



## Joint Legislative Audit Committee



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# "THE CANCER INCIDENCE AMONG WORKERS AT THE LAWRENCE LIVERMORE LABORATORY":

## A SYNTHESIS OF EXPERT REVIEWS OF THE STUDY

Reviews by a variety of national experts of a recent Department of Health Services study of the incidence of malignant melanoma essentially supported the finding of the Department's study indicating a considerably greater than normal incidence of this skin cancer at the Lawrence Livermore Laboratory during the period 1972-77. The reviews by the experts also indicated

- The necessity for extensive, further investigation prior to drawing any conclusions about possible causal factors, including any that might be linked to the Laboratory itself;
- The potential benefit of public health and education measures regarding the general increase of melanoma in the population at-large;
- The need for a fully functioning statewide tumor registry to provide early identification of changes in cancer rates on a routine basis.

REPORT TO THE  
CALIFORNIA LEGISLATURE

REPORT OF THE  
JOINT LEGISLATIVE AUDIT COMMITTEE

"THE CANCER INCIDENCE AMONG WORKERS  
AT THE LAWRENCE LIVERMORE LABORATORY":  
A SYNTHESIS OF EXPERT REVIEWS OF THE STUDY  
JUNE 1980



# California Legislature

## Joint Legislative Audit Committee

GOVERNMENT CODE SECTION 10500 et al

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S. FLOYD MORI  
CHAIRMAN

May 29, 1980

The Honorable President pro Tempore of the Senate  
The Honorable Speaker of the Assembly  
The Honorable Members of the Senate and the  
Assembly of the Legislature of California

Members of the Legislature:

Your Joint Legislative Audit Committee respectfully submits this report prepared by the Joint Legislative Audit Committee staff concerning the Department of Health Services study of the incidence of malignant melanoma at the Lawrence Livermore Laboratory.

This committee staff report contains the comments and recommendations of ten expert scientists and physicians who, at my request, reviewed the earlier Department of Health Services study to assist in identifying what, if any, legislative action or investigation was warranted.

The report of the committee staff concludes that, according to these national experts, appropriate next steps in response to (1) the reported high incidence of malignant melanoma among Lawrence Livermore Laboratory workers and (2) the smaller increase in this skin cancer which has occurred among the population at-large include:

- Thorough scientific follow-up investigations to identify potential causal factors associated with the Livermore melanoma cases;
- Public education measures to address the lesser overall increase which has occurred in malignant melanoma in California and nationally;
- Maintenance of a fully functioning statewide cancer registry with the capacity for systematic early identification of increased cancer incidence rates.

The Honorable President pro Tempore of the Senate  
The Honorable Speaker of the Assembly  
The Honorable Members of the Senate and the  
Assembly of the Legislature of California  
May 29, 1980  
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I wish to express my deep gratitude to the distinguished scholars and medical practitioners whose knowledgeable comments concerning the melanoma study made this document possible.

Preparation of this report was the responsibility of Joan S. Bissell of the committee staff.

Respectfully submitted,



S. FLOYD MORI  
Chairman, Joint Legislative  
Audit Committee

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## SUMMARY

Reviews by a variety of national experts of a recent Department of Health Services report of skin cancer indicated that, in the opinion of this broad-based group of scientists and physicians:

- The reported high incidence of malignant melanoma at Lawrence Livermore Laboratory during 1972-77 appears to be valid. Although study limitations could account for part of the reported incidence, there is a reasonable degree of confidence that, overall, the findings of an unusually high melanoma rate are correct.
- There is no specific factor which can be pointed to as causing the increased incidence of skin cancer, and no conclusions can be drawn about possible links to the Lawrence Livermore Laboratory environment.
- The findings uncovered by the researchers are extremely significant, requiring further study and attempt at explanation. Such investigation could potentially yield added knowledge not only about these melanoma cases but also about this type of skin cancer and cancers more generally.

- The earlier report's findings raise other important policy matters warranting attention, including (1) the potential benefit of public education measures to address increased rates of melanoma generally and (2) the need for a fully functioning uniform statewide cancer registry to assure systematic early identification of changes in cancer rates.
  
- Until thorough investigation is undertaken of the numerous factors which could help explain the observed melanoma rate, no recommendations regarding further health and safety precautionary measures at the laboratory are warranted.



## BACKGROUND

The California Department of Health Services, in April, 1980, released "A Study of Cancer Incidence in Lawrence Livermore Laboratory". The study was conducted through collaborative efforts between the state Department of Health Services (Resource for Cancer Epidemiology) and the Lawrence Livermore Laboratory. It was initiated as a result of the observation of seemingly high rates of a certain type of skin cancer, malignant melanoma, during the mid-1970's, by the laboratory's Medical Services Department and by local clinicians specializing in treating malignant melanoma.

The study reported an incidence of melanoma among laboratory workers from 1972 to 1977 which was approximately five times as high as would be expected from incidence rates reported in Alameda and Contra Costa counties during the same period.

The actual number of melanoma cases reported among laboratory workers from 1972 to 1977 was 19. Based upon standard reporting techniques, this represents an incidence figure of 57.2 per 100,000 compared to the normal case rate of from 11 to 11.9 per 100,000 in surrounding areas. In yearly numbers, the figures represent 3 to 4 cases annually among the laboratory's work force which varied in size during that period from 4,778 in 1972 to 5,756 in 1977. The study did not include time periods earlier than 1972 or later than 1977, but figures from the laboratory's Medical Services Department appear to indicate no unusually high melanoma rates at those times.

Several steps have been taken by various concerned bodies in response to the melanoma study. Immediately after its release, responses of a range of experts were sought by three groups:

- A variety of national experts were asked to review the study and provide their comments and recommendations to the California Legislature's Joint Legislative Audit Committee Chairman by May 15, in order to provide for any appropriate legislative action this year.
- A board of experts was appointed by the federal Department of Energy to look at the issue and report its findings to the Secretary of Energy.

- An internal group of nine senior scientists was established by the Lawrence Livermore Laboratory to examine the melanoma situation in-depth.

Individual members of the State Legislature also requested of the Department of Health Services a description of additional empirical investigations which should be undertaken immediately to further study the reported high incidence of melanoma, and an indication of the funding necessary to undertake this research during 1980-81.

Among the additional investigations proposed by the Department of Health Services were:

- A detailed review of the job assignments, health records, pre-existing medical conditions, and other background characteristics of each of the employees diagnosed as having melanoma;
- An examination of the relationship between melanoma occurrence and employee radiation exposure;
- A broadening of the melanoma research to include other types of cancer;
- An extension of the melanoma research in time to determine the starting and end points of the high incidence of the disease;

- A further assessment of the melanoma risk in surrounding communities.

During late May, legislative fiscal subcommittees approved augmentations to the Governor's budget of one-half of the amount needed for the additional research, with the anticipation of obtaining matching federal funds to provide the remaining necessary funding\*.

The ten national experts whose reviews of the melanoma study are summarized in this report indicated consistently that, in their opinion, further research is essential prior to drawing any conclusions about causal factors in this matter. Their comments on this and other issues are summarized in the next section of this report.

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\* Total funding needed for the additional investigation is projected by the Department of Health Services to be \$227,908. A legislative augmentation (of half this amount) must be approved by the Governor in order to be included within the State's 1980-81 budget.

## REVIEW OF COMMENTS BY NATIONAL EXPERTS

The comments provided by the expert scientists and physicians who reviewed the melanoma study relate principally to four issues: (1) additional scientific investigations which are necessary, (2) appropriate public health and education related to the overall increase in melanoma in California and nationally, (3) the desirability of a fully functioning statewide cancer registry capable of early detection of unusual incidence rates, and (4) related issues pertinent to understanding of the Livermore melanoma "cluster".

### ADDITIONAL NECESSARY SCIENTIFIC INVESTIGATIONS

Additional research activities were considered to be essential by the national experts in order to more fully understand and interpret the high cancer rates reported at the Laboratory. The priority research issues emphasized by the experts largely paralleled the topics independently proposed by the Department of Health Services. For example, the expert reviewers indicated that:

- A number of fundamental medical questions must be investigated in depth before any conclusions about specific causal factors can be drawn. This will necessitate, for example, (1) review of the characteristics of the melanomas identified, (2) thorough study of the incidences of a range of other types of cancer in the study populations, and (3) an assesment of the extent to which reported melanoma cases represented familial occurrences of this cancer (which has a strong genetic component).
  
- There is a need for additional investigation to clarify any possible factors which could have influenced the incidence figures contained in the study. These might include, for instance, (1) potential differences in rates of diagnosis among the laboratory workers and the surrounding community, and (2) possible differences in racial-ethnic compositions between laboratory employees and the comparison population groups (for example, Hispanic individuals might not be equally represented in the two groups, and melanoma is extremely rare among this group).

- Sufficient investigation has not yet been undertaken to assess whether there is any relationship between the reported melanoma cases and exposure to radiation, accidents, chemical exposures, or any other industrial hygiene factors. In the absence of such information, none of the experts believed the meaning of the increased melanoma incidence could be assessed. This issue was of particular concern to the reviewers because there is no previous literature indicating an association between malignant melanoma occurrence and radiation other than ultraviolet, and because there was no reported increase of the types of malignancies usually associated with ionizing radiation.

In summary, the experts consistently indicated the need for further investigation of the melanoma occurrences. They uniformly commented that until such research is completed, it is not possible to determine what, if any, additional or different health and safety precautionary measures might be warranted at the Laboratory.

GENERAL PUBLIC HEALTH  
AND EDUCATION MEASURES

Several of the expert reviewers commented on the need for and the potential benefits of public education about melanoma generally. They noted that there has been a widespread increase both nationally and in the State in the incidence of melanoma in the recent past. In parts of Northern California (the San Francisco and Sacramento areas, for example), present incidences of this skin cancer are at least double what they were a decade ago.

The experts commented upon the efficacy of public education about melanoma. In Australia (Queensland), where the incidence of malignant melanoma is the highest in the world, education of both physicians and the public at-large has resulted in early diagnosis and has significantly reduced the mortality associated with the disease.



It was suggested that an educational program should focus upon the effects of sun exposure on cancer, skin types with propensity for developing melanoma, and early signs of the disease. Additional emphasis was recommended on informing the public of the types of individuals who tend to have an increased incidence of melanoma, on the actions (such as use of sun screens) that may be beneficial in preventing it, and on such basic facts as that (1) malignant melanoma is no longer a rare form of cancer, and (2) it is a disease which affects people in the prime of their life and may be difficult to cure, but it can be curable if found early.

#### A STATEWIDE CANCER REGISTRY

Several of the expert scientists and physicians who reviewed the melanoma study indicated the need for and potential benefits of a fully operational statewide cancer registry to assure early identification of unusual rates of cancer on a systematic basis. Although legislation authorizing such a registry was passed in 1978 (Chapter 1292--Senate Bill 1530, Nejedly), full participation has been achieved only in a limited number of counties for which specific funding has been available.

According to these national experts, such a registry is necessary to routinely identify rates of cancer in the State which could possibly be related to various potential environmental hazards or other factors.

The reviewers also noted the procedures of a number of other states to assure early and uniform reporting of all cancer cases. They observed that while the mechanisms are in place in California for incidence-based tumor registries, the needed reporting procedures are not mandatory and valuable types of data are not collected throughout the State.

As one physician noted:

At this time in the State of California, there [is an incidence-based tumor registry in five counties and other...] tumor registries at many of the larger hospitals both in southern California and northern California; however, [complete and uniform] tumor registries do not exist in [some counties] and in some of the major hospitals and without them, I feel it is difficult always to know what epidemiologic trends are developing in malignant diseases and therefore what might be done to alter these trends.

#### RELATED ISSUES

Two additional noteworthy issues related to the Livermore melanoma rates which were discussed by the national experts were (1) the occurrence of other melanoma "clusters" elsewhere and (2) the overall limited nature of the scientific understanding of melanoma.

Other previous melanoma clusters cited by the reviewers included ones which had been reported in New Jersey and Oregon. It was noted that further examination of the similarities and difference between these clusters and the Livermore cluster might help identify possible causal factors.

Finally, it was repeatedly noted by the experts that melanoma is a little understood disease and that, if factors could be identified which were related to the "cluster" it might be possible to obtain exceedingly vital basic information regarding this cancer and related malignancies. The significance of developing an improved understanding of melanoma and the factors which activate it was consistently emphasized by the scientists and physicians alike.

In summary, the overall conclusions of the experts who reviewed the study were that the questions it raised are highly significant and require considerably more detailed investigation. In their opinion, such research is essential in order (1) to attempt to identify any specific causal factors related to these melanoma cases, (2) to determine whether the cases had any particular relationship to environmental factors or Laboratory work experience, and (3) to contribute to the more basic understanding of fundamental aspects of cancer.

APPENDICES

A STUDY OF CANCER INCIDENCE  
IN  
LAWRENCE LIVERMORE LABORATORY EMPLOYEES

REPORT #1  
MALIGNANT MELANOMA  
APRIL 17, 1980

DEPARTMENT OF HEALTH SERVICES  
RESOURCE FOR CANCER EPIDEMIOLOGY SECTION  
DONALD F. AUSTIN, M.D., M.P.H., CHIEF

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## INTRODUCTION

In late 1976 the Resource for Cancer Epidemiology (RCE) received reports from local clinicians specializing in treating malignant melanoma that an unusual number of their melanoma patients were employees of the Lawrence Livermore Laboratory (LLL). Simultaneously and independently, Dr. Max Biggs, Chief of Medical Services at LLL, began gathering information to help determine whether or not employees at LLL were experiencing an unusual risk of melanoma. In subsequent discussions between Dr. Donald Austin, Chief of the RCE, and Dr. Biggs of LLL it was agreed that the two agencies would cooperate in conducting a scientific evaluation of melanoma occurrence at LLL. By July, 1977, initial planning for the study and negotiations for the necessary employee data files with which to conduct the study were completed. A summary tape of computer files describing the persons employed at the laboratory was subsequently delivered by LLL to the RCE to begin the study.

