

Reports of immunologic effects following human exposure to TCDD have been very rare. An increased susceptibility to infection was noted among workers following the Ludwigshafen accident (Goldmann, 1972). Following the explosion in Seveso, there did not appear to be an increase in number or severity of childhood infections, nor were results of immunological tests found to be abnormal (Reggiani, 1979, 1980; Malizia et al., 1979; Pocchiari et al., 1979).

1.5. Carcinogenic Effects

Several studies indicate that TCDD is carcinogenic in rodents, producing increased incidence of hepatocellular carcinomas and neoplasms in the lung, hard palate, nasal turbinates, and thyroid of the rat (Kociba et al., 1973; Toth et al., 1979; National Toxicology Program, 1982). Hepatocellular tumors, thyroid tumors, and fibrosarcoma of integumentary tissue have been produced in mice (National Toxicology Program, 1982a & b). TCDD may act as a promoter of liver tumors in the rat (Pitot et al., 1980).

An association between phenoxyherbicide exposure in forestry workers and soft tissue sarcoma has been noted in two Swedish case control studies as well as in the combined analysis of four American cohorts of workers industrially exposed to phenoxyherbicides (Coggon and Acheson, 1982; Editorial, 1981). Hardell and Sandstrom (1979) found a significant excess of malignant mesenchymal tumors in individuals occupationally exposed to phenoxyherbicide 10-20 years beforehand (relative risk 5.3, with 95% confidence limits 2.4-11.5). Eriksson et al. (1981) also found a significant association between exposure to phenoxyherbicides and soft tissue sarcoma (relative risk 6.8 with 95% confidence limits 2.6-17.3). The histologic distribution of tumor types in the exposed and unexposed groups was not recorded in either study.

Honchar and Halperin (1981) combined individuals from 4 cohorts industrially exposed to phenoxyherbicides and related compounds and found that 3 of 105 deaths had been due to soft tissue sarcoma compared with 0.07% of deaths in the total U.S. white male population aged 20-84. A fourth (recently deceased) case was subsequently reported in one of these cohorts (Cook, 1981). Additionally, three other individuals with soft tissue sarcomas were reported to have worked in 2,4,5-T production facilities (Moses and Selikoff, 1981; Johnson et al., 1981).

Other studies of workers exposed to phenoxyherbicides during their application have so far failed to confirm this association (e.g., Coggon and Acheson, 1982). However, in most cases the design of these investigations was such that only very high relative risks for soft tissue sarcoma were likely to be detected.

Hardell et al. (1981) found a significant excess of lymphomas in Swedish individuals occupationally exposed to phenoxyherbicides (relative risk 6.0, 95% confidence limits 3.7-9.7). The excess risk was similar for Hodgkin's and non-Hodgkin's lymphomas when analyzed separately. No other epidemiologic studies of this association have been reported. Compromised immunity is the strongest risk factor for development of lymphomas (Greene, 1982). Dioxins have immunosuppressant properties in animal species (see above), which presents an attractive hypothesis for the etiology of their postulated association with both soft tissue sarcoma and lymphomas.

At least two epidemiologic studies suggest a slight excess risk of stomach cancers in cohorts exposed to phenoxyherbicides and related compounds. Theiss et al. (1982) reported a significant excess of stomach cancers (3 observed vs. 0.6 expected) in 74 German workers who were exposed to trichlorophenol and dioxin 20 years before. Axelson et al. (1980) observed an apparent excess of stomach cancer (3 observed and 0.71 expected) among 348 railroad workers exposed to phenoxyherbicides and amitrol.

Hardell et al. (1982) reported that exposure to phenoxy acid herbicides doubled the risk of nasal and nasopharyngeal cancer (relative risk 2.1, not statistically significant). The controls used for this study were the same as those used in the previously mentioned Swedish studies of sarcomas and lymphomas.

Tung reported that primary liver cancer occurred in excess in Vietnam as a result of Agent Orange exposure of the general population, but this reported excess was not verified when his report and pathologic specimens were reviewed (VA lit rev., 1981). Even though human liver damage has been reported as a result of dioxin exposure (see above), no excess liver cancer has been reported.

1.6. Reproductive Effects

The reproductive effects of 2,4-D, 2,4,5-T, and TCDD, alone or in combination, have been examined in a number of different animal species. The effects are variable, depending on dosage, species, and strain. Only animal studies of the effects of 2,4,5-T with levels of TCDD contamination which either are unknown or known to be at least 1 ppm and of the effects of combinations of 2,4-D, 2,4,5-T, and TCDD will be discussed, in the light of the composition of Agent Orange.

