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CAUSAL RELATIONSHIP BETWEEN SERVICE-CONNECTED AMPUTATION AND SUBSEQUENT CARDIOVASCULAR DISORDER: A REVIEW OF THE LITERATURE AND A STATISTICAL ANALYSIS OF THE RELATIONSHIP [a] [b] [c]

PUBLIC LAW 94–433

SEC. 403. (a) The Administrator of Veterans' Affairs shall conduct a scientific study to determine if there is a causal relationship between the amputation of an extremity and the subsequent development of cardiovascular disorders.

(b) The report of the study shall include (1) a comprehensive review and professional analysis of the literature covering other such studies conducted or underway of such relationship; and (2) an analysis of statistically valid samples of disability claims of veterans having service-connected extremity amputation matched by age, sex, and war period with nonamputee veterans.

(c) The report, together with such comments and recommendations as the Administrator deems appropriate, shall be submitted to the Speaker of the House and the President of the Senate not later than June 30, 1977.

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[a] Subtitled: Studies Submitted by the Veterans' Administration (Pursuant to Section 403 of Public Law 94–433) to the Committee on Veterans' Affairs, United States Senate. Dated February 15, 1979.

[b] Reprinted in full from Senate Committee Print No. 6, 96th Congress, 1st Session, printed for the use of the Committee on Veterans' Affairs.

[c] The studies described here were the subject of an editorial (Amputation as Cause of Cardiovascular Disorders) by Lawrence B. Hobson, M.D., Ph. D., Deputy Chief Medical Director for Research and Development, Dept. of Medicine and Surgery, Veterans Administration, appearing in the Bulletin of Prosthetics Research, BPR 10-31, Spring 1979, pp. 1–2.

The complete text became available (as 96th Congress, 1st Session, Senate Committee Print No. 6) too late to reproduce in BPR 10-31. The literature review and epidemiological study are here reproduced in full to make them more widely available in the indexed scientific literature. It is hoped that further study of the subject will be encouraged.

LETTER OF TRANSMITTAL

VETERANS' ADMINISTRATION,
OFFICE OF THE ADMINISTRATOR OF VETERANS' AFFAIRS,
Washington, D.C., February 15, 1979.

Hon. WALTER F. MONDALE,
President of the Senate,
U.S. Senate, Washington, D.C.

DEAR MR. PRESIDENT: As required by the Veterans Disability Compensation and Survivor Benefits Act of 1976 (Public Law 94–433), the Veterans' Administration has obtained a scientific study to determine if there is a causal relationship between the amputation of an extremity and the subsequent development of cardiovascular disorders. The comprehensive review and professional analysis of the relevant literature was sent you on June 30, 1977; another copy of it is enclosed.

The analysis of statistically valid samples of veterans having service-connected extremity amputations matched by age, sex and war period with nonamputee veterans has been completed by the Medical Follow-up Agency of the National Academy of Sciences. The resulting report, "Service-Connected Traumatic Limb Amputations and Subsequent Mortality from Cardiovascular Disease and Other Causes of Death" by Zdenek Hrubec, Sc. D., and Richard A. Ryder, M.D., is enclosed as well.

The literature analysis reported earlier reveals conflicting results from different scientists. The current statistical analysis of American veterans of World War II indicates, however, that amputation of both legs or of one leg at or above the knee increased the relative risk of death to 136 percent that of veterans who were disfigured but had no amputation. The group of amputees had a 158 percent risk of dying from diseases of the cardiovascular system during the intervening years. Amputation of arms, hands, or feet did not detectably increase the risk.

As a result of the Veterans' Administration's review of this study, amended regulations will be proposed to provide service connection for ischemic heart disease or other cardiovascular disease developing in those veterans who have undergone amputation of a lower extremity at or above the knee or amputation of both lower extremities at or above the ankles.

The report by Drs. Hrubec and Ryder speculates on the manner in

which amputation could exert its effects on mortality. The statistical analysis was not intended to explore the causal mechanisms, however, and did not determine them. Research to do so will be undertaken by the Veterans' Administration.

We appreciate the opportunity to give you this report.

Sincerely,

MAX CLELAND
Administrator.

Enclosures.

COMMITTEE ON VETERANS' AFFAIRS

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AMPUTATIONS OF EXTREMITIES AND CARDIOVASCULAR DISEASE

By Richard A. Ryder, M.D.

In accordance with Public Law 94–433, section 403(b), a comprehensive review and professional analysis of the subject of traumatic amputations of extremities and cardiovascular disorders has been undertaken. These results will be presented in a format which will analyze specific studies individually and then analyze coronary artery disease risk factors as they might be related to amputations. The

studies are not arranged in order of importance but in an order which will allow maximal utilization of data from previous studies to analyze subsequent studies.

I. Ministry of Pensions and National Insurance—Ultimate Conclusions of the Advisory Committee on Cardiovascular Disorders and Mortality Rates in Amputees [1]

On January 22, 1953, the conclusions of an extensive British study were submitted to the Director General of Medical Services, Ministry of Pensions, by E. Rock Carling, the Chairman of a nine-man Committee who responded to a request to "consider whether limb amputations and the wearing of a prosthesis predisposed amputees to cardiovascular disorders, and whether, by reason of amputation, their mortality rates differed from the normal for equivalent age and sex groups." This report, which was to adopt the name of its Chairman, "The Rock Carling Study", was further revised in November of 1954 when the "ultimate conclusions" of the Advisory Committee was submitted. This study was done in two parts.

First, from 27,000 amputees from the "1914 War", an investigation was carried out of one in three of the deaths, and compared to both leg wounds without amputation for the same war and the general population. Their results showed that of the amputees alive in 1930 there were 12.6 deaths per 1,000 amputees betwen 1939 and 1950. This compared to an 11.4 per thousand mortality for sex and age matched controls from the general population. When the group who suffered wounds but did not have amputations were compared to their age and sex matched controls from the general population, the annual mortality per thousand was 13.15 as compared to 11.9 per thousand for controls.

Their final conclusions are as follows:

> Limb amputations, and the subsequent wearing of a prosthesis, do not, in time, produce effects on the body as a whole which may initiate or aggravate cardiovascular disorders to any significant extent.
>
> There is no material difference between the mortality rates of amputees, by reason of amputation, and that of the corresponding rates for pensioners who have suffered wounds not leading to amputations. Such excess as there is in both classes over that in the general population is quite small.

The second aspect of this study was to examine 4,500 amputees. These results were to be compared with 1,000 nonamputee pension-

ers who were to serve as controls. These results were "regrettable" and did not provide statistically significant evidence because "considerable numbers" of the amputees did not come for the examination. "So far as it goes the evidence obtained discloses no excess of high blood pressure among amputees and no material excess of cardiovascular disease."

II. A Multidisciplinary Study of Long Term Adjustment to Amputation [2]

In 1965 Nathan and Davidoff published the results of a study performed through the Outpatient Clinic of the Boston Veterans' Administration Hospital. They interviewed and examined two hundred thirty amputee veterans. The length of the study and followup is not given, but it appears to be a one-time encounter. The large majority of those examined were World War II veterans but there were twenty-one World War I and twenty Korean War veterans. The final sentence is:

> The loss of a limb and the wearing of a prosthesis do not shorten the longevity of the amputee.

This statement appears to be based on the fact that twenty World War I amputees had survived an average of 70½ years. There are no controls for comparison and no long term followup of a large group of amputees to determine the number of deaths. Obviously, the conclusions this study draws about longevity of amputees is highly suspect.

III. Causes of Death in a Series of 4,738 Finnish War Amputees [3]

Bakalin examined the records of the State Insurance Department of Finland and presented the causes of death from a total of 4,738 World War II amputees. He states:

> The purpose of this study was to find out whether death from degenerative cardiac and vascular disease is more common among amputees than in the general population.

He found that the mortality rates of the amputees and the general population "was found to be in good agreement," when no division as to cause of death was made. However, when causes of death were differentiated, there was a 63.1 percent greater death rate in amputees than the expected death rate in the general population for degenerative cardiac and vascular diseases. Increased rates were also found for degenerative diseases of the central nervous system and for suicide. The reason the total death rates were comparable is that the higher rates for cardiac, cerebral and suicide deaths were offset by

lower rates for pulmonary tuberculosis and malignant diseases.

When the figures are examined closely several problems arise. First, there appears to be a striking number of young cardiovascular deaths. When the statistics are broken down by cause of death in five-year age group intervals from age 20 to 85, one finds that 24 of the total 219 cardiac and vascular deaths occurred in amputees 39 years old or younger. When the deaths were compared to the general population, there was a 193.2 percent increase over the expected death rate from age 25-44 years as compared to a 38.9 and 28.6 percent increase from ages 45–64 and 65–74, respectively. This can be explained by the fact that of the total of 687 deaths, 44 were before 1945; i.e., during the war, and that the deaths from pulmonary infarction and peripheral embolism are considered under the heading of degenerative cardiac and vascular diseases. It does not seem at all surprising to find an increased death rate if one includes the acute hospitalization period and thereby compares bedridden postoperative patients to normal controls.

