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WOMENS VIETNAM VETERANS HEALTH STUDY
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LITERATURE REVIEW AND BIBLIOGRAPHY

DELIVERABLE A

SUBMITTED BY NEW ENGLAND RESEARCH INSTITUTE

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INTRODUCTION

This review has been conducted as a first necessary step in designing the optimal study of women Vietnam veterans. As originally proposed, the review will, therefore perform the following important functions to inform study design:

- Summarizing current knowledge in related areas of research;
- Noting important gaps in current knowledge which may affect study design;
- Highlighting methodological problems in other research which may be relevant; and
- Acquiring instruments, definitions etc. which, because of wide, accepted use and/or excellence should be considered for inclusion in the planned study.

In order to attain these goals within a very limited time period, the following limitations were put on the literature search:

1. A full literature search was only conducted for work published since January 1, 1980;
2. Selected studies reported before that date were included if they were clearly seminal and frequently cited in later work;
3. Emphasis was given to those areas of research about which least was known, with only key references provided for well-established findings; and
4. Only key references from the comprehensive bibliography on Phenoxy Herbicides already completed by the VA were included and this review was updated with reports since 1985.

An important feature of this task, was evaluation of all original research reports on a three-point scale, according to methodological adequacy of study design. Those at the low end (evaluation = 1) were judged to be so methodologically flawed (usually through inadequate numbers or lack of an appropriate comparison group) that no credence could be given to their findings. In many areas these formed the majority of reports reviewed. Those at the high end (evaluation = 3) met minimal criteria for a study which could be considered methodologically sound, although this did not guarantee a flawless or optimal design. Those

reports rated with an intermediate evaluation score of 2 met sufficient of the criteria for their results to be considered seriously, although not with the same weight given to the most highly rated reports. This evaluation, as well as subject and function indexing is provided for each reference in the resulting computerized bibliography to facilitate the use of this work in the subsequent design tasks. (Not all references in the bibliography are cited in this review - rather the citations are illustrative of the literature reviewed.)

A consequence of this evaluation mechanism is the emphasis given to methodolgical issues in the review, and to the value of certain findings.

In organizing a review which had to encompass a wide range of research fields several options presented themselves. The structure finally accepted followed the proposed basic study design of a retrospective cohort study (in which comparison groups are defined by exposure to hypothesized causes and the hypothesized effects are observed in each group). After setting the stage with a description of women Vietnam veterans as a population group in the first section, subsequent sections address the following exposures which together comprise what is termed the "Vietnam Experience" - combat (or combat-related) stress, drug use (licit and illicit) and chemical exposures (including primarily phenoxy herbicides and their derivatives). An additional section considers the health consequences of nursing as an occupational exposure (given that a conservatively estimated 75% of women Vietnam veterans were nurses). A last subsection reviews some important potential confounding exposures which may pre-date or be unrelated to the "Vietnam Experience" exposures.

Within each section, not only is the exposure itself described and its measurement reviewed, but major known or potential health outcomes of the exposure are also considered.

The review concludes by highlighting some of the important implications of the research (or lack of it) to date, for designing the planned study.

1. WOMEN VIETNAM VETERANS

In reviewing what little has been written concerning the women Vietnam veterans, it is important to set this information in the historical context of women - especially nurses - in combat and in military situations in general.

The history of nurses in the military is the longest and is distinct in many ways. The U.S. Army Nurse Corps was established in 1901 and the Navy Nurse Corps in 1908, following the Spanish-American War, in which civilian women volunteered to nurse the soldiers and were exposed to thousands of troop deaths from tropical diseases and infections under primitive, tropical living conditions. Since then, nurses have always followed troops into combat zones, providing needed care under similar conditions experienced by the troops themselves. This war-time service has always been voluntary, not subject to any draft. During the two world wars, nurses died, both from disease and as war casualties. In World War II, in the South West Pacific, nurses were actively involved in the retreat from Bataan and Corregidor living under fire in jungle conditions and several were imprisoned in Manila for thirty-seven months sharing the privations of male POW's, losing an average of 30lbs in weight and suffering debilitating disease, while continuing to perform nursing duties (Kalisch and Scobey, 1983; Holms, 1982). With the outbreak of war in Korea, nurses again followed the troops into battle zones, with the first unit of 57 landing in Korea only four days after the first soldiers. Approximately 400 nurses served in this war, most of them World War II veterans who had joined the Reserves at demobilization.

As pointed out by both Holm (1982) and by Kalisch and Scobey (1983), there was no hesitation on the part of military command in sending female nurses into these combat situations. Their ability to function effectively under such grueling conditions had been repeatedly documented in military testimony, along with the essential nature of the services they performed. It has been recognized, throughout the wars of this century, by most Western countries (including the U.S., Britain and Canada in particular) that well-trained female nurses are not replaceable with inadequately trained enlisted men. The need for adequate, efficient nursing care appears to have consistently over-ridden concerns in the military this century about exposing women to the combat zones of war.

The experience of Vietnam follows this pattern, with the first nurses arriving in South Vietnam in 1962 as "advisors", attaining a maximum strength of about 900 in 1969. Most of these served in field hospitals exposed to enemy fire and attack.

In contrast, the history of women in other than nursing roles in the military has been much more limited. Although they served in large numbers in World War II in support occupations, first as the Women's Army Auxiliary Corps (WAAC) then as the Women's Army Corp (WAC), with full military status, most did not leave the continental U.S. (CONUS). Their involvement was the direct result of need, to free qualified military men for combat duty (Holm, 1982). The experience was similar in Canada and Britain. Almost all of these women left the forces with the end of the war.

Only in 1947, was the Nurse Corps established as the first permanent staff corps for the Army and Navy. This was followed a year later by the Women's Armed Services Act which formally integrated women into the four permanent armed services (including the newly created Air Force) for peacetime service. At this time, approximately 7,700 women were on active duty in the Services, of whom nearly 1,300 were officers. At the beginning of the Korean War, in 1950, this number had increased to 22,000, including approximately 7,000 in the health professions (mostly nurses).

Despite the increasing numbers of women on active military duty during peacetime, it is important to note that only nurses went to Korea during that war. A few other military women were sent in support (mostly administrative) roles to the Phillipines and to Japan. The pattern was similar in the Vietnam War, with the total number of WAC's in country never exceeding about 160 and all were stationed in or around Ho Chi Minh City (then Saigon), primarily at Tan Son Nhut Air Base or at Long Binh. Other women military personnel were stationed in larger numbers primarily in the Philippines, Japan and Thailand (including nurses).

Even today, women are formally excluded from service in combat occupations, although they may perform equivalent roles (for example flying transport rather than fighter aircraft). The fact that nurses do indeed serve in combat zones has been largely ignored in this debate (Holm, 1982).

Throughout this 80-year history, the image of women in the military has been somewhat schizophrenic as described graphically by both Holm (1982) and Kalisch and Scobey (1983), among others. While the services have recognized the invaluable role of women, especially the nurses and have accepted them as essential - at least in war - the public image has been at considerable variance, as typified by recruitment efforts, movies, other media reports and congressional responses to legislation attempts. This is well-described by Kalisch and Scobey (1983) who note that only the Major Hoolihan character of the television series M.A.S.H. approaches the true image of the army nurse (this was not so for the original movie character). The popular

image is a confusing mixture of a woman of questionable moral character who gives lip service to nursing, or a nurse romantically serving her country in less than real circumstances, minimizing the grueling nature of the combat-zone nursing situation.

As noted by Holm (1982), this confusing image has persisted through the lack of testimony from the women themselves. It has remained true that, after each war most have left active service, merging into civilian life with little or no recognition and little or no reunion or continued contact with their fellow veterans. Perhaps because of their small numbers, perhaps because of negative or indifferent public attitudes, they have remained mostly silent and isolated, not even giving testimony during the land-mark legislation hearings of 1947 and 1948 (Holm, 1982).

Perhaps the most important point made by both Holm (1982) and Kalisch and Scobey (1983), among others, is the glaring lack of any research into exactly how women contributed during the wars of this century and the impact of this service on their subsequent lives. The opportunity for such a study was greatest immediately after World War II during which so many women served for the first time in occupations other than nursing - an opportunity which was irretrievably lost.

It is not surprising, therefore, that very little has been written concerning women veterans of the Vietnam War and almost all of it since 1980, in a decade which is witnessing the emergence of women's voices motivated to close the gap between the reality of war service and the very inadequate public perception of it. Recent literature includes only four systematic research attempts to collect data and an increasing number of witness accounts providing a written oral history of women's experiences for the first time.

History and science are never free of bias. This has been well documented by Kuhn (1970), for example. Oral histories are no exception. Those for whom an experience had a profound impact are most likely to want to describe it publicly. In the climate of anger and denial following the Vietnam War, compounded by fears concerning the health consequences of Agent Orange, most of those veterans who have spoken publicly have been no longer in the Services and negative in their attitudes. This has been true of the women veterans as well as of the men. The very negative description of her experiences provided by Lynda Van Devanter (1983) is a clear recent example. An attempt by Patricia Walsh to verify many of Van Devanter's statements was largely unsuccessful, in some part due to the lack of available military documentation but also because of

contradictory recall by other witnesses (Walsh 1982). Marshall (1987) attempted a more balanced document in her oral history, by deliberately including as wide a selection of experiences as possible, both negative and positive, from military and civilian women serving in Vietnam and provides, perhaps the most complete description ever published of the role of women in a combat zone. Certainly it represents an important first attempt to set the record straight on the reality of such service and verifies many of the inferences from the few systematic research attempts (Boyle et al, 1985; Paul, 1985; Stretch et al, 1985 and Schnaier, 1982).

Of the four recent research studies cited above, only one (Boyle et al, 1985) selected subjects randomly. The number of Vietnam veteran subjects was very small in all four studies, ranging from 28 no longer in active service (Boyle et al, 1985) to 220 nurses still in active service as of 1983 (Stretch et al, 1985). No good estimate yet exists of the total number of female veterans of the Vietnam war although from the numbers cited above and from other estimates available (including estimates from the 1980 Census (Dienstfrey and Byrne, 1984) and from Boyle et al (1985), the numbers are probably of the order of 5000-6000, including about 1500 who served in occupations other than nursing. Over 250,000 women served in the military during the Vietnam War (Vietnam-era veterans), nearly two thirds of them in their early 20's. The small number of veterans who saw service in Vietnam in the survey by Boyle et al (1985) underscores the limited number in this group and is probably a good estimate of their relative numbers among Vietnam era veterans. In this survey, approximately four times as many (120) saw service in nearby Thailand, Japan, Philippines and other South West Pacific and South East Asian Countries.

Despite these and other limitations, these studies and other histories provide a consistent profile of these women veterans and their war experience. A clear majority were well-educated nurses in the commissioned officer ranks, but they were young (predominantly in their early twenties during their Vietnam tour of duty) and inexperienced in the military. All were volunteers and upwards of 20% continued in active military service beyond their Vietnam experience. A majority were exposed to combat zone experience, working in field medical facilities subject to mortar, rocket and other enemy attack.

Apart from the distinctive demography of these women veterans (they were younger, better educated and predominantly nurses, in contrast to women veterans of prior wars; Boyle et al, 1985), their war experience was also distinctive. Their patients were predominantly adolescent soldiers (the average age was 19.2 years, compared to 26 years in World War II, Brende and Parson, 1985), as well as

civilian women and children victims and very young North Vietnam and Viet Cong POW's (many aged 15 or 16). Moreover, efficient transport and deployment of (mobile) medical facilities resulted in treatment of casualties within minutes of occurrence. Cases of massive injury and mutilation were therefore surviving to be treated by medical personnel (and, in fact, surviving treatment) as never before in previous wars. Medical personnel were required to work 12 hour shifts, six days/week or longer under combat conditions, were sometimes short of essential supplies and equipment, and were forced to triage cases for treatment. These conditions were potentially exacerbated by individual rather than unit assignments, leading to transitory supportive relationships.

Because of the apparent predominance of nurses in field assignments among women Vietnam Veterans, exposure to phenoxy herbicides in unknown concentrations was likely. Apart from disease exposure (primarily malaria) and the medications and insecticides to combat them, there is some indication that alcohol, in particular, was used during and after Vietnam service as a coping mechanism (Paul, 1985; Marshall, 1987), although no reliable estimates of any of these exposures are yet available (Ott, 1985).

No reliable data on possible health outcomes are available for this group of women, although the studies of Schnaier, Paul and Stretch and co-workers suggest that these veterans were subject to Post Traumatic Stress Disorder (PTSD) at about the same rate as male Vietnam veterans. Unfortunately the subjects for these studies were self-selected volunteers (Schnaier, 1982; Paul, 1985) or sampled in unknown ways (Stretch et al, 1985). Moreover, the restriction of the sample to those still on active duty in 1983 in the study by Stretch and co-workers limits inference to a distinct, highly selected minority of veterans who were career military personnel.

The health outcomes reported during interviews in the survey conducted by Boyle et al (1985) were compared across groups of women veterans, according to period of service (but not service area) and with comparable samples of male veterans. Unfortunately, for many outcomes which were gender specific (eg. pregnancy termination) or with age and gender-specific prevalence rates (certain cancers, heart disease), extensive comparisons among service area groups, for women veterans could not be made due to small numbers. It is not clear from this study that health outcomes among these women veterans are different from other women. There is no indication from available data on the non-institutionalized civilian population (Ries, 1986) that the health outcome rates estimated in this study are measurably different from what would be expected in a general female population of the same age range.

Finally, it should be noted that a clear majority of the Vietnam era veterans were under the age of 45 as of September 30, 1984. This cohort of women, including Vietnam veterans, has yet to reach the age when most would experience a natural menopause or have hypertension, cancer or heart disease diagnosed. Many have not yet completed child-bearing (Boyle et al, 1985).

The oral histories, supplemented by the four limited studies and other histories indicate that, as in prior wars this century, nurses volunteered for service and were assigned to combat zone hospitals where they served, alongside men under similar stressful conditions. In this respect, the experience of the majority of women veterans was not very different from experiences of women serving in prior wars. Ways in which experience during Vietnam service differs from service in prior wars include:

- Limitation of service to permanent tours of one year (in prior wars women served for the duration);
- The youth of the patients - both soldiers and POW's;
- The stability of the hospital bases in Vietnam;
- The widespread use of defoliants such as Agent Orange and related chemicals;
- The lack of involvement of the civilian U.S. population in the war effort (and wide spread opposition to it);
- The fact that the U.S. did not win this war;
- The lack of a well-defined front-line in the war; and
- The expectation that the U.S. military in Vietnam were not just fighting a war for the U.S. but for the Vietnamese, and the need to support the civilian Vietnam population despite the language and cultural barriers and the infiltration by the Viet Cong - resulting in the Medical Civic Action Program (MEDCAP) and related activities.

No systematic and complete description of this cohort of women currently exists, in terms of its size, age range, occupation, prior and subsequent military experience, Vietnam exposure and subsequent health and life experiences.

2. COMBAT-RELATED STRESS

The literature on war stress has focused on the major post military adjustment problems facing male veterans or what is now labeled post-traumatic stress disorder (PTSD) and chemical abuse. Even in the limited research on women veterans, health outcomes - especially reproductive outcomes - of war stress have not been addressed. This section begins with a description of combat-related stress, including stresses thought to be unique in the Vietnam arena and the relevance of current definitions to a study of women veterans. The next subsection considers the most researched outcome of war stress - PTSD. A final sub-section focuses on the relationship between different types of life stress and reproductive outcomes.

2.1 WAR STRESS

The relationship between combat exposure and the perception of stress has been studied in major wars. However, the stress associated with the Vietnam war exposure has been described as unique in comparison with other wars in that chronic and/or delayed stress reactions or PTSD were more common (Fleming, 1985; Laufer et al, 1985). In testimony for the Royal Commission, Dr. Arthur Blank Jr., head of the American Outreach Program provided a succinct yet comprehensive outline of typical stresses experienced during war-time and post-war, including unusual stresses found in the Vietnam War. This testimony also included a description of the major delayed and chronic stress symptoms seen in Vietnam veterans. Excerpts from this testimony are quoted below as background for review of empirical data.

(a) "Stress Typical of All Wars

- miserable living conditions (deprivation or denial of adequate food, clothing, shelter, cleanliness; exposure to the elements).
- Fatigue.
- Sensory assault.
- The fighting itself.
- Wounds (suffered by self, mates, witnessing of civilian and combat horrors).
- Special stresses of the Combat Situation
  (i) Capture and torture
  (ii) Isolation.
  (iii) Acute survivorship.

(iv) Authoritarian organization
(v) Command incompetence
(vi) Observers (photographers, journalists, casualty clerks, psychiatrists, chaplains, communications operators, intelligence officers).

(b) Unusual Stresses Found in the Vietnam War (but not limited to this war)

- Guerrilla warfare.
- Lack of clear objectives.
- Limitations on offensive actions.
- Terrorism.
- Climate and topography.
- Miscellaneous, bizarre physical dangers (flora and fauna).
- Tropical diseases.
- Immersion in an extraordinarily poor Third World society.
- Chaos.

(c) Psychological Stresses Secondary to the General Political Character of the War

- The experience of absurd waste (including corruption, fraggings, avoidance of unnecessary or purposeless combat.
- Government deceit and misjudgment.
- Massive national conflict.
- Defeat.

(d) Atrocity

Defined as destruction going beyond the usual boundaries of war, lying outside the requirements of military strategy.

- Atrocity directed against the land: Defoliation of forests and fields with herbicides.

- Meaningless destruction of human life: Captives pushed out of helicopters, shooting and napalming of non-combatants, massacres, etc.

(e) Additional Emotional Trauma

- Failure to live up to one's expectations.
- Overwhelming fear reactions.
- Self-inflicted wounds.
- Accidental killing of comrades or civilians.
- Vietnamese left behind.

(f) Stresses of the Immediate Homecoming Period

- Absence of sanction, presence of hostility.
- Absence of normal debriefing.

(g) Long Term Factors Exacerbating the Effects of War Stress

- Further fading of a sense of purpose.
- Impossibility of further contact with Vietnam.
- Unavailability of psychotherapeutic treatment.
- Continuing blackout of the war as history.

Relating the concept of stress to combat was seen also in other major wars. However, the Vietnam war has been described as unique in comparison with previous wars, the differences having been related to the characteristic symptoms of PTSD and especially to the increased prevalence of chronic and/or delayed PTSD (Fleming 1985; Laufer et al, 1985). A succinct yet comprehensive outline of the stresses experienced during war-time and post-war, including unusual stresses found in the Vietnam War, as well as of the major delayed and chronic stress symptoms seen in Vietnam veterans, provided by Dr. Arthur Black Jr., head of the Australian Outreach Program, in testimony for the Royal Commission, is reproduced here as background for review of empirical data.

Major Delayed and Chronic Stress Symptoms Seen in Vietnam Veterans

(a) Type 1. Manifesting Primarily by Psychological Symptoms

(i) Classical traumatic neurosis symptoms. Flashbacks, nightmares, irritability, rage, dizzy spells, anxiety, insomnia, depression.

(ii) Depression. Without other symptoms, masking impacted grief about war experiences and related conflicts (Shatan 1981).

(iii) Psychosomatic syndromes. Headache, low back syndrome, ulcer, migraine, irritable colon, hypertension.

(iv) Violent paranoid states. Without psychotic symptoms, or indicators of pre-war borderline personality disorder, these veterans manifest diffuse hostility, suspiciousness, paranoia, irritability, and crowd phobia. This state represents a persistence of the paranoid, hyper-vigilant state that was lifesaving for

many participants in the terrorized guerrilla atmosphere of Vietnam.

(v) Addictive disorders. Addiction to alcohol, marijuana, heroin, cocaine, thrills, risks, gambling - including gambling with fate as in chronic high-speed driving.

(vi) Exacerbated character disorders. Dramatic exacerbation of character problems, such as impulsive behavior or sociopathy, present in a minor degree before the war.

(vii) Suicides and homicides. These are categorized separately for two purposes: to highlight them as problems, and also to indicate our lack of knowledge of the diagnostic background of Vietnam veterans who kill themselves or others. Fortunately, the number of homicides is quite small. That may not be the case for suicides; there is not a single study of the incidence of suicide in Vietnam veterans; but there is a persistent, almost universal impression among clinicians who work with this group, that the incidence of suicide is high and continuing. (Note that this is not so amongst Australian Vietnam Veterans, see Chapter X).

(viii) Psychotic syndromes. This outcome, long-recognized in the literature from previous wars, has remained largely hidden in Vietnam veterans until recently.

(b) Type II. Manifesting Primarily By General Alteration In Life Course

(i) Underachievement. Lacking, significant symptoms, these veterans' lives are characterized by chronic underachieving or instability in education or work.

(ii) Wandering lifestyle. Though not necessarily underachieving in any obvious way, the veteran goes from job to job, school to school, town to town without progression toward any goal.

(iii) Crime. Some veterans commit antisocial acts not as a result of pre-existing criminality, but as a part of stress disorder.

(c) Type III. Problems Manifested Primarily in Relating to Significant Others

(i) Difficulties in intimacy with spouse or lover.

(ii) Special interferences in relating to children.

(iii) Marked change in relatedness to the country and its institutions. Loss of political attachment may have occurred because the soldier in Vietnam felt himself sacrificed by military and civilian leaders who, out of ignorance or cynicism, did not allow him to win a just war or, from the opposing perspective, sent him to fight an unjust war.

(iv) General alienation. Affected veterans display a pervasive and generalized detachment from most processes of life - marriage, career, social and political institutions community, and friends. Some seem frozen at age 20, have not learned more adult skills for living, and are unsophisticated in subtle and diverse ways.