During the months when review of the files and work on the data summary and analysis plans proceeded the RCE found it necessary to request a second set of files, the annual employee roster, from LLL. These files were also submitted to the RCE for analysis in the fall of 1978.

Slow progress was made during the initial processing of the employee files and the preliminary examination of melanoma incidence rates and trends in Alameda County. Staff assigned to this work were borrowed, on a part-time basis, from other projects. During this process it became clear that the appropriate analysis would require that a more complex method for computing the "expected" numbers of cases among LLL employees be developed than was originally planned. The analytic method selected had to control for possible effects related to the specific place of residence of the employees since this was found to affect melanoma incidence. The resulting study design was established to avoid the possible effects of confounding variables related to residence. Adjustment for these factors required the development of several computer software packages to calculate accurate population estimates by age, race and sex for census tracts containing resident LLL employees; to compute person years of observation for the LLL employees by year, sex, age and census tract of residence.

The crucial objective was to determine whether or not an unusual number of melanoma cases were occurring among the LLL employees. In establishing the study design, the prevailing philosophy was that every effort should be made to make the initial comparisons of observed vs expected cases of melanoma in the employee group as accurate as possible rather than to economize on time and compromise the study by producing a crude risk estimate of dubious scientific value.

Because of early project delays and the necessity for executing a more sophisticated project design, the Lawrence Livermore Laboratory provided funds to purchase needed computer programming and statistical consultant services. These funds were made available early in 1979. A considerable and originally unanticipated staff effort was required to perform the number of different tasks required by the study design. These tasks were eventually completed in about 12 calendar months.

### The Study Population

The LLL is located in Alameda County, approximately 50 miles southeast of Oakland in the Livermore Valley. Roughly 80% of the LLL employees reside in Contra Costa and Alameda counties, coinciding with part of the surveillance area encompassed by the San Francisco Bay Area Cancer Incidence System (CIS) maintained by the RCE under contract to the National Cancer Institute through the Surveillance, Epidemiology and End Results (SEER) Program. Fewer than 1 percent of the LLL employees reside in the remaining counties of the San Francisco-Oakland SMSA (Table 1). The employee computer files provided by the laboratory for the years 1972-77 provided a count of the total number of persons employed during each year. The number of employees varied between 4,778 for 1972 and 5,756 in 1977. There was a steady growth each year. It was not possible to include every employee in the study. Employees residing outside the five counties monitored by the CIS were eliminated from the study because cancer incidence data for these geographic areas were not available. Employees residing in Marin, San Mateo or San Francisco were excluded because valid census tract population estimates for these counties could not be completed with the staff resources available and very few LLL employees resided in these counties. Each year slightly more than 100 employees were excluded because the home address could not be assigned a census tract in Alameda or Contra-Costa counties. These included employees with a P. O. Box address, a motel address or street address that could not be located on a census tract map.

Table 1 summarizes the numbers of employees excluded from the employee roster for each year. Approximately 80 percent of the employees met the criteria of being white and residing in Alameda or Contra Costa county with a home address that could be assigned to a census tract.



### The Study Plan - A Brief Summary

In general, the analysis consisted of comparing the observed and expected numbers of cases of melanoma occurring among the LLL employees over the time period 1972-1977 and statistically testing the difference between the numbers of observed and expected cases. Observed cases were determined by a computerized record linkage, using the annual LLL employee files and the corresponding annual CIS file. Employee cases of melanoma were included in the observed count only if the date of diagnosis was concurrent with employment.

The statistical analyses performed during this study incorporated methods to control for age, sex, race, year of diagnosis and census tract of residence.

The study plan also included computation of age-adjusted incidence rates of melanoma for the LLL employees, for Alameda County, Livermore Valley and selected census tracts where LLL employees resided. These descriptive data were designed to provide information about melanoma in the community surrounding the laboratory facility.

### Details of Methodology

This section of the report covers the specific procedures followed in identification of the observed cases among the employees, and the statistical methodology employed in evaluating the significance of the numbers of these cases.

#### 1. Cancer Incidence Cases Criteria

Cases of malignant melanoma observed for the LLL employee population, and for the comparison population were drawn from Alameda County and Contra Costa County incidence-cases reported through the CIS for the years 1972-1977.

An incidence case is the first diagnosis of a primary tumor in a patient residing within the study area at the time of diagnosis. Case reports are obtained from hospital tumor registries, and through field abstracting activities are cross-validated by review of pathological records and death clearance procedures. Quality control studies have suggested that the completeness of reporting is approximately 98 percent or better.

For the purposes of this analysis two categories of malignant melanoma were used: all melanomas (including in situ), and invasive melanomas only. Since diagnostic staging conventions have changed within the study time period regarding the invasiveness of the 'superficial spreading' histologic type, for comparability "invasive" melanoma is defined by excluding both in situ and superficial spreading melanomas. These

criteria were applied uniformly to both the assessment of observed and expected numbers.

2. Observed Numbers

The ascertainment of observed cases of malignant melanoma among LLL employees during the study period was accomplished via a computerized record linkage between the annual LLL employee files and annual CIS files. Only observed cases diagnosed among white employees residing in Contra Costa and Alameda counties were included. Cases diagnosed subsequent to the date of termination of employment at LLL were excluded. The accuracy of the computerized record linkage was established by a manual review of the computer output. A detailed description of the linkage computer program is in Appendix I.

3. Calculation of Expected Numbers of Cases

To calculate the numbers of cases expected to occur among employees, it was necessary to take into account the exact employment time of each employee during each year. The concept of "person years of observation" was utilized to account for employees who did not work a full calendar year.

a. Person Years of Observation (PYO)

Person years of observation (PYO) refers to the annual distribution of the LLL workforce categorized by age, sex, and census tract of residence (limited here to white employees). It does not address the cumulative experience of any given employee over several years time, but rather is the cumulative total of person-years at risk for each age, sex and census tract group within the employee population for any given year of analysis.

PYO were calculated for each annual employee file, 1972-1977. In a given year, the maximum contribution for a given employee would be one PYO in a particular age-group, sex, census tract cell. For employees who started or terminated during the year, the PYO contribution consists of a fraction of a year, calculated as the number of months worked divided by 12. In order to be included in the PYO tabulation an employee had to have valid birthyear or termination year codes. Two persons were excluded under this criterion (Table 1).

b. Census Tract Population Estimates

In order to compute an expected number of cases for the employee group, the age, race, sex distribution of the population of each census tract in the two counties had to be estimated for each year 1972-77.

In Contra Costa County, a special census for the entire county was conducted in 1975. Considerable work was required to reallocate non-white population data reported for the total county to individual census tract age and sex groups in order to make the population files usable. Data from the 1975 census were used to interpolate, using a straight line method, the changes that occurred between 1970 and 1975 in each sex, age and race grouping of each census tract. These data were then extrapolated to 1978.

In Alameda County a number of special census had been conducted during the intercensal years. The special censuses for Alameda County all occurred at different times, thus making the procedure somewhat more complicated. For each of the individual special census areas, the comparable tracts from the 1970 census were selected and non-white population groups allocated following the procedure for Contra Costa County. Since the race categories between the special censuses were not comparable, race designations were recoded for each special census area to make it as compatible as possible to the 1970 census. Unknown special census designations for age and sex were allocated randomly over all tracts using the known age and sex special census ratios. Subsequently, the percent quarterly change between April 1, 1970 and the date of each special census for each age, race and sex category for each census tract was calculated to interpolate/extrapolate populations for July 1 of each study year.

For the non-special-census areas of Alameda County the percent age, race and sex distributions by tract were calculated for 1970. These distributions were then applied by tract such that the annual sum of non-special-census tracts was equal to the difference between Department of Finance, Alameda County, estimates and the annual sum of special census populations. Cities without a special census included Alameda, Albany, Berkeley, Emeryville, Hayward, Piedmont and San Leandro.

c. Calculation of Rates for the Comparison Populations

Annual rates of melanoma (all melanoma and invasive) were calculated two ways, one for each of the statistical procedures employed. For statistical Method A, approximating the Mantel-Haenszel procedure, age group, sex and census tract specific rates for whites were calculated for all cases of melanoma, including LLL employees in both the numerator and the denominator of the rates. For statistical Method B (the simple ratio of a Poisson to its expectation), annual age group, sex and census tract-specific rates for whites were calculated in which LLL employee cases were excluded from the numerator and tract-specific denominators were modified by excluding the annual LLL PYO from each appropriate cell.

d. Calculation of Expected Numbers

The annual expected number of cases of malignant melanoma required the use of the age and sex specific rates of melanoma occurring in

those census tracts in Alameda and Contra Costa counties for which there was at least some corresponding fraction of a LLL PYO.

Expected numbers were calculated for each of four analytic formulations of the problem. Method A (including LLL employees in the numerator and denominator of the rates) expected numbers were calculated both for all melanoma (including in situ) and for invasive melanoma (excluding in situ and superficial spreading). Likewise, for Method B (excluding LLL employees from the numerator and the denominator of the rates) expected numbers were calculated for all melanoma as well as for invasive melanoma only.

The formula for the calculating expected numbers is the same for each method, what differs is the numerator and the denominator definition. The calculation consists of summing the product of each annual age, sex and census tract specific rate multiplied by the corresponding cell value for PYO. This procedure effectively weights the observed rates of melanoma by the annual residence distribution of LLL employees.

#### Statistical Methods

Two methods of statistical analysis were used to evaluate the results of this study. Both of these statistical methods (A and B) are designed to test the general hypothesis that there is no association between being an employee of LLL and the occurrence of melanoma. Due to theoretical considerations enumerated later, Method A is the preferred method of analysis for this situation.

The general hypothesis of no association between LLL employment and melanoma incidence can be formulated more specifically in the following way:

- $H_0$      The number of observed cases of melanoma during 1972-77 among LLL employees is not different from that expected based on population of the same age group, race, sex and residing in the same census tracts.
- $H_1$      The observed number of cases is significantly greater than would be expected based on a population of the same age group, race, sex and census tracts of residence.

The observed cases included in both statistical analyses are all melanoma cases diagnosed among white LLL employees residing in Contra Costa or Alameda counties during years 1972 to 1977. Diagnoses which occurred when individuals were not currently employed at LLL or not residing in Contra Costa or Alameda counties were excluded from both analyses.

To determine the expected number of cases of melanoma among the LLL employees under the null hypothesis while controlling for age, race, sex, year and census tract of residence, it was necessary to calculate PYO for the LLL employees for each year based on their months of employment during that year and to also calculate the melanoma rates for all

age, race, sex, year and census tract strata which contained LLL PYO. For notational convenience, the strata designated by age, race, sex, year and census tract can be indexed by a single subscript  $i$ . Then the expected number of cases for a particular stratum  $i$ ,  $E_i$ , is defined as the product of the melanoma rate for the  $i^{\text{th}}$  stratum,  $P_i$ , and the LLL PYO for that stratum,  $L_i$ , i.e.,  $E_i = P_i L_i$ . For each stratum it is necessary to assume that the probability of developing melanoma is the same for all members of the stratum, reporting of melanoma cases is complete and that the cases of melanoma are independent from each other. Methods A and B both assume that  $L_i$  and the number of non-LLL individuals in the  $i^{\text{th}}$  stratum,  $M_i$ , are fixed and known.

Method A

The null hypothesis can be translated into a statistical hypothesis which states that  $X_i$ , the number of cases of melanoma among LLL employees of the  $i^{\text{th}}$  age, race, year, sex and census tract and  $Y_i$ , the number of cases among non-LLL individuals from the same stratum, are Poisson variates with expected values given by  $P_i L_i$  and  $P_i M_i$  where  $L_i$  is the number of LLL PYO for the  $i^{\text{th}}$  stratum,  $M_i$  is the number of non-LLL individuals in the  $i^{\text{th}}$  stratum, and  $P_i$  is the common melanoma rate for that stratum. For the  $i^{\text{th}}$  stratum, the maximum likelihood estimator for the common melanoma rate  $\hat{P}_i = \frac{X_i + Y_i}{L_i + M_i}$  is based on the experience of the entire

population and the expected number of cases,  $E_i$ , is then estimated by  $E_i = L_i \hat{P}_i$ .

$$T = \sum_i (X_i - (X_i + Y_i)L_i / (L_i + M_i)) = \sum_i X_i - \sum_i E_i$$

Then, under the null hypothesis,  $T$  has an expected value equal to zero and a variance given by

$$\text{Var } T = \sum_i P_i L_i M_i / (L_i + M_i)$$

which is estimated by

$$\hat{\text{Var}} T = \sum_i (X_i + Y_i) L_i M_i / (L_i + M_i)^2$$

The test statistic

$$|T| - \frac{1}{2} \Big)^2 / \hat{\text{Var}} T$$

is approximately distributed as a chi-square random variable with one degree of freedom. An approximate test of the null hypothesis is obtained

by referring this test statistic to a table of percentiles of the chi-square distribution. Consequently, approximate significance probabilities of observed results can also be determined. This test statistic is virtually identical to the Mantel-Haenszel test statistic for this situation since the occurrence of more than one melanoma case in a single stratum is extremely rare. For the situation where there are no more than one case of melanoma per stratum, this test statistic is algebraically identical to the Mantel-Haenszel statistic with one degree of freedom.

#### Method B

If the melanoma rate for the  $i^{\text{th}}$  stratum,  $P_i$ , is assumed to be fixed and known, then a test of the null hypothesis can be obtained using the ratio of the sums of observed to expected cases among the LLL employees. The melanoma rates for all strata are based on the non-LLL individuals and the expected cases are calculated as before. The total number of observed cases among LLL employees,  $O = \sum_i X_i$  is considered a Poisson variable whose expectation,  $E = \sum_i E_i$ . The test statistic  $O/E$  can be evaluated using existing statistical tables. These tables provide a means of testing null hypotheses at certain specified  $\alpha$ -levels but do not allow calculation of significance probabilities.