Secondly, the comparison of a military population with a control group from the general population is introducing another variable. In the "Rock Carling Study" [1] a wounded, nonamputee control and the amputee population were compared to the general population. Both combat groups had slightly higher mortalities than the general population, but strikingly similar mortalities when compared to each other. Also, as has been shown by Seltzer [4], just the selection process which is used to screen for military induction makes comparison of military and general populations different, irrespective of whether or not they are involved in combat.

IV. Herz und Amputation [6]

In 1960, Meyeringh studied the electrocardiograms of 1,033 traumatic amputees and compared them to 423 nonamputee controls. The ECG's were divided into 10-year intervals from age 20 to 60. Significantly, more abnormal ECG's were found in the less than 40-year-old age group. After age 40 there was no significant difference. Further, they found no more frequent ECG changes in amputees that cannot walk normally as a result of their amputation as compared to amputees who have returned to normal ambulation.

When the less-than-40 age group was further evaluated, the abnormalities were found to be in those patients who had gas gangrene as a complication of their amputation. The authors postulate that this is the result of myocardial involvement by the gas gangrene. This association of infection and myocardial disease is very interesting in

light of the Rock Carling study [1]. In the Final Conclusions (which was followed by the Ultimate Conclusions), there was an association noted between atherosclerotic coronary artery disease and sepsis. This association was not emphasized in the Ultimate Conclusions.

V. Late Sequelae of Amputation: The Health of Finnish Amputated War Veterans [5]

In 1965 Solonen et al. presented this study in which 311 World War II amputees were evaluated by an orthopedist, internist, radiologist and physiologist. Ninety-five nonamputee men (controls) who fought in World War II were age-matched to the amputees. The extensive evaluation of these men included several important cardiovascular studies.

The ECG's of the amputees were pathologic in 7 percent of cases which was not significantly different than the controls. Likewise, there was no statistically significant difference between the amputees and controls in arterial blood pressure or heart size on chest x-ray. Interestingly, the cholesterol of the controls was higher (300.7) than the amputees (267.4). Finally, bicycle ergometry was performed for 5 minutes using either feet or hands with a workload of 10 or 15 kgm/sec. During the test ECG monitoring and maximum oxygen uptake were performed. Only the double lower limb amputees were less fit than controls.

The conclusions drawn by this study were:

> Disorders of the internal organs and peripheral disturbances in the circulatory organs were no commoner in the amputees than in the control group.

Relationship of coronary risk factors to amputations

If traumatic amputations were associated with an increased amount of atherosclerotic coronary artery disease, three logical associations are possible. First, the amputation could be an independent new risk factor for coronary artery disease. Second, amputations could be associated with some new risk factor which is yet to be defined as an independent risk factor. An example of such a factor is the previously mentioned association between amputation, sepsis, and coronary atherosclerotic disease as mentioned in the Final Conclusions of the Rock Carling Study. Finally, the amputation could affect one of the previously described coronary risk factors and thereby result in increased coronary atherosclerosis. An analysis of these risk factors in relation to the presently available literature on amputees should help to further clarify this subject.

J. Willis Hurst, M.D. [7] in his book "The Heart" defines the known coronary artery risk factors. His first category is "Nonmodifiable risk factors" which include age, sex and a family history of atherosclerotic coronary artery disease. It is obvious that a traumatic extremity amputation will not alter any of these. His second category, "Modifiable risk factors," is divided into two subgroups: Major and minor risk factors. His major risk factors are: (1) Elevated serum lipids; (2) habitual diet high in total fats, saturated fats, cholesterol, refined carbohydrates and salts; (3) hypertension; (4) cigarette smoking; and (5) diabetes mellitus. His minor risk factors include: (1) obesity; (2) sedentary life style; (3) personality type; and (4) psychosocial tensions.

Elevation of serum lipids as a result of an amputation seems highly unlikely. The only study which gave cholesterol measurements [5] found the cholesterol to be lower (267 vs. 300) in the amputees as compared to the controls. Certainly, one would want further controlled studies before believing that amputation could lower cholesterol.

The subjects of diet, cigarette smoking and diabetes mellitus, as specifically related to amputees and atherosclerosis, are not discussed in the literature. It is not likely that an amputation would alter any of these risk factors.

The subject of hypertension and amputation has been evaluated. Solonen et al. [5] found no significant increase in blood pressure in his 311 amputees as compared to controls. Loos [8] evaluated 742 amputees and also found no blood pressure elevation.

The minor risk factors of obesity, sedentary life style (physical activity), personality type and psychosocial tension have been evaluated. The subject of obesity is examined by Solonen [5]. He divided his amputees into three weight groups (overweight, normal and underweight) using 15 percent above or below normals. He found no difference between upper limb amputees and controls, but a clearly significant increase in the overweight group among the lower extremity amputees $P < 0.01$). This difference was more marked in the above the knee as compared to the below the knee group, and appears to be even more marked in the double amputees (though the number of double amputees is too small to achieve statistical significance). Loos [8] did not find more obesity among his 647 amputees.

The question of physical activity of amputees and its possible relationship to heart disease is not fully discussed in one article. However, some information can be obtained by analyzing multiple sources. Bakalim [3] states that "The increased consumption of energy taxes the circulation and the heart." Waters [9] found that the higher the level of the amputation the greater the amount of energy expended during prosthetic walking. Furthermore, crutch walking expended

more energy than walking with a prosthesis, except in the subgroup of vascular above-the-knee amputations. The effects of this increased energy expenditure were evaluated by Solonen [5]. He had 311 amputees undergo ergometric testing in which they either peddled or handwound a bicycle ergometer. He found that the physical condition was as good in the amputees as in the controls, with the one exception of the double amputees.

The relationship of increased energy consumption to heart disease presents a more complex problem. Drews [10] evaluated cardiac index and stroke index in amputees and found them to be normal. Paffenbarger [11] evaluated 3,263 male longshoremen between the ages of 35 and 64 over a 16-year period and found the less active group had a 33 percent higher coronary death rate. Frank [12] evaluated 55,000 males and found that the "most active" males were at a significantly decreased risk of dying from a heart attack, as compared to "least active" male matched cohort. The conclusion to be drawn is not that wearing a prosthesis or walking with crutches "taxes" the circulation and thereby leads to heart attacks, but that increased work loads may be protective to the heart as regards coronary heart disease.

It would appear that if physical activity were to be a factor for relating amputation to coronary heart disease, the less active double amputee would be at greater risk.

The final minor risk factors deal with psychosocial interactions. It is obvious (and has been documented by Haber [13]) that amputation of either lower or upper extremity would have a profound effect on one's self-image and social interactions. Bakalim [3] found the suicide rate to be 37 percent higher than expected among amputees. Certainly, the amputee's life has a great deal more emotional stresses which have the potential for increasing atherosclerotic coronary artery disease.

In conclusion, the evidence presently available does not support a statistically significant link between atherosclerotic cardiovascular disease and amputation. The one study which does show a positive link, written by Bakalim [3], does not use a matched control and has mistakenly included the acute injury period in the analysis. A second study [2] claims to show no link between amputation and atherosclerotic coronary artery disease; however, there are no adequate controls to support this claim. Two other studies [5,6] evaluate living amputees and controls with noninvasive (not requiring insertion of needles or surgery) techniques to determine the presence or absence of coronary artery disease. Unfortunately, significant coronary artery disease can be present and go undetected by these

techniques. The only *in vivo* (while the patient is alive) technique which would give unequivocal evidence is cardiac catheterization, which has not been performed in this group. This leaves the Rock Carling Study [1] as the only well-controlled study which looks at mortality rates as an end point. This study did not find a correlation between amputation and cardiovascular disorders.

For one to feel certain about such results one further study conparing deaths of amputees and a matched control group should be undertaken. Such a study should include a comparison of amputees with and without sepsis (infection) to resolve the question raised by Rock Carling [1] and Meyeringh [6]. Also, the study should include an analysis of the level of the amputation to evaluate the possibility that physical inactivity may lead to an increased coronary artery death rate. Finally, the study should attempt to define the weight of the amputees as compared to controls, to evaluate this as a possible risk factor in this group.

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REPORT TO THE VETERANS' ADMINISTRATION DEPARTMENT OF MEDICINE AND SURGERY ON SERVICE-CONNECTED TRAUMATIC LIMB AMPUTATIONS AND SUBSEQUENT MORTALITY FROM CARDIOVASCULAR DISEASE AND OTHER CAUSES OF DEATH

By Zdenek Hrubec, Sc. D.[1] and Richard A. Ryder, M.D.[2]

ACKNOWLEDGMENT

This work was carried out under Contract V101 (134) P-348 with the Veterans' Administration (VA) by the Medical Follow-up Agency (MFUA), National Research Council (NRC). The MFUA program of studies is conducted in cooperation with the Veterans' Administration, the Department of Defense and the National Institutes of Health. Program review is provided by the Committee on Epidemiology and Veterans Follow-up Studies and the Assembly of Life Sciences of the NRC.