(d) Type IV

Veterans in this group have experienced a profound shattering of images of self and humanity. These Vietnam veterans have much in common with the survivors of Nazi death and concentration camps. They have lost some of their basic faith in the capacity of humanity for goodness, as described in Holocaust survivors."

(Royal Commissions on the Use and Effects of Chemical Agents on Australian Personnel in Vietnam, Vol.5, IX-12 to IX-16).

2.1.1 Measurement of War Stress

It cannot be assumed that everyone who served in Vietnam had an equal level of exposure to war stress, nor to the same types of stress. This is especially pertinent to women veterans. Based on the unique character of the Vietnam war in comparison to other major wars, Laufer et al (1984, 1985) argues for a multidimensional measurement of war stress, which identifies three different types of stress (combat exposure, participation in abusive violence, and exposure to abusive violence) and allows for differing levels of exposure to these stresses. While this multidimensional model permits a more exact analysis of the influence of specific war stresses on adjustment outcomes, the model, as used in Laufer's work is not completely pertinent to the probable experience of women veterans. Women did not participate directly in combat nor were they likely to participate in or witness abusive violence. Their war stress differed, more likely consisting of perceived

danger and threat to life, intense exposure to death and destruction, and the excessive physical and emotional demands of their work (Paul, 1985; Stretch et al, 1985; Ott, 1985). In addition, occasional accounts of killing the enemy in self defense do not rule out direct violence as a stressor. For example, Ott (1985) describes the nurse who used a machine gun on three Viet Cong who were attempting to infiltrate her hospital. Brende and Parson (1985) described a similar situation in which a nurse had to defend herself against a North Vietnamese patient for whom she was caring, who attacked her with a pair or scissors. Narrowly escaping, the patient was subsequently killed by military guards, resulting in recurrent nightmares for the nurse. Additional stressors of a more psychosocial nature, such as those suggested by Paul (1985: including exposure to sexual harassment, survival guilt, and interpersonal conflicts) may also contribute to post service adjustment problems.

In conclusion, there is strong evidence to support use of a multidimensional model of war stress in a study of women veterans. However, current models based on studies of men, are inappropriate and must be revised. While the limited data on women veterans identifies some specific war stressors, it is suggested that descriptive data be gathered in a pilot study to inform development of a multidimensional model for women veterans.

2.2 POST-TRAUMATIC STRESS DISORDER

Post-traumatic stress disorder (PTSD) refers to a group of symptoms now commonly associated with the mental disorders of Vietnam veterans. This label first came into use with the issuance of the American Psychiatric Association's Diagnostic and Statistical Manual (Version III) - DSM- III in 1980 with the further identification of subtypes, acute, chronic and/or delayed. The acute subtype is synonymous with that referred to as "shell shock" (World War I) or "combat fatigue" (Korean War). The chronic and/or delayed subtypes are particularly relevant for the veterans of the Vietnam war who manifested relatively fewer neuropsychiatric disorders during the height of the war but rather at the end or during the post-service period. While acute-traumatic stress disorder requires that the symptoms start within 6 months of the trauma and last less than 6 months, chronic or delayed PTSD require that the symptoms exceed six months in duration (chronic) and/or that symptoms are manifested six months or more after the trauma (delayed).

This review begins with a clinical description of PTSD and the DSM-III diagnostic criteria for PTSD, followed by discussion of the unique character of the Vietnam war which contributes to the clinical manifestation of the disorder. A

review of a representative sample of recent and frequently cited empirical studies will be presented, both for female and male veteran populations. This section concludes with a discussion of methodological and measurement issues most pertinent to the purpose of this review.

2.2.1 Clinical Symptoms and Diagnostic Criteria

The majority of material for this section is taken from the comprehensive review of PTSD included in Volume 5 of the Final Report by Australia's Royal Commission in the Use and Effects of Chemical Agents on Australian Personnel in Vietnam, July 1985, and the DSM-III.

According to the DSM-III, the essential feature of PTSD is "the development of characteristic symptoms following a psychological event that is outside the range of usual human experience. The characteristic symptoms involve re-experiencing the traumatic event; numbing or responsiveness to, or reduced involvement with, the external world; and a variety of autonomic, dysphoric, or cognitive symptoms." (p. 236). Further description of these symptoms can be found in the DSM-III's diagnostic criteria (p. 238):

(a) Existence of a recognizable stressor that would evoke significant symptoms of distress in almost everyone.

(b) Re-experiencing of the trauma as evidenced by at least one of the following:

  (1) recurrent and intrusive recollections of the event
  (2) recurrent dreams of the event
  (3) sudden acting or feeling as if the traumatic event were reoccurring, because of an association with an environmental or ideational stimulus.

(c) Numbing of responsiveness to or reduced involvement with the external world, beginning some time after the trauma, as shown by at least one of the following:

  (1) markedly diminished interest in one or more significant activities
  (2) feeling of detachment or estrangement from others
  (3) constricted affect

(d) At least two of the following symptoms that were not present before the trauma:

  (1) hyperalertness or exaggerated startle response
  (2) sleep disturbance
  (3) guilt about surviving when others have not, or about behavior required for survival
  (4) memory impairment or trouble concentrating

(5) avoidance of activities that arouse recollection of the traumatic event
(6) intensification of symptoms by exposure to events that symbolize or resemble the traumatic event

These criteria are currently under some revision.

2.2.2 Prevalence

Scientifically sound prevalence data for the extent of PTSD are lacking. Stretch et al (1985) reported estimates ranging from 18% to 54% of Vietnam veterans in the civilian community who are currently in need of psychiatric care for war-related problems. In contrast, they found lower rates of delayed or chronic PTSD among Vietnam veterans currently on active duty in the Army (5.1%) and the Army Reserve (10.9%). Most of these data have been based on clinical observations in treatment centers. Fleming (1985), on the other hand, claims that a relatively small number have PTSD to the degree that treatment is sought; however, he provides no data as the basis for this statement. Frye and Stockton (1982) surveyed 88 members of an officer candidate school class for the Army infantry during 1968-1969 for signs of PTSD, using DSM-III criteria for diagnosis, and found that 43.2% manifested moderate to strong symptoms. While objective measures and validity checks were employed, application of the findings from this study are weakened by the small sample size, nonrepresentativeness of the sample, questionable calculation of response rate (82%), and a retrospective design utilizing self reports. Therefore, while their estimate falls within the range of previous reports, it cannot be relied upon as a valid predictor of chronic or delayed PTSD prevalence.

2.2.3 STUDIES OF WOMEN VETERANS

Stretch and colleagues (1985) reported an epidemiological investigation of PTSD among Army nurse veterans. Unfortunately, the study was limited to veterans still on active duty. A sample of 361 eligible army nurses (male and female) (RR=75%) were compared to 351 army nurses who had not served in Vietnam (RR=71%), finding a current 3.3% PTSD rate for Vietnam veteran nurses and a rate of only 0.85% for Vietnam-era veteran nurses. However, the difference in rates was not statistically significant. Further, the prevalence of PTSD among the Vietnam veteran nurses was found not to differ significantly from the prevalence of PTSD (5.1%) reported for other active duty army veterans. No gender differences were noted in this study.

The subjects also responded to the same PTSD questions based on their recollection of how they felt in Vietnam,

resulting in rates of 9.1% for Vietnam veteran nurses and 10.5% for other active-duty army Vietnam veterans. Examining both sets of rates revealed that for Vietnam nurse veterans, 7.2% suffered acute PTSD, 1.9% suffer chronic PTSD, and only 1.4% are suffering delayed PTSD. The investigators added these rates, resulting in an overall PTSD prevalence of 10.5%. A similar summative rate of 12.2% was calculated for the other active duty Vietnam veteran group, not a statistically significant difference. Determination of PTSD was based on the DSM-III criteria. However, only limited data were gathered regarding possible sources of trauma among the Vietnam nurses thereby allowing for the influence of non-war related events. Therefore, the investigators caution that this rate is likely to be overestimated. Two design issues are problematic in this study. First, as mentioned, the study was of nurses (male and female) currently on active duty. Consequently, the possibility that Vietnam veteran nurses who chose to leave the military may exhibit a higher rate of PTSD cannot be examined. Secondly, the time interval between the end of the Vietnam tour and the time of the survey was not reported, a potential confounder which might influence the manifestation of delayed PTSD.

Further evidence on symptoms of nervous/emotional problems among women Vietnam veterans can be found in the Harris and Associates national survey (Boyle et al, 1985). However, since measurement of PTSD was not an intent of this study, the data are not conclusive enough to develop an estimate of PTSD prevalence. Limited to descriptive data, it was reported that Vietnam veterans were more likely than other veterans to have experienced seven of nine affective symptoms, including depression, nightmares, troubled thoughts about military experiences, and difficulty making decisions, and guilt feelings. The possible reasons for the similarities between Vietnam veterans and post-Vietnam veterans were not discussed but do not suggest a clear picture of a Vietnam-related stress disorder. Methodological limitations (e.g., not using the DSM-III criteria for PTSD) interfere with the use of these findings for determining prevalence.

In conclusion, while prevalence estimates on both male and female Vietnam veterans are available, data are limited in quality and scope. However, available data do suggest a difference in prevalence rates among active duty and civilian veterans pointing out the importance of a representative sample of all veterans to adequately determine prevalence of PTSD.

Data from two other studies (Schnaier, 1982; Paul, 1985), despite smaller, non-representative samples, provide consistent evidence of the psychological after-effects of the war experience. Current post-traumatic symptoms reported

in the Schnaier (1982) study included: suicidal thoughts (27.6%), feelings of alienation (19%), and feeling depressed between 15-30 times per month (19%). Forty-three percent of the 50% who have sought professional treatment related their problems to the Vietnam experience. Clearly, the data show that these women are currently plagued by significant problems. However, a nonrepresentative sample without a comparison group limits the application of these findings.

In the study by Paul (1985), fourteen adverse after-effects (including recurrent nightmares, depression, flashbacks, and hyperalertness) similar to PTSD symptoms, were identified, with 39% reporting current symptoms at the time of the survey. Additionally, 68% reported current physical problems (headaches, ulcers, gastrointestinal problems) which began in or sometime after Vietnam. In addition, war stressors were identified as: short time in service before Vietnam duty; the number, youth and severity of casualties; nursing roles in specific patient care areas; lack of supplies; sexual harassment; problems with professional relationships; survivor guilt; and threat to life. This study points out the importance of identifying war stressors specific to the experience of women.

The previously cited study by Stretch et al (1985), in addition to estimating prevalence of PTSD among active duty Vietnam veteran nurses, further makes the important point regarding the measurement of war stress among veterans in noncombat positions. While nurses were not directly involved in combat or abusive violence (frequent measures of war stress among men), they routinely experienced the aftermath of such with intense exposure to death and destruction. Therefore, measures of war stress must be adapted to the experiences of women veterans. Investigating perceived danger and exposure to violent combat aftermath as measures of war stress, they found that nurses with high measures of both exposures reported the highest levels of PTSD during Vietnam ($p < .01$) as well as currently ($p < .05$). Further, they found that levels of PTSD were mediated by perceived social support both during and after service, a finding consistent with the large body of literature on the buffering effects of social support (see, for example, McKinlay, 1981).

In summary, while limited, evidence from these data supports the manifestation of delayed and possibly chronic PTSD among women Vietnam veterans. While the larger body of male studies can be used to inform a study design of women veterans, careful attention to development of appropriate measures of war stress/trauma for women is indicated.

2.2.4 STUDIES OF MALE VETERANS

Review of a representative sample of 15 research reports published in the 1980's uncovered only four without serious methodological flaws. The remaining 11 reports suffered primarily from the limitations of small non-representative samples. Several studies focused on the symptoms of PTSD (Amen, 1985; Berkheimer et al 1985; Benedikt, 1986), often attempting to validate the DSM-III diagnostic criteria (Atkinson, 1984; Malloy et al, 1983; Van Kampen et al, 1986). Other studies explored the etiology of PTSD (Borman, 1985), such as the influence of combat exposure or war stress on development of PTSD (Frye and Stockton, 1982) or investigated the other factors potentially influencing PTSD such as social supports (Keave et al, 1985). Finally, a study by Carroll et al (1985) related PTSD to problems with postservice adjustment.

The following studies will be discussed in more detail because of their methodological implications for further studies. All investigate the link between traumatic experiences and subsequent psychological patterns. Laufer (1985) and colleagues (1984, 1985) conclude from their work on the relationship between war trauma and PTSD that discrete dimensions of PTSD are differentially affected by different types or levels of war trauma. Their model of war trauma contains three elements: 1) combat experience; 2) witnessing abusive violence; and 3) participation in abusive violence. In their 1984 study, a sample of 350 veterans was taken from a larger national stratified probability sample (n=1342) of the noninstitutionalized civilian population selected by random digit dial procedures in 10 sites matched in economic and demographic characteristics. Data were collected in 1977 and 1979. Measures included an additive scale of ten discrete events for combat exposure, a set of open-ended questions for abusive violence, and an additive scale of stress symptoms and the Psychiatric Epidemiology Research Instrument (PERI) to measure adjustment. Acknowledging the limitation associated with recall, data on the last two measures were collected for the three periods of before, during, and after service. Control variables included background factors, predispositional factors related to potential adjustment problems, and military and war-related factors (e.g., induction status, service during or after the 1968 Tet offensive, and branch of service). With the addition of these control variables, the investigators could more strongly state their finding that exposure to combat and participation in abusive violence contributed independently to greater incidence of stress. Veterans on average reported onset during the war of two or more stress symptoms if they participated in abusive violence and one or more symptom for every 7 points of combat exposure. The other military-related experiences that

affected symptom level were induction status and branch of service. Marines and those who enlisted reported fewer symptoms. Of the background predispositional factors, only race was significantly related, with blacks and Chicanos reporting an average of one more symptom than whites. Turning to postservice symptoms, much the same pattern appeared, but symptoms were more prevalent at the time of the interview than during the service period (4.2 symptoms on averages. 1.6). The data suggest a pattern of cumulative development in the number of current stress symptoms, a trend which is stronger among blacks. Blacks seemed to respond more immediately to the stresses of war than whites.

In a later study, Laufer et al (1985) attempted to relate their multidimensional war trauma model to discrete dimensions of PTSD based on the DSM-III criteria. With a sample of 257 drawn from the same large probability sample, they used the same measures as previously described but created four subscales from the larger stress scale (intrusive imagery, hyperarousal, numbing, cognitive disruption). Comparing service and postservice measures, the findings suggested a lagged process in which men exposed to life-threatening experiences respond only partially at the time, with the balance of the response emerging at a later point. Participation in abusive violence elicits an immediate unenduring response in terms of hyperarousal, numbing and cognitive disruption while its effect on intrusive imagery diminished with time. Similarly, combat exposure resulted in enduring hyperarousal and intrusive imagery. The effect of exposure to violence, on the other hand, emerged with intrusive imagery well after the experiences occurred. Clearly, the dimensions of PTSD vary over time and according to individual war experience as shown in these data.

The findings of these studies point out important measurement issues in relation to PTSD and war trauma. First, the specific dimensions of PTSD may be related to differing etiological factors as well as adjustment outcomes, and therefore, measurement of specific PTSD dimensions may be useful. Second, the data clearly support a multidimensional model of war trauma looking at different types and degrees of exposure, rather than relying on a unidimensional measure of combat exposure vs. no exposure.

Penk et al (1981) also found that combat veterans rated significantly more stress responses as problems than did noncombat veterans. Further, in this sample of 85 combat veterans and 121 noncombat veterans, post-military adjustment difficulties were not attributable to premilitary adjustment differences between the groups. While producing consistent findings, however, this study was limited by a nonrepresentative sample of drug abusers in treatment and a

cruder, two-dimensional (light vs. heavy) measure of combat relating only to killing the enemy.

Only one prospective study of Vietnam veterans, including measures of PTSD and other post-service adjustment has been conducted (Card, 1983). This study was unique, in that a large battery of psychological and aptitude tests as well as questions on vocational plans and socio-demographic measures had been administered to students in Grades 9-12 in 1960 as part of a large longitudinal study - Project TALENT. To reduce bias in the current study, sample of Vietnam veterans, non-Vietnam veterans and non-veterans were selected from those in the 9th grade in 1960 in the original TALENT study who also responded in a 1974 follow-up survey of the TALENT cohort. The final numbers in each of the three comparison cohorts were 481, 502 and 487 respectively representing response rates of 80%, 89% and 73%. The major design flaw in this study was that Vietnam veteran status was determined in an initial screening question in the 1981 survey, so that respondents were not blind to the purpose of the study. Potential reporting bias could have been investigated by using responses to the 1974 survey, but this possibility was not explored in the report. Despite this problem, a measure of PTSD which, while admittedly crude, contained the important features of this disorder was constructed in the analysis which clearly differentiated not only Vietnam veterans (19 percent with PTSD in 1981) from the other two groups (12 percent with PTSD in 1981) but combat exposure among the Vietnam veterans (from an analytically constructed scale). The reporting of PTSD symptoms was not consistently related to measures of pre-disposition, although most of these were obtained retrospectively in the 1981 survey, not from the 1960 survey. The healthy worker effect was also well controlled in the analysis. Evidence of negative effects of the war in terms of both PTSD and other measures of social adjustment was clear, 15 years after service in Vietnam. An important point to note with this study is that the Vietnam veterans in this particular cohort served prior to the 1968 Tet offensive. Therefore, noted differences between Vietnam veterans and other veteran/civilian groups in relation to PTSD manifestations should be greater among Vietnam veterans serving after 1968. Apart from the importance of this study for assessing the impact of the war on PTSD and other social adjustments, the design and analysis clearly demonstrate; (a) the importance of using non-Vietnam veterans as well as or instead of civilians as comparison groups; and (b) the importance of including pre-war data obtained con-currently, not retrospectively.

A final study by Frye and Stockton (1982) will be discussed in relation to its implications for collection of appropriate background or predispositional data. In their survey of 88 members of an officer candidate school class

(1968-1969) for the Army infantry, they questioned whether level of combat (degree of trauma) is the critical variable in the development of PTSD among Vietnam veterans. Using discriminant analysis, they found that four variables in addition to level of combat distinguished between those who developed PTSD and those who did not: Veterans with PTSD reported a negative perception of their family's helpfulness on return home; a more immediate discharge after the war; an external locus of control; and a more supportive attitude toward the war before they entered the service. Level of combat provided the second largest contribution (22%) to the discriminant function with a total of 62.1% of the variance between the two groups accounted for by the discriminant function. Methodological limitations, however, may contribute to this inconsistent finding regarding the importance of other variables in the etiology of PTSD, i.e., a small nonrepresentative sample (n=21 in the PTSD group), with cruder measures of both combat level and PTSD symptoms than in the work by Laufer et al (1984, 1985). However, the study does point out the importance of collecting background and predispositional data as control variables.

2.2.5 METHODOLOGICAL AND MEASUREMENT ISSUES

Post-traumatic stress disorder appears to be the primary manifestation of post-war emotional adjustment problems in Vietnam veterans. Further, evidence indicates that delayed forms of the disorder, rather than acute, are more likely in this group of veterans as compared to veterans of other wars. A review of the PTSD literature points out two areas of methodological concern important for any future study of women Vietnam veterans: 1) the need for scientifically sound prevalence data on the disorder; and 2) careful measurement of both clinical manifestations of the disorder and possible etiological factors.

(a) Prevalence Estimates. In estimating prevalence of PTSD, as for any other condition, cross-sectional data on current status are used to provide an estimate of "point" prevalence. This estimate may include all current cases (regardless of inception) identified over a defined period - usually a year or less (see for example Monson, 1980). The difficulty in the retrospective studies reviewed is that current status provides (combined) estimates of chronic and delayed PTSD only. Estimation of the prevalence of acute PTSD (occurrence at anytime during war-time service, as defined in the particular study), depends on long-term memory recall. It is clear from studies of both male and female veterans that reliable point prevalence estimates for chronic or delayed PTSD are lacking. Any future study of Vietnam veterans should be carefully designed to obtain valid data on a representative sample of Vietnam veterans. While a prospective study design is the ideal allowing estimates of the incidence of acute, chronic or delayed

PTSD, it is obviously impossible with any new study of these veterans. However, while a retrospective design admittedly has limitations, measurement of the point prevalence of delayed/chronic PTSD, since symptoms are likely to be current, should be possible. Measurement of acute PTSD, typically experienced during war-time service, of necessity will be based on self-reported recall data. None of the studies reviewed attempted to validate their inservice measurement of acute PTSD (if this is even possible); therefore, it is not clear to what extent problems with recall, of the war experiences may affect the validity of these prevalence estimates. Despite these problems, efforts should be made to collect data on at least chronic and delayed PTSD. Although desirable, it is doubtful that the full extent of PTSD, including the acute form, can now be estimated from a retrospective cohort study, as recommended by Laufer et al (1984).

(b) Measurement Issues. Based on his own work and that of others, Laufer (1985) identified four dimensions of measurement central to the field of Vietnam veterans research:

- predisposition;
- the war experience;
- symptomological and behavior outcomes; and
- patterns of life course development after service.

All of these dimensions are relevant to a study of health and reproductive outcomes of women Vietnam veterans.