A study of the effect of exposure of male mice to contaminated 2,4,5-T before mating with unexposed females showed no effect on the loss of fetuses before or after implantation (Buselmaier et al., 1972). Lamb et al. (1980) examined the effects of "simulated Agent Orange" -- i.e., mixtures of 2,4-D, 2,4,5-T, and TCDD -- administered to male mice followed by mating to untreated females. No effects were reported in fertility, implantation, fetal malformations, germ cell toxicity, sperm concentration, motility, or abnormalities and survival of offspring.

Most of the reproductive studies in animals have involved exposure only of the female after conception. In monkeys, fetal size was reduced but no malformations were observed (Wilson, 1971). In the rat, low doses of 2,4,5-T produced cystic kidney and intestinal hemorrhage (Courtney et al., 1970; Sparschu et al., 1971). A slightly increased incidence of cleft palate in the rat was reported in one study (VA, 1981 lit. rev.). 2,4,5-T administered throughout gestation produced maternal toxicity, fetal death or decreased fetal growth (Hall, 1972). In the mouse, 2,4,5-T produced cleft palate, and cystic kidney, the necessary dosage depending on the strain (Bionetics, 1968; Courtney et al., 1970; Gaines et al., 1974). In the hamster, cleft palate was rarely encountered; instead abnormal cranial development was observed (Collins et al., 1971).

Reproductive outcomes have been examined after many human exposures. However, the significance of most of these studies is questionable because of limitations in study design, population size, and inadequate handling of confounding factors. Pazderova-Vejlupkova et al. (1980) considered the frequency of abortion to be normal among wives of workers in the Czech factory. Following the explosion at Seveso, no increase in congenital malformations or developmental abnormalities was noted, but it was not possible to assess the frequency of spontaneous abortions due to an increase in elective abortions following the accident, and no baseline data were available for miscarriages (Reggiani, 1979; Homberger et al., in VA lit. rev.). In the U.S.A., a study of the incidence of spontaneous abortions among women whose husbands were occupationally exposed to 2,4-D as farmers, forest workers, or herbicide applicators revealed no overall association (SRI International, 1981). Human miscarriages near a spray project near Globe, Arizona, were found not to be related to herbicide use; a similar lack of association was found with human malformations in Swedish Lapland (Binns and Balls, 1971; Advisory Committee, 1971). In Arkansas, facial clefts were not associated with the agricultural use of 2,4,5-T (Nelson et al., 1979). A study of birth defects in children born to Long Island Railroad maintenance employees exposed to 2,4,5-T used for weed control revealed that all major birth defects combined and inguinal hernia were less frequent than expected. An excess observed for metatarsus adductus and tear duct obstruction probably resulted from variability in diagnosing these "minor" defects (Honchar, 1982). Reproductive outcomes of wives of Dow Chemical employees exposed to dioxins were surveyed. No statistically significant association between exposure and spontaneous abortions, stillbirths, infant deaths, and congenital malformations was observed (Townsend et al., 1982). The reported association between 2,4,5-T spraying and an increased incidence of miscarriage in the Alsea basin of Oregon (EPA, 1979) has been severely criticized (Wagner et al., 1979; Mantel, 1979).

A number of studies of reproductive outcomes were conducted in Australia and New Zealand. A study in Australia revealed no relationship between 2,4,5-T use and birth defects (Aldred et al., 1978). Another showed a correlation between the season of conception of babies with neural tube defects and the season of maximum 2,4,5-T spraying; a correlation was also found between neural tube defects in animals and 2,4,5-T (Field and Kerr, 1979). Two studies in New Zealand found no association between 2,4,5-T exposure and neural tube defects (McQueen et al., 1977; Hanify et al., 1981). One of these also found no association with cleft lip and palate or malformations of the heart or male genitalia, although it did reveal an association with talipes (malformations of the foot). A study in Western Australia that suggested an association between cleft lip and palate and herbicide exposure (Brogan et al., 1980) has been criticized on methodologic grounds (Bower and Stanley, 1980). A survey of ground agricultural sprayers showed no differences in the occurrence of malformations, stillbirths, miscarriages, or ectopic pregnancies (Smith et al., 1981).

The reports of human birth defects alleged to result from exposure to Agent Orange, which appeared in South Vietnamese newspapers in 1969, caused public and scientific furor (Advisory Committee, 1971; Young et al., 1978). In response, two independent surveys of South Vietnamese hospital records were conducted. An apparent increase in certain birth defects relative to others, which seemed to be associated with periods of herbicide spraying, was noted by

Meselson et al. (1971). Cutting et al. (1970) found no increased incidence of congenital abnormalities, stillbirths, and hydatidiform moles with heavy herbicide spraying. However, the conclusions of both of these studies were seriously limited by incomplete and unrepresentative sampling of births, unreliable birth records, and inadequate estimation of exposure (Advisory Committee, 1971). A subsequent study found an increased prevalence of isolated cleft palate and spina bifida compared with earlier years before widespread defoliant use, which might, however, be attributable to better case-finding and referral (Herbicide Assessment Commission, 1970; Nelson et al., 1979). Tung et al. (1971) and Rose and Rose (1972) reported on malformations and abortions among South Vietnamese refugees in North Vietnam. Lack of specific information about exposure and the lack of an unbiased selection procedure preclude any causal inferences. Studies conducted in South Vietnam in 1972 and 1973 by the National Academy of Sciences (1974) found no conclusive evidence of association between human birth defects and herbicide exposure, although study limitations were recognized.