The U.S. Congress, through Public Law 94-433, mandated the Administrator of Veterans' Affairs to review relevant scientific literature and carry out the study reported here. Veterans' organizations, particularly the Disabled American Veterans and Veterans of Foreign Wars, had made an earlier statement of the relationship reported on in this work. The use of Army medical records in the preparation of this material is acknowledged, but is not to be construed as implying official approval of the Department of the Army of the conclusions presented. The study depended heavily on records of the Veterans' Administration. The records management personnel of the National Archives and Records Service, GSA, were helpful in providing ready access to the required material. The operations staff of the Medical Follow-up Agency was directed by Mr. A. Hiram Simon. Ms. Marcia L. Egge provided project coordination, Mrs. Vivian A. Farley supervised the coding of causes of death, Miss Hatsumi Hamamura controlled records work. Mr. Thomas Preston provided contact with Mrs. Melody C. Warner in the Department of Veterans Benefits, Veterans' Administration, who under the supervision of Mr. J. C. Peckarsky, Director of Compensation and Pension Service, expedited our access to VA records.

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ABBREVIATIONS USED

AH — Army hospital.
BIRLS — Beneficiary identification and records locator subsystem of the VA.
C&P — Disability compensation and pension magnetic tape file of the VA.
ICDA — International classification of diseases adapted for use in the United States.
VA — Veterans' Administration.

Summary

Men drafted into the Army, hospitalized during 1944 to 1945 for service-connected trauma to the extremities, and consequently separated for disability were followed for mortality from January 1946 to April 1977. Three groups were established consisting of those whose injury resulted in

(a) limb amputation,
(b) disfigurement without loss of body part,
(c) loss of part of hand or part of foot.

Group (a) had a mortality, *standardized for age and calendar time,* 1.4 times that of Group (b), matched on age and length of service at admission, and 1.3 times that of Group (c), similar on age and length of service to Group (a). The excess mortality of limb amputees was statistically significant ($P<.05$) for ischemic heart disease, other diseases of the cardiovascular system, suicide by poisoning, alcoholic cirrhosis, and acute pancreatitis. Possibly ($P<.1$) there was also an increased risk of diabetes and cancer of the buccal cavity and pharynx.

Introduction

The cause of most cardiovascular disease, the atherosclerotic narrowings of arteries, and particularly of the coronary arteries, has interested and perplexed medical science for years. Though extensive animal and human research has addressed the subject, we are still left with risk factors that are associated with but are not the direct causes of atherosclerotic coronary artery disease. The science is so imprecise that there are many patients with multiple risk factors who have lived into their ninth decade and other patients who have been reported to have died at young ages with none of the known risk factors.

Dating back as far as 1954 (Carling, 1954) the question has been raised whether amputation of an extremity results in increased incidence of cardiovascular disorders. In this English study, 27,000 amputees from the "1914 War" were evaluated and compared both to soldiers without amputation but with wounds of lower limb and to the general population. The conclusion was that limb amputation does

not "initiate or aggravate cardiovascular disorders to any significant extent".

Several other studies (Nathan and Davidoff, 1965; Solonen et al., 1965; Meyeringh et al., 1960) on a smaller scale also failed to show increased mortality from cardiovascular diseases as a result of amputation. However, Bakalim (1969) examined the results of 4,738 World War II amputees from the State Insurance Department of Finland. For degenerative cardiac and vascular diseases he found a 63.1 percent greater death rate among amputees than that expected for the general population. When this study is examined closely, two problems are seen. First, there was a striking number of young cardiovascular deaths, which may be related to the fact that the study covered the acute hospital period and pulmonary infarction and peripheral emboli were included under cardiovascular deaths. Secondly, the comparison was to mortality of the general population rather than to that of matched combat-injured veterans.

In 1976, Public Law 94-433, section 403(b), mandated a comprehensive review of the literature and analysis of new data on this subject in hopes of clarifying the problem. This report is the culmination of the data analysis carried out by the Medical Follow-up Agency of the National Research Council's Assembly of Life Sciences.

Materials and Methods

The Medical Follow-up Agency, with approval from the Office of the Surgeon General of the Army, has access to files, now on magnetic tape, which contain summary information for Army hospitalizations during 1944 and 1945. All combat related trauma and a 20-percent systematic sample of all other morbidity are included in these files. Selected from them, for further evaluation of eligibility, were male inductees admitted for trauma, who were either discharged or retired for disability incurred in line of duty, and for whom the following final results of the hospitalization were the cause of discharge:

amputation, at or above knee;
amputation, at or above elbow;
disfigurement other than of head, face, or skull;
disfiguring scar, adherent or painful;
loss of part of hand;
loss of part of one foot.

In the analysis described below, mortality in the group of *proximal amputations* (knee or above, elbow or above) is contrasted with that of two comparison groups. One, the *disfigurement* group, includes disfigurement other than that of head, face, and skull, and also the disfiguring, painful or adherent, scars. The other comparison group,

the *distal amputations,* includes loss of part of hand and loss of part of foot.

Additional criteria were imposed to select study subjects in the three study groups. Both proximal and distal amputations identified through the final result codes were included only if the first diagnosis in the tape record was that of a *traumatism of the extremities,* and when present the second diagnosis was that of a *traumatism of the extremities* or a disease. Some records also contained a third diagnosis, but no anatomic location was indicated for it, and therefore it was not examined. Second diagnoses of disease were not considered in the selection to avoid biasing it by excluding concomitant illness that might be associated with subsequent cardiovascular disease. Records with the final result of disfigurement met the following conditions.

The first diagnosis recorded was a *wound or fracture of the extremities without any nerve or artery involvement.* The second diagnosis had to either be absent, or meet the same criteria as the first, or be a disease. Any third diagnosis for which no anatomic location is given had to be either a wound or fracture without any artery or nerve involvement, or a disease. Men whose records indicated an amputation in any of the fields specifying diagnosis or type of surgery have been excluded from the disfigurement group. The diagnoses of disease were retained for the reasons stated above in defining the two amputee groups.

Excluded from all groups were subjects whose Army hospitalization (AH) terminated in death. Age at the AH admission and length of service prior to hospitalization were used to select a matched sample and in the analysis of data. Therefore, all records with unknown values of either variable were excluded, as were records for which the two values were inconsistent, namely, ages at admission of 15 to 24 years with 5 or more years of service. The selection process specified so far employed only the information available in the magnetic tape records of AH admissions. There were 12,197 subjects whose records met the above specified criteria, and these are referred to subsequently as the AH selection. Some were later found ineligible in the review of records described below. The numbers in the AH selection and those among them found ineligible are shown in Table 1 by study group and reason for ineligibility.

The tape records of AH admissions use only the Army service number for identification. Linkage to Veterans' Administration (VA) records was attempted to verify identification and to determine survival. First, these service numbers were matched against the Beneficiary Identification and Records Locator Subsystem (BIRLS) of the VA. Through this operation were obtained, when available, VA identify-

ing number (claim number), name, office of custody of claims folder (VA hard-copy record), and dates of birth and death. Successfully matched were 11,835 of the subjects among those in the AH selection. The remaining 362 were machine matched against the Registry File of the National Personnel Records Center of the General Services Administration in St. Louis, and the 178 not found there were in turn matched in a manual operation against a microfilm file of World War II service numbers where 170 were identified. The eight unidentified subjects could be excluded immediately, and the 354 who were retained were again matched against BIRLS using the new information that had been acquired in the St. Louis searches. Altogether, for 106 subjects no satisfactory relationship between name and service number could be established. Their distribution by study group is shown in Table 1.

A VA death benefit is paid upon death of veterans who served during periods of military action. Previous studies (Beebe and Simon, 1969) have shown that the VA, with high probability, is notified of deaths among such veterans. The fact of death has been ascertained through information obtained from BIRLS for 2,430 subjects and from the VA Inactive Compensation and Pension (C&P) magnetic tape files for another 15 not known to be deceased at BIRLS. Causes of death can generally be determined from claims folders, which were searched for all identified deaths. Even when the claims folder death information is incomplete, place and date of death are generally given. In such instances, certificates have been sought from the Vital Statistics Offices with jurisdiction over the locality of the death. The underlying and associated causes of death were coded according to the International Statistical Classification of Diseases Adapted for use in the United States (ICDA). Also coded was information on autopsy status and place of death.

