, Cohort II's adjusted rates are higher for all age groups except the oldest (figure 6, pg. 60b). Thus phase 2 methods were not simply finding greater proportions of older people.

Why would Cohort II contain a greater proportion of deaths? There are two possible explanations. Either methods employed during the second phase tended to select decedents of all ages when compared with the methods used during phase 1, or at earlier points in the follow-up, living subjects are easier to trace than decedents. In the time between phase 1 and phase 2 follow-up, the accelerating

Figure 5a. Distribution of Living

Subjects by Geographic Region

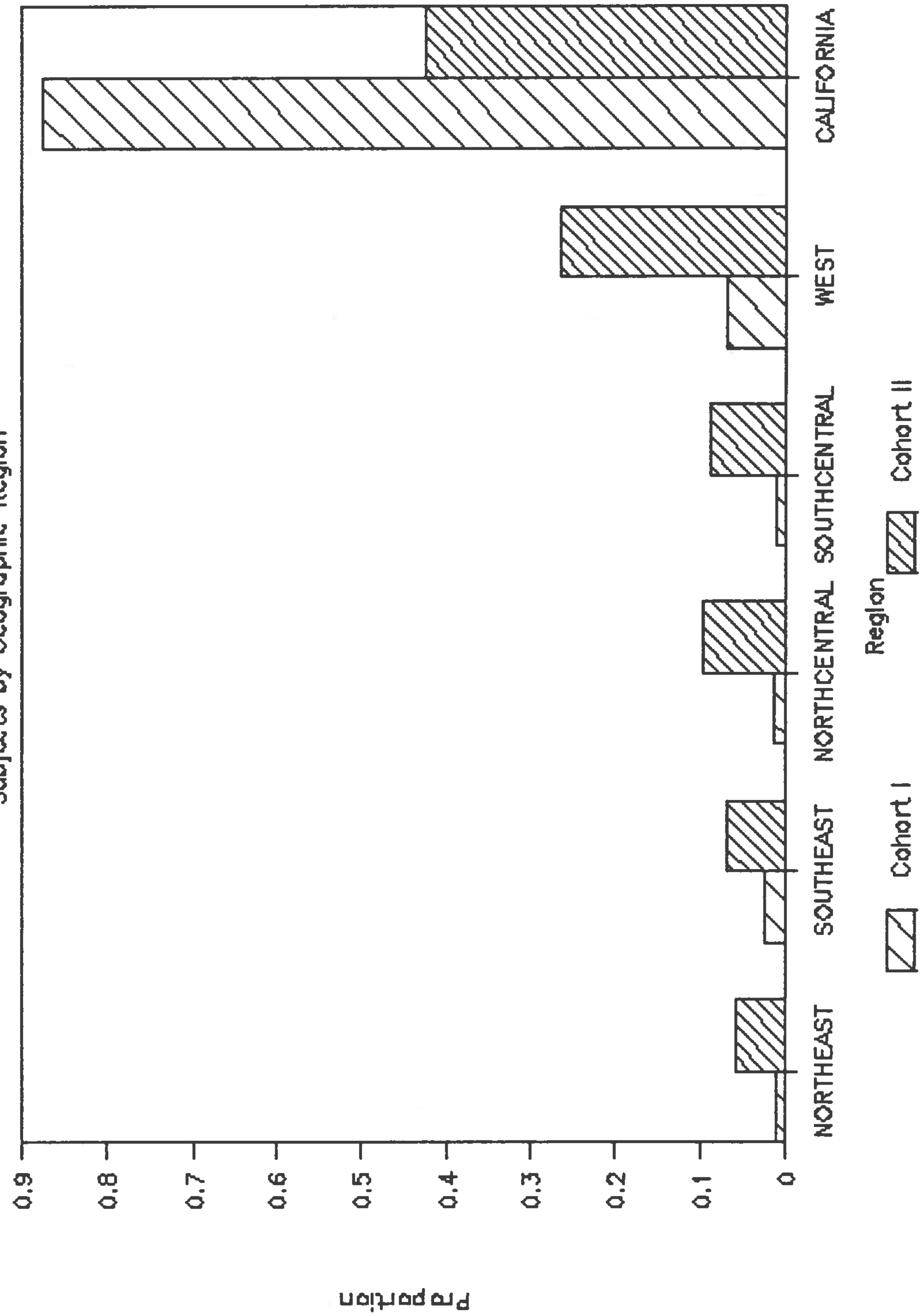


Figure 5b. Distribution of Deaths

by Geographic Region

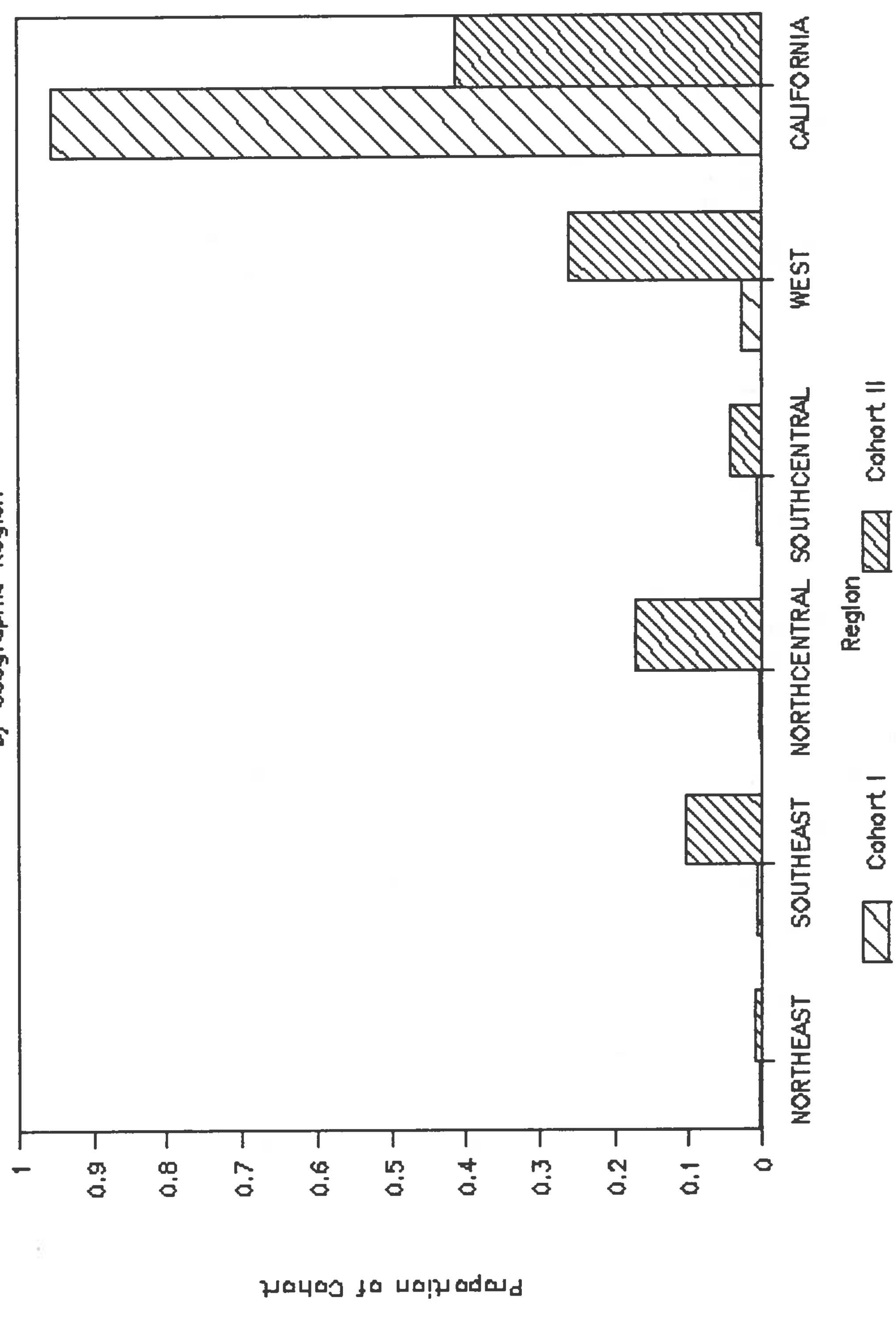
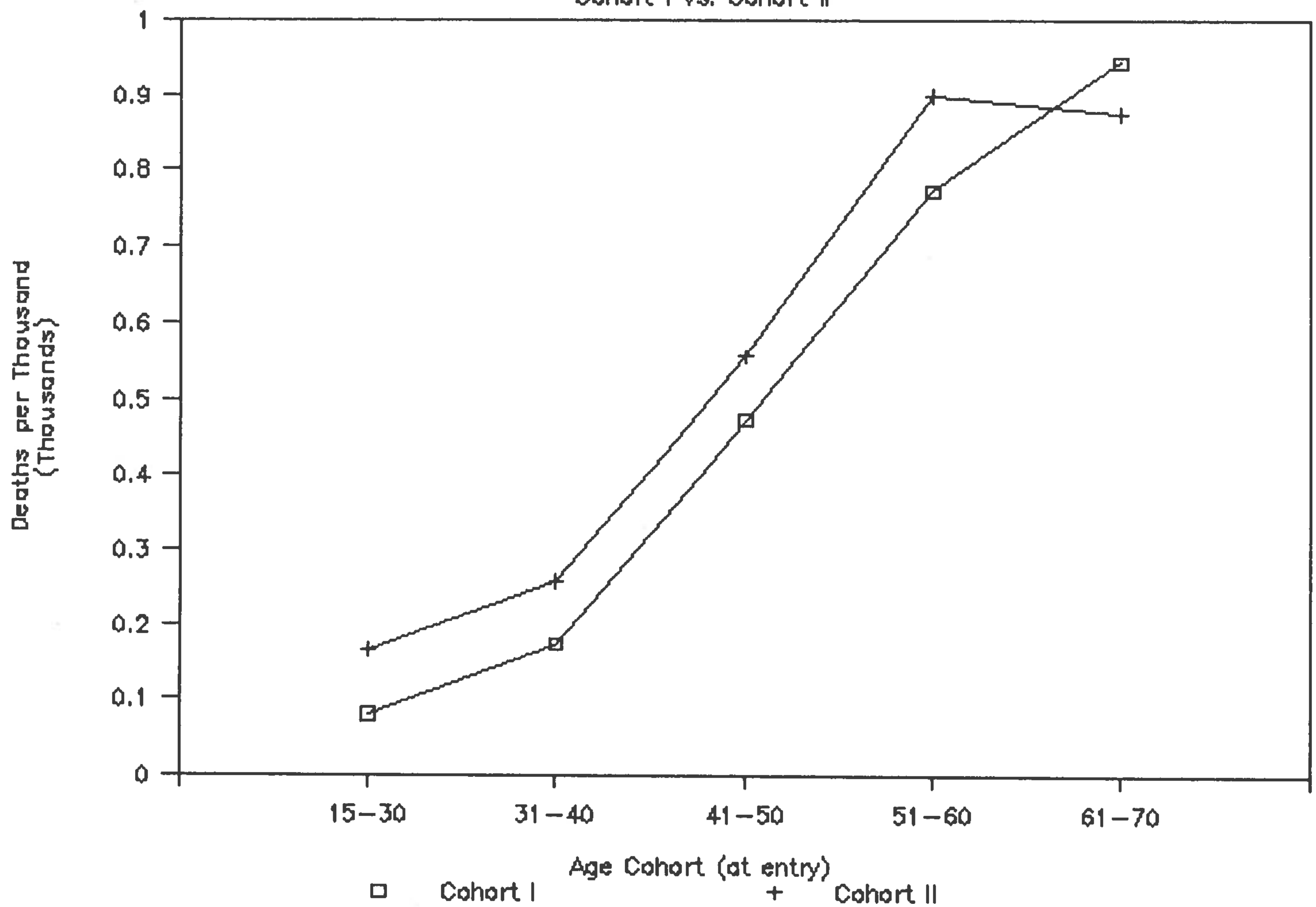