A report has just been released on a large study (Donovan et al., 1983) designed to determine if Australian Vietnam veterans are at increased risk of fathering babies with birth defects. Vietnam veterans had no greater risks than veterans who served elsewhere or than men who were not veterans.

1.7. Other Effects

Gastrointestinal problems have been reported after a number of human exposures. A health survey of workers involved in 2,4-D production revealed that about half complained of dyspepsia, abdominal pains, and constipation (Bashirov, 1969). About 30% of the workers studied at the Newark plant complained of gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pains, or blood in stool) (Poland et al., 1971). Digestive disorders were reported among workers in the factories in Grenoble, France, and in Hamburg and Middle Rhein, West Germany (Dugois et al., 1958; Schulz, 1957; Bauer et al., 1961). Gastrointestinal symptoms, including abdominal pains and indigestion, were among the delayed symptoms which developed 2 to 3 years after TCDD exposure in two of the three government scientists in England (Oliver, 1975).

High levels of serum cholesterol and lipids were also commonly reported among exposed workers. Serum lipids tended to be high among workers following the explosion at the Nitro factory (Suskind, 1978). Ten percent of Newark workers had elevated serum cholesterol levels (Poland et al., 1971). Hyperlipemia and hypercholesterolemia were reported among workers in Grenoble (Dugois et al., 1958). Similar findings were described for the Czech workers, who also exhibited elevated levels of pre-beta lipoprotein and of total blood proteins (Jirasek et al., 1974; Pazderova-Vejlupkova et al., 1980, 1981). All three of the English scientists had hypercholesterolemia (Oliver, 1975). Walker and Martin (1979) reported high cholesterol and triglyceride levels and low high-density-lipoprotein levels in a small group of exposed workers.

2. Diseases Affecting U.S. Troops in Vietnam

This section is included to provide background on the health of U.S. servicemen while they were stationed in Vietnam. Fifty-six to seventy-four percent (mean 70.6%) of hospital admissions during the Vietnam war were for

medical disorders, as compared with battle casualties (15.6%) and non-battle injuries (13.8%), during the period 1965-69 (Ognibene and Barrett, 1982). Despite this fact, the average annual disease admission rate (351 per 1,000 per year) was one-third lower than for the China-Burma-India and Southwest Pacific theaters in WWII, and 40% less than for the war in Korea (Neel, 1973).

Malaria has been identified as the most significant medical problem, accounting for the greatest number of man-days lost from duty during the war. The emergence of a chloroquine-resistant form of malaria, *P. falciparum* malaria, led to the use of Dapsone^R (4,4'-diaminodiphenylsulfone), which is also used to treat leprosy (Neel, 1973).

Infectious hepatitis did not pose a major problem during the Vietnam war, as it did in previous wars. The incidence of hepatitis (6.9 cases per 1,000 per year) varied with the intensity of combat operations and with troop interaction with the civilian population (Neel, 1973). In Vietnam, serum hepatitis was of more concern, occurring most commonly among men who received multiple blood transfusions related to battle injury or among those using illicit drugs intravenously (Ognibene and Barrett, 1982).

Diarrheal disease rates were also lower compared with earlier wars. The prevalence rate ranged from 69 per 1,000 in 1965 to 35 per 1,000 in 1969. Diarrheal diseases may have been related to viruses, bacteria or parasitic agents, but the cause of most cases could not be identified. Troops at greatest risk were those who were unacclimatized and those under combat conditions. Incidence peaked in May or June, corresponding with the monsoon season (Neel, 1973).

Skin diseases were quite prevalent among troops in Vietnam. Those cases severe enough to require hospitalization or retention in quarters varied from 30 per 1,000 in 1965 to 20 per 1,000 in 1968. In 1970, however, skin problems increased again, to 30 per 1,000. The reason for the increase is unexplained. The three major skin problems identified were superficial fungal infection, bacterial infection, and immersion foot (Neel, 1973; Allen, 1977).