One objective of matching against BIRLS was to verify the eligibility of study subjects. Since all of those selected were inductees separated from the Army for disability, it is reasonable to expect that all applied to the VA for disability compensation or pension. Records of VA disability ratings for such awards were sought from magnetic tape files of Active and Inactive C&P claims and from hard-copy claims folders. All of the records may be accessioned by VA claim numbers obtained through BIRLS. Exclusions from the AH selection were made when, for the same claim number, the name representation on either the Active or the Inactive C&P file was not consistent with the name obtained from BIRLS or when there was evidence on the Inactive C&P file that the VA had disallowed a disability claim. Altogether, 169 subjects were excluded for these and other reasons as shown in

Table 1. All remaining 12,028 subjects constitute the total study sample and they all have been considered eligible for the matched sample.

Evaluations of reason for and extent of disability, made by the VA for purposes of awarding compensation, were obtained in coded form from C&P magnetic tape records and as written statements from hard-copy rating sheets. Rating sheets, filed in claims folders, were requested for 2,783 individuals. This included all known deaths for whom rating information is not consistently recorded in the magnetic tape files, and 338 living individuals not machine matched against the C&P files because their VA claim numbers had not at first been available. Analysis of the compiled data revealed that among all otherwise eligible subjects the VA could not provide us with disability ratings from any source for 4.0 percent of the proximal amputees, while among the distal amputees the corresponding figure was only 2.9 percent, and in the matched disfigurement group it was 3.0 percent. Moreover, when all eligible deaths are considered, among the 855 that occurred before 1966, for 22.5 percent no ratings were obtainable from any source, while among the 1,561 that occurred in 1966 or later, 4.8 percent did not have ratings. To avoid excluding early deaths disproportionately between study groups, the individuals for whom no disability ratings could be found have been retained in the study. However, we do evaluate in the Results section the effect of retaining them in the analysis.

A survey of ratings was carried out on a systematic sample of 100 deaths in each study group. The results are presented in Table 2. In this sample no ratings could be found on the C&P tape or through a search of claims folders for 16 percent of the proximal amputee deaths and 9 percent of the deaths in each of the two comparison groups. It appears that, when ratings were found, with high probability they support the AH selection condition and that the level of verification is similar for the three study groups. In the sample of 100 proximal amputee deaths there were 11 records coded on the AH admission records as "loss of lower extremity at the knee" that were rated as below the knee amputations by the VA. A review of the individual rating statements for these cases indicates that among the nine that clearly described the level of amputation, for eight it was given as the upper or middle third of the leg. Obviously the amputations designated by the Army as "at the knee" represent a serious physical impairment and therefore they have been retained in the proximal amputee group.

The relationship between survival status, time of death, and the availability of VA ratings noted above makes the evaluation of the *percent disability* by the VA an unsuitable variable for study. Percent of

disability evaluation is more often unavailable for the early than for the later deaths. The early deaths could well be the most disabled. Overall, information on percent disability was not obtained for 21 percent of the deaths, and this alone suggests that the available percent disability evaluation is not a suitable index for studying mortality. However, in the Results section it is shown that for living subjects there is almost no overlap in the percent disability distributions between the proximal amputees and the other two study groups. The study group classification is an equivalent to a grouping on percent disability if that were generally available. The distribution of percent disability among the 79 proximal amputee deaths is shown in Table 3.

To obtain distributions comparable as to age and length of service at AH admission, the 3,890 proximal amputees were matched to the 5,220 eligible subjects in the disfigurement group, one-to-one, so that at time of admission both were under 20 years old, of the same year of age between the ages 20 to 39, or within groups of 40–44, 45–49, or 50 and over. It was also required that length of service at hospital admission was, for both, less than 1 year, or 1 but less than 2, or 2 but less than 3, or 3 or more years. Within these matching specifications, choices were made alternately among eligible subjects in the disfigurement group with scars and those having other disfigurement until one or the other group was exhausted. The remaining subjects in the disfigurement group meeting the matching criteria were then sampled systematically until either all cases were matched or the entire disfigurement group was exhausted. For 71 proximal amputees, subjects in the disfigurement group could not be found within the age and length of service specifications described above. These 71 were matched to disfigurement subjects with next higher or lower age at admission, or within adjacent length of service groups, or both. The ultimate distribution of age and of length of service at admission is shown by study group in Table 4.

Matching on age at admission does not necessarily match the study groups on year of birth. As is shown in Table 5, the disfigurement group, in the AH selection, closely resembled the proximal amputees on year of birth, but after the matching, the year of birth distributions of the three study groups are almost identical. Deaths that occurred through April 30, 1977 constitute 17.5 percent of the 5,220 eligible disfigurement subjects in the AH selection, while they constitute 17.9 percent of the 3,890 matched disfigurement subjects.

For the major causes of death standardized mortality ratios (SMRs) were computed by dividing the number of such deaths observed in each study group by the number expected during the period of followup among U.S. males of the same age. The expected numbers

were determined by applying age- and calendar-year-specific rates for U.S. males to the actual number of person-years at risk at each age and in each calendar year among study subjects. U.S. mortality data have been coded according to the Eighth Revision of the ICDA only since 1968. To achieve comparability, in the entire followup period, with expected numbers in various cause of death groupings, the deaths that occurred among study subjects through 1967 were classified according to codes of the Seventh Revision of the ICDA. For deaths after that time the Eighth Revision codes have been used. The extent to which the observed mortality in the distal amputation and the disfigurement groups is below that expected at population rates agrees with the favorable mortality experience known to exist in the veteran population (Seltzer and Jablon, 1974).

Age-standardized relative risks (the SMRs) among proximal amputees divided by the corresponding SMRs for one of the other study groups, were evaluated using statistical tests suggested by Haldane (1955–1956). Bilateral amputations and site of loss were evaluated in a paired analysis by examining mortality within proximal amputee-matching disfigurement subject pairs. These contrasts produced relative risks (Mantel and Haenszel, 1959) that were tested as described by Cochran (1950). Mantel-Haenszel adjusted relative risks were obtained to evaluate and correct for possible confounding of the relationship between amputation and later mortality. The adjustment involved co-variables reflecting military career and circumstances of the injury leading to amputation together with age in 5-year groups.

In all analyses, period of observation was from January 1, 1946 to April 30, 1977. The 10 deaths occurring prior to this interval have been excluded from the study. After April 30, 1977 the exact duration of followup varies, and it cannot be accurately determined. The 26 deaths after that date identified among all eligible subjects have been classified as living throughout the followup period.

Results

Table 6 shows, for all living subjects by AH classification of disability, the mean and standard deviation of percent of disability as rated by the VA and recorded on the Active C & P file. It is clear that the proximal amputees have generally been assigned values above 50 percent. Bilateral amputees, almost without exception, have been assigned 100 percent values. The disfigurement subjects generally have values below 50 percent, and the distal amputees span the middle range with ratings in the 40-to-60-percent range. Differences between the two disfigurement subgroups and between the two distal amputee subgroups are trivial.

From the beginning of 1946 to April 30, 1977 there occurred 922 deaths among the proximal amputees, 698 in the disfigurement group matched on age and length of service to the proximal group, and 554 among the distal amputees. The date of death was unknown for three deaths among proximal and one among the distal amputees. These four deaths have been excluded from subsequent analyses because they cannot be used in the expectation computations. Excluding them, the number of person-years accumulated among the proximal amputees was 113,118; among the disfigurement subjects it was 115,746, and among the distal amputees it was 86,012. The number of deaths observed during the followup period and the number expected during this time among U.S. males of the same age is shown by study group for selected cause of death groups in Table 7. Age-standardized relative risks for the proximal group with respect to the disfigurement and to the distal groups are also shown. In one, or the other, or both comparisons there appears to be a statistically significant ($P \leq 0.05$) excess risk among the proximal amputees for overall mortality, deaths due to all diseases, cancer of the buccal cavity and pharynx, diabetes mellitus, and cardiovascular diseases including particularly ischemic heart disease. There is a suggestive ($P < 0.1$), but not clearly significant, excess in the proximal group of deaths from cancer compared to the distal amputees, and in both contrasts of cirrhosis of the liver and of deaths not specifically classified in the designated groups.

To detect differences that may not be apparent in the cause of death groupings in Table 7, individual cause of death codes (Eighth Revision) were contrasted directly between the age and length of service matched proximal and disfigurement groups. Except for the differences shown in Table 7 and those shown below, the two groups were quite similar.

ICDA codes	Cause	Proximal	Disfigurement	Two-sided exact test P
E950-952	Suicide by poisoning	10	2	.02
303	Alcoholism	9	4	>.10
571.0	Alcoholic cirrhosis	34	18	.03
571.8	Other specified cirrhosis	7	5	>.10
571.9	Unspecified cirrhosis	19	21	>.10
577.0	Acute pancreatitis	11	3	.03
582	Chronic nephritis	7	2	>.10

In the category of "other diseases, not above" in Table 7, the 19 excess

deaths among the proximal amputees are contributed to by an excess of various endocrine, nutritional, and metabolic diseases; respiratory system diseases excluding emphysema and bronchitis; diseases of veins; pancreatitits; hepatitis; and cholecystitis. However, within these broad categories the compilation is very heterogeneous, and only for pancreatitis, shown above, can the difference be considered statistically meaningful. Table 8 shows 90-percent confidence limits for the causes of death for which the proximal amputees had excess mortality with $P<.1$ on statistical testing.