Measurement of Predisposition. The importance of gathering data on background and predispositional factors was apparent in the literature regarding drug use among the military as well as in the PTSD literature, especially in assessing the influence of the war experience on subsequent adjustment problems. For example, studies of postservice drug use by veterans consistently report that predispositional factors, particularly preservice drug use, rather than combat experience, account for continued drug use after Vietnam (cf. Robins et al, 1975). Laufer (1985) reviews this predisposition hypothesis in relation to his own work and that of others on PTSD, reporting that predispositional factors have an independent effect, but do not fully explain the effects of the war experience on development of PTSD. In the work of Laufer et al (1984, 1985), war stress clearly has a substantial long-term influence on postservice adjustment of Vietnam veterans. Laufer (1985) suggests, in conclusion, that the combined effects of predispositional factors and war stress be examined in relation to specific manifestations of PTSD or emotional/behavioral maladjustment. In addition to the standard sociodemographic factors, it is recommended on the basis of this review that the following predispositional factors should be considered: drug/alcohol use, school

problems, arrests, attitude toward Vietnam conflict, age at entry into service, peer relationships, family problems (e.g., parental emotional problems or chemical abuse, single parent families, major financial problems) (Laufer, 1985; Carroll, 1985; Robins et al, 1975; Frye and Stockton, 1982).

Measurement of War Experience has already been discussed in section 2.1.1 above.

Measures of Adjustment. PTSD is clearly a major element in post-Vietnam psychiatric symptomatology (Laufer, 1985). The PTSD scale, a single additive scale of stress symptoms based on the DSM-III criteria, is the most frequently used scale to detect symptomatology in empirical research. Other scales, such as the Psychiatric Epidemiology Research Instrument (PERI), have been used less successfully. Since a standardized scale (PTSD Scale) has been used in several male studies, its use is recommended in a study of woman veterans for comparison.

Laufer (1985) suggests that adjustment measures should not be limited to PTSD. Other health outcomes are certainly evident, as supported by the work of Paul (1985). Since systematic data relating war experiences to specific outcomes for women are lacking, data should be gathered in a future study which include not only a broad range of health outcomes (physical and mental) but significant life experiences, including marital and occupational histories.

2.3 STRESS AND ADVERSE REPRODUCTIVE OUTCOMES

In the broader literature on stress and health outcomes, life change events and stress have clearly been related to adverse reproductive outcomes. Therefore, a brief review of the more recent literature in this area was undertaken to identify variables of interest for a study of health and reproductive outcomes of female Vietnam veterans.

2.3.1 Pregnancy Complications

(contributed by Richard Neugebauer Ph.D., Columbia University).

Sociodemographic and medical factors are established as major determinants of adverse reproductive outcomes, including preterm labor (NCHS, 1980; Hutchins et al, 1984; Niswander and Gordan, 1972). Evidence from epidemiologic studies (and those using an animal model) document a role for psychosocial stress in pregnancy complications without specifying any intervening physiological mechanisms.

Studies of psychosocial stress and adverse pregnancy outcome have employed both retrospective case control and prospective cohort designs. These investigations conceptualize "stress" either as an internal psychological

state or as representing the environmental challenges posed by external, so-called stressful life events. Psychological factors have ranged widely from the comparatively elementary constructs of anxiety or depression, assessed with psychometrically sophisticated instruments of adequate reliability (Crandon, 1979), to more complicated concepts of guilt and dependency, where measurement may involve projective tests (Grimm, 1962) and complex inferential processes on the part of clinicians. These latter measures often do not possess satisfactory or even known psychometric properties.

External stressors have usually been measured with one of several life event checklists. Some investigators have adopted without change event inventories produced for work with general community samples (Norbeck and Tilden, 1983); others have developed lists especially suitable for the pregnant women under study (Newton et al, 1979; Chalmers, 1983; Barnett et al, 1983). Objective ratings of event magnitude, each woman's subjective appraisal of her events, event controlability, predictability and indices based on these and other event characteristics have all been evaluated as predictors of pregnancy complications (Norbeck and Tilden 1983; Chalmers, 1983; Newton and Hunt, 1984). Additionally, the temporal focus of the event checklist has either been restricted to pregnancy proper (Newton et al, 1979) or included periods of time prior to conception (Nuckolls et al, 1972; Jones, 1978).

Some investigators have limited outcome to highly specific prelabor pregnancy complications, such as hyperemesis gravidarum (Chertok et al, 1963) complications of labor and delivery (McDonald et al, 1963) or neonatal complications, notably low birthweight and short gestational age (Newton and Hunt, 1984). Other studies have encompassed a wide spectrum of complications, often reflected in a single global index, originating in markedly different biological mechanisms (Nuckolls et al, 1972; Norbeck and Tilden, 1983; Gorsuch and Key, 1974).

Clearly, this diversity of designs and of conceptualization and measurement of dependent and hypothesized independent variables renders interpretation of this literature difficult. However, there is a generally recognized (Chalmers, 1982) and notable failure across studies to demonstrate rigorously a consistent association between stressful life events or psychological symptoms, such as anxiety, and pregnancy complications. For example, while several studies report a positive, unconditional association between life events and risk of adverse reproductive outcome, other investigators fail to discover any association despite adequate sample sizes (Chalmers, 1983), find a negative association (Jones, 1978), or discern an association exclusively in the context of inadequate

social assets (Nuckolls et al, 1972). A number of studies concur in finding a positive association between psychological symptoms and pregnancy complications but differ markedly as regards the period of risk and the specific effected outcomes. Gorsuch and Key (1974) implicated only first trimester anxiety in complications before and during labor and in infant status. However, Norbeck and Tilden (1983), noted an association only between emotional disequilbrium (this construct included anxiety but the time of administration of the anxiety measure was not clearly described) and neonatal complications.

These contradictory findings reflect in part the shortcomings in design or measurement that hobble many of these studies. Case control designs are notoriously vulnerable to biases in subjects' recollection of the hypothesized independent variables. Retrospective designs cannot distinguish, in a compelling fashion, psychological symptoms resulting from and preceding the adverse outcome. Furthermore some studies, presented as prospective investigations, actually measure crucial independent variables during the postpartum period (Gorsuch and Key, 1974). In other studies, comparatively small sample sizes (Davids, Devault and Talmadge, 1961 [N=48]; McDonald and Christakos, 1963 [N=86]). and the unreliability of certain measures, render the lack of statistically significant findings uninterpretable. Small sample sizes have also hindered the use of powerful data analytic strategies to control for the effects of potentially confounding variables. Given the plethora of possible outcomes of interest and the need for biological coherence in the findings, the next wave of investigations in this area should examine individual adverse reproductive outcomes separately, rather than indices combining diverse complications, to permit the specification and testing of defined pathophysiological mechanisms. These studies must also be rigorously prospective.

Three recent studies have investigated possible psychosocial influences in preterm delivery. Using case control designs Newton et al, 1979 and Berkowitz and Kasl, 1983, assessed in a postpartum interview, the frequency of life events during pregnancy of women delivering preterm and at 37 weeks gestation or later. Newton et al, found the mean number of events overall and in the last week of pregnancy was greater for women delivering preterm. During the entire pregnancy, 73 percent of women delivering preterm experienced at least one life event compared to only 43 percent of women going to term. Berkowitz and Kasl using a black and white population in New Haven, reported much the same findings for life events during the entire pregnancy. However, among Blacks this finding held only for women with wanted pregnancies. Finally, Newton and Hunt (1984) examined the role of life events and anxiety in prematurity and low

birth weight in a prospective cohort study involving interviews at three time points during pregnancy and one postpartum. Life events were implicated strongly in risk for prematurity and low birth weight. For example, 73% of women delivering preterm reported at least one life event during pregnancy in contrast to 9% of women with term births.

Despite the apparent consistency of results across these three studies, two used exclusively retrospective designs in which neither interviewers nor subjects were blind to caseness status. Newton and Hunt's study is also not immune to the major threats to validity posed by biased recall. Their final life event interview was conducted postpartum and, perhaps not surprisingly, events reported in this concluding interview contributed decisively to their results. As a consequence, these investigations, while offering provocative early evidence of a role for psychosocial factors in preterm delivery, await confirmation with more rigorous designs and elaborations as regards intervening biological mechanisms.

2.3.2 Menstrual Disorders

Few large scale studies have been conducted on the effects of environmental and social stressors on the menstrual cycle. Studies which have been conducted focus on either amenorrhea or perimenstrual symptoms.

The cessation of menses has been associated with catastrophic events and strong emotional trauma, especially of chronic nature (Summer, 1978). However, the few available studies have instead focused on amenorrhea of psychogenic origin, with little conclusive data. In her review, however, Sommer cites several animal studies which suggest the effect of stress on menstrual function stems from prolonged or chronic stress in contrast to acute stress.

In relation to perimenstrual symptoms, the majority of stress research has examined the influence of life events and daily stressors on symptomatology. These studies have consistently shown that negative life change is associated with reports of perimenstrual symptoms including pain, water retention, behavior change, negative affect, and amount of bleeding (Siegel et al, 1979; Woods et al, 1982; Jordan and Meckler, 1982). While two of these three studies are limited by nonrepresentative samples (typically college students), they do suggest that major life changes, occurring as long as a year prior to the study, were associated with more frequent and more severe symptoms.

A study by Woods and colleagues (1985) is described both for its inclusion of daily stressors, as well as major

life events, in a study of perimenstrual symptoms and for its use of a random sample. Seventy-four women aged 18 to 35, a subsample from a larger study, were asked to complete a health diary for two months, Moos' Menstrual Distress Questionnaire, and Holmes and Rahes's Schedule of Recent Events. Daily stressors were described in the health diary and related to work, familial relationships, etc. The study provided "modest support" for the previously reported relationship between major stressful life events, daily stressors,and perimenstrual symptoms. Notably, daily stressors had a greater effect than major life events or perimenstrual symptoms. Further, the investigators report that "a generally stressful life context is more influential than episodes of stressors during a particular menstrual cycle phase" (p.267).

In summary, the available data, although limited both in scope and methodology, suggest a pattern between stress and menstrual disorder which has clear implications for a study of women Vietnam veterans. It is chronic stress, rather than acute or episodic stress, that has been reported to be more influential on menstrual disorders. If it can be assumed that an average one year tour or duty was experienced as chronic stress, then a higher incidence of menstrual disorders during and possibly following the war experience should be expected. What is not known from available data are the longterm effects of chronic stress on menstrual function, and posssibly fertility. Therefore, to assess the impact of the war experience as a stressor on menstrual function, data (albeit retrospective) regarding typical cycles and abnormalities should be collected for the periods during and after the war.

2.4 SUMMARY

To summarize briefly this lengthy section, it is clear that there is no systematic study to date of the effect of war stress on the general and reproductive health of women veterans. Such a study is clearly needed - at least with respect to the most recent Vietnam conflict. However, in order to implement such a study, new definitions of war stress will be required for non-combatant female military personnel and a broad range of health outcomes beyond PTSD must be included.

3. DRUG USE AMONG THE MILITARY IN VIETNAM

Two types of drug use are considered in this section - prescribed use of antimalarial drugs (Section 3.1) and illicit use of such drugs as heroin, marijuana and alcohol (Section 3.2)

3.1 ANTIMALARIAL DRUGS USE

Malaria was seasonal and endemic in Vietnam and epidemic among U.S. troops, accounting for most of the morbidity from 1965-1969 in the military. Prevention consisted primarily of insecticides (aerial and ground spraying) and chemical phrophylaxis. Of the latter, Dapsone and Chloroquine-Primaquine were the drugs used to prevent and treat malaria in American troops. According to a Department of the Army internal memorandum (12/16/86), chloroquine-primaquine tablets (dose not stated, although typical dose was reported as 300 mgm chloroquine and 45 mgm primaquine; Willerson et al, 1972) were taken once a week, while Dapsone 25 mgm was taken on a daily basis. It is unclear from this memorandum if these two drugs were taken alone or in combination; however, other reports (Willerson et al, 1972; Eppes et al, 1967; Ognibene, 1970) indicated that both regimens were followed. On leaving Vietnam, Army personnel were instructed to continue the chloroquine - primaquine for eight weeks and/or the Dapsone for 28 days. Chloroquine-primaquine is a combination aminoquinoline compound used both in treatment and phrophylaxis of vivax and ovale malaria. Dapsone, a sulfone, was used widely in Southeast Asia from 1966 until 1973 following the discovery of several antimalarial resistant strains of Plasmodium falciparum malaria. The army has no records of how many or which troops took Dapsone. Similarly, data regarding use of Chloroquine-primaquine were not available to the reviewers. However, according to the Army Department memorandum of 12/16/86, "(d)apsone was mainly given to troops in the I Corps and Central Highlands areas where falciparum malaria was prevalent."

Review of available literature focused on these two drug types. A primary source for this review was several chapters in the Handbook of Experimental Pharmacology edited by Peters and Richards (1984) which reviewed data from available studies to date. This review was supplemented with research reports published since 1984. Findings regarding toxicity of each drug group will be discussed separately. It should be noted that the scientific literature on antimalarial drugs is voluminous and highly technical in detail. The limited material presented here is considered that most pertinent to the purposes of this review.

3.1.1 Chloraquine-Primaquine

Chloraquine-primaquine is a combination of two aminoquinoline compounds effective against all stages of human-malaria parasites except for certain strains of P. falciparum resistant to chloroquine. In a review of antimalarial drugs edited by Peters and Richards (1984), serious toxicity of the aminoquinoline compounds has been recognized since the outset of human trials in 1926. The Peters and Richards (1984) volume (Chapter 3 by P.E.Carson) focuses more specifically on the 8-aminoquinolines (primaquine) in its discussion of toxicity, identifying three major areas as follows: 1) specific neurotoxicity of the plasmocid type; 2) general clinical toxicity of the pamaquine type; and 3) induction of hemolytic anemia in genetically predisposed individuals, especially those with G6PD deficiency.

(a) Neurotoxicity. Pathological changes in the central nervous system have been documented in a number of animal studies using lethal and toxic sublethal doses of aminoquinolines. In Peters and Richards (1984) review, neurotoxicity associated with lethal doses of primaquine was less marked than with other compounds in this group. Further, neuronal damage resulting from sublethal, reversible intoxication was described as "low grade." No human studies reporting neurotoxicity were found.

(b) General Clinical Toxicity. Basic studies on toxicity were conducted principally in rats, dogs and monkeys with confirmation in human trials. Several studies cited in Peters and Richards, 1984, (i.e., Clayman et al, 1952; Brewer et al, 1961; Craige et al, 1947; Atchley et al, 1948; Edgecomb et al, 1950; Brewer et al, 1961; Wisclogle, 1946; Alving et al, 1948; Jones et al, 1953; Zubrod et al, 1947) describe the toxic symptoms as primarily gastrointestinal and hematological with the prominent feature of lethal doses being hepatotoxicity. The most prominent toxic symptom is epigastric discomfort with other gastrointestinal symptoms including headache, anorexia, nausea, vomiting, and diarrhea. Drug fever was cited as common. Hematological changes include leucocytosis and neutropenia, with the former more common with primaquine. Reversible T-wave changes, postural hypotension, and cyanosis (primarily related to methaemoglobinanemia associated with high doses greater than or equal to 60 mgm/day) have also been identified. Notable is that reversibility of toxicity was demonstrated repeatedly in the studies cited in this review.

(c) Hemolytic Anemia. Primaquine-induced hemolytic anemia occurs only in certain susceptible individuals, especially those with glucose-6-phosphate dehydrogenase (G6PD) deficiency. However, hemolysis can also be precipitated in these individuals by the stress of serious intercurrent

illnesses such as acute hepatitis, pneumonia, diabetic acidosis, etc. Two other classes of genetically determined conditions also predispose individuals to hemolysis of the primaquine type: enzyme deficiencies of the metabolic system that protects the erythrocyte against oxidant stress; and molecular variants of hemoglobins that are susceptible to oxidant stress (Carson and Fischer, 1966; Carson et al, 1981; Carson, 1968: cited in Peters and Richards, 1984).

(d) Reports of Other Side Effects. Studies completed since the Peters and Richards volume in 1984 have reported both similar and new findings regarding toxic side effects of chloroquine and/or primaquine. While a 1984 review of antimalarials focused on use in Africa (Salako, 1984), one specific finding has important implications for a proposed study of women Vietnam veterans. In this work, ocular toxicity was cited with prolonged prophylactic use, defined as a total dose of 200g of chloroquine ingested over a period of two or more years. The retinopathy is characterized by macula and perimacular degeneration, patchy depigmentation of the macula, and retinal artery constriction. These corneal lesions result in loss of central visual acuity, which may progress to total blindness. Unlike other toxic effects, ocular toxicity is not reversible. Salako (1984) states that chloroquine retinopathy tends to be permanent after discontinuation of the drug. Therefore while it is unlikely that the typical female Vietnam veteran ingested a toxic dose of chloroquine as noted above, this adverse outcome should be of interest in a study of their health outcomes.

Salako (1984) cited other toxic effects not included in the Peters and Richards (1984) volume, namely pruritis dyskinesia, mild neuromuscular disturbances, pigmentary changes in the skin, and lesions of the inner ear. All of these symptoms were either mild, rare, or reversible.

Animal studies report changes in drug metabolizing enzymes in rats (Emerole et al, 1983) and induced cardiomyopathy in chickens with prolonged use of chloroquine, but such findings have not been reported in humans.

(e) Teratogenicity and Carcinogenicity. Reports of the teratogenic effects of the antimalarials have been limited to case studies. Data from large samples are lacking with the exception of a case-control study by Wolfe and Cordero (1985). The teratogenic effects in the fetus, as reported in case studies, appear related to certain dosage regimens or prolonged use in pregnant women and include vestibular changes, deafness, retinopathy, prematurity, and death (Wolfe and Cordero, 1985; Bruce-Chwatt, 1983; Essien and Afamefuna, 1982). Looking at normal dose ranges in their study of 169 pregnant women receiving chloroquine 300mgm/wk,

Wolfe and Cordero (1985) found the proportion of birth defects not significantly different from that in the control group (n=454). However, because of their sample size, the investigators point out that their analysis cannot exclude risks lower than a 5-7 fold increase in the incidence of birth defects.

No reports of other teratogenic, carcinogenic or toxic reproductive outcomes (e.g. infertility) were found. In fact, the literature supports careful and controlled use of antimalarial drugs both for treatment and prophylaxis, pointing out the potential complications of untreated malaria during pregnancy.

3.1.2 Dapsone

Dapsone is a sulfone used in chemotherapy, mainly for leprosy and secondarily in malaria. As previously mentioned, it came into widespread use by U.S. troops in Vietnam following the discovery of resistant strains of P. falciparum malaria. Toxic effects include primarily hematological and neuropathic conditions. A comprehensive discussion of these toxic effects can be found in Chapter 4 by Scholer, Leimer and Richle, in Peters and Richards (1984) and is highlighted below.

(a) Hematological. The hematological side effects were cited as significant in that they occurred with relatively low doses of sulfones, whereas the other side effects were observed mainly with higher doses used to treat dermatological conditions. These hematological side effects included methemoglobinemia, hemolytic anemia, and agranulocytosis.

Methemoglobinemia was reported in cases of high doses of Dapsone for dermatological conditions in seven studies cited in Peters and Richards (1984: Hjelin and DeVerdier, 1965; DeGowin et al, 1966; Cooke, 1970; Shelley and Goldwein, 1976; Elonen et al, 1979; Manfred et al, 1979; Schvartsman, 1979). In addition, a study by Willerson et. al., (1972) cited in this volume documented methemoglobinemia in five of eight army volunteers receiving both dapsone and chloroquine-primaquine prophylactically in Vietnam, suggesting an interaction or synergistic effect between the two drug groups. This effect was independent of any G6PD deficiency.

Hemolytic anemia, induced by dapsone, was first described in a leprosy patient receiving high doses (100-300 mgm daily) as reported by Ramanujam and Smith (1951) in Peters and Richards (1984). However, Eppes et al, (1967) also documented prompt falls in hematocrit values in G6PD deficient black Army soldiers who were on the typical army schedule for malaria prophylaxis, 25 mgm dapsone daily plus

chloroquine and primaquine weekly. Chernof (1967) reported marked hemolysis in some of the G6PD-deficient individuals treated according to this schedule.

As with the other hematological disorders, agranulocytosis was first noted in a dapsone regimen for dermatological problems (McKenna and Chalmers, 1958; Firkin and Mariani, 1977: cited in Peters and Richards, 1984), but was also detected in U.S. soldiers in Vietnam receiving prophylactic dapsone, either alone or with chloroquine and primaquine, for 3 weeks to 3 months, with 8 cases being fatal (Ognibene, 1979; Catalano, 1971; Joplins and Ognibene, 1972: cited in Peter and Richards, 1984). These incidents led to the limitation of dapsone for malaria prophylaxis in the U.S. Army.

(b) Neuropathic. Evidence of peripheral neuropathy is restricted to case studies of dermatological patients receiving high doses of dapsone for prolonged periods (Rapoport et al, 1972; Wyatt and Stevens, 1972; Epstein and Bohm, 1972; Fredericks, et al, 1976; Koller et al, 1977; Homeida et al, 1980; Waldinger, 1984). All of these case studies reported motor neuropathy, but Wyatt and Stevens, (1972) described both motor and sensory symptoms while Homeida et al, (1980) claimed to be the first report of optic atrophy after a daily dose of 600 mgm of dapsone for 10 days. All toxicity was reported as reversible in these case studies. No cases of peripheral neuropathy were reported in individuals using dapsone for antimalarial prophylaxis.

(c) Miscellaneous Side Effects. Hepatotoxicity and hypoalbuminemia have been reported in a small number of individual cases, but again with individuals receiving high doses of dapsone for dermatological conditions (Millikan and Harrell, 1970; Goette, 1977; Stone and Goodwin, 1978; Kingham et. al., 1979; Young and Marks, 1979: cited in Peters and Richards, 1984).