Plague and cholera, endemic in the Vietnam population, did not pose a significant problem for U.S. troops. Melioidosis, an infectious disease of humans and animals endemic in tropical areas, presented a problem to U.S. physicians unfamiliar with its diagnosis or treatment. Two hundred and thirty cases, diagnosed between 1965 and 1971, resulted in 14 deaths (Neel, 1973). The problem of fever of undetermined origin (FUO) presented some of the most challenging diagnostic dilemmas for military physicians in Vietnam. The diagnosis of FUO ranked second only to venereal disease. During the period 1966 through 1969, 58 cases per 1,000 were reported each year, including hospitalized and non-hospitalized patients (Ognibene and Barrett, 1982).

Venereal diseases have been prevalent during most military engagements. In Vietnam, it led other common medical problems in prevalence from 1965 to the conclusion of the war. Gonorrhoea accounted for 90% of all venereal disease cases. The second most frequently occurring condition of venereal origin was chancroid (Ognibene and Barrett, 1982).

Neuropsychiatric diseases did not differ appreciably among troops serving in Vietnam and those serving elsewhere until 1968. During this year, the prevalence of psychosis, psychoneurosis, and of character and behavior

disorders increased among all army troops and particularly among those stationed in Vietnam and became the second leading disease problem by 1970. Concomitantly, the problem of drug abuse escalated during this period, especially among younger, lower ranking enlisted men (Neel, 1973).

3. Current Health of Vietnam Veterans

Very little is known about the health of Vietnam veterans relative to the health of other men of similar age. Some indication of veterans' and others' perceptions about the veterans' health can be found in the reports of Bogen, 1979; Stellman and Stellman, 1980; Texas Dept. of Health, 1983; UCLA-VA Protocol literature review; and Wolfe, 1980. The most frequently reported conditions include dermatologic disorders, neurologic and psychologic disorders (including numbness and tingling in the extremities, headaches, fatigue, depression, memory loss, sleep disturbances, and sexual dysfunction), reproductive problems (birth defects, miscarriages, abortions, reduced fertility), cancer, gastrointestinal disorders, infections, hypertension, hepatic hematologic, genitourinary, respiratory, and cardiovascular problems.

Although there is a lack of data on organic disease outcomes among Vietnam veterans, there are a number of reports on the occurrence of health-related outcomes -- outcomes which may be considered by some to be disease outcomes and by others as possible causes or effects of disease.

Several large surveys have been conducted which provide psychological and sociological data on Vietnam veterans, veterans who served in the Vietnam era but not in Vietnam, and contemporary non-veterans (Starr et al., 1973; Martindale and Poston, 1979; Hammond, 1980; Harris and Assoc., 1971; Egendorf et al., 1981). These surveys present objective data concerning several aspects of social adjustment, subjective reports of psychological adjustment, and attitudes held by and about Vietnam era veterans. Although these surveys employed a variety of methods and focused on different aspects of adjustment, it can be concluded from this literature that Vietnam veterans have encountered more problems in adjusting to civilian life than the other men (Figley, 1977; 1978).

The general areas of observed or suspected sociological differences among Vietnam veterans, other Vietnam era veterans and non-veterans include educational and occupational status, stress-related psychological difficulties, drug and alcohol use, medical problems, and arrests (Boscarino, 1981; Boscarino and Figley, 1981; Segal, 1977; Borus, 1975; Gover and McEaddy, 1974; Stinson, 1979; O'Brien et al., 1980; Mintz et al., 1979). These problems have been found to vary among subgroups of these populations defined by ethnicity, exposure to combat, urban or rural residence, and period of service in Vietnam (Egendorf et al., 1981; Penk et al., 1981).

Post Traumatic Stress Disorder (PTSD) and its association with Vietnam service, exposure to combat, and drug and alcohol use has been widely investigated (Roberts et al., 1982; Boman, 1982; Lipkin et al., 1982; Frye and Stockton, 1982; Wilson & Kruass, 1982; Boscarino, 1980; 1981; Helzer et al., 1979; DeFazio et al., 1975; Horowitz, 1975). PTSD is thought to be a very common condition among Vietnam veterans (Wilson, 1980). However, large-scale psychiatric epidemiology research, which treats PTSD as a distinct diagnosis, has not yet been reported. Reliable estimates of the prevalence of PTSD in

the Vietnam veteran population cannot be derived from the current literature because of the frequent use of unusual (e.g., treatment seeking) samples and because symptom frequencies instead of validated diagnostic criteria have been used as outcome measures.

4. Long-Term Health Status of Servicemen and Veterans

This literature was reviewed to provide background for the Vietnam Experience study. The writers of these protocols expected to find a rich literature, but did not.* Numerous health studies of veteran populations have been conducted, but there are few, if any, which deal with long-term health effects of the general war experience. Disease incidence and prevalence among army personnel is well documented for World War II (WWII) (Anderson, 1968), the Korean War (Army Medical Service Graduate School, 1954), and the Vietnam conflict (Ognibene and Barrett, 1982) (see part 2, this Appendix); however, these reports cover only the period of military action.

