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Australian Veterans Health Studies

Morbidity Study

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PROTOCOL FOR A MORBIDITY SURVEY OF
VIETNAM VETERANS AND CONTROLS

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TABLE OF CONTENTS

		Page
1.	SUMMARY	1
1.1	Background	1
1.2	Rationale for this Study of Morbidity	1
1.3	Descriptive Hypotheses to be Tested	2
1.4	Summary of Study Design	3
1.5	Cancer Morbidity to be a Separate Study	3
1.6	Relationship to Other Studies	4
2.	BACKGROUND TO PROBLEM	5
2.1	Stimulus to Study	5
2.2	Possible Effects of Phenoxy Herbicides and Related Substances	5
2.3	Combat Syndrome and Other Psychosocial Effects of War Service	10
2.4	Effects Related to Specific Concomitants of War Service	13
3.	BACKGROUND TO STUDY DESIGN	15
3.1	Rationale for Study of Former National Servicemen	15
3.2	Enlistment and Training of National Servicemen	15
3.3	Factors Influencing Selection of National Servicemen for Vietnam Service	16
3.4	Comparability of Veteran and Non-veteran National Servicemen	19
3.5	Duration of National Service in the Army	20
3.6	National Service Intakes	21
3.7	Sources of National Service Cohort Data Base	21
3.8	Verifying the Completeness of National Service Cohort	23
3.9	Determining the Accuracy of the National Service Cohort	24
3.10	Rationale for Morbidity Study Subjects Being a Subset of Mortality Study Subjects	24
3.11	Rationale for Subjects being N.S.W. Enlistees Only	25
3.12	Subject Selection	27
3.13	Obtaining Subject Addresses	28
3.14	Areas to be Investigated	29
3.15	Implications of Pilot Study Results	31
3.16	Rationale for Using MEDICHECK Health Screening Centre	32
3.17	Rationale for Method of Measuring Morbidity	34
3.18	Physician Assessment	42
3.19	Rationale for Number of Subjects	44
3.20	Index of Herbicide Exposure	47
3.21	Index of Combat Exposure	49
3.22	Army Dossier Data Held on Each Subject	50

	Page
4. STUDY PROTOCOL	54
4.1 Subject Selection	55
4.2 Obtaining Current Address	56
4.3 Methods of Obtaining Compliance for Medical Examination	59
4.4 Outline of Design of Medical Examination	61
4.5 Design of Examination Procedure for Subjects	63
4.6 Information from Wife/Female Partner	70
4.7 Follow-up of Non-Complying Subjects	73
4.8 Follow-up of Non-Complying Wives/Female Partners	76
4.9 Pilot Testing of Medical Examination	77
4.10 Verifying Data in Medical Records	78
5. ADDITIONAL INFORMATION FROM ARMY SOURCES	79
5.1 CARO Dossier	79
5.2 Central Medical Record	79
5.3 Psychology Record Cards	80
6. DATA ASSESSMENT AND ANALYSIS	81
6.1 Data Acquisition and Verification	81
6.2 Adequacy and Utility of Morbidity Study Data	82
6.3 Hypotheses to be Tested	91
6.4 Outcome Measures to be Used	93
6.5 Principles of Statistical Analysis	97
References	105
APPENDIX 1: SPECIFIC HYPOTHESES AND POWER CALCULATIONS	
APPENDIX 2: PULHEEMS ARMY HEALTH RATING	

1. SUMMARY

1.1 Background

At the request of the Commonwealth Department of Veterans' Affairs, a study group was established in January 1980 to investigate the suggestion that herbicide exposure in Vietnam was responsible for health problems reported by Vietnam veterans and their families.

The investigations, initially known as "Australian Veterans Herbicide Studies", are administered by the Commonwealth Institute of Health. In October 1981, the terms of reference were widened to include all disabilities related to Vietnam service, and not just those which might be due to herbicide exposure. In May 1982, the study group was renamed the "Australian Veterans Health Studies" (AVHS).

1.2 Rationale for This Study of Morbidity

Comments from Vietnam veteran groups have led to suggestions that there is an increased illness rate among veterans, particularly in the following areas: psychological health, behaviour, liver, gastrointestinal system, skin and neurological system. There have also been claims of an increased incidence of cancer amongst veterans, and of marital and reproductive problems affecting veterans and their wives and offspring.

The rationale for this study is to use information on current health and past medical treatment of veterans and their wives to test some of these claims. To achieve this it is proposed to follow-up and examine medically 5,000 former national servicemen who enlisted in NSW (3,000 veterans, 2,000 controls) and obtain reproductive histories from their wives/female partners. The results will be assessed to see whether the disabilities for veterans are more frequent than for national servicemen who did not go to Vietnam (controls).

In the event that disabilities are more frequently found in veterans than in controls, additional data will be analysed to decide whether the excess disabilities are best explained in terms of the physical or social sequelae of combat stress, and/or in terms of herbicide exposure and/or in terms of individual differences which antedated the Vietnam experience (See Sec 3.4).

The rationale for restricting this study to national servicemen is explained in detail in Sec 3.1.

1.3 Descriptive Hypotheses to be Tested

The null hypothesis is that there is no difference in the frequency of disabilities between Vietnam veterans and controls (national servicemen who did not go to Vietnam). This null hypotheses will be tested against each of the following alternative hypotheses:

- (i) That social and behavioural disabilities (unemployment, separation, divorce, motor accidents, alcohol abuse) are more frequent in veterans than in controls.
- (ii) That anxiety, depression and other psychiatric disabilities are more frequent in veterans than in controls.
- (iii) That disorders of the nervous system (including neuropsychological disorders) are more frequent in veterans than controls.
- (iv) That liver disorders are more frequent in veterans than controls.
- (v) That gastro-intestinal disorders are more frequent in veterans than controls.
- (vi) That skin disorders are more frequent in veterans than controls.
- (vii) That infertility, miscarriage or death or disability of children have been more frequent in the families of veterans than in the families of controls.

1.4 Summary of Study Design

Veterans and controls will be former national servicemen who enlisted in those intakes from which veterans were chosen (from June 1965 to February 1971), who served at least 13 weeks, and who were discharged alive or survived for 2 years after enlistment.

From the group of former national servicemen who enlisted in N.S.W., 3,000 veterans and 2,000 controls will attend a central examination site in Sydney. The medical examination will consist of an in-depth medical questionnaire, neuropsychiatric testing, biochemical testing of blood and urine, and physical examination and health assessment by a doctor. Following this examination, certain subjects will undergo more detailed psychiatric and neuropsychological assessment (see Figure 1, chapter 4).

Any subject with illness requiring treatment or urgent investigation will be referred back to his local doctor. Any subject with a suspected disability which requires further investigation for research purposes will be referred to an appropriate specialist, either immediately (option A) or after interim data analysis (option B).

The wives of veteran and control subjects will be interviewed, to seek information about the health of any children of the subject, and about the outcome of all pregnancies.

1.5 Cancer Morbidity Not Addressed by This Study

This morbidity survey is not ideally suited to examining the incidence of cancer (see section 3.19).

1.6 Relationship to Other Studies

Separate studies have investigated the relationship of Vietnam service to birth defects in offspring (Case-Control Study of Congenital Anomalies and Vietnam Service), and are investigating mortality (Retrospective Mortality Study of Vietnam Veterans and Controls Revised Protocol).

2. BACKGROUND TO PROBLEM

2.1 Stimulus to Study

In 1979 Vietnam veteran groups reported that there was an excess of veteran morbidity due to gastrointestinal, neurologic, skin and psychiatric disability and cancer, above that expected in a group of previously healthy young men. This supposed excess was attributed, by some veterans, to exposure to Agent Orange herbicide during Vietnam war service. Health effects other than morbidity are addressed in other documents (Case-Control Study of Congenital Anomalies and Vietnam Service Report, Mortality Study protocol).

While the claimed effects of Agent Orange have yet to be substantiated, it has become apparent that several other environmental exposures, both in Vietnam and back in Australia, could be causally related to any increase in disability in veterans.

Among these exposures are non-phenoxy herbicides (e.g. cacodylic acid), insecticides, infectious tropical diseases and malaria prophylaxis, experiences of social dislocation and warfare, alcohol, tobacco and other drug consumption, and the experiences of homecoming, readjustment and re-establishing a satisfactory life style (Boman, 1982).

2.2 Possible Effects of Phenoxy Herbicides and Related Substances

2.2.1 General Literature Review

The 'Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins', (U.S. Veterans Administration 1981) summarises the known and suspected health effects of herbicides, and the gaps in current knowledge. Points of relevance to a morbidity study of Vietnam veterans are:

TCDD (Dioxin)

- o TCDD has been an important contaminant of 2,4,5-T, and it has not always been possible to distinguish between the effects of the two substances.
- o Chloracne is the most consistently reported health effect of TCDD exposure in humans.
- o Neurasthenia, a series of subjective complaints including irritability, fatigue and insomnia, has been reported after many industrial accidents and exposures.
- o Other neurological disorders (as peripheral neuritis) and hepatic disorders (as hepatomegaly) have been reported after several of the exposure incidents.
- o Porphyria cutanea tarda and gastrointestinal problems have not been commonly reported and seem to be associated with long-term exposure.
- o TCDD is a limited cumulative toxicant; cumulative effects of doses administered within a month of each other have been observed in animals, but not for doses administered beyond about one month.
- o The subacute effects of TCDD are porphyria and depletion of blood cells; these effects are not observed after acute doses.
- o In animal studies TCDD appears to act secondarily or indirectly in enhancing the carcinogenicity of other components (usually unidentified).