As is indicated in Figure 1, the differences in overall mortality between the proximal amputees and the disfigurement group appeared early in the followup period and remained fairly constant throughout. The early mortality experience of both the proximal and distal amputees was similar to that of the U.S. male population. Subsequently, however, mortality in the proximal group increased markedly with time, while the distal group continued to have an experience much like that of U.S. males. The disfigurement group started with a mortality well below that of U.S. males but approached them in the later part of the followup period.

Mortality from cardiovascular disease, shown in Figure 1, in the early part of the followup period was equal for the proximal and the distal amputees and not much greater than mortality among U.S. males and among the disfigurement subjects. These differences increased markedly with time primarily due to increased mortality among the proximal amputees relative to U.S. males. In the disfigurement group, cardiovascular disease mortality was slightly below that expected from the U.S. male experience, and the difference was consistent over time. Among the distal amputees, cardiovascular disease mortality approached that of the U.S. males at the middle of the followup period.

In Figure 2, mortality of the three study groups from all causes and from cardiovascular disease is compared by age at start of the observation period, January 1, 1946. The excess of mortality among the proximal amputees, relative to that expected among U.S. males and relative to that of the other groups, is not much affected by starting age. Relative to the disfigurement group it decreases slightly with age. Particularly among the younger disfigurement subjects, mortality from cardiovascular diseases is well below that of U.S. males of the same ages. In the oldest age group both the disfigurement subjects and the distal amputees experienced mortality much like that of corresponding U.S. males.

As is shown in Table 9, when proximal subjects were compared to the individually matched disfigurement subjects in pairs, bilateral

lower limb amputees had the highest relative risk for all causes and for the cardiovascular diseases. In these same comparisons relative risks were higher for lower limb unilateral amputees than for arm amputees. The excess risk of arm amputees compared to their disfigurement matches was not statistically significant on testing. Included in the sample were only seven bilateral arm amputees and no deaths have been reported among them or among their matching subjects. Relative risks for amputations at the knee, that on review of VA records were shown to include an appreciable number of amputations of the upper or middle third of the leg, were somewhat greater than those for the upper part of the lower limb. The difference in relative risk between levels of lower limb amputation, however, is not significant on statistical tests.

It has not been possible to distinguish right and left proximal amputations of the lower limb, but the distinction can be made for arm amputations. Among 389 right arm proximal amputees, 35 deaths from the cardiovascular diseases have been observed, compared to 33.5 deaths expected from these causes. Among 345 left arm proximal amputees, these numbers are 31 and 27.8, respectively, leading to a relative risk for right arm amputation of 0.94, not significantly different from 1.0. For overall mortality the corresponding relative risk is 0.90, also not significantly different from 1.0.

For a fraction of the sample, one or more of the three diagnostic fields in the tape record summarizing the Army hospitalization indicated that wound infection was associated with the injury. The following diagnoses were considered as indicative of prolonged infection: gangrene, gas bacillus with gangrene, subacute bacterial endocarditis, osteomyelitis, severe wound infection. The presence of prolonged infection has been evaluated in relation to subsequent long-term mortality using the U.S. males as a standard, and this information is presented by study group in Table 10 for all deaths and for deaths due to the cardiovascular diseases. In none of the study groups is there an appreciable increase in overall mortality or in deaths due to cardiovascular diseases among those who were diagnosed with prolonged infection at AH.

A comparison like that presented in Table 7 was also made between the proximal amputees and all of the 5,219 disfigurement subjects in the AH selection. As is indicated in the first column of Table 11, excess mortality among the proximal amputees, significant on statistical testing ($P<0.05$), was found for the same cause of death groupings as in the matched comparison. In addition, a relative risk of 2.17 was noted for diabetes mellitus, of 1.51 for cerebrovascular disease, and of 1.38 for diseases not specifically presented in the table groupings

($P<0.05$). For all cause of death groups, the relative risks obtained in the matched comparison were similar to those in the unmatched one.

One analysis, shown in Table 11, was restricted to subjects with VA disability ratings. As was discussed above, deaths in the early followup period were excluded disproportionately by this restriction, and it has not been employed in other analyses. Nevertheless, as is shown in Table 11, the restriction has little effect on the relative risk values for the causes shown there. In the restricted analysis, no significant mortality differences between proximal amputees and the two comparison groups have been found, other than those shown in Table 11.

The three study groups represent different kinds of injury, and they are not completely homogeneous on a variety of traits on which information is available. In Table 12 are compared percent distributions for various characteristics of the subjects at AH. Also presented for mortality from all causes and the cardiovascular diseases are risks for the proximal amputees relative to the disfigurement subjects adjusted for differences on the characteristics tabulated and age in 5-year groups. When this analysis was carried out considering only age, a relative risk of 1.43 was obtained for overall mortality that is comparable to the value of 1.36 from the analysis that used the U.S. population as a standard. In the comparisons shown in Table 12 it appears that the two study groups have a very similar composition with respect to race, arm of service, and type of case. Adjustment for differences on these traits has practically no effect on the relative risks. There are marked differences between the study groups on the agent that caused the injury for which the subject was hospitalized, the length of hospitalization or of subsequent treatment by the military, and the year of original admission. Adjustment for these differences affects the relative risk values only slightly.

Discussion

The reasons for the statistically significant relationship demonstrated between limb amputation and cardiovascular disorders are not obvious. One possibility is that selection is taking place at the time of the original injury through increased risk of amputation among subjects prone to atherosclerosis. Enos et al. (1953, 1955) have shown that atherosclerosis was already evident in young traumatic casualties of the Korean conflict. In their study they evaluated the coronary arteries of 300 battle casualties whose average age was 21.1 years. They found that 77.3 percent of the hearts had gross evidence of coronary atherosclerosis. This ranged from fibrotic thickening in 35 percent to complete occlusion of one or more coronary vessels in 3

percent. The atherosclerotic process manifest in the coronary arteries of those casualties could also be present in the arteries of the peripheral circulation. At the time of an injury to an extremity it might make the difference between loss of the limb and salvage. This in turn could increase the long-term mortality from cardiovascular diseases among traumatic amputees.

Another means of relating cardiovascular diseases to amputation is to view it as an independent risk factor for atherosclerosis. As we presently understand atherosclerosis, it is difficult to see how loss of an extremity could accelerate this process. It is much more appealing to evaluate how amputation relates to other risk factors.

Our study evaluated one possible new risk factor that was evaluated by the final conclusion of the Carling (1954) study. There the possibility was raised of an increased amount of atherosclerotic coronary artery disease among persons having chronic infections. Also, Meyeringh et al. (1960) found an increased number of abnormal EKG's among amputees who had gas gangrene as a complication of their amputation. The authors postulated that this resulted from myocardial involvement by gas gangrene. No significant relationship could be found in our study between chronic infections and cardiovascular disease.

Hurst (1974) defines the known coronary risk factors. Traumatic extremity amputations cannot alter any of the "nonmodifiable risk factors" that include age, sex, and a family history of atherosclerotic coronary artery disease. The "modifiable risk factors", divided into major and minor, include as the major factors elevated serum lipids, atherogenic habitual diet (high in total fats, saturated fats, cholesterol, refined carbohydrates, and salts), hypertension, cigarette smoking, and diabetes mellitus. The minor modifiable risk factors include obesity, sedentary life-style, personality type, and psychosocial tension.

Elevation of serum lipids as a result of amputation seems unlikely. Our study could not evaluate the lipids of amputees or the comparison group subjects. These have been studied by Solonen et al. (1965), who found that cholesterol in the amputees was lower than in the comparison subjects (267 vs. 300 mg/100 ml). The question of hypertension also was not addressed by our study. Studies by Solonen et al. (1965) and Loos (1957) both evaluated the blood pressure of amputees and found it to be no higher than that of controls.

Smoking habits of amputees have not previously been assessed, and the subject has not been addressed directly in this study. An increased risk of death from malignant neoplasms of the buccal cavity and pharynx was noted among the proximal amputees compared to the

disfigurement group. The number of deaths from this cause is small, and it does not justify postulating a higher level of smoking among amputees as a reason for such an increase. If there were disproportionately more smokers among the amputees, one would expect more carcinoma of the lungs, but the lack of increased risk of neoplasms of the respiratory tract among amputees seems to rule out that possibility.

There is no discussion in the literature about the incidence of diabetes mellitus and traumatic amputation. The numbers of diabetes deaths in the present study are small and findings regarding the risk of diabetes among amputees are inconclusive. Mortality from this cause was slightly, but not significantly, greater among amputees than in the U.S. male population. The amputees tended to have a significantly higher mortality compared to the subjects with loss of part of hand or foot, among whom the number of observed diabetes deaths was inordinately small. The latter deficit may reflect the tendency toward more extensive surgical amputations when the procedure is carried out on diabetics. This would tend to exclude the disease from the distal amputee comparison group.