(d) Teratogenecity and Carcinogenicity. Only two animal studies were cited in Peters and Richards (1984). The teratogenecity study, conducted in Japan (Asano et al, 1975) found no significant increase in fetal defects in rats whose mothers were given high doses of a related sulfone from day 9-14 of gestation. In the carcinogenicity study (Griciute and Tomatis, 1980) rats and mice of both sexes were given daily oral doses of 100mg/kg dapsone five times weekly over 2 years. The incidence of tumors was equal in treated and untreated animals, with the exception of fibrosarcomas and angiosarcomas of the spleen in male treated animals. No human data have been reported, but data from the animal studies do not suggest any concern for teratogenetic or carcinogenetic effects in humans.

3.1.3 Summary

In summary, the available literature on the two antimalarial drug groups used prophylactically in Vietnam troops is limited and provides no outstanding evidence of lasting toxicity at recommended doses. With the one exception of chloroquine-induced retinopathy, all other toxicity is reversible with reduction or termination of dose. Similarly, there is no convincing evidence of teratogenesis or carcinogenesis at recommended prophylactic dose levels. Congenital abnormalities or other conditions have been documented in cases of high doses and/or prolonged administration, usually for conditions other than malaria. Therefore, it appears from existing data of both animal and human studies that prophylactic use of antimalarials does not place the majority of female Vietnam personnel at high risk for adverse health and reproductive outcomes. However, for the most part human data are limited to case and small sample studies. A large-scale epidemiological study of possible long-term effects of antimalarial prophylaxis has not been conducted. Special attention to use of antimalarials during pregnancy or in excess of two years is warranted.

3.2 ILLICIT DRUG USE

Many research studies on illicit drug use among the military in Vietnam have been conducted since the late 1960's with the majority conducted during the 1970's. These studies have focused on the extent of drug use pre-service, in-service and post-service, the types of drugs used, the characteristics of drug users and patterns of use, and the impact of drug use on performance. These studies have focused almost exclusively on male personnel. Only two recent reports (Ott, 1985; Boyle, 1985) were found which addressed the issue in female veterans. This section will cover those studies which are methodologically most sound and which provide findings which are most generalizable. Given the paucity of data regarding female veterans, the studies on male populations can be used to inform investigation of drug use among women in Vietnam.

In reviewing 10 studies of male veterans, conducted over a course of approximately seven years, it becomes clear that the two illicit drugs most frequently used in Vietnam were marijuana and heroin. This trend becomes most apparent in later studies in the 1970's when heroin use increased dramatically in relation to other drug categories. Consequently, with the exception of a study in 1969 by Stanton (1972), data were not gathered routinely (or else not reported) on use of amphetamines, barbiturates, opium, and hallucinogens. Perhaps, as reflected in Stanton's (1972)

report, the numbers of users of other drugs were too small for meaningful analysis. In fact, not only were marijuana and heroin more frequently used, these drugs were also the most socially acceptable, with users of other drugs being ostracized (Ingraham, 1974). Therefore, this review will focus on available data regarding marijuana and heroin use. Results of these studies are summarized in Table 1.

3.2.1 Marijuana

One of the first surveys on marijuana use in Vietnam was conducted by Roffman and Sapol (1970) in 1967 with a sample of 628 Army enlisted men being processed for return to the United States. The sampling frame and strategy limits the generalizability of the findings since only a limited rank distribution was sampled, with the study further restricted to two southern tactical corps areas. The typical respondent was 22 years old, single, white, high school graduate, Protestant, a draftee, and had completed a 12-month tour. The majority of respondents indicated that they had never smoked marijuana. Of the 31.7% who had, 61.1% first smoked after coming to Vietnam, and usually early in the tour. Users were slightly younger, single, from an urban background, of lower rank, and more likely to have experienced combat. One-quarter (n=44) of the users were considered to be heavy users (i.e. smoking on 21 or more occasions). These heavy users were younger, of less rank, more likely to have used marijuana before Vietnam, and used it earlier in the tour. Roffman and Sapol compared their data with estimates of marijuana use at the time in the United States. They concluded that, at that time, the prevalence and incidence of marijuana use in Vietnam was very similar to that in the United States. Rates of use among the military population were similar to rates found among civilian university communities or among the comparable age group in the general population.

In a study two years later (1969), Stanton (1972) reached a similar conclusion despite higher use rates among Vietnam military. The sample in this study was both larger (n=2,547) and more representative, including ranks of E-1 to lieutenant colonel, as well as both incoming and outgoing personnel. Sizeable increases were noted in the reported use of most drugs surveyed when compared to earlier research. In terms of marijuana use, 21.5% used the drug for the first time in Vietnam, a figure only slightly higher than the 19.4% found by Roffman and Sapol (1970). While this may indicate that the rate of increase of users did not increase dramatically between 1967 and 1969, further data on extent of use showed heavier use (i.e., 29.6% as compared to 7.4% in 1967). In a subsequent review, Stanton (1976) compared findings across several studies from 1966-1970, the results of which seemed to indicate a fairly constant increase

TABLE 1. Estimates of Use Among Enlisted Army Personnel

	Roffman 1970 N=584	Stanton 1972 N=997	Rohrbaugh* 1974 N=169	Robins 1975 N=451	Yager 1984 N=1,342	Ritter 1985 N=668
MARIJUANA						
first used before Vietnam	9	35	--	41	--	--
first used in Vietnam	19	22	40-48	28	--	--
used while in Vietnam	25 (used 21 or more times)	50	50-63	69	--	32
used since Vietnam	--	--	37-43	45	37	37
HEROIN						
first used before Vietnam	--	4	--	2	--	--
first used in Vietnam	--	0	71-81	31	--	--
used while in Vietnam	--	2	24-27	34	--	--
used since Vietnam	--	--	10-11	10	1	--

All numbers are rounded percentages based on number of respondents in the study.
-- indicates data not available

* Data based on 2 survey populations, N=169 in each group.

overall in marijuana use in Vietnam. However, in further review of the data, he attributed this apparent increase to the influx of a greater number of pre-Vietnam users who continued use than to an increase in the numbers who initiated use while in Vietnam. In other words, increased use in the U.S. was, in turn, influencing use rates in Vietnam.

Stanton (1972) reported other findings consistent with those of Roffman and Sapol (1970). Marijuana smoking and combat exposure were slightly correlated ($r=.22$, $df=27$, $p=.01$), and the majority of users started smoking in the first three months of duty. Unlike the previous study, however, Stanton did not find any relationship between marijuana use and age, marital status, or volunteer status for duty.

A final study on marijuana use to be reviewed was conducted in late 1974 - early 1975 by Ritter et. al., (1985) of 2510 men, randomly selected from Selective Service records, born in the years 1944 through 1954. Analysis for this study of post-service marijuana use was limited to the subsample of 836 respondents who had served in the military. The sampling frame allowed for three comparison groups as follows: Vietnam service; overseas other than Vietnam service; and U.S. service only. Data on pre-service, in-service, and post-service marijuana use showed that the highest increase from pre-service to in-service use occurred with the Vietnam troops. Further, the higher level continued during the one-year period of post-service. Contrary to what might be expected, regression analysis revealed that service in Vietnam (as compared to other areas) had no significant positive effect on the use of marijuana during military service. However, the period of service did have an effect on marijuana use; that is, marijuana use during service was most probable among men who had served in 1970 or later, a time when drug use was increasing in the U.S. An interaction effect between period of service and location of service was insignificant. Therefore, the time of service, rather than the Vietnam exposure, appears to explain more of the variance in marijuana use. Ritter et. al., (1985) reported other findings consistent with the two previous surveys, mainly that marijuana use was more common among pre-service users, blacks, and younger troops.

In sum, the results of these three studies are generally consistent. The major conclusion is that the Vietnam experience influenced the use of marijuana less than the period of time in which it occurred, a time when drug use was epidemic in the U.S. and drugs were readily available in Vietnam. Therefore, as summarized by Ritter et. al., (1985), it appears that we have a "classic intersection of an historical effect.... and a cohort effect" (p. 129).

3.2.2 Heroin

Stanton (1976) reports that "(u)nlike marijuana, with which so many soldiers had had pre-Vietnam experience, heroin use was clearly a Vietnam phenomenon" (p.562). The "heroin days" in Vietnam began in early 1970 with the influx of 90% to 96% pure heroin. The spread of GI heroin addiction has been attributed to an army crackdown on marijuana use or to boredom and feelings of victimization, driving troops to heroin use. However, McCoy (1972), in an indepth political analysis of heroin trafficking in southeast Asia, claims that the heroin epidemic was related to a "well-organized, comprehensive sales campaign" by the Vietnamese. In addition, the Cambodian invasion in mid 1970 improved smuggling conditions since unlimited quantities of heroin could be flown from southern Laos through Phnom Penh to Saigon.

In terms of the extent of heroin use, data from three studies are available. Stanton's 1969 study (1972) indicated that only 2% of servicemen used heroin for the first time in Vietnam while an additional 4% had used it prior to Vietnam. The year of the study (1969) most likely accounts for these low rates.

In a frequently cited study by Robins and colleagues (1975), a random sample (n=470) was selected from a Department of Defense list of 13,760 Army enlisted men returning to the U.S. in September, 1971. In addition, from a list of 1400 men with positive urine samples for illicit drugs, a random sample of 495 men was selected. Exceptionally high rates were obtained for interview response (95%), military record retrieval (99%), and urine sample reports (92%), the latter allowing for validity checks on the data. As a group the general sample (n=457) did not differ in pre-service drug experience from a national sample of comparable ages. Less than half had ever tried an illicit drug (marijuana, amphetamines, barbituates, or narcotics). Only 2% had ever used heroin, and less than 1% had used any illicit drug more than a few times.

Almost half (n=194 or 43%) of this sample had used narcotics. Approximately one-third tried heroin. Of narcotic users, 25% used these drugs more than weekly for at least 9 months. Forty-six percent were addicted by self report and confirmed by symptoms of dependence. Preferred use was smoking or snorting. Injection was rare but did occur with prolonged use. Similar to patterns of marijuana use, use began early in the tour, i.e., within the first two months. The most common reason for use was the drug's euphoria-producing effects, with no correlation found between use and combat exposure. In fact, according to other descriptive accounts of drug use (Ingraham, 1974; Zinberg, 1972), heroin use was a social event carried on in small groups as

compared to the typical pattern in the U.S. of solitary use. Ingraham described a cohesiveness and loyalty among "heads" or users of heroin, who were accorded higher status than users of alcohol, amphetamines, barbituates and hallucinogens. Finally, Robins et. al., (1975) identified pre-service predictors of narcotic use similar to predictors of in-service marijuana use - younger age, urban background, pre-service drug use, heavy drinking, and behavior problems. Contrary to expectations, they also found that volunteers were more likely than draftees to use narcotics in Vietnam.

In another study regarding effects of the Vietnam experience on subsequent drug use, completed about the same time, Rohrbaugh et al, (1974) found somewhat lower rates of heroin use. A stratified random sample of enlisted men (grade E5 and below) returned to the U.S. was drawn at three points in time: February, September and December, 1971; n=782, 480 and 481 respectively. Data from September and December were used in this analysis. Approximately one-fourth of the returnee group admitted using heroin or opiates at least once in Vietnam, with the greater proportion (51.1% in September, 65.9% in December) reporting daily use. Further, data revealed that the clear majority (71.1% in September; 81% in December) of veterans who had ever used opiates first did so in Southeast Asia.

3.2.3 Alcohol

Alcohol use during Vietnam service has received much less direct attention than other drug use, with data frequently reported secondarily to narcotic or marijuana use. However, there is limited evidence to suggest that alcohol use was extensive among Vietnam soldiers as indicated in the following studies.

In a large national study, Robins and colleagues (1975) found that 92% had used alcohol at least once while in Vietnam with 37% reporting problems with alcoholism post-service. This study did not gather more specific data on extent of alcohol use in Vietnam. Rohrbaugh et. al., (1974) also reported data to suggest extensive alcohol use. In two separate 1971 surveys, they reported that alcohol was used by 83.3% and 79.8% of their samples but that only a small minority (2.7% and 5.2%) began drinking while in Vietnam. No data are available regarding extent of use. These limited data are supplemented by a descriptive account (Ingraham, 1974) of alcohol and other drug use in Vietnam, but no data regarding use rates were reported. Finally, the Veterans Administration reported in 1978 that 107,000 inpatients and 323,000 outpatients were being treated for alcoholism, and public health service figures indicate that as many as half a million Vietnam veterans (of 2.8 million) are alcoholics (Royal Commission on the Use and Effects of Chemical Agents on Australian Personnel in Vietnam, 1985).

Although no systematically methodologically sound collected data are available on alcohol use post-Vietnam, all of the studies which have considered recent alcohol use at all, suggest consistently that it is on the increase and the major drug abused by male veterans. Considerable indirect evidence is available from the recent "Vietnam Experience" mortality studies reviewed in Section 4 of this review. All of them consistently report elevated death rates from Motor Vehicle accidents. Most recently, a report of post-service mortality in the CDC Vietnam Experience Study (CDC, 1987) indicates that, despite small numbers, alcohol-related traumatic (mostly motor vehicle accident) deaths were more likely among Vietnam veterans in the first five years after discharge, then declined. Any future studies of follow-up of Vietnam veterans - both male and female - should include this variable.

3.2.4 Drug Use After Vietnam

Several of the studies cited above also examined whether Vietnam returnees differed in their patterns of stateside drug use from other non-Vietnam soldiers or civilians. The 1971 study by Robins et al, (1975) provides the best evidence. In their sample of 943 men, they found at 8 to 12 months after return that use of particular drugs and combinations of drugs decreased to near or even below pre-service levels. The choice of which hard drug to use reverted to the pre-Vietnam pattern. Only in Vietnam were narcotics used more than barbituates or amphetamines. In addition, on return to the U.S., the susceptibility to addiction among continued narcotics users declined dramatically, resulting in addiction remission rates of 95% for those addicted in Vietnam. The investigators caution that the study period following return was short and that data gathered subsequently might show different use or addiction rates. However, while there was a striking decline in susceptibility to addiction after return to the United States, heavy use of each drug type did not show the same decline. Further, usual methods of administration of narcotics changed from smoking in Vietnam to injection in the U.S. Finally, the type of narcotic most frequently used changed from codeine before Vietnam to heroin after return. In-service predictors of continued narcotic use after Vietnam included injection of narcotics while in Vietnam, narcotic dependence, heavy use of barbiturates or amphetamines in Vietnam, narcotic dependence, and use of narcotics in Vietnam for longer than six months. Drug use in and before Vietnam was determined to be a powerful factor in poor post-Vietnam adjustment, but its effects were contingent on continued drug use. Adjustment problems included arrests, depression, unemployment, and divorce, with narcotics use being the strongest of the drug

predictors except for arrests which were more closely associated with amphetamine use.

Robins and Helzer (1975) followed up this study three years later (1974) with reinterviews of the same sample, adding a group of 300 nonveterans for comparison. The comparison group was selected from Selective Service System files of service eligible men who had not been inducted and was matched with the original sample for age, education, and area of residence. High response rates were again obtained: 94% of the veterans and 91% of the nonveterans. Among the veterans, the low rate of narcotics use and dependency found in the first survey continued to hold after three years. Only 2% of the veterans had been addicted at any time since their return. More than 90% who reported addiction in Vietnam had not become readdicted in the three years since return. Even among those who continued narcotic use (20%), only 12% had become addicted. While heroin continued to be the most frequently used narcotic (55%), opium and codeine were also used. While use of narcotics is a major concern, alcohol and marijuana were actually used more frequently and reported as causing more problems in daily life. For example, while 5% felt that narcotics had interfered with their lives, 18% felt that drinking had.

In the comparison of veterans and nonveterans, for every drug of inquiry, veterans' use was greater in the past two years than was nonveterans' use, and was not related to previous drug experience. The greatest differences were in the use of narcotics, LSD, and barbiturates. Marijuana use was common among both groups. Thus the authors concluded that Vietnam exposure led to increased drug use. However, veterans showed no inclination toward heavy or problem use, and, in fact showed a greater ability to use narcotics without becoming addicted. While this follow up study provides detailed information, no mention is made of obtaining objective measures of drug use (urine samples) as in the earlier study. The investigators do not discuss the implications of reliance on self reported data for validity of the findings. The rates of drug use may be undereported.

Rohrbaugh and colleagues (1974) also used a control group of soldiers who had not served in Vietnam to investigate whether combat zone returnees differed in their pattern of stateside drug use from non-combat zone soldiers. They found greater use by Vietnam veterans only in relation to opiate use ($p < .02$) and only at one point of the three survey times. This relationship held when controlling for age, pre-service drug use, and length of time since return. Consistent with Robins (1975) study, Vietnam returnees reported using the same drugs stateside as in Vietnam but were more likely to discontinue opiate use stateside, supporting the contention that opiate users in Vietnam differ from typical opiate users in the U.S.

Finally, no tendency to use drugs more frequently or heavily was found among Vietnam returnees. Despite consistent results, this study was marked by several methodological flaws, however. First, drug use was based on self report alone and further was defined only as "at least one experience with a given drug in the month prior to the survey." Second, the authors acknowledge the potential for sampling bias by the possibility of underrepresentation of Vietnam drug abuse casualties (e.g. those previously separated from the military for drug problems, AWOL, or actively involved in in-patient rehabilitation programs).

Nace et al, (1978), also found consistent results in a controlled follow up study of army enlisted men who served in Vietnam during a peak period of heroin use (1971-72) conducted two years after discharge. Data were collected by interviews and urine samples. In a sample of 125 detected drug users and 77 controls in the Philadelphia area, selected from four hospitals and two drug treatment center's records, pre-service variables (including drug use) contributed as much to continued narcotic use as did drug use in Vietnam. Rates of addiction post-service were again low (18%) among the 28% who continued use as compared to a 63% in-service addiction rate. Marijuana and barbiturate use also declined since discharge. However, use of hallucinogens and amphetamines increased. Finally, data regarding post-service alcohol use were also collected. Alcohol-related problems were extensive involving 39% of the sample, with 16% categorized as problem drinkers. This study, while limited by a small, non-random sample, nevertheless provides further support for measurement of in-service and post-service drug use by Vietnam veterans.

Finally, two studies are presented, both for their methodological strengths and results contrary to those above (Yager, 1984; CDC, 1987). A national probability sample (n=1342) of draft eligible age during the Vietnam War included 629 nonveterans and 713 veterans, of whom 350 served in Vietnam (Yager, 1984). The sample was stratified by age, race and veterans status. Data were collected in interviews in 1977 and 1979, 6 to 15 years after leaving Vietnam, on a number of outcome variables, including drug use, related to post-service adjustment. Drug use (5 types) was consistently less prevalent among Vietnam veterans than nonveterans. However, use of amphetamines, barbituates and heroin was higher among Vietnam veterans than non-Vietnam veterans. Measures of weekly and daily drinking as well as drinking related problems were highest among Vietnam veterans. Vietnam veterans also reported more stress symptoms. Further analysis revealed that Vietnam veterans who experienced abusive violence reported greater stress and use of heroin and marijuana than did other veterans. Veterans who experienced no violent combat and did not take part in atrocities, however, did not differ appreciably from

nonveterans. While the investigators are not reporting a cause-effect relationship between combat violence and drug use/stress, they do point out that relevant social background and other predisposing factors were controlled for in the analysis. The findings of this large national study, similar to that of Robins (1975) in scope, are roughly, consistent with other studies. Yet, by incorporating measures of exposure to combat violence, they do not support the premise that post-service drug use is more related to pre-service use than in-service use. Incorporating measures regarding both pre-service and in-service drug use as well as exposure to combat violence might uncover an interaction effect between pre-service drug use and combat violence which more completely explains continued post-service drug use.

A rather different Vietnam experience mortality study (CDC, 1987) indicates that, although too small for formal analysis, the number of drug-related deaths remained elevated and was increasing through 1983 in Vietnam veterans, particularly for those drafted into service, in tactical or combat operations and those who served immediately after the TET offensive, in 1969. Approximately 9000 Vietnam veterans and an equivalent number of Vietnam-era veterans, serving in the Army at the pay grade of E5 or below with a military occupational specialty (MOS) other than "trainee" or "duty soldier" were included in this study. In these large cohorts, 446 deaths were identified by the end of 1983.

3.2.5 Studies of Female Veterans

Only two studies were located which even mentioned drug use among female veterans, both of which were published within the last two years. The descriptive account by Ott (1985) of the war experience for women reports only that drugs and alcohol were used to deal with the pain and horror of suffering and death. In the most comprehensive study to date of women veterans by Louis Harris and associates (Boyle, 1985), interviews were completed with 3003 women, not all of whom served in Vietnam. Only one percent of all women veterans reported having problems with drugs. However, Vietnam and post-Vietnam veterans were more likely to have reported drug problems. The differences between groups are reported as small but consistent; however, no data are provided in the report. Further, less than 0.5% of women veterans who served during the Vietnam period (although not necessarily in Vietnam) rated drugs/drinking problems among the two or three most serious problems faced by female veterans since leaving the service.

The Wisconsin Vietnam experience mortality study (Anderson et al, 1986) suggests a significant excess of all external causes of death compared to non-veterans among all

female veterans, which may include an excess of drug or alcohol related deaths, but this finding is not pursued in the report.