2,4-D, 2,4,5-T

- o Both 2,4-D and 2,4,5-T are cleared rapidly from the blood after they are absorbed, with half-times for plasma clearance in humans of 12-23 hours.

- o Neither 2,4-D nor 2,4,5-T has been shown to accumulate in animal fat.
- o 2,4-D and 2,4,5-T are not cumulative toxicants.
- o In animals the cause of death from lethal doses of 2,4-D or 2,4,5-T is unknown; both compounds produce several non-specific effects, such as mild weight loss.
- o 2,4-D produces neurotoxicity in humans and animals, and 2,4,5-T produces neurotoxicity in animals.
- o Animal studies have not produced conclusive evidence that 2,4-D, 2,4,5-T, cacodylic acid or picloram are carcinogenic.
- o The effects of acute exposure to 2,4,5-T in humans are unknown.
- o There is no positive information on the carcinogenic potential in humans of diquat, diuron, dalapon, bromacil, picloram, and tandex and on 2,4-D, 2,4,5-T, or TCDD, (except in the case of concomitant exposure to trichlorophenol or other herbicides).

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Volume 15 gives the following effects of TCDD, 2,4-D and 2,4,5-T as having been described in humans:

TCDD

chloracne

porphyria cutanea tarda

hyperpigmentation and hirsutism

liver damage

raised serum hepatic enzyme levels

disorders of fat metabolism

disorders of carbohydrate metabolism

cardiovascular disorders

urinary tract disorders
respiratory disorders
pancreatic disorders
polyneuropathies
lower extremity weakness
sensorial impairment (sight, hearing, smell, taste)
neurasthenic or depressive syndromes

2,4-D

hyperthermia and tachycardia
nausea, vomiting, diarrhoea
anorexia and gastralgia
increased salivation
sweet taste in the mouth
abdominal pain
fatigue, malaise
headache
sensation of drunkenness
peripheral neuropathy
paralysis
somnolence
muscular weakness, twitching
skeletal muscle damage
severe leg pains
joint swelling
increased blood cholesterol
abnormal serum protein

2,4,5-T

chloracne

liver disorders

neurological changes

behavioural changes

fat metabolism disorders

signs of porphyria cutanea tarda

gastrointestinal symptoms

headache

hypomania

neurasthenic syndrome

The effects listed have generally been observed in subjects after recent chemical exposure, and the pattern of effects varies between reports.

2.2.2 Possibility of Carcinogenic Risk in Man

Soft-tissue sarcoma and lymphoma are suspect as outcomes of exposure to phenoxy herbicides or associated substances (Hardell and Sanström, 1979). The work of Hardell has received some support from reports of at least four cases of soft-tissue sarcoma which have occurred in workers involved in the manufacture of phenoxy-herbicides (Hardell and Ericksson, 1981; Honchat and Halperin, 1981). Several other studies of the effects of herbicides on cancer mortality have failed to demonstrate an effect (Axelson and Sundell, 1974; Riihimäki et al, 1978) and no excess mortality has been demonstrated following the 1976 Seveso dioxin disaster (Regianni, 1980), although the latent period is short.

2.3 Combat Syndromes and Other Psychosocial Effects of War Service

There are no published epidemiologic studies of the effects of Vietnam service on the psychological adjustment of Australian soldiers, nor on their subsequent readjustment to civilian life; however, literature indicates three main areas of psychopathology in U.S. veterans: post traumatic stress disorder; depression; alcohol and substance abuse disorder (review by Boman, 1982; symptoms after DSM III).

2.3.1 Post-Traumatic Stress Disorder

Symptoms:

Re-experiencing of the trauma;

numbing of responses to or reduced involvement with the
external world;

hyperalertness, sleep disturbance, guilt about surviving;

memory impairment or trouble concentrating.

2.3.2 Depression of various types

Symptoms:

Anorexia, weight loss or gain, increased appetite;

sleep disturbance, psychomotor agitation or retardation;

feelings of worthlessness;

loss of interest, loss of energy, fatigue;

complaints or evidence of decreased ability to think;

recurrent thought of death or suicide;

suicide attempt.

2.3.3 Alcohol and Substance Use Disorder

Symptoms:

Alcohol or drug consumption causing impairment in social or

occupational function, with or without tolerance or withdrawal.

2.3.4 Other Psychosocial Disorders

Three other classes of disorder seem possible in view of media reports of the health of Australian Vietnam veterans. These are: anxiety disorders; adjustment disorder with anxious mood; somatization disorder (symptoms again taken from DSM III).

Anxiety Disorders

Symptoms:

apprehension, fear or terror;
dyspnoea, palpitations, chest pain or discomfort;
choking or smothering sensation;
dizziness, vertigo or unsteady feelings;
feelings of unreality, paraesthesias, hot and cold flushes;
sweating, faintness, trembling or shaking;
fear of dying, going crazy or doing something uncontrollable.

Adjustment Disorder with Anxious Mood

Symptoms:

as for anxiety disorder, with nervousness, worry or jitteriness predominating.

Somatization Disorder

Symptoms:

Sickly: Believes that he or she has been sickly for a good part of his or her life.

Conversion or pseudoneurological symptoms: Difficulty swallowing, loss of voice, deafness, double vision, blurred

vision, blindness, fainting or loss of consciousness, memory loss, seizures or convulsions, trouble walking, paralysis or muscle weakness, urinary retention or difficulty urinating.

Gastrointestinal symptoms: Abdominal pain, nausea, vomiting spells, bloating (gassy), intolerance (e.g. gets sick) of a variety of foods, diarrhoea.

Psychosexual symptoms: For the major part of the individual's life after opportunities for sexual activity: Sexual indifference, lack of pleasure during intercourse, pain during intercourse.

Pain: Pain in back, joints, extremities, genital area (other than during intercourse); pain on urination; other pain (other than headaches).

Cardiopulmonary symptoms: Shortness of breath, palpitations, chest pain, dizziness.

Other psychiatric abnormalities may occur, but the number of affected individuals will probably be very small.

2.4 Effects Related to Specific Concomitants of War Service

2.4.1 Alcohol Use

Because of combat stress and the social changes consequent on Vietnam service, it is likely that the consumption of alcohol by Vietnam veterans will prove to be higher than that in non-veterans. This would lead us to expect that there could be a greater incidence of alcohol related disability in veterans than in controls, as has been reported in other army and veteran populations (Mathews 1976).

It is also necessary to consider the possibility that some of the personal qualities which are associated with being a "good soldier" (e.g. vigour, initiative, aggression) may show an intrinsic (genetic) correlation with the propensity to drink more alcohol (Mathews, 1981). If this were the case, then any association of alcohol use with veteran status could be partly consequent on the processes of veteran selection. It will be possible to test this hypothesis in the morbidity study, as data on alcohol consumption will be collected from subjects.

2.4.2 Cigarette Smoking and Other Drugs

Similar considerations apply to cigarette consumption. A particular attempt will also be made to identify any morbidity which could be attributable to illicit drug usage.

2.4.3 Infectious Diseases

It is likely that Vietnam veterans have been at greater risk of several infectious diseases (e.g. malaria, hepatitis, melioidosis, strongyloidiasis), although there is no specific evidence to suggest that this has contributed to any disability in the post-Vietnam period.

Tuberculosis might also be more prevalent in veterans, because of the greater exposure in Vietnam, and the greater susceptibility associated with a history of social disintegration and alcohol abuse. However, because of the efficacy of treatment, it is unlikely that there will be any subjects with tuberculosis.

Because of the social dislocation of the war experience, venereal disease may also be more prevalent in veteran than in control cohorts.

3. BACKGROUND TO STUDY DESIGN

3.1 Rationale for Study of Former National Servicemen

In studying the effect of Vietnam service on subsequent risk of disability, a group of subjects who served in Vietnam (veterans) is required, along with a comparison group of subjects who did not serve in Vietnam (controls). The veterans and controls should have been as similar as possible at the point in time at which the veterans departed for Vietnam. Specifically, the distribution of age, health status and socio-economic status (SES) should be similar between veterans and controls.

Former national servicemen are considered to form a group most closely satisfying these requirements and consequently the study will be restricted to this group. At present it is considered that it would be too difficult to define an appropriate control group for those Vietnam veterans who were in the regular army. If further investigation were to be performed, it may prove feasible to identify acceptable groups of veterans and controls among the regulars, but even so it would still be highly desirable to perform the study with national servicemen for two reasons: firstly, national service veteran and control groups would, in all probability, still be more comparable than groups of regulars, and secondly, within regulars the health effects of Vietnam service could be obscured by the deleterious health effects of peace-time army service (see above).

3.2 Enlistment and Training of National Servicemen

Nineteen year old Australian males were required to register for national service (National Service Act 1957-1971), and those with birth dates selected by ballot were required to present for medical examination and interview by the Department of Labour and National Service. Those accepted were required

to enlist in the army within the next few months, unless deferrment (educational, medical reasons) or exemption (clergyman, conscientious objector) was obtained. Then followed an enlistment medical examination. Some men volunteered for national service independent of the ballot. They had to reach the same medical standard as ballotees. These men can only be identified by examination of individual dossiers.

After enlistment followed 10 to 12 weeks of recruit training, then allocation to corps and 12 weeks Initial Employment (corps) training (except Infantry). The member was then posted to his service unit.

Generally, between 6 months and 1 year after enlistment the veterans were sent to Vietnam for a 1 year tour of duty .

3.3 Factors Influencing Selection of National Servicemen for Vietnam Service

Selection for Vietnam service was based on whether an individual had been allocated to a unit which was subsequently selected for Vietnam service.