The minor risk factors of obesity, sedentary life-style (physical activity), personality type, and psychosocial tension, have not been directly evaluated by this study, but they have been evaluated by others. Sedentary life-style appears important in relation to cardiovascular disease of amputees. Paffenbarger (1970) and Frank (1966) both found an increase in coronary deaths among groups of "less active" males as compared to active cohorts. Our study included 120 bilateral lower limb amputees who are presumed to be the least active. Of them 17.5 percent died of cardiovascular diseases, which led to a risk of 3.5 relative to the 120 disfigurement subjects matched to them on age and length of service. The next lowest level of physical activity would be expected among unilateral lower limb amputees who had a relative risk of 1.64. It is likely that the activity of arm amputees would be the least restricted, and for them a relative risk of 1.2 was noted that could not be distinguished statistically from mortality of the matching disfigurement subjects.

The final minor risk factor is psychosocial tension. It seems obvious, and it has been documented by Haber (1958), that amputation of either lower or upper extremities would have a profound effect on one's self image and social interactions. Bakalim (1969) found the suicide rate to be 37 percent higher than expected among amputees. Our study did not find a statistically significant excess of all suicides in the proximal amputee group, but they had a relative risk of 5.1 for suicide by poisoning. They also had a relative risk of 1.9 for alcoholic

cirrhosis and of 3.8 for pancreatitis. Both of the latter are recognized as common complications of chronic alcoholism (Turner et al. 1977) that frequently is not shown as a cause of death on the certificate. It certainly is possible that amputees have a more stressful existence and thereby increase the potential for cardiovascular disease.

In summary, this study indicates that veterans with proximal traumatic amputations subsequently had excessive mortality due to cardiovascular disease. The study was not designed to test specific hypotheses about the causes of the increased risk. Causation could well be multifactorial. From the data presently available, the most likely factors of importance include increased sedentary life-style among amputees, and increased emotional stress caused by amputation. A greater risk of amputation among those who at the time of injury already had atherosclerotic disease is also a possibility.

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TABLE 1.—SUBJECTS SELECTED FROM ARMY HOSPITAL ADMISSIONS BY ELIGIBILITY STATUS AND STUDY GROUP

Reason for ineligibility and eligibility status	Study group			
	Proximal amputation	Disfigurement	Distal amputation	Total
Ineligibility:				
Incorrect service number	41	44	21	106
VA disability claim disallowed	16	27	10	53
Death before 1946	2	3	5	10
Total ineligible	59	74	36	169
Eligible	3,890	5,220	2,918	12,028
Total Army hospital selection	3,949	5,294	2,954	12,197
Percent eligible	98.5	98.6	98.8	98.6

TABLE 2.—NUMBER OF SUBJECTS IN SAMPLES OF 100 DEATHS FROM EACH STUDY GROUP BY VA DISABILITY RATING STATUS

VA rating status	Proximal amputees	Disfigurement subjects	Distal amputees
Ratings consistent with Army hospital final result code obtained from:			
C & P file (rating sheet not examined)	38	60	36
Rating sheet (no consistent entry on C & P file)	45	30	54
Ratings available, none consistent with Army hospital final result code	1	1	1
No ratings available	16	9	9
Total	100	100	100

TABLE 3.—*Percent distribution of VA rating of percent disability in a systematic sample of 100 proximal amputee deaths*

Percent disability:	*Percent of sample*
40	6.3
50	1.3
60	31.6
70	15.2
80	8.9
90	8.9
100	27.8
Total	100.0
Number with percent known	79

TABLE 4.—NUMBER AND PERCENT OF SUBJECTS AFTER MATCHING [1] BY STUDY GROUP, BY AGE AT ARMY HOSPITAL ADMISSION, AND BY LENGTH OF SERVICE AT ADMISSION

	Study group					
	Proximal amputation		Matched disfigurement		Distal amputation	
	Number	Percent	Number	Percent	Number	Percent
Age at admission:						
<19	532	13.7	532	13.7	388	13.3
20 to 24	1,577	40.5	1,577	40.5	1,176	40.3
25 to 29	1,094	28.1	1,087	27.9	818	28.0
30 to 34	526	13.5	533	13.7	413	14.2
35 to 39	153	3.9	154	4.0	114	3.9
40 to 44	7	.2	6	.2	7	.2
45 to 49	0	0	0	0	1	0
≥50	1	0	1	0	1	0
Length of service at admission:						
<1 yr	741	19.0	741	19.0	671	23.0
1 yr	1,353	34.8	1,370	35.2	969	33.2
2 yr	1,187	30.5	1,166	30.0	888	30.4
≥3 yr	609	15.7	613	15.8	390	13.4
Total	3,890	100.0	3,890	100.0	2,918	100.0

[1] The proximal amputees were matched to the disfigurement subjects, 1-to-1, by age and length of service at admission

TABLE 5.—PERCENT DISTRIBUTION OF YEAR OF BIRTH GROUP BY STUDY GROUP AND MATCHING STATUS

	Percent			
Year of birth	Proximal	Matched disfigurement	Distal	All selected disfigurement
<1900	0	0	0.1	0.1
1900–04	.2	.2	.3	.1
1905–09	3.9	3.8	4.3	3.8
1910–14	14.1	13.9	13.5	12.2
1915–19	28.7	27.9	28.7	26.0
1920–24	40.7	40.4	40.4	44.2
1925–27	12.3	13.9	12.6	13.6
Total	99.9	100.1	99.9	100.0
Number of subjects	3,890	3,890	2,918	5,220

TABLE 6.—MEAN PERCENT DISABILITY RATING ON ACTIVE COMPENSATION AND PENSION FILE, LIVING SUBJECTS BY STUDY GROUP AND ARMY HOSPITAL DISABILITY CLASSIFICATION

Study group and disability	Total	Total with percent disability known	Mean percent disability	Standard deviation
Proximal amputees (N=3,890):				
Bilateral lower limb	76	74	99.5	3.3
Bilateral upper limb	7	6	100.0	0
At thigh and above	1,872	1,799	75.7	15.6
At knee	422	405	66.1	19.1
Arm	574	547	83.9	11.5
Total living	2,951	2,831	76.6	16.5
Total disfigurement (N=5,220):				
Scar	2,144	2,047	40.3	18.9
Other	2,153	2,067	41.7	18.6
Total living	4,297	4,114	41.0	18.8
Distal amputees (N=2,918):				
Part of hand	1,472	1,410	49.8	20.3
Part of foot	888	845	44.8	19.4
Total living	2,360	2,255	47.9	20.1

[illegible] ESTIMATED RELATIVE RISK OF MORTALITY AMONG 3,887[1] PROXIMAL AMPUTEES, 3,890 MATCHED[2] DISFIGUREMENT SUBJECTS, AND 2,917 DISTAL AMPUTEES BY SELECTED CAUSES OF DEATH

ICDA Code, 8th Revision	Cause of death	Number of deaths: Proximal Observed	Proximal Expected[4]	Disfigurement Observed	Disfigurement Expected[4]	Distal Observed	Distal Expected[4]	Risk among proximal relative to[3]: Disfigurement	Distal
000-999	All causes	922	714.1	698	735.1	554	554.1	[5] 1.36	[5] 1.29
800-999	All trauma	127	123.8	115	126.7	101	94.2	[6] 1.13	[6] 0.96
800-949	Accidents	82	83.6	82	85.5	69	63.6	[6] 1.02	[6] 0.90
950-959	Suicide	30	23.2	23	23.8	20	17.7	[6] 1.34	[6] 1.14
960-978	Homicide	11	15.7	8	16.1	12	11.9	[6] 1.41	[6] 0.69
000-796	All diseases	782	590.3	572	608.4	444	459.9	[5] 1.41	[5] 1.37
010-019	Tuberculosis	2	12.2	7	12.3	4	9.3	[6] 0.28	[6] 0.38
140-209	All malignant neoplasms	139	128.3	132	132.6	86	100.2	[6] 1.09	[7] 1.26
140-149	Buccal cavity and pharynx	11	4.9	3	5.1	7	3.9	[8] 3.82	[6] 1.25
150-159	Digestive organs	34	33.5	41	34.6	19	26.2	[6] 0.86	[6] 1.40
160-163	Respiratory tract	44	45.9	47	47.6	34	36.0	[6] 0.97	[6] 1.01
180-189	Genital and urinary organs	13	10.5	13	10.8	7	8.3	[6] 1.03	[6] 1.47
200-209	Lymphatic & hematopoietic	15	15.0	11	15.5	8	11.7	[6] 1.41	[6] 1.46
250	Diabetes mellitus	16	9.6	9	9.9	2	7.5	[6] 1.83	[9] 6.25
390-448	Diseases of cardiovascular system	441	304.4	287	313.9	239	237.8	[5] 1.58	[5] 1.44
430-438	Cerebrovascular disease	36	33.4	25	34.4	20	26.2	[6] 1.48	[6] 1.41
410-413	Ischemic heart disease	346	220.4	229	227.6	187	172.3	[5] 1.56	[5] 1.45
390-404, 414-429, 440-448	Other than above	59	50.6	33	51.9	32	39.2	[9] 1.83	[6] 1.43
582-584	Chronic nephritis & other renal	7	6.1	3	6.2	5	4.7	[6] 2.37	[6] 1.08
470-486	Influenza and pneumonia	12	15.7	10	16.1	11	12.1	[6] 1.23	[6] 0.84
531-533	Ulcers of stomach & duodenum	11	5.3	6	5.3	6	4.1	[6] 1.83	[6] 1.42
571	Cirrhosis of liver	60	27.6	44	28.4	31	21.3	[7] 1.40	[7] 1.49
780-796	Symptoms and ill-defined	9	11.4	8	11.7	8	8.8	[6] 1.15	[6] 0.87
	Other diseases, not above	85	69.9	66	72.0	52	54.2	[7] 1.33	[6] 1.27
	Unknown cause	13		11		9			