Clearly, there are no even minimally adequate data on even in-service, let alone pre-service and post-service, use of drugs among women Vietnam veterans to determine if drug use was an issue of importance as it was with male veterans. Available data are not even adequate to suggest if a serious problem existed or not. As noted by, for example, Anderson et al (1986), the Armed Forces have had access throughout this century to subsidized tobacco and alcohol. The high rates of tobacco product use are clearly evident in all studies reviewed of veteran mortality experience, including the female veterans included in Phase I of the Wisconsin study (Anderson et al, 1986). Elevated death rates due to respiratory cancer, lung cancer and emphysema are typical among veterans in these studies. Moreover, from the oral histories reviewed in Section 1 as well as other oral reports, it is clear that alcohol was the clear drug of choice among nurses serving in Vietnam. Collection of valid data on alcohol and other drug histories will be essential in any study of health and reproductive outcomes of women who served in Vietnam.

3.2.6 Summary

In conclusion, data from a number of sources consistently indicate that the drugs most frequently used in Vietnam were alcohol, marijuana, and heroin although data on the latter two are very limited in women veterans. While heroin use escalated in the 1970's following a decline in marijuana use, use of alcohol appears to have been constant. In relation to the postwar public health concern regarding addicted returning veterans, the fear of continued narcotic use and addiction is unfounded. Both narcotic use and addiction were reported to decline in all studies reviewed which provide this information. This may have been a result of the differing social environments, most notably the social system which supported heroin use in Vietnam, as described by Ingraham (1974), as well as the necessity to change routes of drug administration from smoking to injection in the U.S. Marijuana use continued stateside at higher rates than narcotic use, but there is no evidence to suggest that it was related to the Vietnam experience. Finally, alcohol use/abuse remained at high levels and caused more adjustment problems than other drugs. This may be particularly true of women veterans.

From a methodological perspective, a review of this literature underscores the following points in design of any future studies:

- measures of pre-service, in-service and post-service drug use must be included;

- measures of exposure to combat violence and atrocities must be included to adequately assess any cause-effect relationship between the war experience and subsequent drug use;

- appropriate control groups must be identified for comparison purposes; and

- specific data regarding alcohol use, as well as other drug use, should be collected.

4. CHEMICAL EXPOSURES

This section deals with chemical exposures specifically during Vietnam service. Other confounding chemical exposures likely to occur pre- or post- Vietnam (or Vietnam-era) service are discussed in Section 6, Confounding Factors as well as in Section 5 which addresses Nursing as an important occupational exposure.

The two primary chemical exposures during Vietnam service were: Phenoxy herbicides and insecticides. The health outcomes identified from these two exposures will be reviewed, with emphasis on most recent findings. Measurement issues in the determination of exposure will also be considered.

4.1 PHENOXY HERBICIDES

The most controversial chemical exposure subject to debate, particularly in the last decade, is to the family of phenoxy herbicides - specifically 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5 - trichlorophenoxyacetic acid (2,4,5-T), and a highly toxic contaminant found in the manufacture of the latter (2,3,7,8-tetrachlorodibenzo-para-dioxin or TCDD). Commonly know as Agent Orange, this combination of chemicals was sprayed as a defoliant in South Vietnam in an Air Force operation called Ranch Hand. However, in varying ratios, these phenoxyacetic acids have been used as defoliants at least since the 1940's, in agricultural applications in many countries and in Malaysia, by the British military forces.

The proliferation of studies are reviewed in the following sub-sections:

- Animal studies;
- Human studies of herbicide exposure;
- Vietnam experience studies (including more general Vietnam exposures); and
- Studies of direct exposure in women.

In reviewing these studies, the authors do not intend to replicate the extensive review of studies through 1985, already conducted by the Veterans' Administration (VA, 1981-85). Rather, this section will highlight findings from this extensive work, including methodological evaluation of key studies, and supplement it with a review of more recent reports. The focus is to assess the relevance of these findings for a study of exposed women of reproductive age.

4.1.1 Animal Studies

A considerable number of animal studies on the effects of phenoxyacetic acids and particularly of the contaminant TCDD have been reported since the early 1970's. These studies have been typified by large, unexplainable differences in both toxicity and reactions among the different species tested (recent examples include chickens (Sawyer et al, 1986) and species of fresh water fish (Kleeman et al, 1986a and b). Moreover, the reactions observed in animals do not necessarily resemble outcomes observed in humans. The exact mechanisms of toxic action which can cause death in animals are still not fully understood, either for dioxins in general or TCDD, but include a general wasting and failure to thrive (McConnell et al 1978; Greig et al, 1973; Poland et al, 1982).

Perhaps the most consistently and rapidly established toxic outcomes in a variety of animal species is the carcinogenicity of TCDD - particularly the promotion of liver cancer in rodents (Poland et al 1982; IARC, 1982) - although TCDD does not appear to be mutagenic (even in human tissue) at single or low doses (Beatty et al, 1975; Green et al, 1977; Khera and Ruddick, 1973). The mechanism by which TCDD promotes cancer growth in mice has been identified from recent studies, to be centered on the cytochrome P_1-450 gene in hepatoma cells (see for example, Jones et al 1986 a, b). Other receptor mechanisms whereby TCDD promotes other toxic effects are also being identified (for example, Morrow and Creese, 1986).

A potentially important recent avenue of research indicates that TCDD may have a primarily immunosuppressive effect. This was originally thought to be characterized by thymic atrophy, mediated by the thyroid gland (Knutson and Poland, 1980; Clark et al, 1981, 1983; Greenlee et al, 1984; Rozman et al, 1984 a,b, among others). More recent studies indicate the possibility of direct toxic effects on the suppression of B cell differentiation, without measurable effects on the thymus (Holsapple et al, 1986; Tucker et al, 1986). The latter report, in particular indicates that subchronic exposure (less than 14 days) of mice to TCDD was sufficient to suppress antibody response.

Low doses of TCDD (less than or equal to 0.2mg/kg body weight) administered to pregnant rabbits, Rhesus monkeys and rodents did not accelerate the fetal loss rate, but TCDD appears to be a powerful teratogen at high doses (Smith et al, 1976; Sparschu et al, 1971; Giavini et al, 1982; McNulty, 1983). Silbergeld and Mattison (1986) provide an excellent review of animal and human studies on the reproductive toxicology of dioxins and TCDD. Perhaps most relevant for this review, they note that:

- all human studies have involved exposure to mixtures of dioxins and TCDD in unknown ratios:

- the pathway for reproductive toxicity is complex, involving other organ systems;

- in animal studies, direct gonadal toxicity has been demonstrated, including changes in uterine and ovarian structure (Mattison et al, 1983; Kociba and Schwetz, 1982; Giavini et al, 1982), but equivalent effects have not been considered in human populations, including fertility, hormone levels, timing of menopause and menarche.

In summary, although the wide range of toxic responses in different species has not yet been adequately explained, the major toxic effects of TCDD appear to have been identified. In particular, TCDD promotes cancer at varying doses and suppresses immune function at relatively low (subchronic) doses. Teratogenicity in animals occurs at high doses only, from the work done to date. The potential toxic impact for humans, according to the animal research available, will clearly depend on the strength of acute exposure as well as the duration of chronic exposures.

4.1.2 Human Studies of Herbicide Exposure

For environmental and occupational epidemiologists, the problems associated with reliable exposure measurements are well known (see for example, Monson, 1980). For a substance to be clearly identified as causing a disease or adverse health outcome, the following minimal conditions must apply:

- the substance must exist at a documentably high level in the environment or in measurably variable levels;

- the adverse outcome must be unambiguously observed; and

- the relative risk of the outcome, associated with exposure to the substance, must be sufficiently high not to be explainable by methodological flaws in the study.

A recent example which meets these minimal criteria is the detection of an association between unopposed estrogen use and subsequent uterine cancer in the mid-1970's. Case-control studies indicated that prior use of unopposed estrogen was associated with a four-to-eight-fold increase in uterine cancer (Smith et al, 1975; Ziel and Finkle, 1975; Mack et al, 1976), with evidence of a dose-response relationship (the longer the treatment with estrogen, the higher the relative risk). The exposure was well-defined and

measurable. The outcome was also verifiable through pathology reports and was not a rare cancer. The measured relative risks were high and could not be dismissed despite potential self-selection biases between cases and controls in all of the studies (Kaufert and McKinlay, 1985).

The only study of phenoxy herbicides which meets the first two of these criteria is the "Ranch Hand" study of Air Force personnel who completed the spraying missions in Vietnam (USAF, 1983; Lathrop et al, 1984). It has been estimated that the average exposure of these personnel was at least 1000 times greater than that of a naked man being sprayed with herbicides in an open field (Lathrop et al, 1984). That is, the exposure was documentably high, although not measurable.

All other epidemiologic studies, including studies of Vietnam Veterans, Vietnam residents, industrial and agricultural workers and industrial accidents (See Tables 2 and 3) are typified either by higher levels of exposure than would be expected in a general civilian population, possibly over several years, but within an unmeasurable exposure range or by one or more accidental exposures of short duration at relatively high levels. For example, exposure among New Zealand Chemical Sprayers (Smith et al, 1982a,b) was difficult to determine given the use of aerial spraying techniques. In the industrial accident near Seveso, Italy, heavy exposure was very limited in both area and duration (Reggiani, 1979).

Another recurring problem in these studies has been biased reporting or observation. A subject experiencing a potential adverse outcome would be more likely to "remember" or inflate reports of exposure to herbicides. Similarly, subjects who considered themselves to be dangerously exposed would over-report outcomes (Lathrop et al, 1984; Reggiani, 1979). In most cases, observers could not remain blind to the exposure status of subjects (for example the Swedish studies: Hardell, 1977; 1979; Hardell et al, 1985) thus creating potential bias - particularly in outcome reporting. Notable exceptions were the Australian Vietnam Veterans (Donovan et al, 1983) and CDC (Erickson et al, 1984) studies as well as the study of Kansas agricultural workers (Hoar et al, 1986).

The three primary adverse outcomes associated with phenoxy herbicide exposure to date, are: chloracne - a rare skin disorder associated with TCDD, reproductive abnormalities, (with emphasis on congenital defects and fetal loss) and rare cancers including soft tissue sarcomas (STS) Hodgkins Disease (HD) and non-Hodgkins Lymphomas (NHL). There are two major problems in focusing on such low-frequency outcomes in epidemiological studies. First, diagnosis or definition may be difficult (as in the case of

STS) or unreliable (as in the case of birth defects) and therefore more vulnerable to over-reporting bias under political or public pressure. Second, when the total observed number of outcomes may be less than 10 in a study of thousands of subjects (as with STS and some birth defects), misclassification error and/or spurious clustering of cases can produce artifactual associations or dilute the chance of detecting real associations.

Finally, some of the studies of phenoxy herbicide exposure have been conducted in political climates which have severely compromised their findings. For example, the studies of Swedish Agricultural workers by Hardell and co-workers were conducted during considerable media attention and Dr. Hardell himself took a prominent advocacy position (Colton, 1986). Studies of Vietnam veterans and of the Vietnam civilian populations which involved subject interview have suffered from similar limitations. These political biases can only be overcome by careful validation of self-reported data (for example Hoar et al 1986; Lathrop et al, 1984) or by use of exisiting record systems which are minimally affected by political climate.

The remainder of this section will highlight methods and problems in the measurement of phenoxy herbicide exposure, followed by an attempt to synthesize outcome findings with those of animal studies. A summary of major studies is presented in Tables 2 and 3 divided by population type (Vietnam veterans or civilian).

(a) Exposure Measurement

Three primary methods of exposure measurement have been applied in studies to date: Reported levels, assessed from available documentation, soil analysis and, most recently, analysis of adipose tissue.

The use of existing documentation and verbal reports is the typical method of measurement in industrial settings. This was, for example, used to differentiate long-term occupational exposure among workers at Monsanto's Nitro plant in West Virginia and those involved in the clean-up of a large accidental spill of phenoxy herbicides in 1949 (see for example, Zack and Suskind, 1980; Suskind and Hertzberg, 1984; Hay, 1986 and earlier reports). The resulting exposure classification was into: those exposed to the large, acute doses in the clean up; those exposed directly only during the regular manufacture process; and those minimally or not exposed among Monsanto employees who were not directly involved in production. Because of the time lag (over 30 years) and the changing political climate and memories, existing documentation were not adequate for validation of exposures. In contrast, Hoar et al (1986) validated a sample of self-reported use from suppliers' records. In Swedish and

New Zealand agricultural spraying studies, exposure was estimated according to usual herbicide strength, mode of application and length of time exposed (see, for example, Hardell et al, 1982; Smith et al, 1982) and self-reported mode and length of use was solicited. Other studies have relied on existing records of occupations to indirectly estimate relative exposures without recourse to self-report (Lynge, 1985; Wiklund and Holm, 1986; Nelson et al, 1979).

Use of existing documentation has also been the primary method of exposure measurement in Vietnam. The "Herbs" tapes were compiled from Ranch Hand spraying mission instructions and logs combined with Army Morning Reports to locate troop movements in space and time. The deficiencies in these records have been well documented (see for example The Royal Commission on the Use and Effects of Chemical Agents on Australian Personnel in Vietnam, 1985). Perhaps the best differentiation which can be made in terms of Vietnam military exposure is into three groups: those troops assigned to I Corps where most of the spraying missions were concentrated; those assigned elsewhere in country; and those flying or supporting the Ranch Hand missions themselves (Lathrop et al, 1984).

In the civilian Vietnamese studies, reliance has been on imputed exposures from known location of subjects during the years of spraying (Phuong and Huong, 1983; Trung and Chien, 1983; for example). The unreliability of self-reported exposure, post Vietnam war is well illustrated by the results of an experiment conducted by Korgeski and Leon (1983) on 100 Vietnam veterans. No correlation between self assessed and "Herbs" tape exposure was observed.

Soil sampling has been used primarily to access accidental industrial exposures, notably in Seveso, Italy following the accidental release of TCDD from an industrial plant (Donna et al, 1984; Mocarvelli et al, 1986), and in Missouri where TCDD contaminated wastes were mixed with waste oil and used as dust-control sprays in recreational, residential and commercial areas near St. Louis (see, for example, Hoffman et al, 1986). In these examples, crude categorization was possible into high and low contamination areas. A recent review (Paustenbach et al, 1986) provides a thorough critique of existing U.S. and European guidelines on standards for limits of dioxin contamination in soil by considering the bioavailability to humans. The primary message of this review is that current assumptions on which bioavailability are based are very general and may overestimate the toxic potential of various levels of TCDD in soil. The increased risk to children from low levels is well-argued. The review concludes that amounts in excess of 1 part per billion (the current U.S. soil standard) are required to exceed a virtually safe dose (currently set at 10pg/kg/day). However, this conclusion relies on the same

problematic extrapolations inherent in all of these toxic exposure estimates.

Most recently, techniques have been refined for measuring TCDD levels in human adipose tissue (Patterson et al, 1986a; Gross et al, 1984). A recent report, also by Patterson and co-workers at CDC (Patterson et al, 1986 b) illustrates the use of this measurement as an exposure index in exposed and controls in Missouri. Most recently, Dr. Peter Kahn (1987) reported on the use of this measure as an index of exposure in Vietnam veterans. Both studies indicate that measurement of residual TCDD in adipose tissue is a reliable indicator of actual exposure, but as Patterson et al (1986a) note, the exact relationship between adipose tissue levels, total body burden and actual exposure have yet to be determined from well-defined cohorts. Extrapolation in animal and human studies indicates a half-life of TCDD in human adipose tissue of 5-8 years (Patterson, 1986b). This estimate would further indicate the usefulness of this measure in retrospective studies. Current research at CDC is cross-validating a blood test with adipose tissue measurement. If this test proves to be a viable alternative to a surgical procedure for obtaining adipose tissue samples, wider use of this measurement will be possible.

Finally, added to the problems of measuring exposure <u>levels</u> are the varying <u>combinations</u> of phenoxyacetic acids used, only one of which contains TCDD. Agricultural herbicide use in Kansas, for example, was primarily 2,4-D without TCDD (Hoar et al, 1986), while in Arkansas, the combination varied by crop (Nelson et al, 1979). In Sweden, the primary herbicide was 2,4,5-T (with some 2,4-D use) until the 1970's (Wiklund and Holm, 1986). In Vietnam, Agent Orange was a combination of both herbicides.

In summary, attempts to measure phenoxy herbicide exposure have been generally indirect resulting in relatively crude categorizations into high, low or no exposure. Comparability of exposures across studies have been rendered impossible by both the lack of quantification (in terms of amount/kg of body weight) and by the varying combinations of phenoxy-acetic acids used.

(b) <u>Toxic Outcomes</u>

The primary outcomes which have been clearly associated with phenoxy herbicide exposure fall into three groups:

- chloracne and associated skin problems;
- fetal loss and malformation; and
- a group of rare cancers including STS, HD and NHL.

Each of these outcomes will be considered, in relation to type of exposure and findings from animal studies as appropriate.

Perhaps the best documented result of heavy, acute exposure is chloracne. It was reported in over 50% of workers involved in clean up at the Nitro plant (Cook et al, 1980; Suskind and Herzberg, 1984). It was also reported primarily in children exposed to heavy TCDD contamination in Seveso (Donatelli et al, 1981; Mocarelli, 1986). This distinct skin condition is typically not observed in the absence of TCDD exposure or in the presence of generally low level or non-topical exposure, and is well-defined. Although severe cases of chloracne may persist for 10 years or more, this skin condition generally disappears within 2-3 years (Cook et al, 1980).

The increase in other less severe skin lesions has not been as well documented, although it is suggested in, for example, Hoffman et al (1986).

Fetal loss and congenital malformations have been the outcomes of interest in a number of studies (see Tables 2 and 3). These have been typified by considerable problems and differences in measurement. Early fetal loss is difficult to document as it may appear to be a late menstrual period. Reporting also varies culturally and is affected by recall and political climate. These problems render fetal loss findings for Seveso (Donatelli, 1981; Marni et al, 1982; Tognoni and Bonaccorri, 1982; Bruzzi, 1983; Reggiani, 1983) and for Vietnamese civilians (for example Phuong and Huong, 1983; Trung and Chien, 1983; Can et al, 1983) of doubtful quality.

Data on congenital abnormalities have been somewhat more reliable. The major differences between studies is the time of ascertainment (at birth or later in infancy). Obvious morphological abnormalities such as hydatidiform mole and cleft palate or other facial clefts are readily observed at birth whereas others will only become apparent during post-natal development. Self-report, validated by examination, or medical records are the most reliable sources. Studies in which unvalidated self-reports are likely to have produced biased results include the North Vietnamese studies and those conducted in Seveso (see Tables 2 and 3). Unvalidated self-report was less likely to be biased in the New Zealand studies (Smith et al 1982; Matheson et al, 1981), although it cannot be ruled out.

The results are generally that there is no increase of either fetal loss or defects in exposed (compared to unexposed) groups. The only consistent differences found were in studies of Vietnam villages exposed to spraying (in

which there was direct maternal as well as paternal exposure). The majority of studies have investigated paternal exposure only, through Vietnam exposure or industrial exposure. Agricultural studies have included the possibility of some direct maternal exposure. Despite the methodological problems, the potentially heavy spraying and subsequent soil contamination exposure of the Vietnamese may have been sufficient to cause fetal loss and/or congenital defects, consistent with the animal model. This reproductive effect certainly cannot be dismissed, given the consistently null findings from primarily paternal exposure.

The final group of outcomes includes STS, HD and NHL. These cancers are rare, difficult to diagnose and may have long latency periods. Recent data presented by Hardell and Eriksson (1987) indicate that some STS lesions and lymphomas may have latencies of 30 years. A similar conclusion is reached by Hoar et al (1986) for NHL, given the rapidly increased risk in those exposed prior to 1946. The relationship of NHL in particular, to immune deficiency may provide a further plausible link. Even though the exposure of Kansas farmers to TCDD was very low the primary herbicide was 2,4-D), it may have been sufficient, over a long exposure period to lower immune function sufficiently to increase risk to NHL or there may have been a similar contaminant in the early manufacture of 2,4-D. It is important to note that the only other study relating NHL to herbicides was Hardell et al, 1981. The Swedish exposure was also of long duration (several years) and included TCDD levels through predominantly 2,4,5-T use. In relation to these findings, Hoffman et al (1986) demonstrated that long term low levels of exposure in contaminated soil are associated with depressed cell-mediated immunity, although there were considerable methodological problems - notably inter-reader differences in reading skin test for DTH responses. Elevated levels of alpha-gultamyl transferase (GGTP), AST, ALT and alkaline phosphatase, and lower cholesterol levels were observed in the exposed group.

In studies with latency periods of 20 years or less, exposures at relatively low levels and for shorter periods, the results have been conflicting (see Tables 2 and 4). No cases have been found among the Ranch Hands, but they are young, healthier than average, exposed for a short time period and number only about 1200. With a point prevalence rate estimated at less than 1 in 1000 for STS, HD and NHL combined, in the entire adult population, the chances of observing differences in cohorts is low, unless numbers are very large. The 18,000 in the recent CDC Vietnam Experience Study cohort (CDC, 1987) is insufficient to detect significant differences in current mortality from these causes.

(c) Vietnam Veterans Experience Studies

The most recent studies of Vietnam veterans have avoided attempts at categorization according to Agent Orange exposure and have rather limited comparisons to those with "in-country" Vietnam service and Vietnam-era veteran or civilian controls. These studies are of two general types:

- retrospective cohort studies, comparing veterans groups with respect to mortality; and
- case/control studies of congenital defects or STS relating these outcomes to paternal Vietnam service.