Very few if any national servicemen were prevented from serving in Vietnam for medical conditions and the interval between enlistment and posting to Vietnam (less than 1 year) was insufficient for life-threatening conditions to develop in a significant number of national servicemen which would result in exclusion from Vietnam service.

Many factors influenced the selection of a national serviceman for service in Vietnam. Those currently known to the Study Team are as follows:

a) Individual Soldiers Influence

Completing form NS24, giving details of education, special skills and training.

Completion of a 'dream sheet' which recorded desires to serve in particular corps. It is believed that in a considerable proportion of cases these preferences were recorded on the psychology record cards, which are available. It is thought to have been common knowledge which units were going to Vietnam in the next couple of years, and therefore a national serviceman could steer himself toward a corps which was more or less likely to be sent to Vietnam. Additionally, the field corps (Artillery, Armoured, Infantry, Engineers, Signals) were known to be the most dangerous.

Volunteering for a reinforcement unit.

Expressing a desire to serve in Vietnam.

Performing in a sufficiently unsatisfactory manner so as to be regarded as unsuitable for Vietnam service.

A fear of combat, or conscientious objection to the Vietnam war or combat.

Lack of physical fitness becoming apparent during basic training but not necessitating discharge; lack of psychological fitness for combat service, as evident on enlistment testing or as determined by his commanding officer.

An accident resulting in injury prior to posting to Vietnam, but not necessitating immediate discharge (due to its minimal severity or the need for prolonged medical treatment).

Family circumstance, such as illness, social problems etc. resulting in the national serviceman being granted leave without pay or being posted to a base near home, precluding Vietnam service.

b) Army influence

Requirement lists. These listed the manpower requirements of corps and units. The allocation boards attempted to match 'dream sheets' to 'requirement lists', probably with varying success.

The 49/51 rule. The Army maintained Vietnam service unit strength at 51% regulars or above, although it appears from 1968 onwards the lack of available regulars meant that the ratio sat on 49% national servicemen and 51% regulars.

A national serviceman's superiors regarding him as unsuitable for Vietnam service.

It is probable that these factors, while influencing Vietnam service, would also influence subsequent morbidity and mortality.

The number of national servicemen who sought or avoided Vietnam service is not known.

As this problem is one of confounding, its role may be evaluated, at least in part, at the data analysis stage once the requisite data has been obtained from the army.

It appears possible to identify individuals transferring into or out of Vietnam bound units by searching through individual personnel dossiers.

The proportion of national servicemen who became veterans is similar across all States of enlistment (see Table 3.1) although anecdotal evidence indicates that some units were comprised mainly of enlistees from certain States.

	QLD	NSW	VIC	SA	WA	TAS	NT
Total subjects enlisted in State	14%	32%	30%	10%	10%	4%	0%
% of subjects who are veterans	43%	42%	39%	40%	42%	44%	-

Table 3.1 Origin of subjects by State of enlistment, and % veterans of subjects enlisted in each State.

3.4 Comparability of Veteran and Non-Veteran National Servicemen

As indicated in the previous section, there is ample evidence that the decision to send a national serviceman to Vietnam was not random.

In the absence of random allocation, it is likely that even before the Vietnam experience, those who eventually went (veterans) would have differed, in several important respects, from those who did not go to Vietnam (controls).

This view is supported by evidence that veterans differed from controls in educational level and in scores on the SDI psychological scale at induction.

In as much as these pre-Vietnam differences between veteran and control national servicemen are measurable, they can be treated as potential confounding factors. At the stage of analysis of results it will be possible to see whether factors such as education and psychological type are related to outcome, and if so, to make statistical adjustments to minimise the effects of the confounding.

However, it is important to emphasise that because of (undetected) errors in the measurement of these confounding factors, such statistical adjustments will always be incomplete. Furthermore, no statistical treatment could ever allow for the effects of confounding factors which are unmeasured (and possibly unsuspected).

3.5 Duration of National Service in the Army

Discharge occurred after 2 years service (reduced to 18 months in 1971) unless discharge occurred early for extraordinary reasons (medically unfit, exceptional hardship, change of Government) or late (retention for medical treatment, voluntary prolongation of service).

An analysis of 'discharge reason' by 'duration of service' for those intakes with veterans revealed that 53% of discharges as 'medically unfit' occurred in the first 3 months, 67% by 6 months and by 12 months 80% of all such discharges had occurred (see Table 3.2). For 'expiration of term', 0% occurred in the first 12 months, 29% in 13-24 months, 65% in the 25th month, and 5% after 25 months. The 5% of discharges after 25 months service may be due to errors in enlistment and discharge dates or retention of servicemen in

the Army for medical treatment or voluntary prolongation of service. The reasons for these delayed discharges will be explored by manual searching of the CARO dossiers.

Reason for Discharge	% Discharged in Time Interval of Duration of Service					Total No. 100%
	0-3m	4m-6m	7-12 m	13-24 m	25m +	
Expiration of term	0%	0%	0%	29%	70%	40829
Exceptional hardship	0%	0%	0%	0%	100%	63
Medically unfit	53%	14%	13%	15%	5%	3661
Unsuitable, non-discipl.	34%	19%	22%	19%	6%	874
Unsuitable, disciplinary	6%	4%	13%	23%	52%	316
Other	3%	10%	22%	23%	42%	4138
Total	5%	2%	3%	27%	63%	49881

Table 3.2 Reason for Discharge by Duration of Service

3.6 National Service Intakes

Department of Defence Army Manning Reviews divide national service enlistments into 4 intakes each year. Each intake lasted up to 2 weeks, and they occurred in January, April, July and September. A minority of enlistments occurred in the other months, and for the purposes of this study an intake consists of all national servicemen who enlisted in 1 of the above months or enlisted in the month on either side of that month.

3.7 Sources of the National Service Cohort Data Base

The following information is available from the army for current and former servicemen:

Service number

Surname

Given names

Date of birth
Date of enlistment
Marital status at enlistment
Educational status at enlistment
Occupation at enlistment
Religion
Number of dependents
Place of birth
Army health classification at enlistment
Postings
Dates of postings
Date of discharge
Discharge reason
Army health classification at discharge
Medical record and psychology record data
Other

To date, two army sources have been used to provide data about national servicemen in the Vietnam period. These are the Central Army Records Office (CARO) and the Melbourne Regional Computer Centre (MRCC), both located in Melbourne.

MRCC

An MRCC-supplied computer file contains most of the above data for most study subjects. However, it has several major short-comings. Firstly, it contains initials, not given names (which are required for obtaining subject addresses) and does not contain postings data, medical or psychology data, or other miscellaneous service history data. Secondly, preliminary examination indicates that the data it contains are less accurate than those in the CARO

dossier. As discussed below the first match to obtain addresses will be computerised: matching study subjects' MRCC-file derived names (surname, 2 initials) and date of birth with the Australian Electoral Register. It is proposed to overcome the problems of MRCC file inaccuracy by returning all unmatched subjects names and d.o.b. to CARO for manual verification and addition of 2 given names (CARO contains dossier records for all current and former servicemen). Where corrections have been made, the subjects will be matched with the Australian Electoral Register again, and the residue not matching will be sought in other registers.

CARO

In addition to the above limitations, the MRCC file does not indicate veteran/control status, and neither dates nor names of Vietnam postings. These are contained on a computer file held by AVHS compiled from data manually extracted from individual CARO dossiers. While this file does have 2 given names for all veterans, it only gives data for 17% of controls.

There is evidence of misclassification of veteran/control status, probably less than 1%.

3.8 Verifying the Completeness of the National Service Cohort

The completeness of the cohort has two aspects: firstly, whether we know of the existence of all of the national servicemen, and secondly, whether we have complete details on those known. This work has already been performed as part of the Mortality Study.

All national servicemen have been identified, and the data listed in 3.7 above is present in at least 98% of cases.

3.9 Determining the Accuracy of the National Service Cohort

Generally, data on the MRCC file will be used for the purposes of the Morbidity Study, as this is the only file with complete coverage of national servicemen. The CARO computer file has much greater coverage of veterans than controls and is therefore a biased source.

The MRCC - CARO match was used to determine the error rates in the MRCC data in the following way: If an inconsistency emerged in the MRCC - CARO match the origin of this inconsistency was determined. This involved checking that the computerised CARO data were correctly entered, and, if so, that they were correctly transcribed from the original CARO dossiers. The remaining discrepancies were corrected by referral to army personnel dossiers.

3.10 Rationale for Morbidity Study Subjects Being a Subset of Mortality Study Subjects

Mortality Study subjects comprise all former national servicemen who saw service in Vietnam, and all other national servicemen from those intakes which also included veterans who stayed in the army at least 13 weeks.

The 13 week minimum army service criterion is proposed for several reasons: Initial recruit training lasted from 10 to 12 weeks and the majority (53%) of discharges described as "medically unfit" occurred during this time. Recruit training therefore acted as a further screening procedure to identify and discharge these persons not suitable for army service. By the end of recruit training those remaining in the army would be considered suitable "material" for selection for Vietnam service. A minimum service duration of 13 weeks for subject selection therefore ensures that subjects, both veterans and controls, had an adequate health standard at the time of enlistment.

This rationale for defining mortality study subjects applies equally to morbidity study subjects. Since all 48,600 national servicemen fulfilling the above criteria will be selected for the mortality study and only 5,000 need be studied for the morbidity study, the morbidity study subjects can be a subset of mortality study subjects.