Figure 6. Mortality Rates

Cohort I vs. Cohort II



rate of death for this aging cohort had time to produce more deaths.

Given that subjects lost to follow-up are normally treated as living, the excess mortality in Cohort II would represent a large confounder if follow-up had ceased at 82%. On the other hand, this does not inexorably mean that a greater proportion of decedents will be found in Cohort III. Nearly all decedents may have been found at 95.1% follow-up leaving a higher proportion of living subjects in the lost-to-follow-up group. Only continuing follow-up of Cohort III can resolve the issue of whether treating the remaining subjects (Cohort III) as alive would bias the mortality results.

Morbidity

The LLFS survey questionnaire asks about a variety of general disease categories: previous heart attack, previous bypass surgery or balloon angioplasty, previous stroke, previous cancer, and previous or present diabetes. Although self-reported cardiovascular morbidity may be verifiable in less than 80% of cases, for the purpose of this analysis, a "yes" response defined a "case". Decedents were excluded from morbidity analysis because of incomplete data. Among living males, the frequency of positive responses to these variables are tabulated by cohort in Table 10. Cohort comparisons revealed double the proportion of heart attacks among Cohort II men (19.8% vs. 9.0%, $p<.001$). Not surprisingly, there were also double the proportion of invasive procedures done on Cohort II members (11.7% vs. 6.0%, p<.05). There were no significant differences in rates of stroke, cancer, or diabetes between the two groups. However, the power to detect differences for these categories was not great enough to rule out the existence of such a difference.

Table 10. Self-reported Male Morbidity (% of Cohort total)

		CHRT I	CHRT II	Totals
Heart Attack	Yes	119 (9.0)	32 (19.8)	151
	No	1196	130	1326
Bypass or Angioplasty	Yes	79 (6.0)	17 (10.5)	96
	No	1236	145	1381
Stroke	Yes	43 (3.3)	6 (3.7)	49
	No	1272	156	1428
Cancer	Yes	76 (5.8)	12 (7.4)	88
	No	1239	150	1389
Diabetes	Yes	108 (8.2)	16 (9.9)	124
	No	1207	146	1353
Totals		1315	162	1477

Clearly, inadequate follow-up in this study could have adversely influenced the observed incidence of cardiovascular disease among living men since 21.1% of the "heart attack" cases were in the last 12.3% of the male cohort found. If this rate were to persist in the last 4.9% of men being pursued (Cohort III) and the mean death rate of

55% were also observed in Cohort III, then 11 more cases of heart disease could be expected. If the death rate were lower, there could be even more non-fatal cases. Under the assumption that 11 cases were hidden in Cohort III, if follow-up ceased now, loss of these cases would represent 6.8% of all heart disease cases in the study population.

Two pieces of evidence argue against such a high rate of loss of CHD cases. First, the mean age of Cohort III men is lower so that mortality and morbidity may be less, and second, the proportion of migrants rises as follow-up continues. It is generally believed that migrants have a better health status. Cohort II had a higher proportion of migrants and elevated morbidity and mortality!!

HWE and LTF Bias

Coded work site information from the initial matching of a medical database list with the computerized personnel file provides a good indicator of whether an individual was employed by the laboratory. Employment status as well as year of termination from employment both appear to influence the ability to trace an individual by the methods used. Morbidity and mortality according to employment status was analyzed to discover if there was any favorable selection of healthier individuals either by subjects or the employer.

Examination of personnel record match data reveals that those not hired were significantly younger at entry (33.97 years vs. 35.25 years, $p<.01$), however, this difference was due entirely to the excess of young females in the non-hire group. The mean age of males between the two groups was not significantly different.

The value of personnel record data is apparent when comparing the proportion of non-hires in the three cohorts (Table 11). For those individuals hired, Figure 7 (pg. 66) graphically demonstrates the effect of the age of the last personnel record (the effective termination date) on the probability of locating an individual (for those who were employed). People with later termination dates were preferentially located. The average termination date for Cohort I was 1968, for Cohort II it was 1962, and for Cohort III it was 1959! Apparently the absence of a record or the older age of a record, (potentially less complete as well) adversely affects follow-up. 498 individuals, 82.6% of those not hired by the Laboratory, were nevertheless traceable in the first two cohorts.