[1] For 3 proximal and 1 distal amputee subjects date of death and expected mortality could not be obtained.
[2] Matched on age and length of service at hospital admission.
[3] (Observed/expected (proximal))(observed/expected (disfigurement or distal)).
[4] Based on age- and time-specific U.S. male death rates.
[5] $P \leq 0.001$.
[6] $P > 0.1$.
[7] $0.05 < P \leq 0.1$.
[8] $0.01 < P \leq 0.05$.
[9] $0.001 < P \leq 0.01$.

Note: None of the comparisons of Distal vs. Disfigurement are significant with $P \leq 0.05$.

TABLE 8.—RELATIVE RISK[1] OF MORTALITY AND 90-PERCENT CONFIDENCE LIMITS ON RISK[2] FOR CAUSES OF DEATH WITH EXCESS AMONG PROXIMAL AMPUTEES COMPARED TO THE MATCHED[3] DISFIGUREMENT SUBJECTS YIELDING P<0.1

Cause of death	Relative risk	Lower limit	Upper limit
All causes	1.36	1.25	1.48
All disease	1.41	1.29	1.54
Cancer of buccal cavity and pharynx	3.82	1.32	8.84
Diseases of cardiovascular system	1.58	1.40	1.79
Ischemic heart disease	1.56	1.36	1.79
Other cardiovascular disease	1.68	1.28	2.20
Cirrhosis of liver	1.40	1.01	1.93
Suicide by poisoning	5.12	1.59	21.10
Alcoholic cirrhosis	1.93	1.25	2.88
Acute pancreatitis	3.75	1.40	11.27

[1] For causes of death shown in table 7 see footnote 3 there. For other causes: (deaths (proximal)/113,118)/(deaths (disfigurement)/115,746).
[2] For causes of death shown in table 7 computed as suggested by Haldane (1955–56). For other causes exact binomial computation.
[3] See footnote 2 to table 7.

TABLE 9.—MATCHED[1] PROXIMAL AMPUTEE-DISFIGUREMENT SUBJECT PAIRS—PERCENT MORTALITY FROM ALL CAUSES AND FROM CARDIOVASCULAR DISEASES JANUARY 1946 THROUGH APRIL 1977 AND RELATIVE RISK[2] BY LATERALITY AND SITE OF AMPUTATION

Laterality and site of amputation	Total number of pairs	Percent deaths among proximal amputees	Percent deaths among disfigurement subjects	Number of death concordant pairs	Relative risk
ALL CAUSES OF DEATH					
Bilateral lower limb	120	35.8	18.3	7	[3] 2.40
Total unilateral	3,760	23.3	17.9	180	[4] 1.41
Thigh or above	2,459	23.5	18.4	124	[4] 1.39
At knee	566	24.9	15.5	26	[4] 1.85
Arm	735	21.6	18.2	30	[5] 1.24
Bilateral arm	7	0	0	0	----------
Total	3,887	23.7	[6] 17.9	187	[4] 1.44
CARDIOVASCULAR DISEASES					
Bilateral lower limb	120	17.5	5.0	1	[3] 3.50
Total unilateral	3,760	11.0	7.4	36	[4] 1.57
Thigh or above	2,459	11.8	7.7	20	[4] 1.58
At knee	566	10.4	5.8	9	[3] 2.08
Arm	735	8.8	7.6	7	[5] 1.18
Bilateral arm	7	0	0	0	----------
Total	3,887	11.4	7.4	37	[4] 1.62

[1] See footnote 2 to table 7.
[2] Proximal amputee deaths/disfigurement subject deaths excluding death concordant pairs. Symbols for level of significance as in table 7.
[3] $0.001 < P \leq 0.01$.
[4] $P > 0.001$.
[5] $P > 0.1$.
[6] Two deaths have been excluded because matching proximal amputees had unknown date of death, see footnote 1 to table 7.

TABLE 10.—NUMBER OF SUBJECTS, NUMBER OF OBSERVED AND EXPECTED [1] DEATHS, AND RELATIVE RISK [2] FOR ALL CAUSES AND FOR CARDIOVASCULAR DISEASES BY STUDY GROUP AND BY WOUND INFECTION STATUS

Study group	Wound infection			No wound infection			Relative risk for wound infection
	Total number	Observed deaths	Expected deaths	Total number	Observed deaths	Expected deaths	
ALL CAUSES OF DEATH							
Proximal amputees	1,886	361	348.8	2,001	461	365.3	[3] 1.04
Disfigurement subjects [4]	401	67	77.7	3,489	631	657.4	[3] .90
Distal amputees	601	98	111.4	2,316	456	442.7	[3] .85
CARDIOVASCULAR DISEASES							
Proximal amputees	1,886	222	149.1	2,001	219	155.3	[3] 1.06
Disfigurement subjects	401	31	33.4	3,489	256	280.4	[3] 1.02
Distal amputees	601	48	47.2	2,316	191	190.6	[3] 1.01

[1] See footnote 4 to table 7.
[2] (Observed/expected (wound infection))/(observed/expected (no wound infection)).
[3] $P \leq 0.01$.
[4] Matched, see footnote 2 to table 7.

TABLE 11.—RISK OF MORTALITY AMONG PROXIMAL AMPUTEES RELATIVE TO [1] SPECIFIED SAMPLES OF DISFIGUREMENT SUBJECTS AND DISTAL AMPUTEES BY SELECTED CAUSES OF DEATH

Cause of death	Proximal amputees		
	Entire sample (N=3,887)	With VA disability rating found (N=3,733)	
	Relative to		
	All disfigurement in AH selection, unmatched (N=5,219)	Matched [2] disfigurement, with VA rating (N=3,775)	Distal amputees, with VA rating (N=2,833)
All causes	[3] 1.36	[3] 1.35	[3] 1.26
All diseases	[3] 1.42	[3] 1.43	[3] 1.33
All malignant neoplasms	[4] 1.11	[4] 1.09	[4] 1.24
Buccal cavity and pharynx	[5] 2.96	[5] 3.82	[5] 1.24
Diabetes mellitus	[6] 2.17	[4] 1.83	[7] 6.21
Diseases of cardiovascular system	[3] 1.57	[3] 1.66	[3] 1.39
Cerebrovascular disease	[6] 1.51	[4] 1.46	[4] 1.38
Ischemic heart disease	[3] 1.55	[3] 1.64	[3] 1.40
Other than above	[7] 1.76	[7] 1.98	[4] 1.35
Cirrhosis of liver	[6] 1.36	[4] 1.33	[6] 1.49
Other diseases, not above	[5] 1.38	[4] 1.32	[4] 1.23

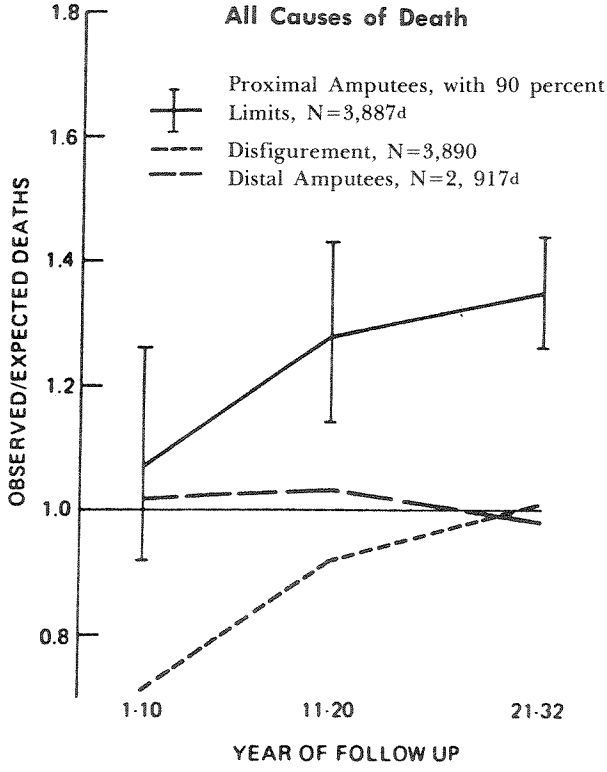
[1] For 3 proximal and 1 distal amputee subjects date of death and expected mortality could be obtained.
[2] Matched on age and length of service at hospital admission.
[3] $P < 0.001$.
[4] $P > 0.1$.
[5] $0.01 < P \leq 0.05$.
[6] $0.05 < P \leq 0.1$.
[7] $0.001 \leq P \leq 0.01$.