Vietnam service generally commenced 9 to 12 months after enlistment. Therefore servicemen discharged between 10 weeks and 9 months after enlistment were not eligible to become veterans. Nevertheless, they will be included, because their exclusion would prevent investigation of the relationship between morbidity and the factors associated with early discharge. If morbidity is found to be related to a history of early discharge in the control sample this will provide evidence of the magnitude of the effects on morbidity that can arise from differences which are not related to the Vietnam experience.

If necessary, these 'short service' controls could be excluded from the analysis at a later stage, to allow comparisons of morbidity to be made in veterans and controls with similar duration of army service.

3.11 Rationale for Subjects Being N.S.W. Enlistees Only

To enhance the logistic feasibility of the morbidity study it is proposed to select subjects who enlisted in N.S.W. N.S.W is chosen as it is the most populous State and the study team is physically located in Sydney, within 200 kilometers of approximately 85% of the State's residents. N.S.W. enlistees who have moved interstate will be sought and encouraged to participate. N.S.W enlistees who have emigrated from Australia will be deemed to be unavailable until they return to Australia.

The assumption underlying this state of enlistment approach is that a large majority of N.S.W. enlistees are still living in the State.

This assumption has been examined by matching former national servicemens' names and dates of birth with the Australian Electoral Register of July 1981 (see Table 3.3) and tabulating the State of residence on the register.

Approximately 6,000 veterans and 9,000 controls enlisted in N.S.W, many more than required for the morbidity survey (see sec. 3.19).

	Veteran	Control
(a) Number of Names Sought	3515	6155
Number of Names Matching	2728	4971
% of Names Matching	78%	81%
% of Names <u>Not</u> Matching	22%	19%

(b) State Distribution of Names Matching with Australian Electoral Register.

Table 3.3 State of Residence of N.S.W. Enlistees.

1981 Electoral Register State	Veteran	Control
NSW	88%	91%
VIC	2%	2%
QLD	6%	5%
SA, NT	2%	1%
WA	2%	1%
TAS	0.4%	0.4%
Not in NSW	12%	9%

The results in Table 3.3 are likely to be the best possible expectation of reality as the 19-23% not matching on the Australian Electoral Register may be more evenly spread across Australia or overseas. In addition, errors in the Electoral Register State of residence due to delays in entering change of address data are likely to over-represent N.S.W. since N.S.W. enlistees started out there.

Nevertheless, the result is encouraging, and also suggests that confining the medical examination facilities to N.S.W. may be the most economical way of executing the study.

N.S.W. enlistees are comparable to enlistees from other states in terms of distribution across corps, proportion of veterans overall, and proportion of veterans within each year of enlistment.

An alternative approach is to select current N.S.W. residents irrespective of State of enlistment. There would be the potential for major bias, in that mobility after Vietnam service could be strongly correlated with morbidity, and, in terms current State of residence, differ among the States (e.g. mobile people heading to Qld and NT).

3.12 Subject Selection

To be eligible for subject selection, a former national serviceman must fulfil the following requirements:

- (i) Served in the Army at least 13 weeks, to ensure uniform enlistment health status (see section 3.10);
- (ii) Be enlisted in an intake from which Vietnam veterans were subsequently drawn. Intakes after February 1971 contain no veterans;
- (iii) Be enlisted in N.S.W. (see section 3.11).

The pool of former national servicemen fulfilling these three criteria will be stratified by veteran/control status and enlistment intake. With regard to the total number of veterans required (see section 3.19), random selection of a constant proportion of veterans within each intake will be made.

For every intake from which veterans have been selected, 2 controls will be randomly selected for every 3 veterans.

This will ensure that both the structure of ages and chronologic years of army and Vietnam service are similar for veterans and controls.

3.13 Obtaining Subject Addresses

Inviting subjects to a medical examination requires knowledge of their current address.

Initially, address will be obtained from the Australian Electoral Register, (probably 80%) and drivers licence registers (a further 10-15%). Follow-up data from the Mortality Study would be useful in this regard. Additional negotiation will be required to obtain addresses from licence registers.

However, in the Pilot Study it was found that only 87-90% of subjects could be located using a known Electoral Register address. It is proposed therefore, that when a morbidity study subject is unable to be located through an address obtained via the mortality study, additional address searching will be carried out.

Since all subjects will be sought in the Australian Electoral Register and computerized licence registers, there will be no additional search requirement for these sources. Additional searching will involve manual drivers licence registers (Vic, Qld) the latest Electoral Register microfiche, commercial

credit bureaux, telephone books and Telecom customer files, and Social Security records, if available. It is probable that 10% of morbidity subjects will have to be sought in this way. This second stage searching, specific to the morbidity study requirement for current addresses, will be carried out concurrently with the medical examination field work, as the failure to contact a subject will only become evident at this stage.

If available, the current Australian Electoral Register tape will be used as the initial source of the addresses of subjects.

Addresses, once obtained, will be held on computer file to facilitate the control and monitoring of subject contact and participation.

3.14 Areas to be Investigated

Veterans have expressed concern about the health of themselves and their offspring in several areas. However, confining investigation to these areas alone would ignore many areas of disease which might have arisen from service in Vietnam, and which might, at a later stage, become significant to the veterans.

3.14.1 Veterans Areas of Concern

Birth defects - see Case-Control Study of Congenital Anomalies;

Death from a variety of causes - see Retrospective Mortality Study;

Cancer - to be investigated in part via the Mortality Study;

Abnormalities of behaviour (eg outbursts of rage);

Substance abuse (eg excessive use of alcohol, tobacco, illicit drugs, prescription drugs);

Relationship difficulties (eg divorce, social disabilities);

Psychiatric disorders (eg depression, anxiety);

Reproductive disorders (eg miscarriages, infertility);

Liver disorders;

Gastrointestinal disorders;

Neurological disorders of both the C.N.S. and P.N.S.;

Skin abnormalities.

3.14.2 Morbidity Related to Concomitants of War Service. - . . .

Combat injuries, disability and crippling

Psychiatric disorders (see sec. 2.3):

Post-traumatic stress disorder

Substance abuse:

alcohol - gastrointestinal ulceration, liver disease,
hypertension, degeneration of nervous system and
heart, psychoses

tobacco - chronic obstructive pulmonary disease,
respiratory tract infection, cardiovascular
disease, cancer

miscellaneous drug dependancies

Depression and anxiety disorders:

wide variety of concomitant symptoms

Somatization disorders:

wide variety of concomitant symptoms affecting nervous
system, gastrointestinal system, cardiopulmonary
system, psychosexual functioning

Infectious diseases

Only four diseases endemic to Vietnam could (arguably) still
affect veterans:

Melioidosis

Strongyloidiasis

Syphilis

Tuberculosis

All other infections will have either spontaneously resolved or become sufficiently florid to necessitate treatment and cure. Although vivax malaria can persist in a latent phase for long period of time it is not considered that this could be a significant cause of morbidity.

3.14.3 Morbidity Implicated in Herbicide Literature

Occupational studies of the long term effect of human exposure to chlorinated phenols have revealed cases of soft tissue sarcoma, and the Swedish case-control studies, suggest that phenoxy herbicides could cause soft tissue sarcoma and lymphoma (Hardell and Sandstrom, 1979, see also section 2.2).

3.15 Implications of Pilot Study Results

The Pilot Study has provided information about the value of many aspects of methodology which have been considered in the planning of this morbidity protocol. Information from the Pilot Study will also be used in the planning of detailed procedures if this present protocol is approved in principle.

Briefly, the pilot study results show that:

- o telephone and face to face interviews were more expensive (\$100 and \$95 respectively) than self-administered questionnaires (\$60) posted to the home
- o response rates were higher for telephone and face to face interviews than for self-administered questionnaires
- o veterans responded to the request for an interview more frequently than controls
- o self reports on army unit, subunit, corps and veteran status are likely to be useful

- o self reports on posting dates and operations in Vietnam are unlikely to be useful
- o self reports on exposure to chemicals in Vietnam are unlikely to be useful
- o self reports on exposure to chemicals at work and home are more likely to be useful
- o cigarette smoking was reliably reported
- o the use of alcohol was reliably reported, but with the instrument used drinking frequently was less reliably reported
- o false positive and false negative rates for conditions reported in the medical history were high, especially for conditions occurring more than one year prior to interview
- o separation of the medical history and physical examination meant that the examining physicians were hindered by a lack of contextual clues in making judgments about morbidity in the subjects studied
- o morbidity was detected in both veteran and control subjects; target conditions based on subjective responses were found at highest frequency
- o the psychology tests used were insensitive in detecting psychopathology
- o a proportion of the reports from wives on miscarriages, birth defects and handicaps in children could not be confirmed.

The implications of these findings have been considered in more detail elsewhere in this protocol.

3.16 Rationale for Using MEDICHECK Health Screening Centre

Comprehensive medical evaluation of several thousand men requires complex logistical arrangements. The MEDICHECK Centre in Sydney has extensive experience in processing large numbers of people through a medical evaluation procedure. As the majority of subjects will be living in or near Sydney,

compliance will be maximized by having the examination site in Sydney. MEDICHECK is convenient, as it is located in the centre of Sydney, close to public transport.