It was concluded that the statistical analysis described in Method A is preferable to that of Method B. Method A does not require the assumption that the melanoma rates among non-LLL individuals are fixed. Both methods assume that the number of non-LLL individual in each stratum is known and this potential source of error is recognized. The population estimates used in this study were the best possible in a period so removed from the 1970 U.S. census. Although the impact of possible error in this estimation cannot be readily quantified, the population estimates used could not account for the findings of this study.

## Findings

There was a total of 19 cases of malignant melanoma identified among white LLL employees living in Alameda County or Contra Costa County during 1972-1977 (Table 2). The number of cases varied from a high of six cases in 1977 to no cases in 1973. Two of the 19 cases occurred in female employees. The analysis of findings was based on a total 28,473 person years of observation for the six year period.

Of the total of 19 cases of malignant melanoma, 16 were of the invasive type and three were non-invasive (Table 3). Only three of the cases occurred in employees who were 39 years of age or younger, while 11 of the cases occurred in the age group 40 to 49. The comparison cohort used for computing the expected numbers of cases for employees had a total of 185 malignant melanoma cases (Table 3). Of this number 162 or about 88 percent were invasive.

The Lawrence Livermore Laboratory Study population provided, on the average each year, 3,958 person years of observation for white males and 787 for white females (Table 4). The number of person years of observation is fewer than the total employee count for each year since some employees leave and new employees are added. A comparison of a 10 percent random sample of persons employed in 1974 with the employment list of 1975 indicated that 93 percent of the persons employed in 1974 were still employed in 1975. About 13 percent of the employees of that year reported address changes between 1974 and 1975. Six percent maintained a residence in the same city and seven percent moved to a different city.

For male employees, 58 percent of the person years of observation were between ages 30 and 49 while 53 percent of the PYO for the females were in this age range. However, about 1/4 of the PYO for females was in the age group under 30 while only 1/8 of the male PYO was in the younger group (Table 4).

Table 5 presents the results of computations of age-adjusted truncated incidence rates which were developed to compare the melanoma experience of white male employees, age 20 to 64, to other males, age 20 to 64, living in the same census tracts as employees, living in the immediate geographic area of the LLL or living in nearby residential communities.

The rate for white male employees, age 20 to 64, was 57 per 100,000, nearly five times greater than the rate for white males living in the same census tracts of the employees (Table 5). The rate for Livermore was identical with that of the total Livermore/Pleasanton Valley area. The rate for white males age 20 to 64 in Alameda County was only slightly lower than the Livermore area i.e., 11 per 100,000 compared with 12 per 100,000.

This table supports a conclusion that the high rate of melanoma is related to LLL employment. The rates among non-employees living in the same area is very similar to the rate for the total county.

The number of cases that were expected to occur among the LLL employees was determined in two ways during the analysis of findings, by Methods A and B described previously. The expected number of cases and the summary test statistics (Z statistics) presented in Table 6 are the results for Method A. The Z statistics reported in this table are measures of the significance of the difference between the numbers of observed and expected cases under the null hypothesis. The differences between 17 observed and 5.13 expected cases of all melanoma and 14 observed and 4.08 expected cases of invasive melanoma, for the male LLL employees are statistically significant ( $p < 6 \times 10^{-8}$  for each result). For white female employees the results of this analysis do not permit a conclusion that there is an increased incidence of either melanoma or invasive melanoma.

The findings for Method B (Table 7) corroborate those of Method A, i.e., there is evidence of an elevated-risk of both melanoma and invasive melanoma among white male LLL employees. Similarly there is insufficient evidence to conclude that white female LLL employees share this association. Exact significance probabilities for the results for white males are not readily calculable. It is possible to state that the ratios of 3.87 and 3.74 observed to expected cases for melanoma and invasive melanoma respectively among white male LLL employees are significantly different from one.



## Discussion of Findings

The analysis of malignant melanoma in LLL employees had a major objective; to determine conclusively whether or not a significantly higher number of diagnoses of malignant melanoma was occurring among the employees than would be expected based on the rate of occurrence in a similar population. In conducting this analysis, several alternatives were possible in statistical methods and in case definition.

The first alternative was in selecting the definition of malignant melanoma for purposes of the analysis. If the diagnosis of melanoma "in situ" is excluded, a significant number of cases may be excluded from the analysis. In situ cases are those diagnosed at a stage so early that they have not yet begun to invade surrounding tissues. Consequently, the chance of erroneous diagnoses are greater with invasive melanoma. Another problem to be resolved was how to deal with melanoma cases diagnosed as "superficial spreading melanoma". During the study period the classification of this type of melanoma changed from the early period, when it was often classified with in situ cases, to the later period when it never was.

The definition issue was resolved by making two separate definitions for malignant melanoma. A liberal definition included all skin cancers labeled as melanoma, including in situ cases. A conservative definition excluded both in situ and superficial spreading types of melanoma. The analysis was then conducted for each of the definitions. The conclusions were identical for each analysis.

The second alternative was in the definition of the group used as a control, also referred to as the general population or "normal" group. The choice of the control group dictates the type of statistical methodology which can be used and the type of interpretation which can be made of the results. Again, the decision was to do the analysis both ways. The first way, Method A, is an analysis which compares the LLL employees to a general population which includes the LLL employees. This comparison has two advantages; it permits answering the question, "Are the LLL employees different from a general population with respect to melanoma occurrence?", and it permits the computation of an estimate of the probability that any such difference found could arise by chance.

The second way, Method B, compares the LLL employees to a general population minus all LLL employees. It permits answering the question, "If the employees are different from the general population with respect to melanoma occurrence, how large is that difference and what is the melanoma occurrence in the normal population without this different group included?" Once again, when the analysis was done both ways, the conclusions were the same.

From Method A, the number of diagnoses of melanoma, all types combined, expected among the LLL employees was six cases over the six year period. The actual number that occurred was 19 cases, over three times the expected number. The probability that this finding could occur by chance is less than six chances in a hundred million. The majority of the difference between the expected and observed number was in males. The difference in females, although in the same direction, was based upon such small numbers that statistical significance was not reached.

The results from Method A were similar by either definition of malignant melanoma and can be illustrated by the difference in the computed truncated incidence rates between LLL employees and the general population which includes the employees. The general population for this comparison is the population residing in the same census tracts as the employees, excluding persons under 20 and over 64 years. Therefore, although the truncated incidence rates can be compared with each other, they cannot be compared to non-truncated rates as usually computed for other areas. The age-adjusted truncated incidence rates for all white LLL employees for the study period was 57.7 while for the general population including LLL employees, it was 14.1 per 100,000 per year.

It can be concluded that, with respect to the occurrence of malignant melanoma, the LLL employees are different from the general population. To illustrate the magnitude of the difference, the rates among LLL employees may be compared to the general population with the LLL employees removed. The average annual age-adjusted truncated incidence rate in the white male LLL employees was 57.2 per 100,000. By comparison, the rate for white males in general population in the Alameda County census tracts where employees lived was 11.7, for the Livermore area was 11.9, for the Livermore-Pleasanton area combined was 11.9 and for all of Alameda County was 11.0 per 100,000. This comparison illustrates that the rate of melanoma among the LLL employees was approximately five times that of the general population. More significantly, with the LLL employees removed, the truncated rate among the white male residents of Livermore is identical with the combined rate of Livermore and Pleasanton white males and is nearly identical with the rate for white males for the entire county of Alameda. This suggests that the excess in risk for melanoma was limited to employees of the Laboratory and did not extend into the general population.

In most population groups, malignant melanoma usually ranks no higher than the tenth most common type of cancer. During the study period, malignant melanoma was the most frequently diagnosed malignancy among the LLL employees. Continuing analyses will determine whether or not any other types of cancer are increased among the LLL employees. Data on only one additional site has been analyzed to date and not in such great detail as for melanoma. That additional site is leukemia, defined for the analysis as leukemias of the chronic lymphocytic and acute myelocytic types. This definition was chosen because those types of leukemia have most frequently been found to have excessive occurrences in groups exposed to ionizing radiation. No cases of these types of leukemia were found among LLL employees during the study period.

The analysis completed to date permits certain conclusions to be drawn. The following statements are summary conclusions from the investigators at the Resource for Cancer Epidemiology, a section of the California Department of Health Services.

1. During the period 1972-77, a significantly greater than expected number of malignant melanomas were diagnosed among the employees of the LLL. The cases occurred at a rate approximately five times greater than normal.
2. During that time period, malignant melanoma was the most common malignancy diagnosed among the employees of the LLL.

3. The greater than expected number of cases of malignant melanoma among the employees of the LLL during that period is very unlikely to have occurred by chance.
4. The greater than expected number of cases of malignant melanoma among the employees of the LLL during that period is not the result of an unusual pattern of disease reporting, diagnosis or medical care.
5. The elevated rate of malignant melanoma during that period appears to have been limited to employees of the LLL and did not extend to members of the local community.
6. Preliminary analysis to date fails to suggest that during that period, other types of malignancies usually associated with radiation occurred at a rate any greater than normal.
7. Malignant melanoma has never been associated with any type of radiation other than ultra-violet radiation. In well studied populations having received radiation from medical, nuclear fission or radioisotope sources, increased malignant melanoma risk has not been reported. Any other statement about the possible cause of the greater than expected rate among LLL employees would be conjecture.

STUDY OF LAWRENCE LIVERMORE LABORATORY EMPLOYEES

TABLE 1 - Employees Included and Excluded from Melanoma Study

Inclusion/Exclusion Eligibility	Computer File Year					
	1972	1973	1974	1975	1976	1977
Total employed during year	5998	5906	6170	6335	6820	7408
Non-white race	424	424	439	420	481	583
Not a resident of five Bay Area counties	653	674	697	734	769	923
A resident of Marin, San Mateo or San Francisco	29	28	23	19	35	41
Total, White and living in Alameda or Contra Costa County	4892	4780	5011	5162	5535	5861
No census tracted address	113	112	111	102	108	105
Invalid dates	1	-	1	-	-	-
Total Study employees	4778	4668	4899	5060	5427	5756

STUDY OF LAWRENCE LIVERMORE LABORATORY EMPLOYEES

TABLE 2 - Number of White Employee Cases of Melanoma  
and Person-Years of Observation  
by Year 1972-1977

Year	Number of Cases All Melanoma	Person-Years of Observation
Total	19	28,473
1972	3	4,467
1973	-	4,390
1974	4	4,516
1975	3	4,767
1976	3	5,001
1977	6	5,332

## STUDY OF LAWRENCE LIVERMORE LABORATORY EMPLOYEES

TABLE 3 - Number of White Cases of Invasive and Non-Invasive Melanoma by Age for LLL Employees and the Comparison Cohort

AGE	NUMBER OF CASES					
	LLL EMPLOYEES			COMPARISON COHORT (1)		
	Total	Invasive	Non-Invasive	Total	Invasive	Non-Invasive
TOTAL	19	16	3	185	162	23
15-19	-	-	-	2	1	1
20-24	-	-	-	3	3	-
25-29	1	1	-	21	17	4
30-34	2	2	-	20	20	-
35-39	-	-	-	22	19	3
40-44	5	5	-	28	27	1
45-49	6	4	2	32	28	4
50-54	1	1	-	29	26	3
55-59	3	2	1	13	11	2
60-64	-	-	-	10	7	3
65-69	1	1	-	5	3	2

(1) Those cases that occurred in the age-sex-tract-specific categories for which there was an associated person-year of observation provided by an-LLL employee.

STUDY OF LAWRENCE LIVERMORE LABORATORY EMPLOYEES

Table 4 - Average Number of Person Years of Observation, Per Year by Sex and Age with Percentage Distribution

AGE	AVERAGE PERSON YEARS OF OBSERVATION PER YEAR					
	NUMBER			PERCENT		
	Total	Male	Female	Total	Male	Female
TOTAL	4,745	3,958	787	100.0	100.0	100.0
15-19	19	7	12	0.4	0.2	1.5
20-24	196	121	75	4.2	3.1	9.5
25-29	461	339	122	9.7	8.5	15.5
30-34	640	527	113	13.5	13.3	14.4
35-39	678	566	112	14.3	14.3	14.2
40-44	719	616	103	15.1	15.5	13.1
45-49	714	624	90	15.0	15.8	11.5
50-54	637	562	75	13.4	14.2	9.5
55-59	471	411	60	9.9	10.4	7.6
60-64	185	163	22	4.0	4.1	2.8
65-69	25	22	3	0.5	0.6	0.4

STUDY OF LAWRENCE LIVERMORE LABORATORY EMPLOYEES

TABLE 5 - Comparison of the Number of Melanoma Cases, and Truncated Age-Adjusted Rates <sup>(1)</sup> White Males, 1972-1977

COMPARISON GROUP	NUMBER OF CASES AGE 20-64	AGE-ADJUSTED RATE PER 100,000
LLL Employees	16	57.2 (a)
Census Tracts Where Employees' Live (2)	137	11.7 (a)
Alameda County (2)	159	11.0
Livermore/Pleasanton Valley (2)	14	11.9
Livermore Area (2)	6	11.9

- (1) All melanoma cases, in the white male population age 20-64 were used to compute age-adjusted rates by the direct method using Alameda County population of 1970 as a standard.
- (2) The case count and population used for computing age-specific rates in all comparison groups excludes LLL cases and population.
- (a) Only Alameda County cases and population were used in computing the rate.