Such studies, categorized by the above two types, are presented in Table 4. The case/control studies of congenital defects (Donovan et al, 1983; Erickson et al, 1984) are both well-done and show no consistent associations. The studies of STS (Greenwald et al, 1984; Kang et al, 1986) also show no association with Vietnam service. Both studies verified cases of STS from pathology reports.

The remaining retrospective cohort studies have used death and cancer registers to identify Vietnam and/Vietnam era veterans or civilians as comparison groups. These studies have all documented that veterans, compared to civilians, have higher rates of tobacco-related and accidental deaths (particularly motor vehicle accidents). Varying excesses of accidental and alcohol-related deaths have been found in Vietnam veterans compared to Vietnam veterans (CDC, 1987; Kogan and Clapp, 1985), the latter group of deaths indicating recent increases.

With the exception of the CDC (1987) study, all of these report on STS cases. All have few such cases and only Kogan and Clapp (1985) appear to have verified cases through pathology reports. Holmes et al (1986) report three STS cases in West Virginia Vietnam veterans, none in Vietnam-era controls. Kogan and Clapp report a similar significant excess (9 versus one expected). No differences are found by Anderson et al (1986) in their Wisconsin study (5 cases in each group). Holmes et al also report an excess of HD deaths (4 versus 1) and an excess of one testicular cancer death.

These variable results may be the result of small numbers and short latency periods (generally 15-20 years). They may also reflect socio-economic differences related to the drafting of men into service and general health status, which could not be investigated in these data sets.

(d) Studies of Women

The only studies of phenoxy herbicides which have included women exposed directly, have been general population studies in Vietnam (Cutting et al, 1970; Kunstader, 1984; Sterling and Arundel, 1986) in agricultural areas exposed to relatively high levels such as Arkansas (Nelson et al, 1979) and Kansas (Hoffman et al, 1986), New Zealand (Hanify et al, 1981), Hungary (Thomas and Czeizel, 1982) and other occupational groups (Honchar, 1982; Axelson et al, 1974; Hardell, 1977, 1979; Hardell et al, 1981; Huff et al, 1980) and from industrial accidents such as in Seveso, Italy (Reggiani, 1979; Donna et al, 1984). All of these studies exhibit major methodological problems which render findings doubtful and/or report no adverse reproductive outcomes, as discussed above. As noted above for the Vietnam studies, heavy maternal exposure may be necessary to produce measureable adverse reproductive effects. Donna et al (1984) reported an isolated case/control study which estimates a four-fold risk of ovarian cancer in exposed Seveso women, although numbers are barely sufficient (only 60 cases) and exposure is crudely measured. This finding has not been replicated.

Other reproductive outcomes such as infertility (in the woman) and menstrual disorders have not been considered as outcomes in any study reviewed. These are outcomes indicating ovarian or hormonal dysfunction which may result from toxic exposures (Silbergeld and Mattison, 1986). Recent human studies indicate that ovaries are sensitive to toxic exposures such as cigarette smoking and that this sensitivity can be manifest in delayed fertility (Baird et al, 1985; Olsen et al, 1983), menstrual irregularity (Hammond, 1961) and early menopause (McKinlay, 1985; Baron, 1984). These findings are corroborated by animal studies (Mattison, 1983).

4.2 INSECTICIDES

There have been no direct studies of the impact of insecticides either applied directly to the skin or clothing (dimethyl phthalate, dibutyl phthalate) or sprayed (primarily malathion) to reduce exposure to mite-born and mosquito-born diseases such as malaria and scrub-typhus. The methodologically sound Vietnam veteran experience studies which compare Vietnam veterans with other groups, irrespective of chemical exposures (Donovan et al, 1983; Erickson et al, 1984, for example - See Table 4), by including all chemical exposures, provided some indirect evidence of no adverse reproductive outcome from chemicals other than dioxin.

It is important to note that Hoar et al (1986) in their study of agricultural exposure found no independent effect of insecticides. Most studies - including those of Vietnam veterans - are unable to separate out the effects of insecticides and herbicides.

4.3 SUMMARY

To date, the only methodologically sound studies of dioxin exposure (Donovan, 1983, Lathrop et al, 1984; Erickson et al, 1984; Smith et al, 1982a,b) have not shown any significant associations between dioxin exposure and adverse reproductive outcomes, including spontaneous abortion, sterility and congenital defects. The highly exposed Ranch Hand personnel have shown small, statistically insignificant but consistent increases in a majority of adverse reproductive outcomes which are suggestive of a toxic effect. The Vietnam veteran cohorts are still too young for adequate observation of potential cancer outcomes and results to date are conflicting (for example, Kogan and Clapp, 1985; Greenwald et al, 1984), primarily because of small numbers of cases. All other studies report small relative risks of adverse health outcomes including soft-tissue sarcomas (generally under 1.5 in magnitude), most of which can be explained by methodological problems such as those discussed above or confounding factors which were inadequately controlled in comparisons.

It is plausible that relatively low levels of toxic exposure in women will produce measurable changes in fertility or menstrual function but not necessarily in fetal loss rates or rates of congenital malformation. This is in contrast to the lack of a toxic effect on sperm produced by the relatively high levels of exposure in the "Ranch Hand" personnel (Lathrop et al, 1984). Other potential health outcomes from dioxin and other insecticide exposure are more problematic, including rare soft-tissue sarcomas, and possible increases in heart disease. As most of the veteran cohort will be under 50 years of age at the time of the planned VA study, the chances of observing sufficient cases of these diseases to make any valid estimates of association are small. A potentially important outcome to be considered in any future study of depression of immune function, which may result from relatively low, long term exposures to TCDD.

TABLE 2. VIETNAM DIOXIN EXPOSURE STUDIES
A. MILITARY

STUDY	REFERENCES	DESIGN	POPULATION & SAMPLE SIZE	EXPOSURE MEASURE	OUTCOMES	FINDINGS	EVALUATION
RANCH HAND II STUDY	USAF (1983) Lathrop (1984)	Retrospective Matched Cohorts (1:5) Matching Variables: job, race, age	Surviving Veterans of Period 1962-1971 1269 (Operation Ranch Hand) Matched on other USAF Viet. Vets	Severe (highest) Dioxin exposure vs. minimal exposure (not measured)	All mortality (100 deaths) Cause-specific mortality Fertility Fetal loss Birth Defects (last 3. self-report)	Healthy worker effect Generally lower mortality in all veterans. Ranch Hands more fertile. No diffs. in fetal loss, birth defects.	3 Cohort still too young for some endpoints. Some bias in self-report.
AUSTRALIAN VETERANS BIRTH DEFECTS STUDY	Donovan et al (1983)	Case/Control Matched 1:1 Matching Variables: hospital, maternal age, YOB, payment method.	Cases: 8517 Infants born with anomalies in NSW, Vict & ACT 1966-1979 incl. with identified fathers Controls: infants matched with fathers identified	Fathers Vietnam Veterans Non Vietnam Vets 1962-72	Abnormalities ICD-9 codes 553,740-759	No difference	3 No bias in observat 90% power to detect RR = 1.5 Only included defec detected at birth.
CDC BIRTH DEFECTS STUDY	Erickson et al (1984)	Case/Control 1:1 Matched Matching Variables: Race, YOB, hospital	Cases: 7133 births 1968-80 Atlanta, GA	Fathers Vietnam and Non Vietnam Vets 1962-72	Abnormalities ICD-8 codes (not given) first year of life	No consistent differences.	2 Used 2 Interviews to minimize bias Low reponse rates: 70% mothers, 56% fathers 100% Power to detec
MINNESOTA VETERANS STUDY	Korgaski & Leon (1983)	Experiment	100 subjects from free Agent Orange Screening at VA Hospital All Vietnam Veterans (male)	Two Measures for Dioxins (a) Objective - using HERBS tapes. (b) Self-rated.	Psychological and medical problems subsequent to exposure.	Psychological and psychomatic symptoms related to self-rated but not objective exposure measure.	2 Sample limited Problems of inaccuracies in "objective" measure of exposure.
NEW YORK VETERANS STUDY	Greenwald et al (1984)	Case/Control 1:1 Matched Matching Variables: Age, residence	Cases: 281 (130 dead) from N.Y. Cancer Registry ICD-9 code 171. Controls (a) 281 live from Registry of N.Y. files. (b) 130 deceased controls from N.Y. Death Certs. - no cancer deaths. All were males.	Vietnam Service cases = 10 controls (a) = 18 controls (b) = 9	Soft Tissue sarcoma (ICD-9 code 171) + histological typing on subset.	No Signficiant Difference	2 Insufficient power to detect Otherwise careful study.
MASSACHUSETTS VETERANS STUDY	Kogan and Clapp (1985)	Cohort Study Not matched. Viet Veterans Non-Viet Veterans Civilians.	White males only. All deaths in Massachusetts 1972-83 incl. 840 Vietnam Veteran deaths.	Veteran Status determined from benefits claimed.	Cause-specific deaths. (ICD-9 codes)	Significant Diff. for ICD-9 code 171 compared to both groups.	2 Soft-tissue Sarcomas (9 in Viet Vets) Not verified.

TABLE 1. VIETNAM DIOXIN EXPOSURE STUDIES

A. MILITARY (continued)

STUDY	REFERENCES	DESIGN	POPULATION & SAMPLE SIZE	EXPOSURE MEASURE	OUTCOMES	FINDINGS	EVALUATION
KANSAS STUDY	Hoar et al (1986)	Case/Control 1:3 match on age and vital status	Cases: 139 STS, 132 HD and 172 NHL from population based cancer registry Controls: 1005 white men from the general population	Self-report Survey of pesticide suppliers	Soft tissue sarcoma Hodgkin's disease Non-hodgkin's lymphoma	Increased risk of non-Hodgkin's lymphoma among exposed. No association for other outcomes.	3 Careful validation of self-reported data. Separated effects of insecticides and herbicides.
GRAY SUMMIT, MISSOURI STUDY	Hoffman et al (1986)	Cohort (retrospective)	Residents of the Quail Run Mobile Home Park (N = 154) and residents of a similar park not exposed (N=155)	Soil samples Dust samples from mobile home interiors	Abnormal cellular immune function Liver damage	Exposure associated with depressed cell-mediated immunity However, no excess of clinical illness. Subclinical alterations in liver functions among exposed.	2 Self-selected sample, otherwise well done. Analysis completed without knowledge of exposure. Adjustments in analysis.

B. ACCIDENTAL EXPOSURE

SEVESO ITALY, 1976	Donatelli et al (1981) Marni et al (1982) Tognoni and Bonaccorsi (1982) Bruzzi (1983a,b) Reggiani (1983) Mocarelli et al (1986)	Cohort (retrospective)	Plant employees & families and Seveso residents (varying numbers)	Soil samples Plant records Wind direction etc.	Chloracne Fetal loss Birth defects Cancers Liver damage	Short term increase in Chloracne. No clear association for other outcomes.	1 Lack of pre-accident records of known quality and political climate post-accident render all data questionable except perhaps choracne cases.
NITRO, WEST VA., 1964	Cook et al (1980) Zack and Suskind (1980) Suskind and Hertzberg (1984) Hay (1986)	Cohort (retrospective)	Plant employees (varying numbers)	High/low exposure areas Plant records	Chloracne-like lesions Mortality Cardiovascular disease Renal damage CNS problems	Diff. in rates of skin lesions, not in other outcomes.	1 Probable healthy worker effect. Small number of deaths. Documentation inadequate to validate exposure.

TABLE 3. NON-MILITARY EXPOSURE STUDIES

A. INDUSTRIAL

STUDY	REFERENCES	DESIGN	POPULATION & SAMPLE SIZE	EXPOSURE MEASURE	OUTCOMES	FINDINGS	EVALUATION
NEW ZEALAND APPLICATOR STUDY	Smith et al (1982) Matheson et al (1981)	Cohort (retrospective)	Agricultural Sprayers (registered) and other agricultural workers. Total Sample: 989 Period: 1969-80	Spraying year of pregnancy or prior year	Fetal loss Congenital defects	No difference	2 Excellent response rates (89% and 83%) Potential for reporting bias.
NEW ZEALAND CANCER STUDY	Smith et al (1984)	Case/Control 1:1 Matching Matching variables: age, year of registration	Cancer Registry Cases (95% coverage of NZ) Male only. 1955-1979 (212 Ca. cases).	Exposure to phenoxy herbicides in industry.	Soft tissue sarcoma (ICD-9 code 171) + histological confirmation.	No difference.	2 Design minimizes recall bias and sample size adequate. Problems with ascertaining exposure to herbicides.
HUNGARIAN STUDY	Thomas (1980) Thomas and Czeizel (1982)	Registry Study	Congenital malformation registry for Hungary 1968-1977 Census data.	Increased use of phenoxy herbicides in agriculture.	Congenital malformation rates by year.	No association.	3 Well-documented registry and national statistics.
NEW ZEALAND ECOLOGICAL STUDY	Hanify et al (1981)	Ecological descriptive study.	Birth defects at area hospitals 1959-60 & 1972-76	Use of time period 1972-76 as proxy for heavy spraying.	Malformations at birth.	No consistent association.	2 Problem with exposure measure.
DOW CHEMICAL COMPANY	Townsend et al (1982) Cook and Bodner (1983)	Cohort (retrospective) Matched 1:1 Matching variable: date of hire.	Male employees of Dow 1939-1975 (370 exposed at least one month + 345 matched controls Response rate 63%,62%	Exposure to phenoxy herbicides from company records.	Fetal loss Malformations.	No differences.	2 Well done but self-reported malformations and low response rates.
DANISH STUDY	Lynge (1985)	Cohort (retrospective)	Pension contributors from manufacturers of phenoxy herbicides linked with National Cancer Registry. (n=4563, male & female)	Exposure to herbicides by deparment.	Cancer - all types.	No consistent differences.	2 Problems in determining exposure, but large numbers well analyzed.
ITALIAN STUDY	Donna et al (1984)	Case/Control Matched 1:1 - 1:4 Matching Variables: Year of diagnosis, residence.	Cases: 60 ovarian tumors 1974-1980, one clinic source. Controls: 127 other tumors Same source	Exposure - self-reported use herbicides or farmer after 1960	Diagnosis of Cancer	RR = 4.4	2 Design minimizes bias in reporting. Exposure measure careful but still prob. Adj. in analysis. Numbers barely adequate

TABLE 3. NON-MILITARY EXPOSURE STUDIES

A. INDUSTRIAL (continued)

STUDY	REFERENCES	DESIGN	POPULATION & SAMPLE SIZE	EXPOSURE MEASURE	OUTCOMES	FINDINGS	EVALUATION
SWEDISH STUDIES	Hardell (1981a,1981b) Hardell et al (1982) Hardell and Bengtsson (1983)	(a) Case/control 1:1 matching Matching variables: age, residence	(a) Cases: specific cancers, referred to Oncology Dept. or Swedish Cancer Registry (males only). Controls: same source-Oncology Dept./ Registry	(a) Exposure to herbicides by occupation.	(a) Lymphoma, STS, Colon Cancer, Hodgkin's Disease, etc.	(a) RR less than 3.5 for agriculture and forestry workers.	(a) 2 Measure of exposure to herbicide self-report only. Not clear on adjustments or selection of controls.
	Wiklund and Holm (1986)	(b) Cohort (retrospective)	(b) 354,620 agriculture and forestry workers potentially exposed to phenoxy herbicides. 1,725,845 men employed in other industries.	(b) 1960 National Census "Estimates" of herbicide use in occupational categories.	(b) Soft tissue sarcoma	(b) No significant difference	(b) 2 Indirectly estimate relative exposure from occupational records. No self-reported data.
ARKANSAS STUDY	Nelson et al (1979)	Ecological Descriptive Study.	Countries categorized according to crop. Birth certificates 1943-74 screened for facial clefts + records of Rehab Svcs. (n=1,201)	Countries categorized by crop as surrogate for herbicide spraying.	Facial clefts	No consistent association	2 Carefully done. Well analyzed. Potential biases in case finding in records.

TABLE 3. NON-MILITARY EXPOSURE STUDIES

B. ENVIRONMENTAL

STUDY	REFERENCES	DESIGN	POPULATION & SAMPLE SIZE	EXPOSURE MEASURE	OUTCOMES	FINDINGS	EVALUATION
TWO-COMMUNITY STUDY	Nguyen Thi Ngoc Phuong & Le Thi Diem Huong (1983)	Cohort, Retrospective	Village + 10th district of Ho Chi Minh City All women and all pregnancies. 1249 women in village 1126 women in 10th Dst.	Herbicide exposure from heavy spraying (village)	Fetal loss Congenital abnormalities Hyatidiform mole	Higher risk in village for all 3 outcomes	1 Sample selection? No adjustment for maternal diffs. Potential observer and respondent bias.
FOUR VILLAGE STUDY	Cung Binh Trung and Nguyen Tran Chien (1983)	Cohort, Retrospective	Families in all villages. (Total # pregnancies/ village, 436-824)	Heavy spraying in 3 villages not in one.	Fetal loss Birth defects (external)	Before/After diffs. in rates in exposed villages only.	1 Incorrect analysis No adjustments for maternal diffs. Respondent recall and interviewer bias Sample selection? Numbers small.
HOSPITAL STUDY	Le Diem Huong & Nguyen Thi Ngoc Phuong (1983)	Cohort (and Case/Control)	(a) All births at one hospital in Ho Chi Minn city, 1952-1981, minus 3 yrs. (b) Cases of Hydatidiform moles. 1982 & age, admission matched controls.	(a) Year of birth. (b) Exposure to Herbicide spraying.	(a) Rate of Hydatidiform mole. (b) Presence of Hydatidiform moles	(a) Increase by Year. (b) Increased Risk (RR = 12)	1 No adjustments for maternal diffs. Incorrect analysis. Unavailability of complete records. Problem of referrals to this main hospital. Bias in recall.
NORTH VIETNAM STUDY I	Nguyen Can et al (1983)	Cohort (retrospective)	Women in 3 North Vietnam districts. 29,041 married to possibly exposed men. 11,023 married to unexposed men.	Military service in South Vietnam.	Still births external birth defects. Fetal loss.	38% increase in major congenital defects. 19% increase in fetal loss.	1 No adjustments. Incorrect analysis. Potential observer and recall bias. Not clear on sample selection.
NORTH VIETNAM STUDY II	Ton Duc Lang et al (1983)	Case/Control matched on age	Cases: 21 liver cancers Controls: 42 stomach cancers, ulcers. Admitted to one hospital, 1982.	Exposure to Herbicides.	Liver Cancer	Risk of liver cancer increase (RR > 5.0)	1 Numbers too small and no adjustment. Use of cancer control questionable
HOSPITAL RECORD STUDY I	Kunstadter (1982)	Cohort (retrospective)	Hospital case records in Ho Chi Minh City for 4 hospitals, Periods of study not clear.	Maternal Herbicide exposure (using HERBS tapes)	Congenital Abnormalities Sex ratio	No consistent results.	1 Too many potential problems with the hospital records.
HOSPITAL RECORD STUDY II	Cutting et al (1970)	Cohort (retrospective)	22 Public hospitals in Sth. Vietnam. Records of deliveries 1960-1969 incl. 470,200 live births 15,812 still births ,2840 Hydatidiform moles.	Year of record as surrogate for herbicide spraying 1960-65 (pre-herbicide)	Still births Hydatidiform moles. Malformations	No difference.	2 Careful study. Limitations in data well documented.

* An important source is the excellent review by Sterling and Arundel, 1986.

TABLE 4. VIETNAM EXPERIENCE STUDIES
A. CASE CONTROL

STUDY	REFERENCES	DESIGN	POPULATION & SAMPLE SIZE	EXPOSURE MEASURE	OUTCOMES	FINDINGS	EVALUATION
AUSTRALIAN VETERAN BIRTH DEFECTS STUDY	Donovan et al (1983)	Case/Control Matched 1:1 Matching variables: hospital, maternal age, YOB, payment method.	Cases: 8517 infants born with anomalies in NSW, Vict & ACT 1966-1979 incl. with identified fathers. Controls: infants matched with fathers identified.	Fathers Vietnam veterans Non-Vietnam vets 1962-72	Abnormalities ICD-9 codes 553,740-759	No difference	3 No bias in observation 90% power to detect RR=1.5 Only included defects detected at birth.
CDC BIRTH DEFECTS STUDY	Erickson et al (1984)	Case/Control 1:1 Matched Matching Variables: race, YOB, hospital.	Cases: 7133 births 1968-80 Atlanta, GA	Fathers Vietnam and Non-Vietnam Vets 1962-72	Abnormalities ICD-8 codes (not given) first year of life	No consistent differences	2 Used 2 interviews to minimize bias Low response rates: 70% mothers, 56% fathers
NEW YORK VETERANS STUDY	Greenwald et al (1984)	Case/Control 1:1 Matched Matching variables: age, residence.	Cases: 281 (130 dead) from N.Y. Cancer Registry ICD-9 code 171. Controls (a) 281 live from Registry of M.V. files. (b) 130 deceased controls from N.Y. Death Certs. - no cancer deaths. All were males.	Vietnam service cases = 10 controls (a) = 18 controls (b) = 9	Soft-tissue sarcoma (ICD-9 code 171) + histological typing on subset.	No significant difference	2 Insufficient power to detect Otherwise careful study
VETERANS ADMINISTRATION STUDY	Kang et al (1986)	Case/Control	Cases: 234 Vietnam-era veterans with STS. Controls: 13,496 Vietnam veterans from the same era as the cases, selected from all Vietnam-era veteran patients.	Vietnam service	Soft tissue sarcoma (ICD 171) and pathology report review	No significant difference	3 Well done Records located and abstracted for all cases and 90% of controls.