Detailed evaluation of the comparative economics of MEDICHECK versus AVHS - established centres has not as yet been performed. However, initial indications are that MEDICHECK compares favourably with Pilot Study costs. Apart from economics, there are other advantages of using MEDICHECK:

1. The use of MEDICHECK facilities would significantly reduce the time required to commence the medical examination of subjects and would therefore bring forward the date of reporting of the morbidity survey.
2. The experience and skill of currently employed staff ensures maximum efficiency in subject processing, even at the commencement of examinations.
3. MEDICHECK uses a computer-guided VDU-type questionnaire which is acceptable to clients, does not permit invalid or inconsistent answers, and does not require staff to administer. (It is constrained by permitting only yes/no answers and will therefore be supplemented by a pencil and paper instrument when more complex responses are required).
4. Facilities and staff are in place for blood pressure measurement, electrocardiogram, chest x-ray, pulmonary function, audiogram, anthropometric and biochemical evaluation. The Centre operates its own biochemistry and microbiology laboratories, and participates in a standards programme supervised by the College of Pathologists of Australasia.

5. The entry of all data onto computer files is the routine method of data handling, and will increase the efficiency of the morbidity study.

While the use of MEDICHECK is indicated for the above reasons, certain additions and modifications to the usual programme will be made to ensure quality control of critical items (eg blood pressure measurement) and to ensure that additional items of data of particular interest to the morbidity study are collected. These are discussed below.

3.17 Rationale for Method of Measuring Morbidity

Additions to the usual MEDICHECK programme are required to meet the requirements of the morbidity study. The data to be collected by the usual MEDICHECK evaluation and those to be collected by additional sections of the examination are listed below, along with their rationale (see section 3.14).

3.17.1 VDU Questionnaire.

Item	Rationale
Marital status	Veterans, war service
Job satisfaction block	War service
Financial status/problems	Veterans, war service
Sleep/worry	Veterans, war service
Depression and state of mind	Veterans, war service, TCDD, 2,4-D, 2,4,5-T
Drinking habits	War service
Smoking habits	War service
Exercise	War service
Tablets	War service
Bereavements and family history	Confounding variable
Coronary symptoms	War service, TCDD

Leg pain symptoms	War service, TCDD
Heart beat/hypertension	War service, TCDD, 2,4-D
Breathlessness, numbness, varicose veins	War service, TCDD, 2,4-D, 2,4,5-T
Ankle oedema symptoms	War service, TCDD
Lung problems and diseases	War service, TCDD
Abdominal diseases and history	Veterans, Vietnam service, TCDD, 2,4-D, 2,4,5-T
Sexual problems	Veterans, war service, TCDD, 2,4,5-T
VD and U/G history, infections, operations	War service, TCDD
Joint & muscle pains/arthritis	War service, 2,4-D
Neurological symptoms	Veterans, war service, TCDD, 2,4-D, 2,4,5-T
Skin disease and allergies	Veterans, war service
Vision and eye problems	TCDD, 2,4,5-T
Ear, nose and throat problems	2,4-D
Tropical diseases	Veterans, Vietnam service
Infections and miscellaneous diseases	Veterans

3.17.2 Components of the AVHS Questionnaire

Self Report of Current Conditions and Symptoms

At reception, all subjects will be asked to list all current medical conditions and symptoms, to indicate a grading of severity (from 1-trivial to 5-incapacitating) and to give a duration for each complaint. This data is being sought in addition to questionnaire data for several reasons:

- to identify intercurrent and trivial illness which may affect pathology tests (e.g. white cell count)
- to permit an unprompted description of the subject's problems, which may reveal unsuspected or unconventional symptomatology
- to improve the accuracy of clinical judgements made by the doctor about the subject's health.

Pencil and Paper Questionnaire

Item	Rationale (see section 3.14)
Occupation, employment	Veterans
Education	Veterans
Social and behavioural functioning	Veterans, war service
Marital and offspring history	Veterans, war service
Wife/partner identification	Veterans, war service
Social desirability questions	Confounding variable
Reasons for Vietnam/non-Vietnam service	Confounding variable
Combat experience	Explanatory variable
Combat injuries	Explanatory variable
Alcohol and tobacco consumption - diary of past week	War service
Other drug consumption, including tea and coffee	War service
Medical and hospital consultations - reasons, when, duration, name and address.	Confirmation of reports
Herbicide exposure in Australia	Confounding variable

3.17.3 Neuropsychiatric Screening

Test	Rationale
Interview:	Veterans, war service
present state examination	
post-traumatic stress disorder	
interpersonal relationships	
psychological well-being	
AVHS schedule of life events:	
Eysenck Personality Inventory	
Army Self Description Inventory	
Symbol-Digit Modalities Test	
Supra-Span Digit Learning Test	
Trail Making Test	
Nelson Adult Reading Test	
Army Speed and Accuracy Test.	

3.17.4 Pathology and Other Tests

Test	Rationale
Electrocardiogram	War service, TCDD
Chest x-ray	Vietnam service: tuberculosis
Spirometry	War Service
Hearing	War service
Anthropometry	War service

Test	Rationale
Blood:	
Glucose, lipids	TCDD, 2,4-D, 2,4,5-T
Uric acid	Alcohol related, 2,4-D
Liver enzymes	Veterans, Vietnam service, TCDD 2,4-D
Haematology	Alcohol, Vietnam service
Hepatitis B serology	Vietnam service
Strongyloides, melioidosis, and syphilis serology	Vietnam service
Drug screen	War service
Urine	TCDD, 2,4,5-T

3.17.5 Physical Examination

Item	Rationale
Skin	Veterans, Vietnam service TCDD
Hepatosplenomegaly	War service, TCDD, 2,4-D
Neurological screen	Veterans, war service, TCDD, 2,4-D, 2,4,5-T
Thoracic auscultation	War service, TCDD, 2,4-D
Legs - vascular, reflexes, sensation	Veterans, war service, TCDD, 2,4-D
Blood pressure	War service, TCDD, 2,4-D
Auditory canals and tympanic membranes	Confounding variable in hearing testing

In addition, the examining doctor will have the questionnaire responses for each subject, and will elicit additional historical details and additional examination findings as indicated by the

history. He will then record all physical signs found and make clinical judgements as to the presence or absence of particular conditions (see section 3.14), and record other diagnoses suggested by the data. Later, when test results are available he will have the opportunity to modify or add to his clinical judgements.

3.17.6 Hierarchical Structure

One component of the on-site medical examination will be conducted on a sample of subjects only. This is the phase 2 neuropsychiatric evaluation. This area is of particular importance to veterans and relates directly to the putative effects of both war service and herbicide exposure. It is therefore desirable that detailed evaluation be carried out in this area. As this will require 1 hour of additional testing per subject, it is not feasible to evaluate all subjects without reducing the total number of subjects studied.

A random sample of 10% of all subjects plus subjects with high scores on the neuropsychiatric screen will undergo additional testing. This allows for accurate diagnosis of those with suspicious scores on the screening test, and the evaluation of the random sample of non-high scorers will enable inferences to be made about the prevalence of psychopathology in the total sample.

3.17.7 Referral Policy

3.17.7.1 Referrals Indicated for Medical Reasons

Any subject with illness requiring treatment or urgent investigation will be referred back to his local doctor, with a brief note from the MEDICHECK physician explaining the problem and asking for follow-up information. Subsequent investigation and treatment would be arranged by the local doctor.

With the prior approval of each subject, a summary of the complete evaluation will be sent to his local doctor.

3.17.7.2 Options for Referrals Indicated for Research Reasons

For some subjects, although there may be no indication for treatment or urgent investigation, there may be symptoms and/or signs which cannot be explained without specialist consultation or referral.

There are two alternative methods for obtaining the opinions of medical specialists in regard to subjects who are thought by the examining doctor to be suffering from a medical condition that the doctor is not able to diagnose accurately.

The first alternative (option A) is to confine specialist examination to the 3 areas of particular concern to veterans and of significance in relation to herbicide exposure. These are dermatology, gastroenterology and neurology. For this option, if the examining doctor is of the opinion that the subject has a condition in any of the 3 areas of interest which the doctor is not able to diagnose accurately the subject will be referred to co-operative specialists for full clinical evaluation at AVHS expense. The results of the clinical evaluations of all subjects referred would then be available at the time of data analysis.

The second alternative (option B) is to perform the standard medical examination on all subjects prior to referral of any subjects, and at the stage of analysis, if the data suggested that veterans were suffering from particular forms of disability more frequently than controls, selected veterans and controls would be referred to the

appropriate specialists. This approach has the advantage that there is no prejudgement of areas requiring specialist assistance, thereby throwing the net wider to catch unexpected areas of morbidity; specialist evaluation (and consequent expenditure) is confined to those areas in particular need of investigation; the number of subjects to be investigated is much more readily controlled than would be the case with a comparatively open-ended referral system; referral is confined to those subjects that, on full consideration of all data, have inexplicable disabilities.

Difficulties are that in the interval between initial examination and subsequent referral some subjects will have changed addresses, and therefore all subjects will be required to notify the Study of all changes of address; subject motivation may have waned, resulting in lower compliance rates. Option B will also delay the completion of the study.

In both option A and option B specialist reports would be made available to the Study.

3.17.8 Questionnaire for Wife/ Female Partner

Considerable anxiety has been experienced by veterans in relation to decreased fertility and abnormal reproductive outcomes. The separate Case-Control Study of Congenital Anomalies has addressed part of this area, but not infertility, death or disability of offspring, or miscarriages.

These will be investigated using a structured telephone interview with the current and previous partners. Attention will be confined to

women who have cohabited with the subject for at least 12 months (or who became pregnant while cohabiting for a lesser period). If contact cannot be made by telephone, a home visit will be made to all wives who live in a capital city, otherwise a postal questionnaire will be sent, to be completed at home. There is no requirement for the partner or children to be present at the examination site, as all abnormal pregnancy outcomes will be verified through medical records. For any treatment received in relation to these outcomes, the year of treatment and name and address of the doctor or hospital will be obtained, to allow verification of the data supplied.