Table 11. Proportion of Hires by Cohort

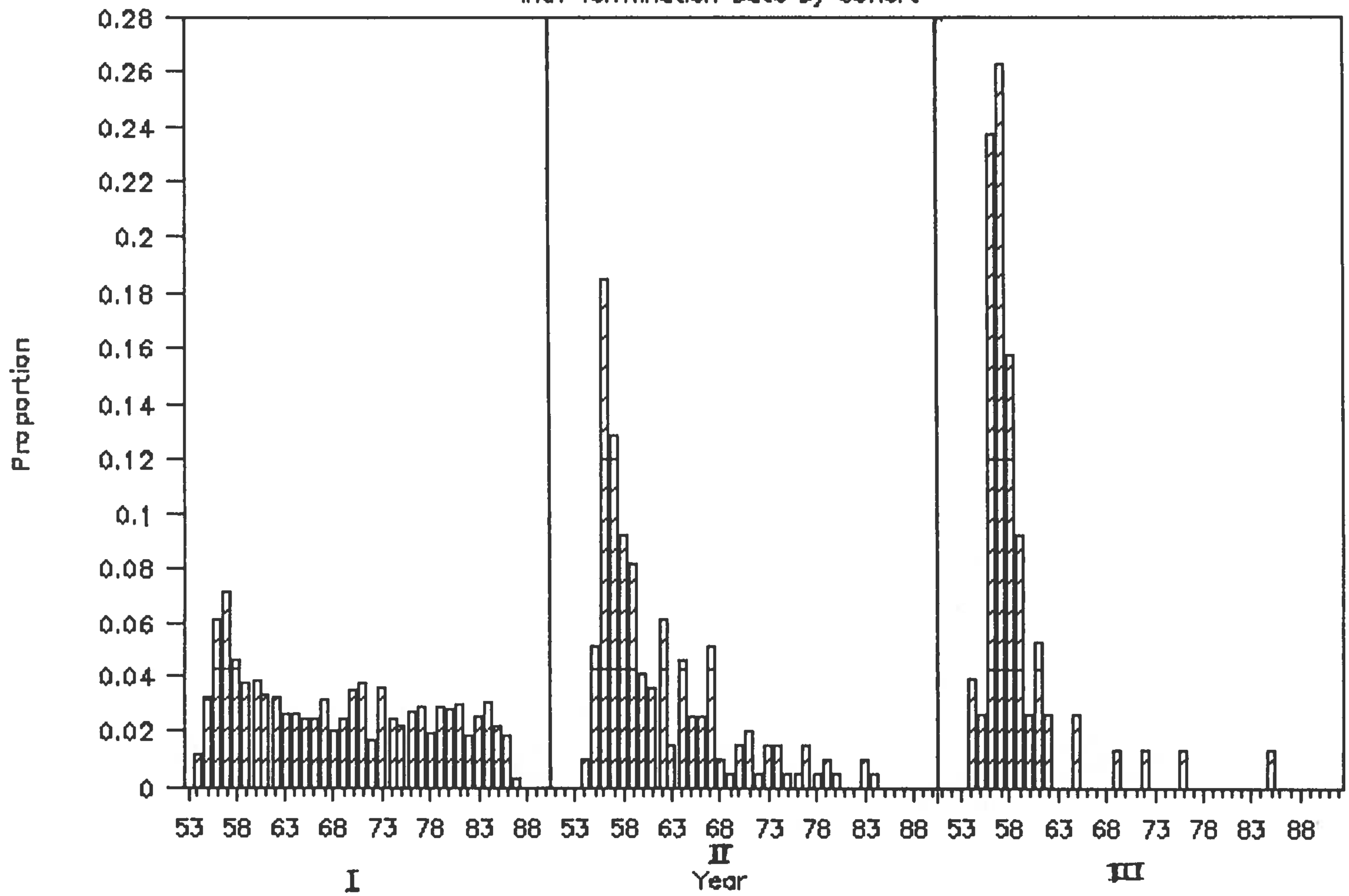
	Not Hired	Hired	Pct Not Hired
CHRT I	373	1645	18.5
CHRT II	125	196	38.9
CHRT III	105	74	58.7
Total	603	1915	23.9

In the attempt to detect the presence of the HWE, neither the mortality nor the morbidity of the hired or non-hired groups was significantly different. This may have been because not being hired by the Laboratory was not a sufficiently consistent predictor of whether that person was employable or not. If that was the case, the negative finding suggests either that employer selection of healthy employees played less of a role in this type of occupational cohort than self selection. In other words, those who were in poorer health never even applied for jobs with the laboratory. Another possibility is that the HWE, which some authors believe dissipates after the first 5-15 years as previously covert disease manifests itself in the employed population as well as the unemployed, must be observed with a shorter follow-up period of less than thirty years.