TABLE 4. VIETNAM EXPERIENCE STUDIES
B. RETROSPECTIVE COHORT STUDIES

STUDY	REFERENCES	DESIGN	POPULATION & SAMPLE SIZE	EXPOSURE MEASURE	OUTCOMES	FINDINGS	EVALUATION
WEST VIRGINIA STUDY	Holmes et al (1986)	Cohort study Not matched Vietnam veterans Non-veterans	All deaths in West Virginia 1968-83	Vietnam service	Mortality	Excess mortality among veterans	2 Self-selected sample Small numbers for some cause specific mortality rates.
MASSACHUSETTS STUDY	Kogan and Clapp (1985)	Cohort study Not matched. Vietnam veterans Non-Vietnam veterans Civilians	While males only. All deaths in Massachusetts 1972-83 incl. 840 Vietnam veteran deaths.	Veteran status determined from benefits claimed	Cause-specific deaths. (ICD-9 codes)	Significant difference for ICD-9 code 171 compared to both groups	3 Soft-tissue sarcomas (9 in Viet Vets) verified by pathology.
CDC STUDY	(1987)	Cohort	9,234 in country Vietnam veterans 8,989 Vietnam-era veterans. Selection from National Personnel Records Center	Vietnam service	Mortality	Excess mortality among Vietnam veterans, mainly in first five years after discharge.	2 Validation of death certificate data by physician review of pertinent medical and legal documents. Insufficient numbers for some cause specific mortality rates.
WISCONSIN STUDY	Anderson et al (1986)	Cohort study Not matched Vietnam veterans Other veterans Non-veterans	Males and white females. All deaths in Wisconsin in 1960-1983	Vietnam service	Mortality	Excess mortality among Vietnam veterans and all other veterans.	2 Small numbers for some cause specific mortality rates.

5. NURSING: OCCUPATIONAL RISKS

As previously indicated, the majority of female personnel in Southeast Asia served as nurses. Therefore, in order to more comprehensively assess the impact of Vietnam duty on health and reproductive outcomes, occupational risks associated with the nursing profession were explored. In the context of an epidemiological study, these risks fall into three major categories: exposures, outcomes, and confounders. The primary exposure relevant to this population was trace anesthetic gases in operating room environments. Other potential exposures such as antineoplastic drugs or radiation are acknowledged but were not included in this review since the likelihood of this type of exposure during a Vietnam tour was low. The major outcome with implications for this population is stress and/or mental disorders, assumed associated with work conditions or type of nursing practice. Stress may also be considered a confounder in the analysis of certain research questions, e.g. in relation to reproductive outcomes. Finally the major confounders to be considered are smoking and substance abuse. A representative sample of recent literature in each category will be critically reviewed for both content and methodology.

5.1 EXPOSURE: TRACE ANESTHETIC GASES

5.1.1 Clinical Studies

In view of the fact that approximately 75 percent of female personnel serving in Vietnam were nurses, teratogenic risks associated with occupational exposure to chemicals must be considered. A likely frequent exposure in both field and base hospitals during that era was to volatile anesthetics. Waste anesthetic gases are widely distributed throughout the operating room (Cohen, et. al., 1975). It is assumed that neither scavenging apparatus nor air conditioning were used widely in field hospitals to remove waste gas in operating rooms. Further, while air conditioning may have been more prevalent in large base hospitals, scavenging equipment was not routinely used in the 1960's or early 1970's (Cohen et. al., 1974). A review of the literature regarding possible harmful effects of trace concentrations of anesthetic gases on operating room personnel is inconclusive, resulting in part from methodological flaws. Three of the more frequently cited studies as well as two major reviews will be discussed to illustrate the problems and issues.

A survey (Cohen et al, 1971) to evaluate the possible relationship between spontaneous miscarriage and exposure to the operating room was carried out by personal interview

with operating room (n=67) and general duty nurses (n=92 between the ages of 25-50 years. Data from a second study of female anesthetists (n=50) and physicians in other specialties (n=81) in the same age group were also reported for comparison. Data from this sample were collected via mailed questionnaires, however. The investigators report that both exposed groups had a substantially higher frequency of spontaneous abortions (29.7% and 37.8%) when compared to the controls (8.8% and 10.3%). Marginal significance (p=0.045) was reported. Further, it was noted that spontaneous abortions occurred earlier in the pregnancies of exposed women than in controls (i.e., eighth vs. tenth week of gestation). Several methodological problems raise skepticism about these findings. First, the small sample sizes makes the significance of the finding suspect (Ferstandig, 1978). Secondly, data consisted only of self-reports. Rushton (1976) points out that none of the aborted pregnancies were confirmed by a positive pregnancy and/or examination of the products of conceptus. Third, a non-specific measure of exposure, i.e. "practiced anesthesia any time during pregnancy," was utilized, preventing any analysis of a dose-response relationship. Finally, the retrospective design, in addition to self-report, raises the possibility of recall problems (e.g., with time of spontaneous abortion) which may influence the validity of the data.

A British epidemological study analyzed frequency of congenital abnormality, spontaneous abortion, and involuntary fertility in 563 married female anesthetists and 828 female physician controls (Knill-Jones et al, 1972). Three groups were analyzed: anesthetists at work, and anesthetists not at work and other physicians as two control groups. The study reports that anesthetists working during pregnancy had a significantly ($p < 0.02$) higher frequency of congenital abnormality (6.5%) than those not at work (2.5%) but not significantly different from the control group of other doctors (4.9%). The authors neglect to discuss the implications of the significantly higher mean age ($p < .001$) in this latter control group for this finding. In addition, spontaneous abortion was significantly higher (p less than .025) in the working anesthetists (18.2%) than in the control physician group (14.7%), but not when compared to the anesthetists not at work (13.7%). As pointed out by Ferstandig (1978), the lack of congruence between the two control groups as well as the reversal of effects between the control groups "mitigates against any logical conclusion in this study." Finally, the study also reports that 12% of the anesthetists were infertile for unknown causes, twice as many as the controls ($p < .001$). However, how this was determined was not described. In addition, the small numbers involved make any relationship between exposure to anesthetics and fertility questionable (Ferstandig, 1978). Overall, this study also suffers from limitations of the

previous study, i.e., a retrospective design, with no objective estimate of exposure, and reliance on self-reported data.

The final epidemological study (Cohen et al, 1974) to be discussed is perhaps the most comprehensive study on this issue, yet is still characterized by methodological limitations. A mailed survey was conducted with 49,585 operating room personnel belonging to three professional societies and 23,911 medical personnel in two other societies who served as an unexposed comparison group. Comparisons were made to detect differences in occurrence rates of five major characteristics: spontaneous abortion,congenital abnormality, cancer, hepatic disease, and renal disease. Rates were standardized by the direct method adjusted for both age and smoking in the case of spontaneous abortion and congenital abnormality rates, and age alone in the case of disease rates. Exposure estimates were defined as work in an operating room during the calendar year prior to the event for both sexes, as well as exposure during the first trimester of pregnancy for women. Data regarding use of scavenging apparatus in the operating room were also collected. The investigators report that female members in the operating room-exposed group were subject to increased risks of spontaneous abortion, congenital abnormalities in their children, cancer, and hepatic and renal disease. The increased risk of congenital abnormalities was also present among the nonexposed wives of male operating room personnel. An increase in cancer and renal disease was not found among the exposed males, while an increased incidence of hepatic disease was found. With the exception of leukemia and lymphoma, there was no evidence of a specific type or location of cancer.

While the report of this study appears convincing, several authors have raised sharp criticism which call the results into question. Ferstandig (1978) and Mennuti (1980) point out the inconsistencies of the data both within and across groups in this study, e.g., that operating room workers least exposed to anesthetic gases had the highest rate of spontaneous abortion; or that there is no statistical significance in differences in spontaneous abortion rates for female anesthesiologists exposed or not exposed to operating rooms. These inconsistencies and others weaken the argument for deleterious health and reproductive outcomes of operating room/anesthesia exposure. A further flaw in the study is the use of pediatricians as a control cohort. According to Ferstandig (1978), this group has the lowest mortality rate of any medical specialty which biases comparative statistics. The study also shares the limitations of self-reported data collected retrospectively.

None of the three above studies has fully tested the hypothesis that a cause-effect relationship exists between

exposure to trace concentrations of anesthetics and possible adverse health effects. While the nationwide survey by Cohen et al, (1974) considered age and smoking as confounders, the other studies did not, notably the study by Knill-Jones et al, (1972) where a statistically significant difference in mean age between exposed and non-exposed groups was reported. To detect a cause-effect relationship, other possibly significant causes, such as the stress of operating room work must be ruled out (Ferstandig, 1978). Similarly, differences in the characteristics of study samples (e.g., social class, health and reproductive history, substance abuse, stress levels) must be included in the analysis. A recent, excellent review of these and other studies (Buring et al, 1985) included a pooled analysis. The conclusion was that, although their findings were suggestive, studies to date have been beset by major, compromising methodological problems which devalue their findings.

5.1.2 Animal and Tissue Studies

The comprehensive review of the toxicity of anesthetics by Ferstandig (1978) was used to review animal and tissue studies. From approximately 46 tissue studies and 40 animal studies, Ferstandig concluded that only high levels of anesthetics and long times of exposure cause significant histotoxicity in laboratory studies on cells and animals. Trace concentrations, as typically found in operating room environments, produce none of these effects; "therefore, studies using high concentrations have no value in predicting the effects of trace concentrations" (p.341). Further, laboratory studies provide no evidence that commonly used anesthetics produce cancer in animals.

5.1.3 Summary

In conclusion, despite some superficially convincing data, the epidemological studies to date on anesthetics and adverse health and reproductive outcomes are methodologically flawed and inconclusive. A properly designed study would include the following elements: a prospective design; random sample of adequate size; an appropriately matched control group; field methods, (including medical record abstraction) to ensure collection of valid data; ascertainment of a more specific exposure estimate than merely operating room exposure; and consideration of potential confounders in the analysis (Buring et al, 1985). A study of women Vietnam veterans, by its very nature, cannot incorporate all of these methodological elements. For example, a prospective design is not possible, nor is precise estimation of exposure likely. It is probable that scavenging systems on the Navy hospital ships were effective. The effectiveness of systems in the land-based hospitals - especially the mobile units are likely to have been very variable. No good measurement

of exposure is likely to be obtainable. However, attention can be given to choice of an appropriate control group, adequate sample sizes and response rates, appropriate field methods and data collection protocols, and comprehensive analysis of potential confounders.

5.2 STRESS AND MENTAL DISORDER

In a review article regarding stress among nurses (Marshall, 1980), several sources of stress were identified: specific nursing tasks; workload/overload; uncertainty and concerns about responsibility (especially in emergency room duty); relationships with patients, families, or other professionals; dealing with death and dying; role conflicts; the need to fulfill others' expectations (including sanctions against showing stress); and the organizational structure in which nursing care is provided. In Marshall's model, only two sources of satisfaction which balance these pressures are identified: a feeling of having helped patients and receiving positive feedback from patients. If considered in the context of Vietnam duty, the potential for high levels of pressure and low levels of satisfaction are obvious. Most nursing duty took place in field hospitals where the work environment was less than ideal and the wounded, mutilated, and often near-dead were received constantly. Nurses were continually faced with uncertainty, death and dying, work overload, and unpleasant nursing tasks. Further, these field hospitals served as centers for triage and emergency care. Those soldiers who did not die typically were transferred to larger base hospitals for further treatment and recovery. Therefore, the satisfaction of seeing a patient recover or receiving feedback was unlikely sufficient to balance the pressures. It seems safe to assume that nurses in Vietnam experienced stress with little outlet for therapeutic expression of that stress.

The literature on stress among nurses does not include any study of Vietnam duty. The majority of available work is descriptive or anecdotal, often in conjunction with recommended strategies for dealing with stress. Most of the limited research has been conducted by nurses.

One of the better studies (Cronin-Stubbs and Schaffner, 1985) surveyed a random sample of 296 female nurses (response rate not stated) to explore the relationship of stress, social support and burnout in diverse groups of staff nurses. Using valid and reliable measures, data were collected by mail or in-person. The rationale and circumstances for the two field modes was not described, but the authors state that "standardized procedures" were used. In a stepwise multiple regression analysis, 35% of the variance in burnout (measured with the Staff Burnout Scale for Health Professionals) was explained by the following factors: intensity of occupational stress, negative and

positive life stresses, low social support, and work setting. Regarding the last variable, critical care and medical nurses experienced more frequent and intense occupational stress than psychiatric and operating room nurses, yet all four groups experienced similar amounts of burnout. This apparent inconsistency was not discussed. Further findings indicated that burnout was positively and significantly correlated with absenteeism, tardiness, physical illness (undefined), use of prescription "calming" drugs, and job searches undertaken. Smoking and alcohol use were not mentioned. Clearly these data suggest that occupational stress and burnout are related to health outcomes and other exposures/confounders such as drug use.

Another study (Gray-Toft and Anderson, 1981) of 122 nurses on five hospital units (medicine, surgery, cardiovascular surgery, oncology, and hospice) of a midwestern hospital found somewhat consistent results as to sources of stress: workload, dying patients, and inadequate preparation to meet the emotional needs of patients and their families. However, unlike the previous study, the investigators found that these major sources of stress were similar, regardless of unit or type of care. Further, path analysis indicated that the nurse's level of trait anxiety along-with level of training were significant predictors of stress. Sociodemographic variables (race, age, marital status, religious commitment, and nursing experience) were not found to be predictors of stress. As hypothesized, stress was found to have significant effects on job satisfaction and turnover.

A third recent study on perceived job stress (Norbeck, 1985) is of interest because of its focus on critical care nursing, which along with emergency room nursing most closely approximates Vietnam nursing duty. However, unlike the previous two studies, a comparison group of nurses in other settings was not available. Data were gathered via mailed questionnaires to examine the relationships between job stress and both job satisfaction and psychological symptoms. Established and tested scales were employed for all major study variables. After controlling for work experience and shift (both correlated with job satisfaction), perceived job stress accounts for 6% of the variance in job satisfaction and 10% of the variance in psychological symptoms. Further, factors associated with perceived stress are consistent with other study findings: number of rapid decisions required, cardiac arrest, death of a patient, amount of knowledge needed, and workload. Clearly these findings have implications for any study of stress and health outcomes of nurses serving in Vietnam.

While increasing attention in the professional literature has been given to burnout of nurses, little focus has been aimed at the analysis of other emotional or mental

disorders. While a recent study by VanServellen and colleagues (1985) is limited methodologically, the findings do suggest that staff nurses may suffer higher rates of affective disorders in proportion to the general female population. A convenience sample of 64 nurses was administered six standardized survey instruments and an expert-administered diagnostic interview for depression. The incidence of clinical depression was significantly higher than that found in the female population at large. Further, major depressive illness was more prevalent than dysthymic disorder. The investigators point out the importance of recognizing and separating out clinical disorders from the more general burnout syndrome. Although the small convenience sample limits generalizability, and no attempt to control for major sociodemographic factors or life situation was reported, the study does emphasize the need for valid and reliable data on the prevalence of psychiatric disorder in the profession. This need is further underscored by an analysis of death certificate data from 1963-1977 (Katz, 1983) showing that when compared to a control group of other female workers, nurses have an elevated risk of death from suicide.

In summary, the literature on occupational stress and related factors is limited and characterized by the following methodological limitations: primarily descriptive designs, small and non-random samples, and lack of control or comparison groups. However, the few studies reviewed here show general consistency regarding sources of stress, almost all of which are highly relevant for a study of a nursing population in Vietnam. Further, the suggested higher prevalence of depression and suicide among nurses warrants careful analysis in any study of nurses' Vietnam duty to determine if any evidence of stress or mental disorder can be attributed to the Vietnam experience itself or is related to the occupational stress of nursing in general. Selection of an appropriate control group, perhaps nurses in a critical care setting outside of Southeast Asia, will be critical to such an analysis.

5.3 SMOKING

As discussed further in the next section, smoking is a confounder when investigating both health outcomes such as lung cancer and cardiovascular disease and reproductive outcomes, including birth weight and gestation. The literature was reviewed regarding smoking habits of nurses to determine if they differed from the female population at large.

Among health professionals, smoking rates consistently have been reported higher for nurses than for physicians and dentists. While the actual rates have differed, the data indicate that a sizeable proportion of nurses smoke. For

example, the American Cancer Society's prospective Cancer Prevention Study I found that, in 1959, 36.3% of female nurses were smokers and by 1972, 25.9% were still smoking (Garfinkel and Stillman, 1986). In an analysis of the 1975 Public Health Service Survey, Stillman and Stillman (1981) reported that 32.1% of female health professionals were current smokers. This figure, however, may include professionals other than nurses. A 1981 study of Connecticut nurses showed that 25.5% smoked (Morra and Knobf, 1983), while 28.3% were smokers in a western New York sample (Wagner, 1985). In a sample of 601 nurses in North Carolina, 31.9% were smokers (Dalton and Swenson, 1983), whereas in Michigan, only 19.1% of a sample of 448 hospital nurses reported smoking (Tagliacozzo et. al., 1982), suggesting possible regional differences in smoking rates.

While these data clearly indicate that a large proportion of nurses smoke, comparison with smoking rates of the female population in general reveal that nurses have higher smoking rates. The more recent Cancer Prevention Study II, started in 1982, reports that even with a decline of 2.3% in nurses' smoking rate between 1972 and 1982, their current rate of 23.6% exceeds the rate of 21.5% for all women. Furthermore, important to a study of women in the Vietnam era cohort, the cohort of nurses with the highest smoking rate in CPS II is the 30-39 year age group, which contains a sizeable proportion of the cohort of interest.

Data are limited concerning the characteristics of nurses who smoke or their reasons for smoking. No definitive explanation for differences in smoking patterns between men and women, or nurses and other professionals has been formulated. However, two interesting pieces of data from the western New York study (Wagner, 1985) and the North Carolina study (Dalton and Swenson, 1983) indicate respectively that almost half (43%) began smoking when studying nursing and that the vast majority of smokers were staff nurses.

Occupational stress is frequently offered as a reason for the high smoking rate among nurses (Stillman and Stillman, 1981). Data from the few available studies provide only limited support for this hypothesis. In a mailed survey of 823 randomly selected nurses in Minnesota with a response rate of 82% (Feldman and Richard, 1986), two of the reasons for continued smoking were stress reduction (43%) and a primary means to relax (38%). The investigators did not inquire as to the source(s) of stress to determine if it was occupationally related. However, they did compare the characteristics of the sample with nurses nationally as reported by the American Nurses Association and concluded that the Minnesota sample was representative of nurses nationally. Further, consistent with the New York study by Wagner (1985), the data indicated that over 50% of both current and former smokers started to smoke between the ages

of 17 and 19 years, a period coinciding with the beginning of their nursing education.

A study by Tagliacozzo et al, (1982) examined specifically the relationship between work-related stress and smoking among hospital nurses. Prevalence of smoking in a sample of 448 nurses was low (19.9%) in comparison to other studies. However, this finding may well have been influenced by the low response rate of 49.3% to a mailed questionnaire. Work-related stress was measured by Kahn's Job Tension Index, modified by the investigators to incorporate items specific to nursing. Subscales of this index were developed for analysis of several dimensions of work stress. Data revealed that nurses who smoked had an overall tendency to produce higher stress scores than nonsmoking nurses. More specifically, smoking nurses who were most likely to perceive the physical and emotional demands of the job as stressful were younger, single, had a BSN degree, work 40 or more hours per week, and worked on rotating shifts. The authors caution, however, that their data do not show a cause and effect relationship between work stress and smoking. In fact, for the majority of nurses, smoking was an established habit before starting work. The study does not explore if work-related stress contributes to continued smoking.

In conclusion, therefore, smoking rates for nurses are generally higher than for other health professions despite a recent decline, and further, nurses are more likely than the general female population to smoke. Limited data regarding the tendency to start smoking at an early age and for continued high rates for the 30-39 year old cohort suggest that the cohort of nurses serving in Vietnam was likely to have high smoking rates. This is supported by findings that smoking nurses who perceived their job as stressful were young, single, and worked long hours and/or rotated shifts, a description most apt to fit nurses serving in Vietnam. These data support the inclusion of smoking as an important confounder in a study of women serving in Vietnam.

5.4 CHEMICAL ABUSE

The lack of scientific data regarding chemical dependency among nurses has been repeatedly pointed out (Canfield, 1976; Bissell and Jones, 1981; Caroselli-Karinja and Zboray, 1986) and confirmed by this review. The majority of literature on this issue has been written by the nursing profession and consists of case studies to illustrate the problem (Pierce, 1976; Booth and Gillard, 1981) or descriptions of programs/approaches to deal with the problem (Pierce, 1976; Reed, 1983; Naegle, 1985; Caroselli-Karinja and Zboray, 1986; Penny, 1986).

Concern with professional and legal reprisals, compounded by denial of the problem, is considered to contribute to the difficulty in obtaining reliable data (Bissell and Jones, 1981). Canfield (1976) asserts that any available data are likely to be underestimates of incidence for similar reasons. The few available studies are described here for informational purposes, i.e., to provide some estimates as to the extent of the problem and to describe characteristics of addicted nurses. All of these studies have obvious methodological flaws, openly acknowledged by the authors, but they provide what little data are available.