For all children biologically fathered by the subject the following data will be sought (from the most recent child, back in time):

Sex and birthdates

Difficulties with any pregnancies

Disabilities or death of any of the children.

Additional data will also be obtained:

Miscarriages leading to curettage in hospital

Mothers date of birth.

3.18 Physician Assessment

Based on a retrospective assessment of Pilot Study data, two AVHS physicians made judgments about the presence and absence of a number of target conditions, taking into account the symptoms, physical signs and results of special tests. This work has also been incorporated in the Pilot Study Report.

The following recommendations can be made about the need for physician assessments in the proposed morbidity study:

- (i) An assessment by a physician has high face validity, provided that it is based on a contextual analysis of symptoms, signs and results of special tests. Therefore, in the proposed study each subject should have a brief interview (15 minutes) with a physician, working in the MEDICHECK environment, who will:
- o assess the results of the MEDICHECK and pencil and paper questionnaires
 - o ask additional direct questions
 - o carry out a physical examination
 - o record judgments about:
 - the quality of the history
 - the presence of designated signs
 - the presence of designated conditions
 - other morbidity
 - o re-assess his judgments when the results of special tests have been made available.
- (ii) No case can be made for separating the assessment of the history from the assessment of signs and special tests.
- (iii) To minimise subjective bias in physician judgments, objective indices should be sought, wherever possible, to support the judgments based on the assessments of symptoms and signs.

For example, to precisely document the prevalence of peripheral neuritis in veterans and controls, a "council of perfection" would be to recommend that clinical examination and nerve conduction studies by a trained neurologist be carried out on (a) all subjects with symptoms and signs suggestive of peripheral neuritis and (b) a random selection (e.g. 1 in 20) of subjects.

However, such an option is probably precluded by considerations of cost and acceptability to subjects. The lesser option, i.e. of referral on the basis of suspected signs alone, would be less informative because of the subjective nature of neurological signs when elicited by a physician who is not a practised neurologist.

- (iv) Ideally, the physicians who carry out the 15 minute interviews and assessments at MEDICHECK should have post-graduate training as physicians (i.e. FRACP qualifications or MRCP) or general practitioners (FRACGP), and they should be specially selected for the purpose of this study.

- (v) The exact protocols and proformas for the recording of physicians judgments will be finalised after consultation between MEDICHECK physicians and AVHS physicians.

3.19 Rationale For Number of Subjects

The number of subjects to be examined is influenced by several constraints:

- o The need to complete examinations in 12-18 months to allow the submission of a report in an appropriate time frame.
- o The total number of subjects available that fulfil the criteria outlined above.
- o The need for the study to have sufficient power to detect moderate relative risks for conditions of interest possibly associated with Vietnam service.
- o The need to have sufficient numbers of veterans to test the hypothesis that variables such as combat exposure, herbicide exposure and corps, are predictive of morbidity within the Vietnam cohort.

Approximately 120 subjects could be examined per week, for a total of 5,760 in a 48 week period. Taking into account delays introduced by not being able to locate subjects at known addresses, and initial failure of some subjects to keep examination appointments, a more realistic total in one year is probably 5,000 subjects.

As approximately 6,000 veterans and 9,000 controls enlisted in N.S.W., total numbers available are adequate.

For 5,000 subjects, maximum study power is achieved when the numbers of veterans and controls are equal (2,500 of each). Increasing the number of veterans studied to 3,000 (to increase power in relation to explanatory variables within the veteran group) and reducing the number of controls to 2,000 reduces the power of veteran/control comparisons by 4%, a minimal loss. The effect on study power of further increasing the number of veterans is shown in Table 3.4.

Table 3.4 Effect of Veteran/Control Ratio on Power.

Veterans	Controls	Loss of efficiency
2,500	2,500	0%
3,000	2,000	4%
3,500	1,500	16%
4,000	1,000	36%

Therefore, it is proposed to examine 3,000 veterans and 2,000 controls.

For selected conditions of particular interest, the minimum relative risk that would be detected (80% power, $P_{(1)} = 0.05$) is shown in Table 3.5. The expected prevalence rates are mostly derived from complaints of controls in the Pilot Study. A more detailed table is given in Appendix 1.

Table 3.5 Minimum Relative Risks Detectable as Statistically Significant with 3,000 Veterans and 2,000 Controls

Condition	Estimated prevalence	Minimum Relative Risk
Anxiety	10%	1.2
Sleep difficulties	16%	1.1-1.2
Depression	10%	1.2
Temper outbursts	20%	1.1-1.2
Hypertension	5%	1.3-1.4
Numbness and tingling	5%	1.3-1.4
Dizziness	7%	1.2-1.3
Loss of strength	5%	1.3-1.4
Severe acne	3%	1.3-1.4
Burning /itching of skin	13%	1.1-1.2
Persistent rash	13%	1.1-1.2

Up to 100 deaths are anticipated to have occurred since discharge (18 months to 2 years post enlistment) in this cohort of 7,000. These will be detected via the mortality study.

A minimum detectable relative risk of 1.4 for the common conditions of interest indicates that 5,000 is a satisfactory number of subjects. Rare conditions such as melioidosis, strongyloidiasis and syphilis will, if significant causes of morbidity among veterans, have much larger relative risks than 1.4. Lack of adequate general population prevalence rates makes power estimation impossible. Rare manifestations of common exposures such as

alcohol (eg Korsakow's psychosis) are not of relevance here, as there are much more common manifestations that will allow evaluation of veteran/control differences arising from any differences in patterns of alcohol use.

Any infrequent but distinctive effect of Vietnam service or herbicide exposure might be provisionally identified on clinical grounds even if its frequency was not statistically increased in veterans (e.g. 6 cases in veterans, none in controls). For instance, there would be only 2 or 3 cases of a condition with the incidence of multiple sclerosis in this group of 5,000 men.

This study will not specifically investigate cancer incidence for the following reasons:

- i. The study would have very low power to detect veteran/control differences due to the infrequency of cancer in this young age group.
- ii. The mortality associated with cancer would reduce the number of subjects giving a past history of cancer.
- iii. Subjects with cancer may not be sufficiently well or motivated to present for medical examination.
- iv. The long latent period for developing cancer.

3.20 Index of Herbicide Exposure

3.20.1 Objective Determination of Herbicide Exposure

Determining individual herbicide exposure in Vietnam from spraying mission and troop movement data is considered in other reports (Adams et al., 1981).

3.20.2 Subjective Reports of Herbicide Exposure

The relationship between subjects reporting of herbicide exposure and morbidity will be difficult to interpret for several reasons:

- The events occurred 12 to 17 years ago and therefore recollection is likely to be inaccurate.
- At the time the spraying was taking place the soldiers did not know what chemicals were being sprayed.
- It may be anticipated that as a result of the publicity surrounding the issue and the desire for compensation those subjects with morbidity will be more likely to recall being sprayed independent of whether they were actually sprayed.

It may be possible to analyse this latter problem, one of recall bias, by determining the relationship between current morbidity, reported exposure to herbicide and the likelihood of herbicide exposure determined by the HOPPS programme. In spite of this potential bias it is important to collect and assess the utility of subjective reports of herbicide exposure.

3.20.3 Quantity of Herbicide Sprayed Each Year

The volume of herbicide sprayed in the RANCH HAND programme in Phuoc Tuy in each year of the Vietnam War is known (Table 3.6).

Table 3.6 Annual Herbicide Usage in Phuoc Tuy Province by Agent According to HERBS Tapes 1965-1971

Amount of RANCH HAND herbicide sprayed in Phuoc Tuy (in thousands of litres)				
Year	Agent			Total
	Orange	White	Blue	
1965	90	-	-	90
1966	200	-	-	200
1967	490	140	50	680
1968	240	570	-	810
1969+	-	-	-	-
Total	1020	710	50	1780

Thus the chronologic year of service in Vietnam is useful as an explanatory variable, although herbicide usage and level of combat are probably highly correlated.

3.20.4 Exposure to Herbicide in Australia

If herbicide exposure does have a measurable effect on morbidity, the relationship between herbicide exposure in Vietnam and current morbidity is potentially confounded by herbicide exposure in Australia. Therefore data will be sought from subjects on occupational exposure to herbicides.

3.21 Index of Combat Exposure

American literature suggests increased prevalence of war-related disorders amongst those troops closest to the 'front-line' of combat (Penk et al., 1981). In analysing relationships within the veteran group it is therefore important to assess the degree of combat or danger to which veterans were subjected. This will be done in several ways:

1. Chronologic Year of Vietnam Service.
The risk of death or wounding as a function of year of Vietnam service will be determined and used as an explanatory variable.

2. Corps
Subject's Corps will be used as an explanatory variable, as some Army Corps (Engineers, Infantry, Armoured, Artillery, Signals) engaged in contact with the enemy, and other did not.

3. Subjects Injured in Combat
The Central Medical Record of each subject will be reviewed

and the presence of any combat injuries recorded, along with their nature, cause and duration of hospital treatment (see section 3.22.2).

4. Casualty Rate of Units (Combat Index)

With 'Casualty Reports' (the completeness of which is not yet known) and Vietnam Unit postings data, the incidence of combat wounds and deaths will be compiled for all Units, if feasible. With data on each subject's Vietnam postings from his CARO dossier (see section 3.22.1) the risk of combat injury and death will be calculated for each subject.