Another approach that could be taken to detect the HWE in the LLFS cohort is to determine whether date of termination has any predictive value for mortality or morbidity. A more refined analysis seeking a correlation between length of employment, age, and risk of morbidity and mortality cannot be done with presently available data, but is planned for the future.

Figure 7. Proportion of Subjects

with Termination Date by Cohort



Part VI. Conclusion

The benefits of observational approaches to data gathering are increasingly recognized (Greenfield, 1989). Compared to randomized trials, observational studies avoid ethically difficult assignment of subjects to treatment or placebo. Larger numbers of subjects can enter a study with less cost and effort on the part of investigators. It is hoped that this examination of follow-up in a retrospective contact setting contributes to an understanding of the gains and pitfalls of follow-up in research.

This investigation of the follow-up of the LLFS cohort demonstrates that a high percentage of detailed follow-up (beyond mere determination of vital status) is achievable. Such follow-up is attainable in spite of a long period since last contact (30 years) with many subjects. That subjects may be traced with little more than a name, birthdate and former address has been illustrated by a greater than 82% trace rate for subjects who were never hired, but had only pre-employment medical exams. This study confirms the finding by others that a major share of follow-up resources, effort, and time will inevitably be spent locating the last 20% of the study cohort (Modan, 1965; Feinlieb, 1985).

In terms of biases introduced by follow-up, this study identified four potential LTF biases. First, as found in other studies, women are more difficult to trace than men (Boice, 1978). Since many diseases differ in presence rate and degree between men and women, selection of a cohort for follow-up must take gender into account. An investigator who wishes to study a phenomenon of interest in women must be prepared to approach their follow-up with techniques more suited to women as described above. Vital record databases are less useful and individualized "detective's methods" are more useful.

Secondly, those who are younger or older at time zero will be missed by initial follow-up methods. Presumably, the young are more mobile while the elderly have died within a time frame that makes their death certificates more difficult to retrieve. The "missing elder" bias can be expected to abate as the National Death Index ages, but may not disappear (Curb, 1985). The "missing younger" bias is not likely to change.

Thirdly, there may be a mortality bias with a greater proportion of deaths in the LTF group, which runs contrary to the usual assumption whereby those lost to follow-up are treated as alive.

Finally, the morbidity in the LTF group may differ from the initially located 80%. In this study unlike those of Boice (breast cancer risk of radiation) and Modan (polycythemia), the later cohort members had double the incidence of heart attack, the opposite of what would be expected under the assumption that migrants have a generally better health status.

No conclusion could be drawn about the presence or absence of a healthy worker effect with available data.