*For reports of studies on the long-term health effects of war experience, we reviewed the Cumulated Index Medicus for the years 1975 through March 1983. In addition, several computer-based literature searches were conducted against these on-line data bases: Medline, 1966-83; Cancerlit, 1963-83; American Statistics Index, 1974-82; Social Science Citation Index, 1972-83; Psych Info, 1967-83; and Sociological Abstracts, 1963-83. The holdings of the libraries maintained at the Centers for Disease Control, Veterans Administration (VA) Hospital (Atlanta), VA Central Office (Washington) and Emory University School of Medicine were reviewed for appropriate reports. Finally, relevant studies completed on veteran populations by the Medical Follow-up Agency of the National Research Council within the National Academy of Sciences were included in the literature search. When relevant studies were identified, we used a branching technique to search for other cited references. A total of 135 journal articles and books were brought to CDC offices and reviewed.

A summary of the studies reviewed follows, even though they are not especially useful for the task at hand.

Hawryzluk (1975) studied prevalence ratios of diagnosed conditions among 813 army officers. Hearing loss, musculoskeletal disorders, and skin disorders were among the most frequently occurring medical problems. This study was limited to officers, most of whom were between 33 and 37 years old and had had 10-14 years of military service. They were selected for leadership positions and for their potential ability to do college work; thus, they were probably not representative of the general military population.

Medical records from the Armed Forces and the VA offer opportunities for followup studies. The Armed Forces system records all illnesses and injuries, even minor ones, among its active duty members, and it stores the clinical records in a central repository when the individual is separated from service. In the VA system, records documenting most of the agency's contacts with a veteran are maintained in a single file. Because benefits to veterans are many and varied, the VA maintains contact with most veterans, and many thousands of records are thus accessible for study (DeBakey and Beebe, 1962), (Beebe, 1951), (Cohen, 1953). However, because only a fraction of veterans receive their health care at VA facilities, and because those who do may be less educated and have more severe service-connected physical and mental disabilities, the records are of questionable usefulness for epidemiologic purposes, since their health experiences may not reflect those of the overall veteran population.

Armed Forces and VA records have been used for clinical followup studies of various medical and traumatic conditions, such as leprosy (Brubaker et al., 1969), rheumatic fever (Engleman et al., 1954), missiles in the heart (Blano and Beebe, 1966), and psychoneuroses (Brill and Beebe, 1951). These studies have been conducted for the purpose of describing the natural history and progression of the disease or condition and were conducted without control groups. Other studies with control groups, on the basis of the Armed Forces and VA data bases, have been directed at the veteran population receiving health services through the VA system, for example: studies of amyotrophic lateral sclerosis (Kurtzke and Beebe, 1980), asthma (Robinette and Fraumeni, 1978), scrub typhus (Elsom et al., 1961), coronary heart disease (Hrubec and Zukel, 1974), lumbar disc lesions (Hrubec and Nashold, 1975), splenectomy (Robinette, 1977), infectious mononucleosis (Miller and Beebe, 1973), cirrhosis of the liver (Beebe and Simon, 1970), esophageal cancer (Rogers et al., 1982), traumatic limb amputations (Hrubec and Ryder, 1980), and learning and reaction time (Milligan and Powell, 1981). Generally, the controls for these studies have been other veterans. Since the diseased and control veterans in these studies were not stratified with respect to their combat participation, the effect of that experience on the occurrence of the disease or its clinical course cannot be evaluated.

Veterans or their families have been participants in several studies on the effect, on subsequent health, of exposure to certain risk factors. Wallis (1968) reported on stress in service families, but his study did not include control families. Other studies have examined the effect on veterans of exposure to adjuvant influenza virus vaccine (Beebe et al., 1972), microwave radiation (Cleary et al., 1965), mustard gas (Beebe, 1960), (Norman, 1975), and smoking (Rogot and Murray, 1980). These studies included control groups.

but they were also selected from among other veterans. For the reasons discussed above, these data cannot be used to evaluate the effect of war service.

The literature contains reports from several studies that examined the morbidity and mortality experience of prisoners of war (POW's). Nefzger (1970) found that standardized mortality ratios and death rates indicated a clear early excess of deaths among prisoners held by the Japanese in WWII. Prisoners from the European and Mediterranean theatres of WWII did not have an adverse mortality experience to 1965. Keehn (1980) followed the same groups through 1975 and found that their increased risks of death, though diminished over time, persisted for 9 and 13 years, respectively. Mortality in Korean War prisoners has been more like that in Pacific than European WWII prisoners (Nefzger, 1970). Mortality from tuberculosis and from trauma contributes to the increase among Pacific ex-prisoners, whereas for Korea the increase is limited to trauma. An excess of deaths due to cirrhosis of the liver was apparent in all three former prisoner groups, WWII (Europe, Pacific) and Korean, from about the 10th followup year (Keehn, 1980).