5. Subjective Combat Exposure

Figley (1980) has developed a questionnaire which quantifies combat exposure, which he has validated on a small sample. Only minor modification is required to make it applicable to Australian Vietnam veterans. Only veterans will be asked to complete this instrument, as it is not applicable to controls.

3.22 Army Dossier Data Held on Each Subject

The personal (CARO) dossier, Central Medical Record and psychology record cards together contain a wealth of information about almost every aspect of a serviceman's period of service. This material is potentially available, is not subject to recall bias, and constitutes a valuable source of baseline data for each subject, enabling comparisons of veterans and controls at the time of enlistment and during the period of service. More specific uses of these data are outlined below.

For all 5,000 subjects it is proposed to extract certain data from these records for use in the analysis and interpretation of findings from the medical examinations and to compare the enlistment and Army service characteristics of subjects who present for examination with those who do not. The extraction of these data therefore need not precede the medical examinations, but will be concurrent.

3.22.1 CARO Dossier

Data to be extracted:

Verification of veteran/control status

Verification of Vietnam postings for veterans.

Disciplinary proceedings

Promotions

Volunteer/ballotee

The CARO dossiers of all current and former members of the army are held in the Central Army Records Office (CARO) in Melbourne, except for those of serving Officers (Military Secretary's Office, Canberra).

These data will be used to derive each subject's risk of combat injury or death (Sec. 3.21), and to see if ability in the army or disciplinary problems are related to current morbidity and social and psychological functioning.

3.22.2 Central Medical Record:

Data to be extracted:

1. From enlistment medical examination:

Weight, height

Significant past medical history

PULHEEMS rating (Army fitness ratings, see Appendix 2).

2. Hospital admissions:
 - Type of disease
 - Duration of admission
 - Residual disability
3. From discharge medical examination:
 - PULHEEMS

These data will be used to determine to what extent current morbidity existed at the time of army service, or has arisen subsequently.

3.22.3 Psychology Record Card

Three types of data will be extracted from the psychology record card:

- i. Enlistment psychology test results.

The comparison of these test results between veterans and controls, and with scores obtained when retesting subjects 10 to 15 years later, will permit valuable comparisons of veteran and control subjects both prior to and after army service. The relationship between test scores and subsequent morbidity is also of interest.
- ii. Corps preferences expressed by recruits.

The preferences for corps reflects the desire of a member for combat (e.g. prefers Armoured, Infantry, etc) or non-combat (e.g. Ordnance, Catering, Band, Transport) roles, and are therefore potentially valuable explanatory variables in analysing the relationship between desire for Vietnam service and subsequent morbidity. The completeness of these data is adequate, although not 100%.

iii. Referral for Psychological Opinion.

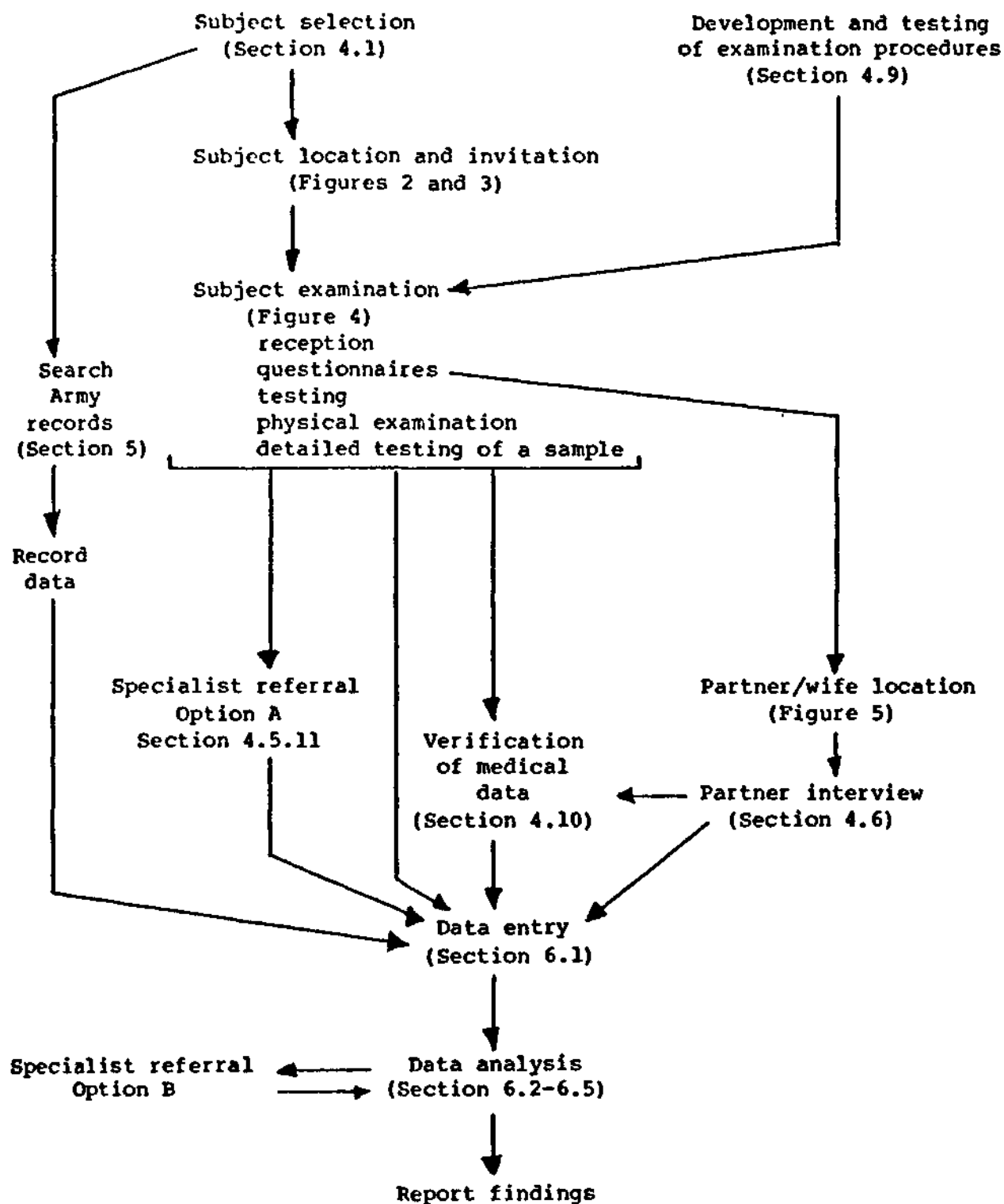
The referral of a soldier for psychological evaluation may bear significantly on current morbidity and therefore such data will be obtained.

Data from all three types of records will be transferred directly onto a data entry sheet for ease of computer entry and analysis.

4. STUDY PROTOCOL

The outline of the design of the Morbidity Study is shown in Figure 1.

Figure 1. Overall Plan of the Morbidity Study



4.1 Subject Selection

4.1.1 Definition of Veteran Status

A Vietnam veteran is a national serviceman who served at least 13 weeks who went to Vietnam within two years of enlistment during the period of the war, irrespective of the duration of Vietnam service, and who was discharged alive or survived for two years after enlistment.

4.1.2 Definition of Control Status

A 'control' subject is a national serviceman who served at least 13 weeks, who did not go to Vietnam but was drafted in an intake from which national servicemen were sent to Vietnam (June 1965 to February 1971), and who was discharged alive or survived for two years after enlistment.

4.1.3 Process of Subject Selection

- Former Vietnam war period national servicemen only;
- N.S.W enlistees only;
- Date of original enlistment February 1971 or before;
- Served at least 13 weeks;
- Discharged alive or survived for 2 years post enlistment, whichever occurred first;
- Randomly select a uniform proportion of veterans from all intakes to yield 3,000 veterans;
- Randomly select 2 controls for every 3 veterans from each intake (to yield 2,000 controls);
- Randomly allocate veterans and controls to 10 blocks, each with 300 veterans and 200 controls;

- Blocks of subjects are invited to participate sequentially until 5,000 subjects have been examined. For the subjects within each block selected, full measures will be taken to maximize the participation rate (see section 4.3).

4.2 Obtaining Current Address

Current addresses will be sought only for the 5,000 subjects selected.

1. Current serving member of the army. Address from CARO and serving unit. If not a current serving member, go to stage 2.

2. Subjects names matched with computerised registers:

Current Electoral Register, and
N.S.W drivers licence register, and
S.A. drivers licence register, and
N.T. drivers licence register, and
Tas drivers licence register, and
(possibly) W.A. drivers licence register.

If a name matches and an address(es) is found, it is stored on the study subject file.

If no match occurs go to stage 3.

3. Subject whose names are unmatched after stage 2:

Names matched with manual registers:

QLD drivers licence register, and
Vic drivers licence register, and
Immigration and Ethnic Affairs 'arrivals and
departures' microfiche.

If a name matches and an address is found it is stored on the study subject file.

Note: Matching in stages 1,2, and 3 has been performed in the Mortality Study.

4. Subjects whose names are unmatched after 3:

Names matched with:

Commercial credit bureaux and

Criminal Records Bureau (if available), and

Department of social Security files (if available).