TABLE 6 - Number of Observed and Expected Cases and Z Statistics for all Melanoma and Invasive Melanoma Among White LLL Employees, By Year and Sex

METHOD A

ALL MELANOMA		YEAR					TOTAL	Z	
		1972	1973	1974	1975	1976			1977
Male	Observed	2	0	3	3	3	6	17	
	Expected	0.34	0.17	0.80	0.68	1.20	1.94	5.13	5.61
Female	Observed	1	0	1	0	0	0	2	
	Expected	0.21	0.05	0.10	0.21	0.19	0.04	0.80	0.81
TOTAL	Observed	3	0	4	3	3	6	19	
	Expected	0.55	0.22	0.90	0.89	1.39	1.98	5.93	5.70
<b>INVASIVE ONLY</b>									
Male	Observed	2	0	3	3	3	3	14	
	Expected	0.34	0.17	0.80	0.68	1.15	0.94	4.08	5.34
Female	Observed	1	0	1	0	0	0	2	
	Expected	0.21	0.05	0.10	0.17	0.09	0.04	0.66	1.05
TOTAL	Observed	3	0	4	3	3	3	16	
	Expected	0.55	0.22	0.90	0.85	1.24	0.98	4.74	5.56

TABLE 7 - Number of Observed and Expected Cases and O/E Ratios for all Melanoma and Invasive Melanoma Among White LLL Employees, by Year and by Sex

METHOD B

ALL MELANOMA		YEAR					TOTAL	O/E	
		1972	1973	1974	1975	1976			1977
Male	Observed	2	0	3	3	3	6	17	4.40
	Expected	0.31	0.17	0.94	0.78	1.07	0.59	3.87	
Female	Observed	1	0	1	0	0	0	2	2.74
	Expected	0.19	0.05	0.04	0.22	0.19	0.04	0.73	
TOTAL	Observed	3	0	4	3	3	6	19	4.13
	Expected	0.50	0.22	0.98	1.00	1.26	0.63	4.60	
<u>INVASIVE ONLY</u>									
Male	Observed	2	0	3	3	3	3	14	3.74
	Expected	0.31	0.17	0.94	0.78	1.01	0.52	3.74	
Female	Observed	1	0	1	0	0	0	2	3.36
	Expected	0.19	0.05	0.04	0.18	0.09	0.04	0.60	
TOTAL	Observed	3	0	4	3	3	3	16	3.69
	Expected	0.50	0.22	0.98	0.96	1.10	0.56	4.34	

## RECORD LINKAGE

A study of this nature is not practical without the assistance of a record linkage computer program. The fundamental problem of record linkage is that two large files must be compared to determine which records are common to both, with no unique, reliable, and common record identifier available for matching purposes. Use of the Social Security number does not satisfy this requirement for several reasons: (1) it may be missing from one or both files; (2) it may be in error on one file (or both); or, (3) the Social Security number may be correct but different on each file, because some individuals have more than one social security number. The Social Security number is missing for over 20 percent of the cases in the CIS file.

In the absence of a unique identifier, record linkage is predicated on pairwise comparisons of items of identification which are common to the records of each file, e.g., name, birthdate and/or Social Security number. These items of information are utilized in record linkage to evaluate the likelihood that a particular comparison pair is a match.

The problem of performing record linkage is exacerbated by the fact that these items of identification are products of a record generating process which can significantly affect the form in which these identifying components appear on the records which are to be compared. Although most changes which occur in the record generating process do not pose problems for clerical review, these changes do present serious difficulties to computer assisted record linkage. For example, the occurrence of nicknames (e.g., Bill for William) may be more frequent in one file than in the other. Therefore, record linkage computer programs must be sufficiently flexible to accommodate the occurrence of these and other interfile characteristic differences in addition to the possible presence of transcription and/or reporting errors in the records of each file.

The LLL annual files which were desired to be matched with the CIS reference file are referred to as the transaction files in record linkage nomenclature. These transaction files required additional preprocessing before linkage could be performed. For all record linkage applications the transaction file must be sorted into a configuration similar to the reference file. The reason for this is that when matching two large files (the most current CIS master file has 100,197 records), it is not possible to compare all possible pairs of transaction and reference records. Therefore, each file is blocked and only transaction and reference records occupying the same blocks are compared. The system currently employed involves blocking each file by NYIIS (New York State Identification Information System) surname phonetic code and sex.

Record linkage software was developed for this study adapting the Fellegi-Sunter record linkage model. This is a two-sample variant of the linkage procedures employed in the ongoing file updating for the CIS.

The record linkage program generates all possible pairs of records within a surname phonetic code and sex block (one record from each file) and makes one of three decisions for each comparison pair, viz., the pair is a certain match, the pair is a possible match, and the pair is a non-match. This decision rule involves the assessment of the magnitude of a summary linkage weight relative to fixed threshold values. This summary linkage weight for each comparison pair is calculated as the log of the ratio of two conditional probabilities which are each composed of products of conditionally independent and empirically estimated probabilities. The estimation of the parameters of probability distributions for the nine linkage components, i.e., surname, first name, middle initial, day, month and year of birth, and Social Security number (partitioned into its three components) was performed using the CIS master file immediately prior to the LLL record linkage production runs.

The record linkage software is designed so that the two threshold values (upper and lower) which determine whether a pair of compared records is a non-match, possible match or certain match, can be set by the user, depending on the degree to which one wishes to rely on the automated linkage decisions, and the degree to which one is willing to review those record pairs falling between the threshold values (possible matches). The threshold value which separates the possible matches from the non-matches was chosen to be as low as possible and this choice substantially increased the number of possible matches for review. In fact, all linkage decisions which resulted in certain or possible matches were reviewed. Following manual review it was determined that all "certain" matches did represent the same person, and that there was either insufficient information available for "possible" matches to make such a determination or that they clearly represented different people.

The structure of record linkage processing which requires blocking of the comparison files can result in the occurrence of false negative matches. This type of failure in record linkage is referred to as the problem of implicit non-matches--the failure of an individual to occupy the same comparison block on each file. There are several occurrences which can result in implicit non-matches, including sex code errors, surname changes or gross errors in surname transcription, and Chinese name transposition. For this study, additional record linkage computer runs were performed with the transaction and reference files blocked by year of birth. Consequently, the only possible implicit non-links which may not have been detected during record linkage would consist of those cases where intra-file discrepancies existed for both surname and birth year.

In summary, the employee cases used in the study as "observed" include only those "certain" matches which also resided in either Alameda or Contra Costa counties at the time of diagnosis and were diagnosed concurrent with active employment at the LLL.

## UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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May 14, 1980

Honorable S. Floyd Mori  
Chairman, Joint Legislative Audit Committee  
State Capitol  
Sacramento, California 95814

Dear Assemblyman Mori:

I have examined the recently completed study conducted by the California Department of Health Services, which you enclosed in your letter to me, and I believe this report makes a persuasive case that the incidence of malignant melanoma among the employees of Lawrence Livermore Laboratory is indeed elevated at a rate approximately 5 times that to be expected.

Your letter makes two requests, (1) "comments on the study itself including any additional investigation necessary to provide a thorough understanding of the reported cases of malignant melanoma", and (2) "recommendations for appropriate action in response to the research findings including any health and safety precautionary measures."

I believe this preliminary study answers the question originally raised, namely, is the alleged rate of malignant melanoma among LLL employees greater than that expected? The evidence that this is indeed the case seems convincing. The next question to be answered is why should this be so. The study itself points out a feature which is considered to be of considerable importance; namely, that despite this increase in the rate of melanoma, that other types of cancer have not increased. In particular, the types of cancers that one might expect to be caused by exposure to radiation—one of which was specifically looked for (leukemias) was found not to be increased. The study did not specifically evaluate other types of cancers in any detail. Melanoma is a rather uncommon tumor which has not been associated with exposure to radiation. It is significant that it should now become the most common malignancy diagnosed among the employees of the LLL.

In order to answer your second question regarding preventive steps or safety measures to be taken, we will have to have more information as to why this particular population is at an increased risk for melanoma. When an explanation for this increased risk is at hand, then the design of appropriate health and safety precautions may be devised. In its present form, this study, while establishing the fact of increased risk, can give no clue as to the cause of it.

In order to account for the increased incidence of melanoma, while at the same time explaining a lack of such increase for other cancers, one's attention is drawn to the differences between melanoma and other cancers. There is a considerable amount of information available regarding the biology of melanoma, which accounts for some of the known differences between the behavior of this tumor and cancers more generally, and it is along these lines that the next phase of the investigation might well be directed. In particular, since this Livermore problem is one of melanoma specifically, and not carcinogenesis generally, it would appear sensible to investigate this matter through the use of current knowledge of this particular tumor. We have had some experience with such matters at the University of California Medical Center, San Francisco, and if we can be of any help, we would be most pleased to do so. Some of the steps that could be taken in this respect are briefly described in the appendix to this letter.

I understand your deep concern about this matter and I believe the quickest way to make progress that would lead to effective prevention would be accomplished by carrying out studies along the lines of those proposed in the appendix.

Very truly yours,



Richard W. Sagebiel, M.D.  
Associate Professor of Pathology  
and Dermatology  
Co-Director, Melanoma Clinic  
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RWS:db  
Enc.

## LAWRENCE LIVERMORE LABORATORY REVIEW

The following suggestions seem pertinent from a review of the Department of Health Services Report #1, dated April 17, 1980:

- I. GROUP MEETING OF CONSULTANTS
  - A. Local Consultant Group
  - B. National Consultant Group
  
- II. CLUSTER STUDY
  - A. Histologic Review
  - B. Patient Interview
    - 1. Ultraviolet exposure history, recreational, occupational
    - 2. Chemical exposure
    - 3. Radiation, criticality areas, accidents
  - C. Physical Examination of Patients
    - 1. Skin type and degree of pigmentation
    - 2. Unusual sites outside of demographic norms
    - 3. Psychosocial evaluation of patients, co-workers and controls
  
- III. PUBLIC EDUCATION OPPORTUNITY
  - A. Queensland Melanoma Group Record
  - B. Increased Incidence of Bay Area Malignant Melanoma Compared to LLL
  
- IV. APPENDICES

## I. GROUP MEETING OF CONSULTANTS

Individuals from various specialties have been asked to review the report on the incidence of cancer in the Lawrence Livermore Laboratory employees. They must have a varied background regarding the biology of malignant melanoma. Prior to such a meeting, circulated suggestions regarding specific studies could be circulated to the consultants for study and the meeting could accomplish two purposes:

1. Brief introductory remarks regarding special characteristics of malignant melanoma as a representative "cluster" cancer.
2. Discussion of the proposed recommendations for further study.

It would seem efficient to form a local group committee to over-see the recommendations, review the pathology and examine the patients. The National Consultants could then review policy and results.

## II. CLUSTER STUDY

Previous clustered high incidence reports of malignant melanoma are known from New Jersey, Oregon, and Sacramento. These have not been studied as to demographic or histopathologic characteristics. The fact that clusters of this neoplasm exist is of extreme importance in possible etiologic factors, perhaps related to Public Health measures of specific environmental health factors.

If unique factors could be identified related to the increased incidence of melanoma in the LLL, it might be possible to obtain exceedingly vital information regarding the biology of this neoplasm and presumably related malignancies. Depending on job history, one might be able to obtain information regarding the latent period of induction of cancer from exposure to clinical disease. One might prevent development of



neoplastic transformation by appropriate protective measures.

### III. PUBLIC EDUCATION OPPORTUNITY

The experience of the Queensland Melanoma Group in Australia, where the incidence of malignant melanoma is the highest in the world, has demonstrated that education of both lay and physician public can result in early diagnosis and subsequent improvement of mortality in melanoma. Education regarding sun exposure, skin types with propensity for developing melanoma, and early changes in pigmented lesions could be emphasized. A large amount of public information regarding the Livermore incidence has already been disseminated and the public is ready for further educational opportunities.

### IV. APPENDICES

The following forms regarding patient interview, histopathologic examination and psychosocial evaluation are currently in use in the Pigmented Lesion Study Group at the Melanoma Clinic, University of California, San Francisco.

As a primary referral resource for Northern California, the University of California, San Francisco, Melanoma Clinic has provided consultation for over 1,500 melanoma patients since its founding in 1971. This Clinic was a member of the Malignant Melanoma Cooperative Group, a four institution group (together with Harvard, New York University, and Temple) which accessioned 1,200 successive patients during the period 1973-77. We are currently developing a melanoma clinical data base in conjunction with the University of Pennsylvania and SRI International, under a grant from the National Cancer Institute.

These circumstances are mentioned since one important extension of the study conducted by the State Department of Health Services would be to compare the melanoma cases at Lawrence Livermore Laboratory in much more detail with cohorts of cases taken from the San Francisco Bay Area, and from Northern California. Such a comparison should include such patient attributes as site, type and level (the LLL cases should be reviewed by our reference pathologist to permit this comparison), clonism, presence of regressive phenomena, skin type, presence of pre-existing nevi, etc. This more detailed study will be necessary to determine whether the LLL cases represent an increased incidence of melanoma per se, or whether a different type of melanoma may be involved.

(1) There has been a widespread (indeed national) increase in the incidence of melanoma, which appears to be beyond that explainable on the basis of more thorough case detection. In the San Francisco Bay Area for example, the incidence has approximately doubled over the past decade. This observation cannot account for the LLL cases, but it might suggest that whatever factors are responsible for this general increase, might be operative in the LLL cases to a larger degree.

(2) The LLL cases do not represent the only instance of a microgeographical role in melanoma, although it is probably the one best documented. A localized area near Portland has been reported to show an increased incidence of melanoma which is statistically significant. We understand informally from colleagues in melanoma research that there may be a similar cluster of melanoma cases in New Jersey. Finally, we suspect that there may be another such microgeographical group in California, but since we do not have the resources to study this, it is still a conjecture.