Beebe (1975) studied morbidity, disability, and maladjustments among WWII and Korean prisoners and compared them with veteran controls from the same wars who were not taken captive. In this study, sequelae of the POW experience were both somatic and psychiatric and were of greatest extent and severity among Pacific WWII POW's. Among European WWII POW's, only psychiatric sequelae were apparent. Somatic sequelae were most prevalent in the early years after liberation, but for Pacific WWII POW's they persist in the form of higher hospital admission rates for many specific causes. Klonoff et al. (1976) investigated the long-term or residual effects resulting from severe and extended exposure to stress among POW's captured in Japan (high-stress group) or Europe (low-stress group) during WWII. The low-stress group was divided into long-term and short-term internment periods. Neuropsychological, psychiatric, and physical/neurological outcomes were compared, and significant differences were found among these three groups. The high-stress group scored significantly lower in operational intelligence, exhibited more signs of psychiatric maladjustment, and had more physical illnesses, especially of the neurological and musculoskeletal systems. Residual effects increased in proportion to length of internment, though numbers in each category were small when stratified in this way. The authors concluded that terms such as "survival syndrome" (Chodoff, 1963) and "war neurosis" (Maskin, 1966) describe identifiable phenomena with long-term residual effects (Klonoff et al., 1976).

Davies (1978) found an excess of leukemias, lymphomas, myelomas, and polycythemia vera among Australian servicemen with overseas and tropical area service as compared with those serving in temperate Australia; however, he did not control for confounding variables (such as age) and, for some controls, the area of service was doubtful. A diagnosis of malaria and/or an interaction of nitrates and nitrites with the malaria prophylactic drug chloroquine were suggested as possible risk factors. In a followup study, Giles et al. (1980) investigated the possibility that exposure to malaria may have led to later development of lymphoma in 62 men resident in Tasmania, Australia, and found no association.

In two studies which covered 29 years (1946-1974), Jablon and Miller (1970, 1978) found no statistically significant differences between army x-ray technologists (n=6,560) and controls (n=6,826) who served as medical, laboratory, or pharmacy technologists for total deaths from cancer, individual site of cancer, or deaths from other causes. Norman et al. (1981) investigated exposure to tetrachloroethane by comparing age-specific mortality among 1,099 males assigned to chemical processing companies during WWII and 1,319 veterans not involved in the impregnation process of protecting clothing against mustard gas. Overall cancer mortality for exposed subjects was 1.26 times higher than for controls. The risks for leukemia, lymphoma, and cancers of the genital organs were moderately elevated, but the numbers were small and no significant excesses were observed.

The Medical Followup Agency of the National Academy of Sciences - National Research Council established a Twin Registry comprising 16,000 pairs of white male twins, both members of which had been in military service, mainly in WWII. This data base has provided information for the study of multiple sclerosis (Bobowick et al., 1978), cardiovascular and respiratory symptoms (Cederlof et al., 1969), (Hrubec et al., 1973), psychopathology (Pollin et al., 1969), (Allen and Pollin, 1970), (Hoffer and Pollin, 1970), (Stabenau et al., 1970), intraocular pressure (Schwartz et al., 1972, 1973), corticosteroid response (Schwartz et al., 1973), allergy (Bazaraal et al., 1974), skin diseases (Lynfield, 1974), hypertension (Oglesby, 1975), headache (Ziegler et al., 1975), plasma cholesterol and triglycerides (Christian et al., 1976), personality traits (Horn et al., 1976), earnings (Taubman, 1976), dietary intake (Fabsitz et al., 1978), weight changes (Fabsitz et al., 1980), electrocardiographic characteristics (Havlik et al., 1980), alcoholism (Hrubec and Omen, 1980), and familial factors in early deaths (Hrubec and Neel, 1981). These studies have not classified the veterans according to their combat experience.

Seltzer and Jablon (1974) found evidence for a "healthy warrior" effect when they examined the effect of health selection at induction on subsequent cause-specific mortality in a series of 85,491 white male WWII U.S. Army veterans followed for 23 years, 1947-1969. They found that mortality rates were well below those of the general population during the first few years after discharge. After 23 years the mortality rates of the veterans were still lower than, but approaching, those of the general population. The effect of military selection varied considerably according to the nature of the cause of death.

Three studies have demonstrated an association between mortality and military rank at separation from military duty. Keehn et al. (1978, 1974) and Seltzer and Jablon (1977) found that mortality during 24 years following separation declined with each successive advance in rank through the enlisted grades. Furthermore, mortality of privates was very close to expectation based on population rates; non-commissioned officers had a 23% advantage and commissioned officers about a 40% advantage. The advantage held for deaths from all causes and also for most specific causes examined. Over the 24-year period of followup, the tendency for the differences to diminish was only small.