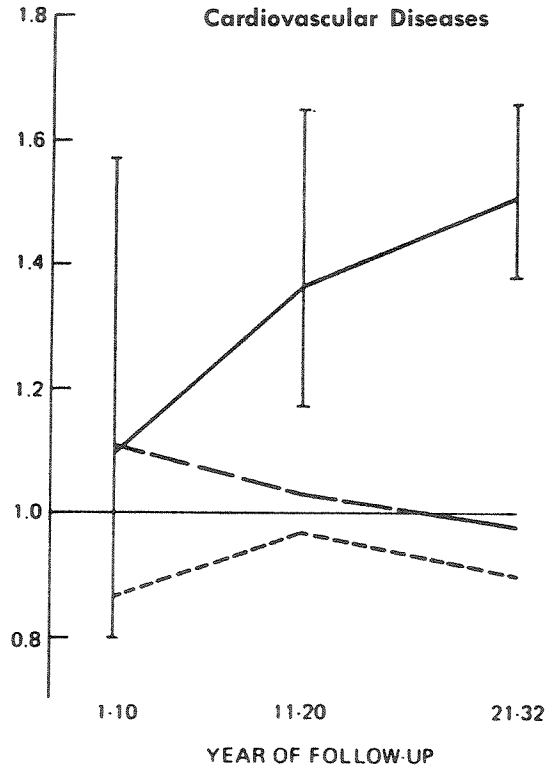
TABLE 12.—PERCENT WITH SPECIFIED CHARACTERISTIC, BY CHARACTERISTIC, AND THE RISK OF DEATH FROM ALL CAUSES AND FROM CARDIOVASCULAR DISEASES AMONG PROXIMAL AMPUTEES RELATIVE TO MATCHED DISFIGUREMENT SUBJECT ADJUSTED[1] SIMULTANEOUSLY FOR AGE AND CHARACTERISTIC

Characteristic	Percent with trait		Adjusted relative risk	
	Proximal (N = 3,887)	Disfigurement (N = 3,890)	All causes	Cardiovascular diseases
Race:				
White	99.2	98.0		
Nonwhite	1.8	2.0	[2] 1.43	[2] 1.60
Total	100.0	100.0		
Arm or service:				
Infantry	78.6	82.3		
Armored divisions	3.5	3.1		
Medical department	3.3	3.0	[2] 1.43	[2] 1.59
Other	14.7	11.7		
Total	100.1	100.1		
Type of case:				
Battle casualty	95.4	91.1		
Battle injury	2.1	3.5		
Nonbattle injury	2.6	5.4	[2] 1.44	[2] 1.60
Total	100.1	100.0		
Causative agent:				
Enemy artillery	62.5	54.6		
Enemy small arms	15.7	23.9		
Enemy land mine	11.9	3.8		
Aerial operations	6.8	4.7	[2] 1.46	[2] 1.60
Accidents with equipment, etc	2.9	3.9		
Total	99.8	99.9		
Duration of treatment, days:				
<249	19.7	43.2		
250-299	16.5	18.1		
300 to 499	47.9	29.4	[2] 1.40	[2] 1.47
≥500	15.8	9.4		
Total	99.9	100.1		
Year of admission:				
≤1943	5.0	0.6		
1944	54.8	41.9		
1945	40.2	57.4	[2] 1.40	[2] 1.57
Total	100.0	100.0		

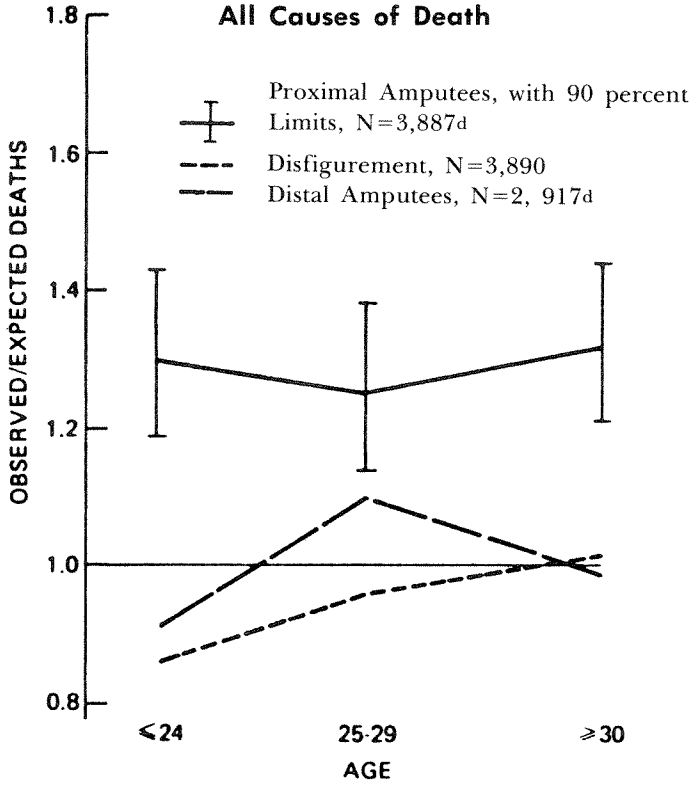
[1] Mantel-Haenszel method (Mantel, 1963) using 5-year age groups.
[2] $P \leq 0.001$.

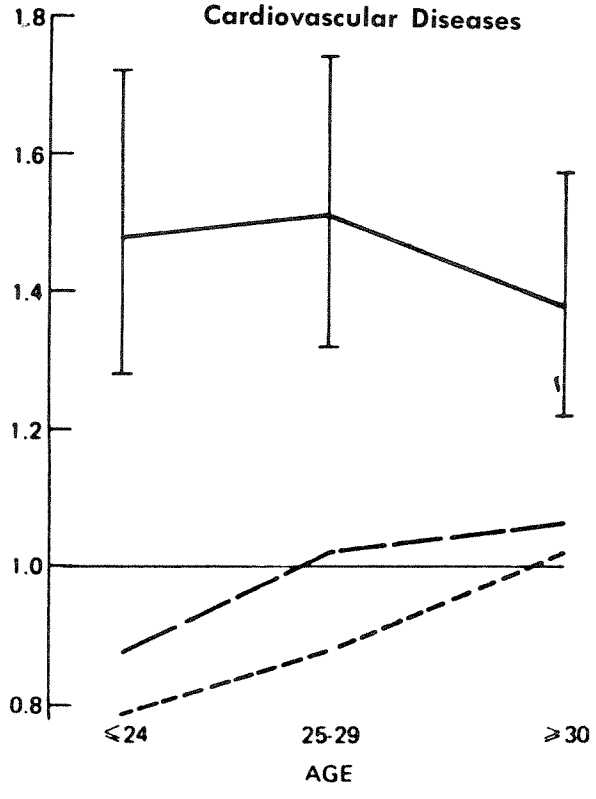
FIGURE 1. (opposite)—Ratio of observed to expected[a] deaths, 90 percent confidence limits of ratio and relative risk[b] from all causes and from cardiovascular diseases (ICDA 390-448) among proximal amputees, matched[c] disfigurement subjects, and distal amputees by year of followup.
NOTE: a, b, c, d: See footnotes d, c, b, a, respectively, to Table 7.





Risk Relative to						
Disfigurement:	1.50	1.39	1.33	1.26	1.42	1.67
Distal Amp.:	1.05	1.24	1.37	0.99	1.33	1.53





Risk Relative to						
Disfigurement:	1.51	1.30	1.29	1.87	1.72	1.35
Distal Amp.:	1.43	1.14	1.32	1.68	1.48	1.29

FIGURE 2. (opposite)—Ratio of observed to expected[a] deaths, 90 percent confidence limits of ratio and relative risks[b] from all causes and from cardiovascular diseases (ICDA 390-448) among proximal amputees, matched[c] disfigurement subjects, and distal amputees by starting age, 1 January 1946.

NOTE: a, b, c, d: See footnotes d, c, b, a, respectively, to Table 7.