(3) A feature commented upon briefly, but importantly, in the report is the observation that melanoma is not considered to be associated with exposure to ionizing radiation. On the basis of present knowledge, if a population of individuals were to be exposed to increased levels of ionizing radiation, the first forms of cancer to be found would probably be the leukemias which Dr. Austin mentions. Next, perhaps would be lymphomas and then carcinomas of various tissues. Last of all would probably be tumors of components of the nervous system. The melanocyte, being of neural crest origin, and the cell of origin for melanoma, shares many biological features with nervous tissues including an increased resistance to ionizing radiation. This is not to argue that ionizing radiation should be dismissed from consideration in the LLL cases, but that since it presumably cannot account for the rise in melanoma incidence in the general population, nor the other proposed clusters, that there are other more promising hypotheses. The most significant finding in the LLL study, is that a greatly increased incidence of melanoma is found without any increase observed (at least so far, though this was looked for in the case of leukemia) in the other forms of cancer. This all raises a final point.

(4) If it turns out the melanoma alone is so dramatically increased, then one's attention is drawn not to general issues of carcinogenesis, but specifically to the question 'what distinguishes the melanocyte from other cells, which could have a bearing upon the way these cells respond to environmental influences?' This line of reasoning seems most promising. The most striking difference between melanocytes and other cells is their having a wholly unique biochemical apparatus for the synthesis of melanin pigment. The final product of this synthesis is a material, melanin, which has unusual--but well known properties--with the ability to bind and accumulate toxic or other exogenous materials. The retinopathy caused by chloroquine, for example, may arise through this mechanism. We suggest therefore that a most promising line of inquiry into this matter would be the study of environmental factors which could act via this mechanism and thus to account for the remarkable difference between the production of melanoma and the non-production of other malignancies.

## UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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SANTA BARBARA • SANTA CRUZ

DEPARTMENT OF RADIATION ONCOLOGY

SAN FRANCISCO, CALIFORNIA 94143

12 May 1980

S. Floyd Mori  
Chairman, Joint Legislative Audit Committee  
925 L Street, Suite 750  
Sacramento, California 95814

Dear Mr. Mori:

I have reviewed the study of cancer incidence in Lawrence Livermore Laboratory employees. I find it an exceedingly interesting study and well done in so far as it goes. However, it raises more questions than it answers. I believe the questions are highly significant and thoroughly merit an additional and more detailed investigation.

The study indicates the incidence of malignant melanoma in LLL employees is approximately 5 times that expected. The increased risk does not extend to the local community. There was no increase of the types of malignancies usually associated with ionizing radiation in the LLL employees. I am unaware of any literature associating the occurrence of malignant melanoma with radiation other than ultraviolet. These points are all brought out by the author of the manuscript.

I understand that in personnel exposed to "Operation Smokey" there is approximately twice the expected incidence of melanoma. The difference is of borderline significance. If real, it is presently unexplained. Dr. Glyn C. Caldwell (Chief, Cancer Branch, Center for Disease Control) is familiar with this study.

I think it necessary to attempt to identify the factor(s) responsible for the increased incidence of malignant melanoma. Some possibilities follow. Is there a difference in life style, before and/or during their employment at LLL that might lead to an increased ultraviolet exposure? Is or was there occupational exposure to UV radiation? What types of chemical exposures have they had? On what part of the body did the lesions occur? Were they limited to areas exposed to sun, other UV sources or chemicals? If so, such features as sunbathing and hiking (particularly at high elevations) would need investigation. Is there a relationship between duration of employment and risk of malignant melanoma? Duration of exposure(s) and interval between exposure(s) and appearance of the malignant melanoma need investigation. Which employees developed the melanomas? Did they have a particular type of prior history (for example, residence in Los Alamos, New Mexico) or of common types of occupational tasks?



DEPARTMENT OF RADIATION ONCOLOGY

SAN FRANCISCO, CALIFORNIA 94143

In summary, Dr. Austin and his staff have uncovered a very interesting and significant finding which requires further attempt at explanation. I would think both Federal and State agencies would be interested in this problem. I suggest that a local task force be established and charged with designing an appropriate study. Such a group, of course, should make use of all information and recommendations submitted by the various authorities whom you have solicited.

Until there is an adequate explanation of the reported increased risk of malignant melanoma, I would not know what additional health and safety precautionary measures to recommend.

I hope that these comments are of help to you. If I can be of further assistance, please let me know.

Sincerely,

A handwritten signature in cursive script, reading "Glenn E. Sheline".

Glenn E. Sheline, Ph.D., M.D.  
Professor and Vice-Chairman  
Department of Radiation Oncology

GES:cls

## UNIVERSITY OF CALIFORNIA, BERKELEY

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SANTA BARBARA • SANTA CRUZ

SCHOOL OF PUBLIC HEALTH  
DEPARTMENT OF BIOMEDICAL AND  
ENVIRONMENTAL HEALTH SCIENCES

EARL WARREN HALL  
BERKELEY, CALIFORNIA 94720

May 20, 1980

S. Floyd Mori, Chairman  
Joint Legislative Audit Committee  
California Legislature  
State Capitol  
Sacramento, CA 95814

Dear Assemblyman Mori:

Please forgive my delay in answering your letter of April 30, 1980 concerning the "study of cancer incidence in Lawrence Livermore Laboratory employees." Today I have spoken with your administrative assistant and have given her the gist of my comments. I am, herewith, providing you with written confirmation.

First, let me say that I do not think that any specific actions of a precautionary nature can be recommended as a result of the research findings to date. As you know, radiation has not been implicated heretofore as a risk factor for malignant melanoma. I would expect that all research facilities which handle radioactive materials are already exercising maximum safety measures.

With respect to the study itself, I think that one can be reasonably confident that the findings are valid. The methodology employed by Dr. Austin was perfectly straightforward and appropriate. Unless some serious procedural errors affected his operation, the excess incidence demonstrated is unlikely to be due to the methodology employed. Nevertheless, I would want a statistician to take a look at the statistical methods section to be sure that it is correct, and I would like to see appendices to the paper containing the actual calculations from which the expected cases were generated. The key problem in analyses of this kind is the validity of the calculated expectancies.

It seems likely that a very high proportion of cancers occurring in research workers in a radiation laboratory will be properly reported to a cancer registry. It is not quite as likely that all cases occurring in a population will be reported. While Dr. Austin states that the tumor registry is 98% accurate for all cancers, he provides no evidence that malignant melanoma is also fully reported. It is conceivable that because this is a skin tumor and skin cancers are generally not reported to registries, that there may be some underreporting. Nevertheless, I would not expect that this could account for the large excess demonstrated.

One way to assess the comparability of the reporting would be to provide information on deaths among the nineteen laboratory cases and the 180 odd population cases. Of course, other factors can affect case fatality but it would be interesting to see this information and it could be easily generated.

Having demonstrated the excess incidence of malignant melanoma to be valid, it is important to proceed with a study to elucidate the reason for the excess. The minimum effort should include a case-control study in the laboratory personnel to see how the cases differ from the rest of the laboratory population with respect to a variety of characteristics which might influence the occurrence of this disease. High on my list of putative risk factors would be: cigarette smoking, radiation exposure, chemical exposure, and interactions between these and other factors.

If I can be of any additional assistance in this matter, please do not hesitate to call on me.

Sincerely yours,



Warren Winkelstein, Jr.  
Dean and Professor of Epidemiology

WW:dd



## UNIVERSITY OF CALIFORNIA, DAVIS

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SANTA BARBARA • SANTA CRUZ

SCHOOL OF MEDICINE

Reply to:

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May 12, 1980

Assemblyman S. Floyd Mori, Chairman  
Joint Legislative Audit Committee  
California Legislature  
State Capitol  
Sacramento, CA 95814

Dear Assemblyman Mori:

I greatly appreciate the opportunity to review and comment on the report, "A Study of Cancer Incidence in Lawrence Livermore Laboratory Employees." The results of this study raise a number of concerns which are readily apparent but also suggest the need for further evaluation which would place this study in a more realistic perspective. It is clear from the report that the suspected high incidence of melanoma was first brought to light because employees from LLL were seeking medical care for melanoma. In response to this, a retrospective study was carried out utilizing the California Tumor Registry, and the suspected high incidence was confirmed. This is a classical approach to identifying high incidence rates, but when dealing with small populations, such as was done in this study, the mere fact that the incidence rate appears higher does not negate the possibility that this could be an example of "rare things happening rarely." By that I mean that malignant melanoma is a rare disease and that by chance alone there are apt to be higher incidences of this disease at one time among one population and a lower incidence of this disease among another population. It is now currently felt that a number of so-called epidemics of acute leukemia which have been reported over the past 20 years in various parts of the country are best explained by "rare things happening rarely."

Should the data be valid, and should this represent a true high incidence of malignant melanoma among LLL employees, one must then identify why this occurs. Based upon our current knowledge, this is not the result of radiation injury since this disease has not been previously reported to be caused by radiation. Were this to be the cause, then one would have anticipated an increased incidence of epidermoid and basal cell malignancies of the skin as well as increased instance of leukemia, lymphoma, and perhaps Hodgkin's disease, cancer

of the lung, and osteogenic sarcoma since these diseases are known to be induced in some cases by radiation. Only the incidence of leukemia was sought for in these studies, and there were no cases of leukemia reported, suggesting that working at LLL protects one against leukemia since the incidence of leukemia is generally twice that of malignant melanoma. I realize that it does not seem reasonable to interpret the data from LLL in this light, but would suggest that it may be just as valid to interpret these limited data as being protective of certain types of malignancy as it is to publicize these data as indicating there is a higher incidence of melanoma at Lawrence Livermore, particularly when there is no identified cause at LLL.

I would suggest that these studies be looked at as preliminary and that in-depth evaluation of these data be carried out. For instance, a careful case study of each of the 19 individuals with malignant melanoma should be undertaken with review of the pathologic slides by a competent dermatopathologist. The location of the malignancies should be noted since it is well known that melanomas which are at times secondary to ultraviolet radiation appear on the exposed portions of the body, that is the face, arms, legs, etc. Was this the case at LLL, or did melanomas occur in unexposed areas of the body, suggesting that perhaps it was something on the clothing which was responsible, or did this appear at random over the body surface? Since melanoma is known to have a higher incidence rate in those who are exposed to the sun, it would be important to know the work habits of those individuals at LLL who develop melanoma. Perhaps they were employees who worked the night shift, thus having at least a portion of the day during which they were out of doors, exposed to ultraviolet radiation. It may also have been that the individuals were day-time workers assigned to outdoor jobs and thus had a higher incidence of exposure. In this review of the 19 patients with melanoma, a careful family history should also be obtained. A small number of melanomas are familial, and among families where melanoma is common, up to 5% of members of the family will have melanomas. These melanomas tend to occur earlier in life with a peak age of 42 instead of the peak age of more nearly 50 which is associated with non-familial melanoma. Twenty-six percent of the melanomas in LLL employees occurred between the ages of 40 and 44, whereas in a comparison cohort, only 17% occurred within those age ranges. Perhaps there are several families with familial melanoma in the Alameda County area who work at Livermore, giving a suspected higher incidence of this disease at the Laboratory.

In reading the report, I was surprised that there was not attention given to relating the duration of employment at LLL to the incidence of melanoma. If indeed this is a disease which occurs because of industrial exposure, then there should be an increased incidence with longevity of employment. These data would be extremely easy to come by since there were only 19 cases reported in the study. In addition, a very careful work history should be obtained on these individuals as suggested above with relationship to not only what their jobs were at the laboratory and

Assemblyman S. Floyd Mori

May 12, 1980

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how long they worked at these various jobs, but also what was their industrial exposure prior to coming to the laboratories.

In attempting to look at all sides of the problem, I have considered the possibility that earlier detection of melanoma among LLL employees might account for the supposed higher incidence. This phenomenon is certainly well known in medicine, but I think probably does not apply to these studies, although I am quite certain that workers at the laboratory would be more apt to contact their physician if there was a change in a mole on their skin than perhaps employees working elsewhere, since their awareness of a potential higher incidence of malignant melanoma has most certainly been brought to their attention.

Apparently there has been no attempt made to follow up on individuals who have been employed at the laboratories and then left that employment. Although this would be somewhat difficult, I would anticipate that such a review could be carried out, perhaps using social security numbers which would at least identify the majority of former workers at the laboratory. If the incidence of melanoma could be confirmed as being high among these individuals also, I think this would lend greater credence to this study. A very careful epidemiologic evaluation of these patients, in addition to the 19 who have already been identified, might very well lead us to a rational explanation for why this higher incidence appears to exist at LLL. It is very doubtful, based upon our current information, that this higher incidence, if confirmed, would be related to radiation exposure.

I believe there is probably an error in the report. On page 11, second paragraph, it states that "consequently the chance of erroneous diagnoses are greater with invasive melanoma." I believe that should probably read "non-invasive." Another error in the report is to be found on page 12, third paragraph. Chronic lymphocytic leukemia is not associated with radiation exposure. Those leukemias which are include acute myelogenous leukemia, acute lymphocytic leukemia, and chronic myelogenous leukemia. With reference to the conclusions on pages 12 and 13, certainly the first five appear to be substantiated by the report, although I believe they should be looked at as only preliminary since the concerns I have raised above I feel should be investigated before any firm conclusions would be made. The sixth conclusion, for reasons stated, is indeed preliminary and really requires additional evaluation before such a statement can be made. The seventh conclusion is indeed true, and since there is no obvious cause and effect, one must raise the question as to whether or not the effect seen has any relationship at all to employment at LLL. Were one trying to develop a case for the laboratories being hazardous secondary to low-level radiation exposure, one would first want to document the fact that such radiation exposure does exist, and I see no data on this at all in the document, and that those malignancies which are associated with radiation exposure are indeed higher among employees of the laboratory. These have been mentioned earlier and include epidermoid cancer of the

Assemblyman S. Floyd Mori

May 12, 1980

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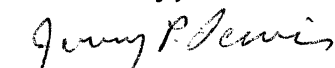
skin, certain leukemias, osteogenic sarcoma, etc. This type of evaluation has not been done.