In summary, many health studies have been conducted on veteran populations, but because of the lack of control groups, the selection of control groups from among veterans who were not classified as to their combat experience, and the selection of study subjects from specific military occupational specialties, the studies are not useful for evaluating the overall effect of war service. CDC's review of this literature revealed little which could be used to generate specific hypotheses about health effects of military service in the Vietnam war.

APPENDIX C
SAMPLE SELECTION USING TELEPHONE RANDOM DIGIT DIALING

Random digit dialing is a telephone sampling method that produces a random sample of households with telephones, regardless of whether or not the number is listed in the telephone directory. It appears to be an efficient and inexpensive means of obtaining an unbiased random sample, and a preferable alternative to time-consuming and costly door-to-door screening and to random selection of numbers from telephone directories or specially compiled lists. The latter approach misses unpublished and new listings and requires the difficult task of removing duplicates when large geographic areas and multiple overlapping directories and lists are involved. Further, since 90.2% of all U.S. households had telephones in 1976 (thought to be around 95% in 1983), biases attributable to underrepresentation of those households that do not have telephones are not likely to affect results appreciably (Klecka and Tuchfarber, 1976). One factor to be aware of, however, is that availability of telephones is related to income. According to the 1970 Census of Population and Housing, 76% of households with incomes \$5,000 had telephones, compared with 95% of households with incomes \geq \$25,000; 89% of white households had telephones, compared with 70% for black households (Waksberg, 1978).

Random digit dialing methods range from dialing a 7- or 10-digit random number to compiling a listing of area codes plus 3-digit exchanges used within the geographic bounds from which a study sample is to be drawn and randomly appending the last 4 digits. The 7- and 10-digit random numbers are estimated to produce households for only 1 in 30 and 1 in 200 numbers dialed, respectively (Cooper, 1964; Glasser and Metzger, 1972). Sampling within the listing of area code plus 3-digit exchanges involves one of several approaches to randomly append the last 4 digits and to deal with non-residential and not-in-service numbers. Klecka and Tuchfarber (1974a) report that the proportion of not-in-service numbers ranged from 37.3% in an urban setting to 70.6% in a rural region for 3 random digit dialing samples; and the proportion of business numbers were 11.3% and 3.2%, respectively. Cooper (1964), who uses blocks of 3-digit exchanges plus 1 digit and randomly selects the remaining 3, reports 32% of the numbers were ineligible. Waksberg (1978) contends that simple random sampling within existing exchanges is inefficient, since about 80% are businesses, institutions, government, or not in service. Waksberg's method seems to eliminate making large numbers of nonproductive calls to non-residential and not-in-service numbers by making multiple calls within a block of numbers (block=area code + exchange + 2 random numbers) only if the first number dialed within that block is residential.

To support the hypothesis that random digit dialing yields an unbiased sample, such a sample must be scientifically compared with samples drawn by conventional means in the field. In 1974, Klecka and Tuchfarber (1976) compared their random digit dialing sample on crime victimization of 800 households and 1,685 respondents in Cincinnati, Ohio, with the Census Bureau's survey of 9,708 households and 19,903 respondents. Race, age, sex, education, income, household density of persons over 12 years of age, and ownership status of the residence were among the demographic variables examined. Excepting education, there were no statistically significant differences between the two populations when tested by chi-square. Thus, the authors concluded that random digit dialing and Census Bureau's complex approach had produced samples from the same population. References cited above and others documenting the efficacy of random digit dialing are found in section 12.

APPENDIX D

TOPICAL LIST OF QUESTIONNAIRE ITEMS* FOR
AGENT ORANGE AND VIETNAM EXPERIENCE STUDIESADMINISTRATIVE

Name
Identification Numbers
 Military Service Number
 Social Security Number
Telephone Number
Interviewer Name
Date of Interview
Quality of Interview
Names and addresses of friends who will know future whereabouts

SOCIODEMOGRAPHIC

Date of Birth
Place of Birth
Current Residence
Race/Ethnicity
Marital History
Education
Religion
Occupation and Income
Problems in Obtaining Employment

MEDICAL

Height and Weight
General Health Status
All Hospitalizations and Operations
Physician Treatment, Physician Diagnosis, or Self-Diagnosis of:
 Neurologic Disorders
 Psychologic Disorders
 Impaired Fertility
 Endocrine Diseases
 Cardiovascular Diseases
 Cancer
 Gastrointestinal Disorders
 Genitourinary Disorders
 Respiratory Diseases
 Musculoskeletal Condition
 Dermatologic Conditions
 Other Complaints
Trauma
Reproductive History
Blood Transfusions

*Some data items listed may be derived from military records.