Chemical addiction includes both alcohol and drugs, prescription and illegal. However, the literature to date focuses only on abuse of alcohol and prescription drugs by health professionals. The extent of use of illegal drugs such as cocaine and marijuana is not mentioned. Canfield (1976) cites 1973 data from the American Medical Association's Council on Mental Health indicating that 15% of known drug addicts are nurses or pharmacists. Several other studies from the late 1960's and early 1970's cited in this work reported on drug use by physicians, pointing up the dearth of data regarding nurses. Bissell and Jones (1981) estimate that roughly 5% of American women are alcoholic so that if nurses are considered at the same risk, then 5% of nurses can be considered alcoholic.

In an attempt to learn more about alcoholism among members, Bissell and Jones (1981) conducted interviews with 407 professionals who were actively involved in Alcoholics Anonymous during the early and mid 1970's. One hundred of this sample were nurses and female. All were abstinent at the time of the study. Data revealed that 35% of the sample abused drugs in addition to alcohol, with barbiturates and amphetamines cited most frequently. The rates for combined chemical abuse were highest for physicians and nurses, in that order, when compared to other professional groups. The sequence of drug use was typically alcohol first, followed by non-narcotics and finally hard narcotics. The major flaw of this work is its nonrepresentative sample but it remains one of the few available studies.

Suggested reasons for chemical abuse by nurses have included accessibility of prescription drugs and alcohol and work stress (Bissell and Jones, 1981; Reed, 1983; Naegle, 1985). Naegle (1985) proposes an interactional rather than causative role in the phenomenon of impaired practice, pointing out that while role strain and job stress pose challenges for the nurses, most nurses do not resort to drug/alcohol abuse as a coping mechanism.

This latter point is consistent with the findings from a study of the characteristics of nurse addicts conducted in

the late 1960's (Poplar, 1969). Among 90 nurse addicts admitted to a federal treatment facility, three basic reasons were found for drug abuse: physical illness, emotional problems too great to handle, and work pressure too demanding emotionally and physically. Psychological testing revealed that nurses used drugs to alleviate pain and escape from reality not for curiosity, desire for pleasure, or nonconformity as was typical for other addicts. Further, drug abuse began later in adulthood and was usually a solitary, not social, activity. Finally, more than other addicts, nurses claimed to be able to work while using drugs.

To summarize, valid and reliable data regarding the extent of alcohol and drug abuse by nurses are unavailable. However, a few case reports and descriptive studies provide evidence that it is a problem, and one which is increasingly recognized of late. Data from more extensive studies on chemical use among the military, as reported elsewhere in this review, would strongly suggest that some nurses serving in Vietnam were likely abusers and may continue to abuse drugs, especially alcohol. A study of woman Vietnam veterans provides an opportunity to collect data for careful consideration of drug and alcohol abuse as a confounder in analysis of health and reproductive outcomes.

5.5 CONCLUSIONS

In reviewing the literature on occupational risks, there are data, admittedly flawed, to suggest that the work of nursing itself may contribute to higher levels of perceived stress, higher rates of smoking, and, possibly, of chemical abuse, as well as exposure to possible toxins, such as volatile anesthetic gases. These factors may exist independently of the Vietnam exposure, but may also be intensified in a sample of Vietnam nurses. Therefore, it will be important to determine how much influence the Vietnam exposure had on these factors above and beyond what might be expected in a nonexposed population of nurses. The implications for a carefully matched control group are clear.

6. CONFOUNDING FACTORS

In observational studies in which the hypothesized exposure or cause cannot be randomized, it becomes particularly important to control for potential confounding factors likely to affect the outcomes(s) or likely to mask an association between exposure and outcome (Cochran, 1972; McKinlay, 1975; Schlesselmann, 1982). In the proposed study of Women Vietnam Veterans, the potential for confounding factors is further complicated because important potential confounding factors for health outcomes such as cancer and heart disease, and abnormal reproductive outcomes may themselves be important health outcomes resulting from exposure to the Vietnam war experience. Some obvious candidates for this category are: use of (licit or illicit) drugs including marijuana and tranquilizers; heavy alcohol use; and smoking. Some evidence is emerging that alcohol use in particular may be increasing among male Vietnam veterans (see the above on Drug Use in Vietnam section)

With respect to other potential confounding factors, it is already well documented that full-time nurses - the major occupational category among women Vietnam veterans - are some of the heaviest cigarette smokers and are prone to increased alcohol and drug use (see section 5 above).

This section, therefore, reviews current knowledge concerning the association of important potential confounders with outcomes of interest to the planned study. The two primary factors included here are cigarette smoking and alcohol use. The potential roles of caffeine, antihistamines, tranquilizers, and marijuana use are also considered. A final section reviews other potential intervening or confounding exposures which must be considered in designing a study of women Vietnam veterans.

6.1 SMOKING

Of all the substances, the use of which is not generally restricted, cigarette smoking is almost certainly the most damaging to human health. It has been well-established as a primary risk factor for lung cancer (Hammend, 1961; Doll and Hill, 1952; Bross, 1968), heart disease (Shurtleff, 1974; Harlik and Feinleib, 1979), other cancers (Hammond, 1961; Levin et al, 1950) and Chronic Obstructive Pulmonary Disease - COPD - (Spinaci et al, 1985). The literature on these associations is considerable and will not be included here, beyond the key references cited above.

The effect of cigarette smoking on the reproductive system is less well understood. The early finding that it results in increased fetal loss and pre-term deliveries as well as lower birth weight (adjusted for gestational age)

has now been well documented. The early seminal work of Yerashalmy, among others on this effect (Yerashalmy, 1964; see also Wainright) has been recently confirmed in Sweden (Cnattingius et al, 1985), Australia (Lumley, 1985), United States (Kleinman and Madans, 1985; Shiono et al,1986), Finland (Pulkkinen, 1985) and France (Schwartz et al 1972). These and similar studies have been typically well designed using large samples with adequate response rates and independent outcome assessment. Potential confounding factors, given the large numbers, have also been adequately controlled in these studies.

Apart from confirming these early associations, recent studies have considerably extended knowledge on the effect of maternal smoking on the fetus. It has been established in several studies that the effect of smoking on fetal outcome is independent of any effect of alcohol (Kline et al, 1981; Stein and Kline, 1983; Lumley, 1985; Shiono et al, 1986; Wright et al, 1984; Berkowitz et al, 1982; Hingson et al, 1982). A recent U.S. study (Kline et al, 1981) demonstrates that spontaneous abortions in smokers are of chromosomally normal fetuses. In other words, smoking is not teratogenic in humans. This is confirmed in an excellent review of recent literature (McIntosh, 1984) which synthesizes results from methodologically sound studies. McIntosh (1984) also identifies an increased risk of uterine bleeding during pregnancy among smokers. Three recent studies have documented increased infant mortality and/or morbidity, excluding neonatal mortality, for maternal smokers in Finland (Rantakallio, 1979), in New Zealand (VandenBerg, 1985) and in Sweden (Stjernfeldt et al, 1986). The last study focussed on an increase in childhood cancers.

The impact of smoking during pregnancy appears to be immediate, with pre-pregnancy quitters showing no differences from non-smokers in fetal outcomes (Pulkkinen, 1985; Schwartz et al, 1972). The presence of a dose-response curve is well established for low birth weight, but there are indications that the dose-response relationship is small for fetal loss (Kline et al, 1981; Shiono et al, 1986).

The association of smoking with other aspects of reproduction is not well understood and the literature is sparse, most of the reports being recent. Two recent studies in very different populations have demonstrated reduced fertility among smoking women. Baird and co-workers (1985) showed a marked increase in time to pregnancy for smokers in a representative sample of pregnant women who had been trying to conceive for less than two years. A similar effect was observed in a large sample of infertility referrals in Denmark who had not conceived in at least 2 years (Olsen et al, 1983). Both studies controlled for confounders and other biases in assessing their findings.

In the well-known U.S. study of smoking effects, Hammond (1961) found an increase among smoking women in irregular menstrual patterns which is consistent with the recent findings on infertility but which has not been confirmed in more recent large studies.

Also consistent with these findings relating to infertility are recent reports of an earlier natural menopause among cigarette smokers (McKinlay, 1985; Baron, 1984; Adena and Gallagher, 1982; Kaufman et al, 1980). These reports, although reporting consistently that the median age at menopause (last menstrual period) is 1.5 - 2.0 years earlier in smokers than in non-smokers, are inconsistent in reporting a dose response and the effect for past smokers. On balance, from the evidence available, there does not appear to be a strong dose response, most of the effect deriving from any cigarette smoking, regardless of how much. This is consistent with similar findings by Baird et al (1985) regarding the impact of smoking on fertility and with the impact of smoking on fetal loss (Kline et al, 1981; Shiono et al, 1986).

Apart from these studies, evidence of the toxic impact of smoking on the reproductive system as a whole has come from animal studies (see for example, Mattison, 1983).

6.2 ALCOHOL

Apart from being classified as a disease itself, heavy alcohol consumption has been related causally to such degenerative health outcomes as cirrhosis of the liver, some cancers and brain disorders, (see NIAAA, 1980 for comprehensive data and review). As with smoking, these associations have been well-established from consistent studies and only key references are provided here.

The potential effect of heavy alcohol consumption on aspects of the reproduction system has not, however, been systematically researched. Animal (primarily rodent) studies (for example Krueger et al, 1982; Van Thiel et al, 1980; Ryback, 1977) have demonstrated that in both males and females, heavy alcohol ingestion produces hypogonadism directly. There is also evidence for an indirect effect on the endocrine system through liver dysfunction (Ryback, 1977). In female rodents exposed to ethanol, fewer estrous cycles are observed (Ryback, 1977; Krueger et al, 1982), and Ryback cites two clinical cases of human amenorrhea apparently caused by heavy alcohol consumption.

The studies of infertility and smoking (Baird et al, 1985; Olsen et al, 1983) also noted that the smokers reported higher alcohol consumption, but that this factor did not influence infertility, which seems to contradict the animal results. However, both studies were too small to

adequately investigate this effect. Baird and co-workers included 678 women of whom 136 were smokers. Ten percent of smokers (14 subjects) and 3% of non-smokers (16 subjects) reported more than 7 drinks/week. The Danish study was larger (278 infertile and 2947 fertile couples), but the rates of smoking and alcohol use were not provided. If rates are assumed equivalent to those for the Minnesota study (Baird et al, 1985), then the number of couples providing information on the effect of alcohol use is still small (less than 300). These null results, therefore can only be considered suggestive and require confirmation in a much larger study.

Perhaps the most controversial issue regarding alcohol and reproductive function has been its hypothesized effect on the fetus. Fetal outcomes attributed to alcohol include fetal loss and growth retardation (as for smoking) as well as a cluster of fetal abnormalities labeled the Fetal Alcohol Syndrome (FAS) by Jones et al (1973). This syndrome comprises central nervous system dysfunction including irritability, microcephaly and mental retardation, growth deficiency and distinct facial characteristics (including short palpebral fissure, abnormal jaw protrusion, marked vertical skin folds, thin upper lip etc.). Reports on this subject fall into three distinct groups: animal studies; epidemiological studies of the joint effects of smoking and alcohol (among other factors); and epidemiological studies of FAS.

Adverse toxic effects of ethanol crossing the placenta, have been well documented in animal fetuses (see for example, the reviews by Furey, 1982; Strobino et al, 1978). The primary effects appear to be growth retardation, including microcephaly and central nervous system dysfunction.

Recently, well-designed and analyzed epidemiological studies have investigated the potential joint effect of smoking and alcohol on the fetus. Lumley (1985), Kline et al (1981), Shiono et al (1986) have all demonstrated, using large samples that the effect of smoking on the fetus is independent of alcohol consumption, even though smoking women are much more likely to drink than non-smokers. Prager et al (1984) provide excellent statistics on these behaviors in mothers from the 1980 National Natality Survey). Only very heavy maternal alcohol consumption (generally the equivalent of at least 2 oz. absolute alcohol/day) is apparently associated with low birth weight (Kline et al, 1981; Wright et al, 1984; Berkowitz et al 1982).

Studies of FAS have been typified by methodological problems. Studies including specialized neo-natal and/or pediatric examinations have either not blinded the examiner to maternal alcohol status (Sokol et al, 1980), have been

unclear on such potential biases in the study (Streissguth et al, 1981; Ouellette et al, 1977) or have demonstrated lack of reproducibility in physician examiners (Alpert et al, 1981). Others, such as Marbury et al, 1983, used existing records to determine fetal outcome. While removing problems of observer bias, this approach suffers from lack of standard definitions among a large number of clinicians completing the records. Despite methodological difficulties, only the Boston Study (Alpert et al, 1981; Hingson et al, 1982) is large enough, with unbiased physician examinations. With adequate control of potential confounding factors, this study does not find an excess of adverse fetal outcomes due to alcohol except for shorter gestation (Hingson et al, 1982). Thirty-one cases consistent with FAS were identified in 1,384 infants examined.

In summary, the adverse effects of alcohol on reproductive function possibly include reduced fertility and some retardation of fetal growth, although only in heavy drinkers. Stein and Kline (1983) provide an excellent review of these findings.

6.3 CAFFEINE AND OTHER DRUGS

The health outcomes of heavy caffeine use (generally equivalent to more than three cups of coffee per day) are not clear. Most of the studies have been too small, have not consistently or reliably measured caffeine exposure (Wetherbee et al, 1977) or have been subject to other biases (Jick et al, 1973; Rosenberg et al, 1980). An excellent review recently completed by James and Sterling (1983) indicates that there is no sound evidence for an increase in myocardial infarction, that there is probably an increased risk of pancreatic cancer but that the evidence for bladder cancer is unclear. With respect to reproductive outcomes, there is no sound evidence of excess fetal loss or congenital abnormalities such as cleft palate or neural tube defects. Watkinson and Fried (1985) indicate a possible decrease in birth weight, but a relatively low response rate combined with retrospective data on caffeine consumption make these results questionable. Kurpa et al (1983) show no effect of caffeine on congenital abnormalities in a Finnish population, consistent with Linn et al, (1982) in the U.S.

In another excellent review of factors affecting fetal outcomes, Goldman (1980) indicates that antihistamines and tranquilizers can produce cleft palate abnormalities in the fetus. Fried (1980) documents nervous system abnormalities in the offspring of maternal marijuana users and Hingson et al (1981) estimate that marijuana users are 5 times as likely to have offspring with features consistent with FAS, although the numbers are small.

6.4 OTHER POTENTIAL FACTORS

Apart from the major factors discussed above, the possibility of longer term TCDD exposure either from residential or occupational exposure must not be overlooked. For example, residents exposed near St. Louis, Missouri or other toxic waste sites may exhibit depressed immune function.

Another factor emerging from oral histories and verbal reports is marriage to a Vietnam veteran, thus increasing exposure to fetal abnormality or loss.

A recent report (Hogstedt et al, 1986) indicates that ethyline oxide, used as a sterilizer in hospital and commercial sterilization facilites may increase the risk of leukemia and possibly stomach cancer, although exposure in Vietnam veteran or Vietnam-era nurses post-Vietnam to this substance is probably low.

6.5 SUMMARY

The literature reviewed in this section is not intended to be exhaustive, but highlights the current state of knowledge with respect to health outcomes of smoking, alcohol use and other drug use including caffeine and marijuana. Major adverse health effects are generally well documented for these factors indicating that smoking and alcohol at least must be included in any comparison of veterans involving disease endpoints such as cancer and heart disease. The state of knowledge is not so clear for outcomes relating to the reproductive system, but there is sufficient, consistent evidence from both animal and human studies to include both smoking and alcohol use in all comparisons involving reproductive health outcomes. To the extent feasible in the proposed study, other drug use should also be considered, particularly those possibly associated with congenital abnormalities (including marijuana, tranquilizers etc.).

Other important confounders to be considered are spouse, residential, and occupational exposures to toxic substances, including TCDD in particular.

A major methodological difficulty will be reliable ascertainment of these confounding exposures before and immediately after Vietnam or Vietnam-era military service.

SUMMARY AND CONCLUSION

The literature reviewed here has clearly indicated the need for:

- A study of women war veterans; and
- A study of women Vietnam veterans.

The distinction is made between these two types of studies, because although, both are needed they have separate goals.

The first type of study would have as its goal, the investigation of how women function under war conditions and the accompanying stresses as well as the impact of this experience on subsequent life. Are there differences according to occupation (nurse versus other military role) or according to age or prior life experience? Is subsequent post-war integration into society different for those who stay in the military compared to those who return to civilian life?

Ideally such a study should be prospective, defining and measuring a cohort before it goes to war, immediately after completion of war service and subsequently. The chances of completing such a study, however, are negligible. The most feasible design is to begin immediately on completion of war service, to minimize recall problems, tracing difficulties and costly access to archived records. The proposed study of women Vietnam veterans can provide an investigation of the direct effect of war experience on women. It will however be limited in the following ways:

- Already 15-20 years have passed since completion of war service, increasing the problems of recall;
- The Vietnam war was a unique experience for the U.S., with a concurrent and subsequent political climate which created difficulties for veterans not usually expected after serving in a war; and
- The period of war service was limited, for the first time, to one permanent tour of duty (one year).

The second type of study has a more focused goal to investigate the effect of the Vietnam Experience (VE) on women veterans. This experience includes: the exposure to war as would be investigated in the first study; the potential exposure to phenoxy herbicides; the exposure to an unconventional guerrilla war with no well-defined front line; the knowledge that the U.S. did not win the war; and the lack of mobilization for (developing into active hostility towards) the war in the civilian U.S. population.

Thus, while a study of women Vietnam veterans can address both sets of goals, to varying extents, it must be recognized that it will not provide a representative portrait of how war in general affects women who are participants. The impact of the war experience will be confounded with the impact of the unique Vietnam experience.

In designing the proposed study, several issues must be addressed which are highlighted in this review. Some of the major issues are:

- The retrospective nature of this study (requiring recall over 20 years, on average);
- The impact of the intervening and current political climate on participant responses (this is clearly demonstrated in the experiment by Korgeski and Leon, 1983 and is further emphasized by Colton, 1986);
- The difficulties inherent in measuring exposure to phenoxy herbicides;
- The need to define and develop measures for combat exposure and PTSD for women; and
- The complex relationship between exposure, intervening and outcome variables. Each of these issues is reviewed briefly below.

(a) Retrospectivity

Reliance on memory recall, even over one year, is risky. Over longer periods, reliable data can only be obtained on major events or changes. In designing this study, decisions must be made on what data can be feasibly collected from an interview and what independent sources can be used to supplement or validate interview data. Potential supplemental sources include:

- Results of medical examinations required by the military (minimally at in-take and discharge); and
- Hospital and other medical records.

(b) Political Climate and Value-Free Data

This phenomenon clearly exacerbates memory recall by biasing it in certain directions. Vietnam veterans are more likely to respond positively concerning PTSD symptoms and possible toxic outcomes from Agent Orange exposure. In combination with the well-known problems of memory recall, this issue underscores the need to validate key items of

information and/or to obtain independent, value-free assessments. This is true of both exposure and outcome variables.

In terms of exposure, the "Herbs" tapes should be considered, if it is feasible to determine exposure in time and space from independent records. If a large proportion of nurses were moved around frequently between units then this may not be feasible. Alternatively, blood sampling (at least on a sub-sample could be considered for eventual determination of residual body TCDD levels. Exposure to combat situations, including enemy attack should also be determined, if possible form independent documentation (if available).

All major health outcomes should be verified on either 100% of cases or a sample (depending on cost constraints and the reliability of self-report). Disease diagnoses (including cancers in particular) can be verified from medical records and pathology reports (if available in the 15-20 year time span being considered). Congenital anomalies in offspring can be verified from medical records and from pediatric examination. Potential low level effects of TCDD on immune function can be determined from a variety of blood, urine and skin tests. Psychological disturbance (including chronic or delayed PTSD in particular) can be determined from a series of tests and/or clinical examination.

(c) Development of Measures for Women

The currently available measures of combat exposure and PTSD in particular are designed primarily for men. Certain exposures are not within the likely experiences of women military (at least to date), including direct confrontation and killing of the enemy and combat field living conditions. The definition and measurement of PTSD must also be modified accordingly.

(d) Changing Roles of Variables

The relationships among the variables and between different measures of the same variable are complex. For example, alcohol consumption in Vietnam becomes a component of the Vietnam Experience (if it was high and ubiquitous). It is also an important intervening variable, post-war, in assessing, for example, any reproductive effects of either prolonged stress or phenoxy herbicide exposure. Finally, current alcohol consumption may itself be considered an important outcome of the war experience. A similar set of roles can also be proposed for tobacco smoking.

The confounding role of nursing as an occupation deserves special attention, as the majority (estimated at

about 80%) of all women Vietnam veterans were nurses. This is well-known as a high-stress occupation which in this study will be confounded with a variety of unique stressors related to war. It may be that women able to successfully manage such stress differentially self-select from this occupation and for war-service.

Design Recommendations

The methodologies of prior studies reviewed here indicate that the strongest design will be a retrospective cohort design that compares Vietnam veterans with Vietnam-era veterans who were otherwise eligible for Vietnam service but did not have a tour of duty "in country". This direct comparison can be supplemented for key health and socio-demographic characteristics, with comparisons involving civilian population data sets such as those generated by the National Center for Health Statistics.

Within the cohort design, case-control studies should be imbedded which compare women with and without key outcomes, including measurement to verify these outcomes. For example, all women reporting offspring with congenital abnormalities could be matched with women of equivalent fertility and normal offspring. Pediatric examinations (done blind to group status) would then be conducted on all off-spring in these two groups. Women with any cancer diagnosed and alive at interview could be matched with cancer-free women for immunological assessment.

The final design will, therefore, include a subset of possibly over-lapping case-control studies for in depth study and verification of key outcomes. Because in-person measurement will be costly in this nationwide study, this design approach is considered the most efficient.

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