The overall implications of this for state health planning can be looked upon in its narrowest sense and one can focus merely on the particular question of melanoma occurring because of exposure at the work place at the LLL, or it can be looked at in a much broader context, that of--are there other areas in the state where there is a higher incidence of malignancies which might possibly be related to industrial exposure. What one sees in this report is a chance occurrence of several clinicians making the observation that there appeared to be a higher incidence of melanoma at Lawrence Livermore Laboratories. If one is truly serious about identifying an increased incidence of malignancy, one cannot rely upon the alertness and astuteness of busy practitioners to bring this to the attention of the proper authorities. What is needed is an incidence based tumor registry, such as was finally used in this report, to develop proper statistical relationships to support an increased incidence. A number of states are mandating cancer as a reportable disease and mandating funding by third party carriers for tumor registries to permit the development of such data. Although the mechanisms are in place in California for such population tumor based registries, they are not mandated as yet, and thus such data are not uniformly available throughout the state. It would be prudent for the state to require the reporting of cancer incidences and to provide mechanisms for the epidemiologic studies which need to be done when suspected areas of higher incidence are detected. Our current mechanism of recording incidence by death certificates is far too late, imprecise, and cumbersome to permit a direct attack on cancer caused in the work place.

In closing, I would like to bring to your attention that malignant melanoma is an excellent example of a tumor which is best managed by early detection. Programs in such areas of the world where malignant melanoma has a very high incidence have developed a high level of awareness on the part of the population and very early melanomas are recognized and treated. When these malignancies are treated early, the cure rate is exceedingly high. If it is decided that there indeed is a higher incidence of melanoma at LLL, regardless of the cause, then it would be appropriate to institute such an educational program for employees at the laboratory so that when a mole changes its character it can be immediately evaluated, removed if necessary, and if it is a malignant melanoma, chances of cure would be considerably higher than if such an educational program does not take place and a lesion becomes far advanced before the employee becomes concerned.

I have found this study of considerable interest. I hope that you will find my comments of some help.

Sincerely,



E-4

Jerry P. Lewis, M.D.

Professor of Medicine & Pathology  
Chief, Section of Hematology  
and Oncology

JPL:lb

## The Permanente Medical Group

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May 12, 1980

S. Floyd Mori, Chairman  
Joint Legislative Audit Committee  
State Capitol Building  
925 L Street, Suite 750  
Sacramento, California 95814

Dear Mr. Mori:

This correspondence is in answer to your letter sent to me on April 30, 1980 concerning the apparent increased incidence of malignant melanoma in the employees of the Lawrence Livermore Laboratory. I am writing this letter to you as a practicing oncologist at the Kaiser Permanente Medical Health Center, a prepaid health plan serving greater than a quarter of a million patients. We see a great deal of malignant melanoma and are cognizant of its increased incidence. It is a very difficult disease to treat, often striking people in their most productive years of life. Although initial surgical therapy is often effective, there is no treatment of significant proven benefit for recurrent disease, despite a great deal of research in progress at this time.

I have several comments as to the study which was submitted to me. First, in the definition of malignant melanoma, I feel that the histologic group superficial spreading melanoma cannot be excluded from the definition of malignant melanoma, as this type can be as potentially dangerous and lethal as other histologic groups. It is also the most common type of malignant melanoma. Secondly, I would be very interested to know more about the patients that developed malignant melanoma while working at the Lawrence Livermore Lab, specifically, how long had they been employees at the laboratory, what type of occupational history did they have prior to joining the laboratory, and were there any common denominators in their prior occupational history? I would also be interested in knowing if any of the cases of malignant melanoma occurred in the same family. Thirdly, I would also be interested in knowing the specific histologies of the malignant melanomas, specifically, how many represented nodular histologies, how many represented lentigo maligna histologies and how many represented superficial spreading histology. I would also be interested in the number of lesions stratified as to the depth of invasion, either in millimeters or by Clark's method of level of invasion. Fourthly, I would be interested in knowing whether other laboratories doing similar activities

as the Lawrence Livermore Laboratory have also noted increase in incidence of malignant melanoma.

As far as appropriate action to be taken in response to the research findings, I feel that a strong educational program must be employed. As you well know, the general public knows very little about this disease. I think there should be educational maneuvers initiated which would stress that certain types of people have increased incidence of malignant melanoma, specifically those with fair and ruddy complexions, and those with a family history of malignant melanoma. Certainly these patients should be aware of this and know that perhaps the use of sun screens may be beneficial. It should be reiterated to all people that malignant melanoma is no longer a rare form of cancer, that it is probably more common than Hodgkin's disease at this time, and that it affects people in the prime of their life but can be curable if found early. Any change in skin pigmentation such as color changes, advancing margins, bleeding, ulceration etc. may be ominous symptoms and would warrant the consultation and evaluation by appropriate physicians.

Finally, I should tell you that the incidence of malignant melanoma has increased greatly at our institution from an incidence of three tenths per ten thousand patients in 1972 to an incidence of 1.4 per ten thousand in 1975 to an incidence thus far in 1980 of 2.2 per ten thousand patients. Whereas this incidence as yet is not as great as being experienced in the Livermore area, it is certainly of some concern. Along these lines, I feel that we are not always able to know what the true incidence of malignant melanoma and other malignancies are without the implementation of tumor registries which document the incidence of all malignancies. At this time in the state of California, there are tumor registries in existence at many of the larger hospitals both in southern California and northern California; however, tumor registries do not exist in some of the major hospitals and without them, I feel it is difficult always to know what epidemiologic trends are developing in malignant diseases and therefore what might be done to alter these trends.

I hope that my comments will be of some use to you. I certainly agree that we need to take a hard, fast look at why melanoma is increasing both in the Livermore area as well as in other areas in the United States.

Sincerely yours,

*Ed Hearn MD*

Edward W. Hearn, M.D.  
Chief, Medical Oncology & Hematology

EWH/jl

Addendum: The best definition of malignant melanoma includes all histologies which are invasive--i.e., Clark's level II or greater (goes deeper than epidermis).



## NEW YORK UNIVERSITY MEDICAL CENTER

Institute of Environmental Medicine  
Health Survey Unit

341 EAST 25TH STREET, NEW YORK, N.Y. 10010  
AREA 212 685-5930

May 16, 1980

The Honorable S. Floyd Mori  
Chairman Joint Legislative  
Audit Committee  
California Legislature  
State Capitol  
Sacramento, California 95814

Dear Assemblyman Mori:

Enclosed are my comments on Dr. Austin's study of cancer incidence among Lawrence Livermore Laboratory employees. The first section provides a somewhat detailed critique of specific points, while the second and third sections provide a general critique and recommendations.

I believe it would be premature to mandate unusual health and safety measures at the Lawrence Livermore Laboratory at this point, since Austin's study has provided no evidence that the malignant melanoma excess is related to radiation. However, as I discuss in my recommendations, a preliminary study could be performed in 4-6 months time which would give a fair estimation as to whether radiation is a culprit. At that point a reasonable decision could probably be made as to whether stringent actions are necessary, even though the definitive study I also recommend would only be nicely started.

Sincerely,

Roy E. Shore, Ph.D.  
Associate Professor

RES:ly  
Encl.

Comments on the Report: "A Study of Cancer Incidence in  
Lawrence Livermore Laboratory Employees" by Donald F. Austin, M.D.

(Dated 4/17/80)

By

Roy E. Shore, Ph.D.  
Dept. of Environmental Medicine  
New York University Medical Center  
341 East 25th Street  
New York, New York 10010

This evaluation will be made in three sections: specific comments, overall evaluation, and recommendations for further research.

#### SPECIFIC COMMENTS

There are several methodologic points of varying importance which merit comment. Two of these have to do with potential biases in the study.

First is the potential bias introduced by taking only a cross sectional slice in time (1972-77) for the Lawrence Livermore Laboratory (LLL hereafter) workers, especially when there was already a suspicion of an excess during that period. In a methodologically correct follow-up (or "cohort") study, workers would be considered "at risk" for a suspected occupation-related hazard from the time of initial exposure (or following some assumed latent period after the onset of exposure in the case of cancer) until the time of most recent observation. Thus the expected values (as in Table 7) would be accumulated across all years of follow-up post-onset of exposure. By way of contrast, in the LLL report, only recent years of observation, during which there was already suspicion of a malignant melanoma excess, were accumulated to define the observed and expected values. The observed values during this period may well represent a chance upward excursion (compared to the average long term rate in the LLL population). Thus, there is reason to suspect that the observed malignant



melanoma rate may be an overestimate of the prevailing rate, caused by an ad hoc selection of the time frame. The expected values, although correct for that time frame, are underestimates of the expected values for a LLL worker cohort. Hence the observed/expected ratio probably has a nonconservative bias, of unknown magnitude.

Second is the ethnic composition of the LLL worker population versus the general population of the area. In particular, if the percent who are Hispanic/Chicano/Latin (called Hispanic hereafter) differs between the worker and general populations, the results could be seriously biased. Hispanic groups have much lower rates of malignant melanoma than other whites, apparently because of protection by their skin coloration from the carcinogenic effects of sunlight ultraviolet exposure. MacDonald ("Epidemiology of Melanoma." In, *Progress in Clinical Cancer*, vol. 6, 1975, pp. 139-149) compared malignant melanoma incidence rates in Texas for caucasians of Hispanic and non-Hispanic origin. She found that the non-Hispanic rate was over 6 times as great as the Hispanic rate. Similarly, in the New Mexico Tumor Registry during 1969-72, the non-Hispanic rate was 8-10 times as great as the Hispanic rate for both males and females (Waterhouse J, Muir C, et al: *Cancer Incidence in Five Continents*, vol. 111, Lyon, France: International Agency for Research on Cancer, 1976, pp. 212-219).

Because of this differential in malignant melanoma rates, if there is a greater percent of Hispanics in the tumor registry population than in the LLL worker force, the LLL group would appear (spuriously) to have a higher malignant melanoma rate. Whether the percent Hispanic is comparable in the two groups is not known to this reviewer, but can be determined from the author of the LLL report. Obviously, the degree of spurious bias (if any) introduced by the ethnic factor would depend upon the degree of discrepancy between the two populations in the percent Hispanic.

The limitation of the study to current LLL employees is not the preferred way to conduct a cohort study, and may lead to some bias caused by not following those who terminated employment. Such a bias would probably be small and could surely not account for difference of the magnitude found, but it might contribute along with the several other factors.

The LLL report does not indicate why the rather unconventional approach of using specific census tracts to define expected malignant melanoma rates was used. It may have been to help control the ethnic factor referred to above, since individual census tracts are probably more ethnically homogeneous than a whole county or region. However, census tract-based melanoma rates for individual years would be very unstable; the LLL report indicated that most of these sex-, age-, census tract- and year-specific rates were based on either zero or one malignant melanoma case. Thus the result could be an aberrant expected value. The saving grace of the method is that the summation of many unstable rates is likely (but not guaranteed) to produce a reasonable average estimate. Also, the similarity of the rates using different population bases in Table 5 suggests that this method probably did not yield substantial bias.

On page 13 of the LLL report it states that the excess of malignant melanoma "is not the result of an unusual pattern of disease reporting, diagnosis or medical care." Nowhere in the paper could documentation be found for this assertion. In view of the past publicity over malignant melanoma at LLL, one wonders if that assertion is entirely or even approximately true. If the publicity has sensitized workers to seek more intensive medical surveillance, a nonconservative bias may thereby have been introduced.

On page 12 of the LLL report, the analysis of chronic lymphocytic leukemia of an hypothesis of radiation induction is peculiar, in that chronic lymphocytic leukemia is the primary leukemia type which has not been found associated with ionizing radiation in other studies. G-4

GENERAL COMMENTS

Basically this study does not address the issue of whether exposure to ionizing radiation is related to the apparent excess of malignant melanoma at LLL. There is no defined group of radiation-exposed workers which can be compared to a similar non-exposed group by ascertaining their malignant melanoma experience from date of employment to the present. Much less is there any quantitative information on cumulative radiation dose to permit an examination of a dose-response relationship (where malignant melanoma or other selected cancers would be the "response" in question). Nor has any alternative hypothesis been examined as to whether the apparent malignant melanoma excess may be due to exposure to some other agent by the LLL workers.

Thus one is left with the bare finding of an apparent excess of malignant melanoma, but with absolutely no information to provide an etiologic interpretation of the excess. This deficiency makes the study of dubious value. One wonders how the decision was made to spend resources on this kind of study rather than using them to conduct a proper etiologic study.

It would clearly be a non sequitur to infer from the present LLL study that the malignant melanoma excess was caused by ionizing radiation. Not only has no evidence been marshalled to support the radiation hypothesis, but there are two additional lines of evidence against it.

First is the fact that the LLL report indicated there was no evidence that leukemia or "other malignancies usually associated with radiation occurred at a rate any greater than normal" (p.13). If the tissues known to be sensitive to radiation carcinogenesis fail to show any excess in these presumably exposed workers, then it is most unlikely that malignant melanoma, which is not known to be very radiosensitive, would be in excess because of radiation effects.

Secondly, one might entertain the hypothesis that the workers' irradiation was primarily from skin exposures by "hot" particles which yielded alpha or beta irradiation. These two forms of irradiation do not penetrate far (especially alpha particles), so that the skin would be the primary irradiated tissue (i.e., the bone marrow, thyroid gland and other radiosensitive organs would receive little or no irradiation). This hypothesis would explain the failure to find excesses of leukemia and other internal malignancies. However, in this case one would expect to find primarily large excesses of non-melanotic skin cancers. There is evidence that the skin is quite sensitive for the induction of basal cell carcinomas and to a lesser extent squamous cell carcinomas. But in a recent review of the literature on ionizing radiation and skin cancers (Draft Report to the BEIR Committee, 1978) I could find no study which showed a clear relationship between ionizing radiation and malignant melanoma. If there is any relationship at all it is much weaker (probably by at least an order of magnitude) than that between radiation and non-melanotic skin cancer. Thus if there is a large radiation skin hazard at LLL, one would have seen a major epidemic of basal cell and squamous carcinomas, plus perhaps a small number of malignant melanomas. Given that the former has not been reported, it is doubtful that skin irradiation is implicated in the apparent malignant melanoma excess.