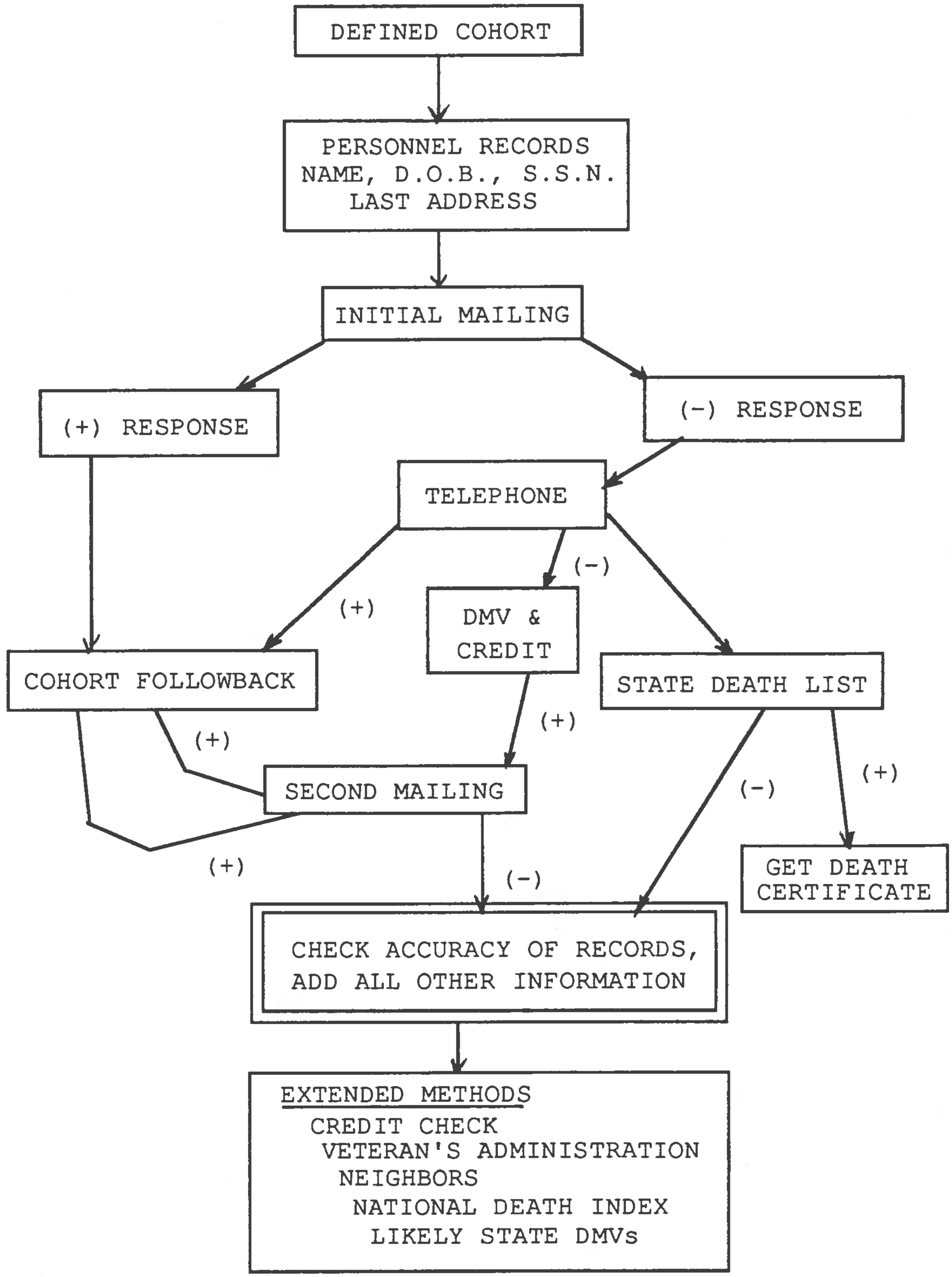
However, the absence of a mortality or morbidity difference between hired and non-hired individuals would argue that employer selection was a less important component of the HWE than other components. Further analysis will be required to resolve this issue.

It was a goal of this analysis to determine how best to implement follow-up of an occupational cohort. Some methods will obviously be applicable to locating members of other types of cohorts as well. A flowchart of a hypothetical application of procedures appears in figure 8 (pg. 70a). The rational approach must initially begin with local searches, in spite of their inherent bias against migrants, on the assumption that the investigator can counteract such biases at later stages of follow-up. After an initial mailing to all last known addresses, the department of motor vehicles is the best way of establishing new addresses or validity of existing addresses. A search of state death records either by computerized data searching (such as CAMLIS) or by hand-searching death indexes should remove the bulk of decedents. If applicable, cohort follow-back, sending a list of remaining subjects' names to those located should produce more addresses and other information. In an occupational cohort this method is quite effective, it would not be at all effective for hospital or treatment-based cohorts. Finally, a credit bureau check using social security numbers is a valuable addition.

Phase two of the approach generally extends the search beyond state borders through the use of local methods as well as national and other state databases. Before undertaking the extended search it is vital to recheck all data. To do so before phase one searching would be wasteful because a large number of people will be located in spite of inaccurate data. Phase one thus serves as a filter which keeps individuals with inaccurate data in the group not located. Not to check the data before embarking on searches involving much more labor is counterproductive because of the duplication of effort entailed upon finding that information was inaccurate.

As noted above, LLFS follow-up continues in phase 3 for 179 individuals. Because these individuals were generally not hired by the laboratory and therefore do not have extensive information available, the methods used to trace them will depend more on "shotgun" approaches such as sending a list of male names to every department of motor vehicles in the United States. For the women, methods that permit location of a spouse or child, such as reviewing birth records, marriage records, and divorce records for the region and time of their last known whereabouts may permit further construction of a trail that can be followed by the above methods. At this stage, there is every reason to believe that virtually complete ascertainment of vital status will be accomplished.

Figure 8. Algorithm for Follow-up



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