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

Page 80

Smoking

Alcohol

Abbreviated Occupational History Focusing on Exposures to Herbicides

Illicit Drug Use

MILITARY HISTORY

Drafted/Enlisted

Countries of Assignment

Occupational Duties

Combat Intensity

Injuries, Wounds in Service

Herbicide Exposure

APPENDIX E
 TOPICAL LIST FOR EXAMINATION AND LABORATORY TESTING*
 AGENT ORANGE AND VIETNAM EXPERIENCE STUDIES

PHYSICAL EXAMINATION

The physical examination will be modified from those of the National Center for Health Statistics' Health and Nutrition Examination Survey and the Ranch Hand Study, with special attention given to the dermatologic and neurologic systems.

General: habitus, weight, height, blood pressure, pulse, respiratory rate
 Skin: rash, scars, ulcers, acne, masses, spider angiomas, pigmentation
 Head: movements, hair pattern
 Eyes: movements, fundi, Snellen testing of acuity, conjunctiva, icterus
 Ears: audiometry, otoscopic exam
 Nose: polyps, sinusitis
 Mouth: teeth, tonsils, tongue, cheeks, throat, gingiva
 Neck: thyroid and parotid palpation, cervical lymphadenopathy
 Chest: movements, bony abnormalities, axillary lymphadenopathy
 Lungs: rales, rhonchi, wheezes, dullness, hyperresonance
 Heart: extra sounds, murmurs, rubs, size
 Abdomen: liver and spleen size, tenderness, masses, hernias, testicular size and masses, inguinal lymphadenopathy, rectal exam
 Back: scoliosis, kyphosis, tenderness
 Limbs: movements, edema, arthritis, varicosities, nail clubbing, peripheral pulses, lymph nodes
 Neurologic: mental status, cranial nerves, motor system, reflexes, sensory deficits, nerve conduction studies (conduction evaluation only for Agent Orange study)

PSYCHOLOGIC AND NEUROPSYCHOLOGIC TESTING

Minnesota Multiphasic Personality Inventory
 Diagnostic Inventory Schedule
 Psychiatric Epidemiology Research Interview
 Battery from Halstead-Reitan Neuropsychological Tests
 Armed Forces Qualification Test--this is the intelligence test given to the veterans on their induction into service
 Wechsler Memory Scale

* May be modified as a result of consultations to take place in late 1983 and early 1984 with experts in several specialties, e.g., neurology, immunology, psychology.

BLOOD:

Complete Blood Count: hematocrit, red cell count, white cell count
and differential, platelet count
Fasting Blood Glucose
Cholesterol and Triglycerides
Creatinine
Bilirubin and GGPT
Thyroxine
Hepatitis B Core Antibody
Serum Stored for Future Serologic Testing

URINE:

Protein
Glucose
Hemoglobin
Porphyrins

STOOL:

Qualitative Test for Occult Blood

MISCELLANEOUS:

Delayed Cutaneous Hypersensitivity Battery:
Mumps
Candida
Tuberculin
Streptococcus
Proteus
Diphtheria
Tetanus
Control

APPENDIX F

TOPICAL LIST OF QUESTIONNAIRE ITEMS FOR
SELECTED CANCERS CASE-CONTROL STUDYADMINISTRATIVE

Name
Identification Numbers
 Military Service Number
 Social Security Number
Telephone Number
Interviewer Name
Date of Interview
Quality of Interview
Friends who will know future whereabouts

SOCIODEMOGRAPHIC

Date of Birth
Place of Birth
Current Residence
Race/Ethnicity
Marital Status
Education
Religion
Occupation and Income

FAMILY HISTORY OF CANCER

Occurrence of soft tissue sarcomas, lymphomas, and other cancers in first-degree (parents, siblings, and children) and second-degree (aunts, uncles, and grandparents) blood relatives and spouses.

MEDICAL

Height and Weight
Possibly Predisposing Conditions
 Immune Deficiency Diseases
 Rheumatoid Arthritis
 Other Cancers
 Celiac Disease/Gluten Enteropathy
 Hemophilia
 Infectious Mononucleosis
 Neurofibromatosis
 Trauma
Medical Exposures
 Immunosuppressive Therapy
 X-irradiation
 Dilantin
 Iron Dextran
 Blood Transfusions
Surgery, Hospitalizations, Long-term Medications
Medical Care Utilization

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

Smoking
Alcohol
Lifetime Occupational History, Including Probes to Exposures Such As:
 Asbestos
 Herbicides
 Pesticides
 Irradiation
 Organic Solvents
 Vinyl Chloride
 Benzene
 Arsenicals
 Wood dust
Illicit Drug Use

MILITARY HISTORY

Drafted/Enlisted
Training
Countries of Assignment
Military Occupational Specialty
Occupational Duties
Combat Intensity
Herbicide Exposure

Use of trade names is for identification only and does not imply endorsement of the Public Health Service or the Department of Health and Human Services.

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