Although several possible nonconservative biases in the present study have been discussed in the "specific comments" section (above), it seems doubtful that they can, even collectively, fully account for the large discrepancy between observed and expected malignant melanoma values in the LLL report. There does seem to be an excess of malignant melanoma whose etiology clearly needs to be studied as quickly and thoroughly as possible.

#### RECOMMENDATIONS

There are two types of studies which seem worthwhile performing. The first is a "cohort" (or "follow-up") study of LLL employees. A cohort study is the only way

to provide definitive data as to the relationship between malignant melanoma and radiation or other exposures.

The cohort study would entail developing a complete historical roster of LLL employees and assembling radiation exposure (and other exposures) data for them. They would be traced, using various case-location methods, to determine their vital status and to obtain cause of death for decedents. Although one could stop with a mortality study, it would be much preferable to use tumor registries and subject questionnaires (with medical verification of pertinent diseases) to determine if there are excesses of cancer morbidity related to radiation (or other) exposure. A morbidity study of the cohorts is desirable because some cancers are not very lethal, and mortality data alone may therefore not give an accurate picture. (For instance, for malignant melanoma the average 5-year survival rate is about 70 percent, and the 10-year survival rate about 60 percent). Once the data were obtained one could validly compare exposed and unexposed groups and could examine dose-response relationships, etc. to confirm or disconfirm etiologic hypotheses.

Since the cohort study takes a considerable length of time to perform, a preliminary case-control study is also suggested to quickly examine if there is any apparent relationship between radiation (or other) exposure and malignant melanoma. This would entail choosing some number of matched control (i.e., non-melanoma) workers for each known malignant melanoma case, where matching variables would have to be carefully and appropriately defined. The exposure histories of the cases and control would then be compared to determine whether malignant melanoma status is related to the degree of exposure to ionizing radiation or other agents. While this study would not be definitive (because all the malignant melanoma cases may not have been detected as yet, and those detected may be a biased sample) it nevertheless would provide a quick and reasonable guide as to whether there is any large radiation (or other exposure) effect involved. If the study results are negative, it will

provide a temporary basis for calming public apprehension over radiation (or other occupational exposures) at LLL. Obviously, if it were positive it would be an indication that exposure control measures need to be reviewed.

While I normally would not recommend a preliminary case-control study based on the incomplete ascertainment of cases, in this instance in which 3 1/2 years have elapsed since a possible hazard was identified and no etiologic study has been begun, it does not seem responsible to require another 3-5 year wait (for the cohort study results) before any answer is provided. A preliminary estimate based on a case-control study performed by capable epidemiologists who are aware of the pitfalls in designing and analyzing such occupational studies, would seem to be in order. A cohort study should also clearly be mounted as soon as possible to provide the definitive answers.

I would stress that the studies should be performed by a capable investigator who is experienced in these kinds of studies, because, in this circumstance, a second-rate study is almost as bad as none. There should also be a panel of outside experts in radiation epidemiology, biostatistics and other pertinent specialties to provide continuing review and guidance for the studies at all stages of their development and execution.



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20205

May 9, 1980

NATIONAL CANCER INSTITUTE

Mr. S. Floyd Mori, Chairman  
Joint Legislative Audit Committee  
California Legislature  
925 L Street  
Suite 750  
Sacramento, California 95814

Dear Mr. Mori:

I am writing in response to your letter of 30 April regarding the Austin report on malignant melanoma among Livermore Laboratory employees. I think it would be most unfortunate, in view of the public concern for, and lack of understanding of, the effects of ionizing radiation, if the results given in this report were, without a great deal of further study, taken to have any relation to ionizing radiation.

It appears to me that Dr. Austin has done a careful job of calculating the expected number of melanomas for comparison with the observed number among the Livermore employees. But his study, as reported in his 17 April 1980 manuscript, is not really an epidemiologic study of melanoma in the usual sense. Although stimulated by a specific concern, it seems not to represent the pursuit of a scientific hypothesis and merely confronts us with an unexplained excess related to no specific environmental exposure, genetic background, personal characteristics, or life-style. There is no information about the 19 cases. There is no examination of the material from the standpoint of potential etiologic factors although there is a fairly extensive literature on the epidemiology of melanoma with rather good evidence of a relationship to UV radiation, socio-economic characteristics, genetic background, and life-style. If ionizing radiation were to be seriously entertained as an etiologic hypothesis it would be necessary not only to establish the ionizing radiation exposure (dose) distribution of the cases and of a much larger and representative sample of the Livermore employees from which they are drawn, but also to take into account the influence of these other factors that are believed to influence the likelihood of the disease.

Mr. S. Floyd Mori, Chairman  
May 9, 1980  
Page Two

From his introduction it would appear that Dr. Austin originally undertook the study with minimal resources and that he may not have had more than statistical help available to him. Before anything is made of the finding a much broader look should be taken of the factors that are believed to be significant in the epidemiology of the disease. There are several epidemiologists in the U.S. who have taken an active interest in malignant melanoma, Dr. J. A. H. Lee, Professor of Epidemiology at the University of Washington in Seattle, Dr. Thomas Mack, epidemiologist at the University of Southern California, and Dr. Mark Greene, epidemiologist in the National Cancer Institute here. With some funds for consultation and for the field work that a deeper investigation would require, I should think that Dr. Austin might be able to throw considerably more light on the reported discrepancy than his 17 April report provides. Until such a broad epidemiologic study is performed I believe no inferences should be drawn about the possible relation of the apparent excess to ionizing radiation.

Sincerely yours,



Gilbert W. Beebe, Ph.D.  
Clinical Epidemiology Branch  
A521 Landow Building  
National Cancer Institute-NIH  
Bethesda, Maryland 20205

GWB:ahs





DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20205

May 13, 1980

NATIONAL CANCER INSTITUTE

Mr. S. Floyd Mori  
Chairman, Joint Legislative Audit Committee  
California Legislature  
925 L Street, Suite 750  
Sacramento, CA 95814

Dear Mr. Chairman:

In your letter of April 30, 1980, to Dr. Vincent T. DeVita, Acting Director of NCI, you requested an evaluation of the report recently prepared by the Department of Health Services entitled "A Study of Cancer Incidence in Lawrence Livermore Laboratory Employees." Dr. DeVita has asked me to prepare a reply.

This report is a careful statistical survey of malignant melanoma among employees of the Lawrence Livermore Laboratory (LLL). An enormous amount of attention has been paid to methodologic detail in the conduct of this study. By virtue of the existence of a cancer registry that is part of the NCI SEER Program in the geographic area of interest, the authors were able to apply incidence rates (age-, sex-, race-, time period-, and census tract-specific rates) to develop a precise estimate of the number of melanoma cases expected in the study population. From the outset, this eliminates one of the most frequent criticisms of this type of analysis, namely that the incidence rates used in the calculation of an expected value almost always do not come from the same population being studied. The cases of melanoma were identified through the SEER registry, which has an excellent case ascertainment record. The authors are experienced in the type of record linkage studies employed in the analysis, and have been careful to consider the various known sources of error. Where appropriate, alternative methods of analysis have been offered. On statistical and methodologic grounds, the analysis appears to be sound, and supports the conclusion that "a significantly greater than expected number of malignant melanomas were diagnosed among the employees of the LLL." Given the relative rarity of malignant melanoma in the general population, and the relatively small size of the population under study, the finding of 19 cases of melanoma cannot be dismissed lightly.

However, no effort was made to provide a biological explanation for this observation. Thus, some readers may assume that the melanoma excess is related to occupational exposure to ionizing radiation, despite the authors' brief disclaimer to the contrary. It should be emphasized that Conclusion 7 (page 13) of the report is correct, that is, no epidemiologic or experimental evidence exists to support the notion of a causal relationship between melanoma and ionizing radiation. Many variables beyond those

considered thus far in the analysis could contribute significantly to the observed melanoma excess. These need to be explored further before the biological and regulatory implications of this study can be understood.

Additional information should be collected on the 19 LLL melanoma cases and controls as a first step to epidemiologic inquiry.

1. Case histories. Data should be obtained on ethnic background, social class, associated medical conditions, lifestyle description, and other antecedent factors pertinent to melanoma risk.
2. Familial occurrence. Melanoma has a strong genetic component, compared to most other cancers. It would be important to determine if any of the cases occurred in persons from melanoma-prone families.
3. Careful occupational history. This should include assessment of specific job exposures, including contact with ionizing radiation, UV radiation, and chemicals.
4. Exposure to UV radiation. This is the major known risk factor in melanoma, so that data should be collected to determine if the patients were heavily exposed recreationally, or unusually sensitive to sunlight. This would include data on eye and hair color, complexion, skin response to sun exposure, and patterns of recreational exposure.
5. Histologic review. This is needed to confirm that the diagnosis of melanoma is correct in all cases. An expert panel of pathologists might be required for such an undertaking. Other characteristics of the melanomas should be evaluated, including location on the body, histologic subtype, depth of invasion, and presence of pre-existing nevi, in a search for clues which might suggest something unusual about these cases.
6. Industrial hygiene. A survey to measure radiation and chemical exposures is called for, particularly if there are areas of the plant where melanoma patients have clustered.

Once these data are obtained, the problem will be in clearer perspective, although further epidemiologic studies may still be needed to clarify the risk of melanoma and find the explanation in this population. The Introduction to the report suggests that the original investigation was impeded by lack of adequate resources, so it is important to ensure that funding and manpower are sufficient to rapidly and efficiently complete the task. In the meantime, based on the available Livermore data and what is known about the origins of melanoma, it would seem premature to institute special health and safety measures until the epidemiologic and industrial hygiene studies are finished.

Sincerely yours,

*Gregory T. O'Connor*

Gregory T. O'Connor, Director  
Division of Cancer Cause and Prevention

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
OFFICE OF THE ASSISTANT SECRETARY FOR HEALTH  
WASHINGTON, D.C. 20201

May 23, 1980

Mr. S. Floyd Mori  
Chairman, Joint Legislative Audit Committee  
California Legislature  
925 L Street, Suite 750  
Sacramento, CA 95814

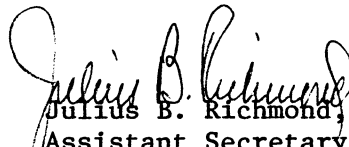
Dear Mr. Chairman:

I am pleased that members of the Public Health Service have been able to assist in the follow-up of the report recently prepared by the Department of Health Services entitled "A Study of Cancer Incidence in Lawrence Livermore Laboratory Employees."

I understand that you have sent copies of the study report to selected PHS scientists at the National Institutes of Health and the National Institute for Occupational Safety and Health for their review and comment and that they are responding to your request. I hope their comments will be sufficient in critiquing the study, and addressing the matters of needed additional research and implications for occupational health and safety which you identified in your letter to me. While these experts are providing detailed comments, it appears to me that the study conducted by the California Department of Health Service provides very interesting and useful epidemiological data and raises a number of important questions that should be explored further.

We will be pleased to provide further technical assistance to the Department of Health Services and the State Legislature in further pursuit of this matter if it should be needed.

Sincerely yours,



Julius B. Richmond, M.D.  
Assistant Secretary for Health and  
Surgeon General



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL  
SAFETY AND HEALTH  
5600 FISHERS LANE  
ROCKVILLE, MARYLAND 20857

MAY 23 1980

Mr. S. Floyd Mori  
Chairman  
Joint Legislative Audit Committee  
California State Legislature  
Sacramento, California

Dear Mr. Mori:

This is in response to your letter of April 30, 1980 requesting comments on the study of malignant melanoma incidence in the worker population at the Lawrence Livermore Laboratory (LLL). NIOSH is conducting several studies of occupational hazards in workplaces where radiation is a factor, and the California Department of Health Service's investigation is of interest to us.

The study is adequate, as far as it goes. However, we feel that many additional factors must be studied before it is clear whether the malignant melanoma excess is an artifact or real for the population studied.

Malignant melanomas have been correlated with inherited predisposition, ethnic grouping, and exposure to sunlight. The lifestyle of Livermore Laboratory personnel may differ substantially from that of the control group - for instance, their outdoor exercise patterns may be quite different. Livermore employees are better educated, better paid, and less transient than the control population. All the above factors should be considered in comparing incidence in different population groups, as well as the fact that malignant melanoma statistics have not been stable during the last two decades. Incidence in the San Francisco area rose 60 percent in the 1970-75 period. A study might also be started to compare incidence with that at a sister laboratory where very similar work is performed, the Los Alamos Scientific Laboratory, and could be expanded to include incidence of all cancers.

Consideration should also be given to conducting a retrospective cohort mortality (cause of death) study, which would permit inclusion of ex-workers who were employed at the laboratory years ago. Information about latency period for the disease, and about its relationship to length of employment could be gained in this manner.

Our consultations with LLL staff indicate that the melanoma cases were scattered through many departments, some professional, some not. It is not clear that sufficient data exists, but it might prove worthwhile to characterize the stricken population by work-site. Anecdotal histories which include work habits, recreation patterns, and life style of the deceased melanoma victims could prove useful.

In considering causal factors, it must be cautioned that malignant melanoma incidence has never been correlated with ionizing radiation. All possible occupational hazards should be characterized including exotic chemicals utilized in warhead construction, and sources of ultraviolet radiation. Long-term employees have indicated that, for many years, high-energy explosives were tested in fields immediately adjacent to the then modest facilities. Additionally many "one-shot" radiation experiments were performed on site. Attempts should be made to compile a history of all such events for later comparison with work-sites for the study population, particularly since the one common bond amongst that population is long-term employment. In short, a complete industrial hygiene survey should be completed. NIOSH possesses particular expertise in this area, and we would be available to perform such a characterization if it is deemed appropriate.

There is some literature which suggests that ionizing radiation, while not causative, is synergistic with ultraviolet radiation. That is to say, it may magnify the effects of U.V., which in itself has been correlated with the presence of malignant melanomas. Given the sun conditions in the Livermore Valley, and the presence of ionizing radiation at the laboratory, it may prove interesting to study this synergy if the melanoma excess still holds after reevaluation.

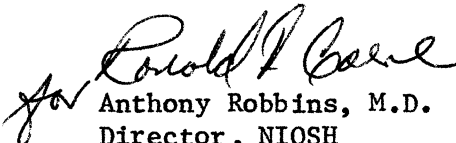
The phenomenon of malignant melanoma clusters has been reported previously. Dr. Arthur Sober of the Department of Dermatology at Massachusetts General Hospital reports a never explained grouping of 14 cases among white officers on the Washington, D. C. Police Force. Ionizing Radiation was not known to be a factor and exposure to toxic chemicals was not demonstrated. That is to say, it cannot be taken for granted that the LLL cluster, if it is confirmed, necessarily relates to a causal factor within the laboratory.

I understand that several groups have been formed to further investigate the phenomenon, one, an LLL group headed by Dr. J. Lowry Dobson, and the other a group headed by Dr. Arthur Upton of New York University, sponsored by the Federal Department of Energy. Until these groups have presented their findings, it may be premature to suggest health and safety precautions, especially since there is so little information about causal factors. However, in the interim, it would be wise to have employees watch for changes in warts or moles. Early detection improves survival rates from this disease.

Page 3 - Mr. S. Floyd Mori

We look forward to the findings of the two study groups currently investigating the phenomenon, and would be happy to assist them in occupational safety and health aspects of the research.

Sincerely yours,

  
Anthony Robbins, M.D.  
Director, NIOSH

## DEPARTMENT OF HEALTH SERVICES

714/744 P STREET  
SACRAMENTO, CA 95814  
(916) 445-1248



May 5, 1980

Honorable S. Floyd Mori  
State Assembly  
State Capitol  
Sacramento, CA 95814

Dear Mr. Mori:

We too are concerned over the recent incidence of malignant melanoma at the Lawrence Livermore Laboratory. The findings of an increased cancer risk among employees at the Laboratory is the product of a recently implemented program of this Department that was specifically designed to identify such risks. The second half of the program should, when supported, lead to the identification of the occupational or other environmental factors responsible.

Your request is most timely as I had previously asked Doctor Donald F. Austin, Chief of the Resource for Cancer Epidemiology Section, to provide me with a description of the additional support necessary for a thorough epidemiologic investigation of the possible causes of this increase.

He has estimated that five full-time professional, technical and support staff will be required to properly carry out the necessary tasks associated with such an important study. Based on current salary levels, the cost is estimated at \$227,908 on an annual rate.

Doctor Austin has projected what he considers to be a tight time schedule in a step-wise research approach. He acknowledged the possibility that at any point in the investigation a breakthrough might occur. However, it is more likely that the investigation must be carried to the end point.

I have attached a summary and budget for the major tasks required to proceed with an in-depth study of the cancer increase at the Lawrence Livermore Laboratory.

We expect that our efforts to identify cancer risks in specific groups will give rise to a continuing need for investigation of the causal factors of those risks. We already know of a need for such investigation regarding leukemia in Ventura County, brain and kidney cancer in a Bay Area Plumbers' Union, melanoma in Woodland, bowel cancer in San Diego County, testicular cancer in a high school water polo team in Stockton, and cancer among chemists at a plant in Sacramento.

Honorable S. Floyd Mori


-2-

If this portion of the program is permanently supported, when the Lawrence Livermore Laboratory study is completed, we will immediately deploy this cancer response team to investigate apparent high risk groups among other workers or geographic areas of the State.

Your request is essentially identical to one we received at the same time from Senator Nejedly. I am sending you both the same information.

I appreciate your interest in this problem.

Sincerely,

  
for  
Beverlee A. Mers  
Director

Enclosures

cc: Senator Nejedly



## RESOURCE FOR CANCER EPIDEMIOLOGY SECTION

### Research Procedures Necessary to Complete Investigation of Malignant Melanoma Cases at Lawrence Livermore Laboratory

A thorough investigation of the increased melanoma risk at the Lawrence Livermore Laboratory will require a determination of the most probable mechanism of exposure to the risk factor responsible so that corrective steps may be taken. Other important determinations include whether or not additional health risks from the same hazard can be identified among those exposed, whether or not the risks can extend outside the physical boundaries of the Laboratory, whether the risks from the risk factor can be expected to be in effect for some time in the future and when the hazard began, so as to identify all individuals exposed to elevated risk.

A brief description of the steps that will likely be necessary to investigate the melanoma problem at the Lawrence Livermore Laboratory (LLL) are as follows:

1. Detailed record review. The selection of a set of matched "controls" from among the LLL employees for each employee melanoma case will create a comparison group. Both the control and case groups would be the subject of an intensive review of records to determine any possible differences in the duration of employment, job assignment, pre-existing medical conditions, etc. This step would attempt to identify a specific building, project, job classification, etc. that is associated with the elevated melanoma risk so that an in-depth and focused study of the indicated factor can be mounted.
2. Assess the association of melanoma to radiation exposure. Because of the nature of the work at LLL it is essential to determine whether or not the incidence of melanoma or other cancer is related to radiation exposure as measured by cumulative radiation dosimetry badges.
3. Assess the relative frequency of melanoma cases in each job or account number. Existing computerized records of LLL employees make it possible to see whether certain job classifications or projects have had an abnormally high proportion of persons with melanoma. This procedure, if productive, will provide an early means of focusing further investigative efforts. Similar procedures will also provide an evaluation of personnel in special groups such as those working at Site 300.
4. Extend the analysis to other cancer types. The presence of a hazard for one type of cancer raises a distinct likelihood that the hazard may also cause cancers of other types. Other types of cancer should be analyzed to determine whether or not evidence for this possibility exists.
5. Extend the analysis to other years. The melanoma incidence among LLL employees for the years 1969-71 and 1978-79 will be added to the analysis in an attempt to characterize the starting point and conclusion of the melanoma epidemic. This will assist in identifying the factor involved and will provide one of the measurements necessary to identify all those exposed to the factor. It will also help in determining the latency period so that it can be estimated when the period of greatest excess risk begins and is completed among the exposed persons.

6. Melanoma risk assessment in surrounding communities. The incidence of melanoma and of cancer commonly associated with radiation exposure should be determined in the communities at near, moderate and far distances from the LLL. The incidence should be determined for children, as well as adults, since children are more susceptible to many carcinogenic effects, including radiation. This will help determine whether or not any extension of the LLL hazard into the community has occurred.

7. Examination of a control occupational group. In order to determine whether the elevated melanoma risk is imparted by a factor in the immediate environment, from a non-classified process used by other workers in similar research, or from a specific process used only at LLL, an occupational group from the same geographic area will be examined for melanoma occurrence.

8. Case-control interview study. An interview to determine the effect of job assignment, work location, skin color, other medical conditions, smoking, etc., will be conducted among all available melanoma cases from LLL or their survivors. The responses will be compared to those of an appropriately drawn sample of persons without melanoma. This procedure, using strict survey research epidemiology techniques, can test causal hypotheses suggested by other steps, can identify the presumptive cause of the elevated incidence and can suggest possible control mechanisms.

Joint Legislative Audit Committee

Synthesis of Expert Reviews of Cancer

Incidence Among Workers at Lawrence Livermore Laboratory

1. P. 10 and Appendix B-4. Statement is made of reports of high incidence of melanoma in Sacramento (and other areas). We have no knowledge of any incidence study in Sacramento.
2. Appendix A-13, paragraph 2. The word, *invasive*, is in error in third sentence. The sentence should read "Consequently, the chance of erroneous diagnoses are greater with in situ melanoma."
3. Appendix A-14, paragraph 3. Error in fourth sentence. The sentence should read "That additional site is leukemia, defined for the analysis as leukemias of the acute lymphocytic and chronic myelocytic types."
4. P. 8 and Appendix G-3. Concern is expressed that bias may have been introduced if there were a difference in percent Hispanic between worker and general populations compared. In the Resource for Cancer Epidemiology Section report, Hispanic is included with white in both worker and comparison populations. However, it is known that the percentage in each group is small. Even if fifty percent of the comparison population and zero percent of the worker population were Hispanic, the effect could not be greater than an observed rate in Lawrence Livermore Laboratory workers two times that of the comparison population. Since the Lawrence Livermore Laboratory rate is five times higher, inclusion of Hispanics cannot have caused sufficient bias to account for this finding.



May 13, 1980

Assemblyman S. Floyd Mori  
California Legislature  
925 L Street, Suite 750  
Sacramento, CA 95814

Dear Assemblyman Mori:

Thank you for your interest and concern regarding the incidence rate of malignant melanoma at the LLNL, as described in the study recently conducted under the leadership of Dr. Donald Austin of the California Department of Health Services. I share your concern and will see to it that the Laboratory does whatever we can to identify possible causes, and to mitigate them if causes are found which involve LLNL operations.

In response to Dr. Austin's study, we have established an internal LLNL task group to work on this matter. The group consists of nine senior Laboratory scientists, chosen for their ability and breadth of knowledge, who will take whatever time is necessary during the next several months to pursue an in-depth study of the problem. The group is chaired by Dr. Lowry Dobson, from our Biomedical Sciences Division, and includes Dr. Max Biggs, the Head of our Medical Department, a biologist, two chemists, a statistician/epidemiologist, two physicists, and one specialist on industrial hygiene from the Laboratory's Hazards Control Department. In addition to their own areas of technical knowledge, most of these people are familiar with a wide range of Laboratory operations.

The LLNL task group will examine the melanoma situation broadly and in depth. It is charged with doing a thorough review of what is known about melanoma and its possible causes, reviewing the statistical basis and the conclusions of the Health Service study, investigating the backgrounds, habits, and medical and work histories of those individuals at LLNL who have contracted melanoma, reviewing current and past Laboratory operations, and finally, trying to find relations among this information so as to identify possible causative factors for the observed melanoma incidence.

As you know, Dr. Austin plans to continue his study, but along somewhat more specific lines. On May 7, Dr. Austin discussed with Dr. Biggs what his future plans are. While I cannot speak for Dr. Austin, I will list our understanding of his plans to put the relationships among the studies in some perspective for you.

(1) The records of the 19 cases will be reviewed in detail and will be compared with the records of a suitable control group. The records used will include medical records, radiation exposure records and personnel records.

(2) A correspondence between melanoma cases and radiation exposure will be searched for and evaluated, if found.

(3) A positive correlation between melanoma incidence and job assignments and payroll account numbers will be sought and evaluated, if found.

(4) The incidence rates of other cancers at LLNL besides melanoma will be calculated and compared with rates in appropriate control groups.

(5) The "Melanoma Study" will be expanded to include the time period since 1977 and extended back before 1972 as far as the data will allow.

(6) Melanoma associated risk will be evaluated in the communities surrounding LLNL as a function of distance.

(7) The melanoma rates at LLNL will be compared with the rates in other but similar occupational cohorts.

(8) Personal interviews are planned with the cases and controls.

Dr. Austin was unable to give final details of how these studies were to be financed and hence could not estimate time intervals required for each portion of the study. He felt that his financial needs and arrangements would be clarified at the State level within a week or so.

An additional investigation board has been appointed by Ms. Ruth C. Clusen, Assistant Secretary for Environment, DOE, to look at the problem and report within 60 days to the Secretary of Energy. I believe you are familiar with the personnel on this Federal Board; however, I have listed them in the attachment. As of this time, I do not know the details of how this Board will proceed. It will bring a group of very distinguished and capable professionals together to work the problem. I have been advised that they will visit the Laboratory for an unspecified period beginning June 23, 1980.

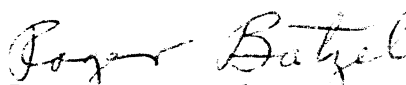
A major responsibility of the LLNL task group will be to assist and cooperate with Dr. Austin in his further studies and to assist the DOE Board in any way it can. During the next week or two, we expect to have more detailed discussions with Dr. Austin and his coworkers regarding his plans for continuation of his study, how the work of our task group and the DOE Board may complement them, and possible needs for additional LLNL funding

support for Dr. Austin's work. The Laboratory supported the Health Service study in the past by providing funds for a computer programmer and statistician to the extent of \$26,389 between mid-1978 and the present. We are already committed to providing additional support for his continuing study, if it is needed, perhaps in amounts roughly comparable to what we have contributed in the past, provided that the work proposed seems to us to make sense.

Each of these three groups brings a useful perspective and background to these studies. Together, I believe that their efforts as outlined above are necessary and, from what we can see now, sufficient. It is difficult, at this time, to say what "leads", if any, may be identified by any of the three groups involved. Therefore, we cannot say what additional effort may be required to pursue such leads. I do not believe that it is warranted at this time to plan to undertake additional basic biomedical or environmental research on the causes of melanoma in support of these studies. There is a large national program in cancer research and, with what we know now, it would be hard to add much to it which is specific to this situation. As you know, the biomedical research program at LLNL is intimately involved in this national program and we will, of course, draw on the knowledge of our people in this area as needed. If any of the study groups identifies specific additional biomedical research needs, the Laboratory, and I am sure, DOE, will address them as appropriate.

I would be glad to discuss and expand any aspect of this problem and plans to solve it with you as necessary. The Laboratory is pledged to cooperate in any way it can to a final solution.

Sincerely,

  
Roger E. Batzel  
Director

Attachment

cc: Members of the Legislature  
Office of the Governor  
Office of the Lieutenant Governor  
Secretary of State  
State Controller  
State Treasurer  
Legislative Analyst  
Director of Finance  
Assembly Office of Research  
Senate Office of Research  
Assembly Majority/Minority Consultants  
Senate Majority/Minority Consultants  
California State Department Heads  
Capitol Press Corps