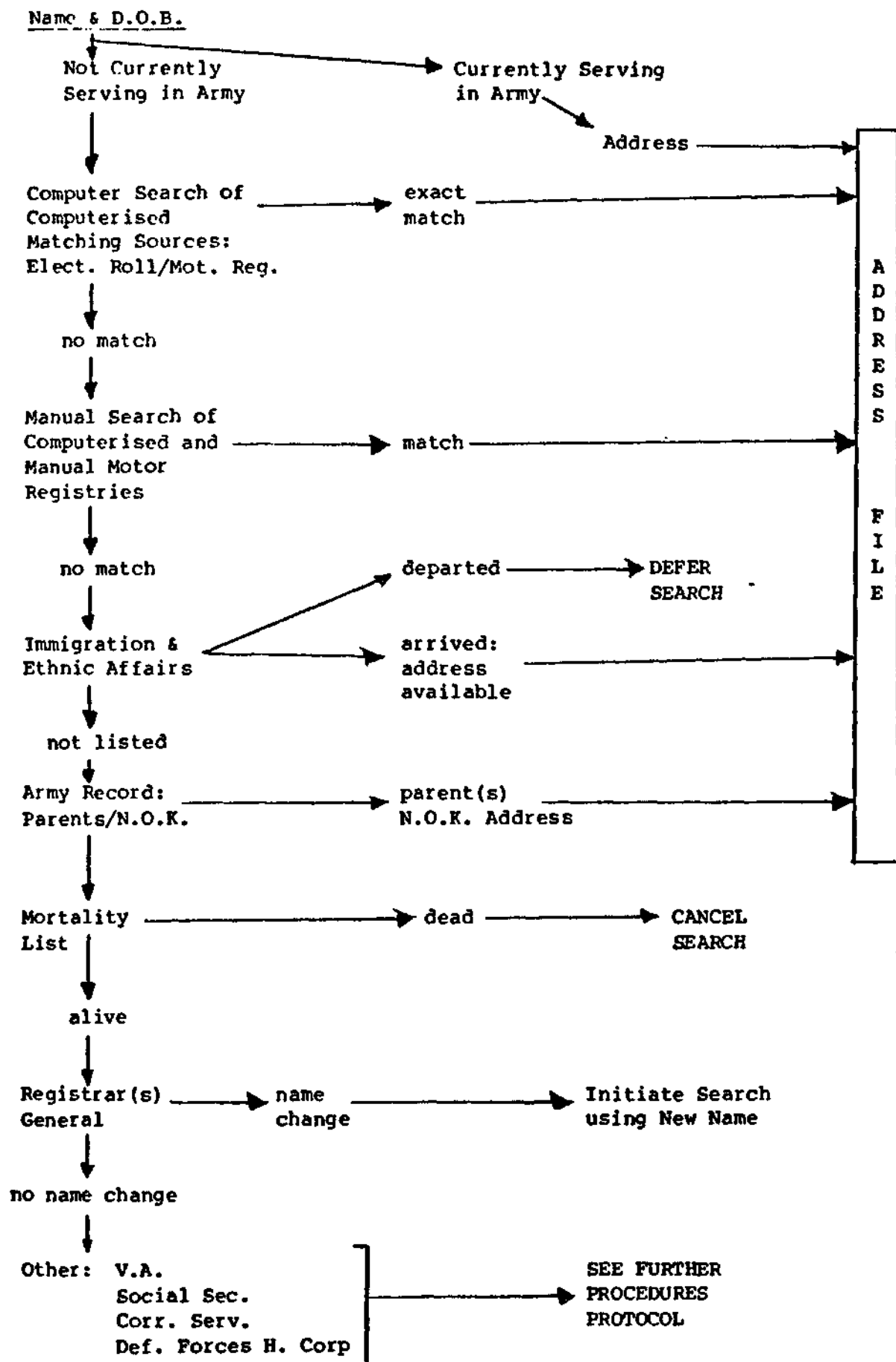
If a name matches and an address is found it is stored on the study subject file.

5. If an address is found, yet subsequent tracing fails to locate the subject, the name will be matched with those registers in stages 2,3 and 4 not yet used for that name. This stage can only occur after an attempt at initial contact has been made.
6. Once an address has been found, telephone books and Telecom will be consulted to obtain a home telephone number if required.

See Figure 2 for plan for obtaining subject addresses.

Figure 2

Schematic Address Tracing Procedures



4.3 Methods of Obtaining Compliance for Medical Examination

4.3.1 Contact Procedures

For each address obtained, a sequence of contacts will be made until an appointment is made for the subject to attend for examination (see Figure 3). A record will be kept of all attempts made to contact each subject. For subjects living in the country, telephone calls will be substituted for personal visits.

Stage 1.

Sequence until contact made:

1st mailing - introductory letter followed by an appointment card.

2nd mailing - letter plus appointment card.

Telephoning (if possible)

Personal visit to enlist participation.

If no contact has been made with the subject go to stage 2A.

If contact has been made with the subject but he has not presented for medical examination, go to stage 2B.

Stage 2A

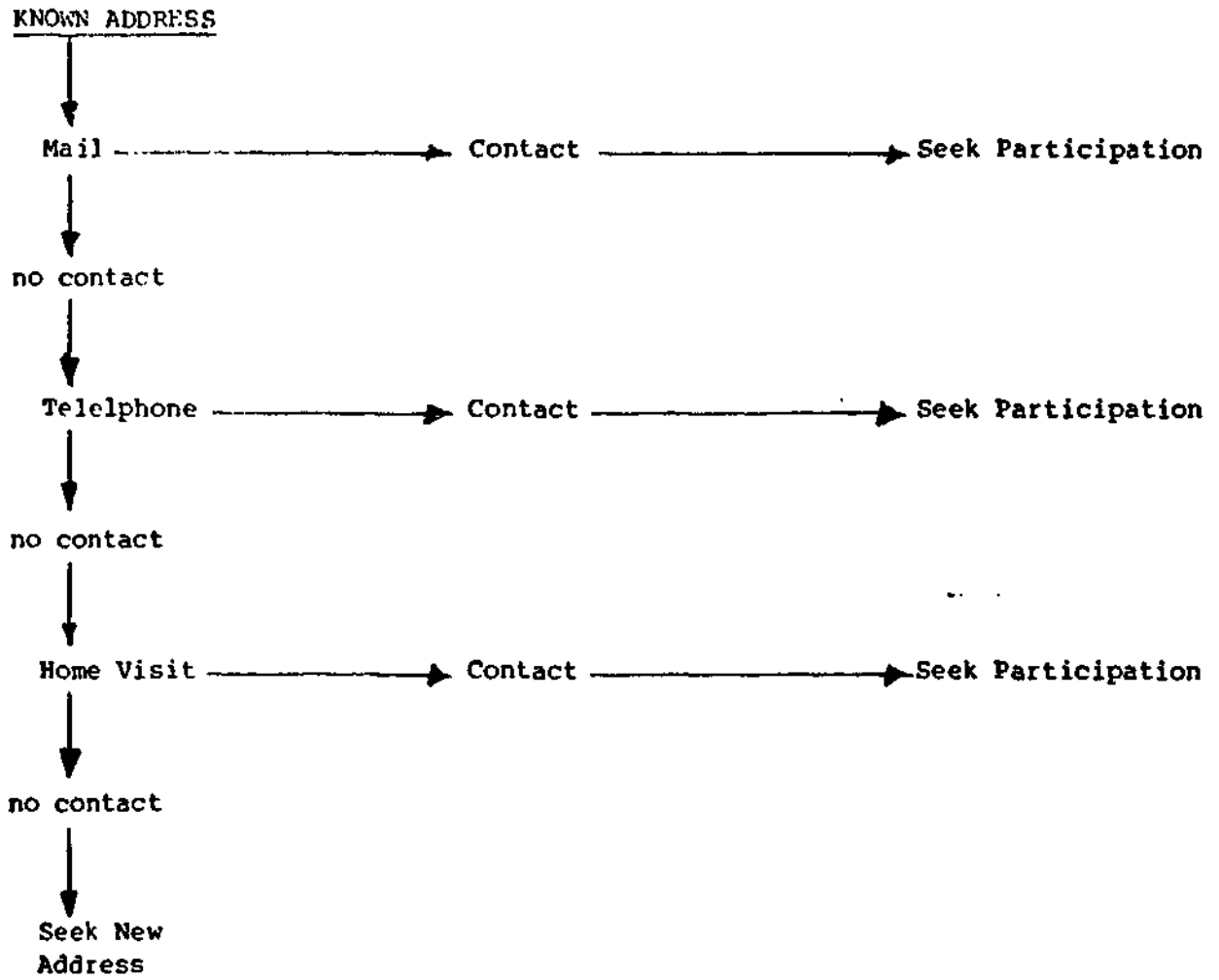
Seek new address, firstly by visiting or telephoning the most recent address found on register searching, and then if no contact is made, seek another address on the registers (see section 4.2, stage 5).

Stage 2B

Contact subject again by telephone and make another appointment. If 2nd appointment not kept, or no telephone contact possible, make personal visit to arrange appointment if the subject is a capital city resident. If the subject still fails to attend, see section 4.7.

Figure 3

Male Subject Contact Procedures



4.3.2 Financial Compensation

Full economy class return fares for travel between home and the examination site by taxi, country train or aeroplane will be paid to all subjects. Full compensation for lost earnings will be provided to the subject or his employer upon receipt of appropriate documentary evidence.

4.3.3 Additional Means of Maximizing Compliance

A covering letter signed by the Minister for Veterans' Affairs will be sent to all subjects, mentioning that the investigation is supported by the leaders of the major political parties, the Returned Servicemen's League and the Vietnam Veterans Association of Australia, if such endorsement can be obtained. Advertisements and feature articles and programmes in the public media would be valuable.

4.4. Outline of Design of Medical Examination

All subjects presenting for examination will undergo:-

V.D.U. questionnaire

Pencil and paper questionnaire

Neuropsychology and psychiatric screening tests

Blood and urine testing

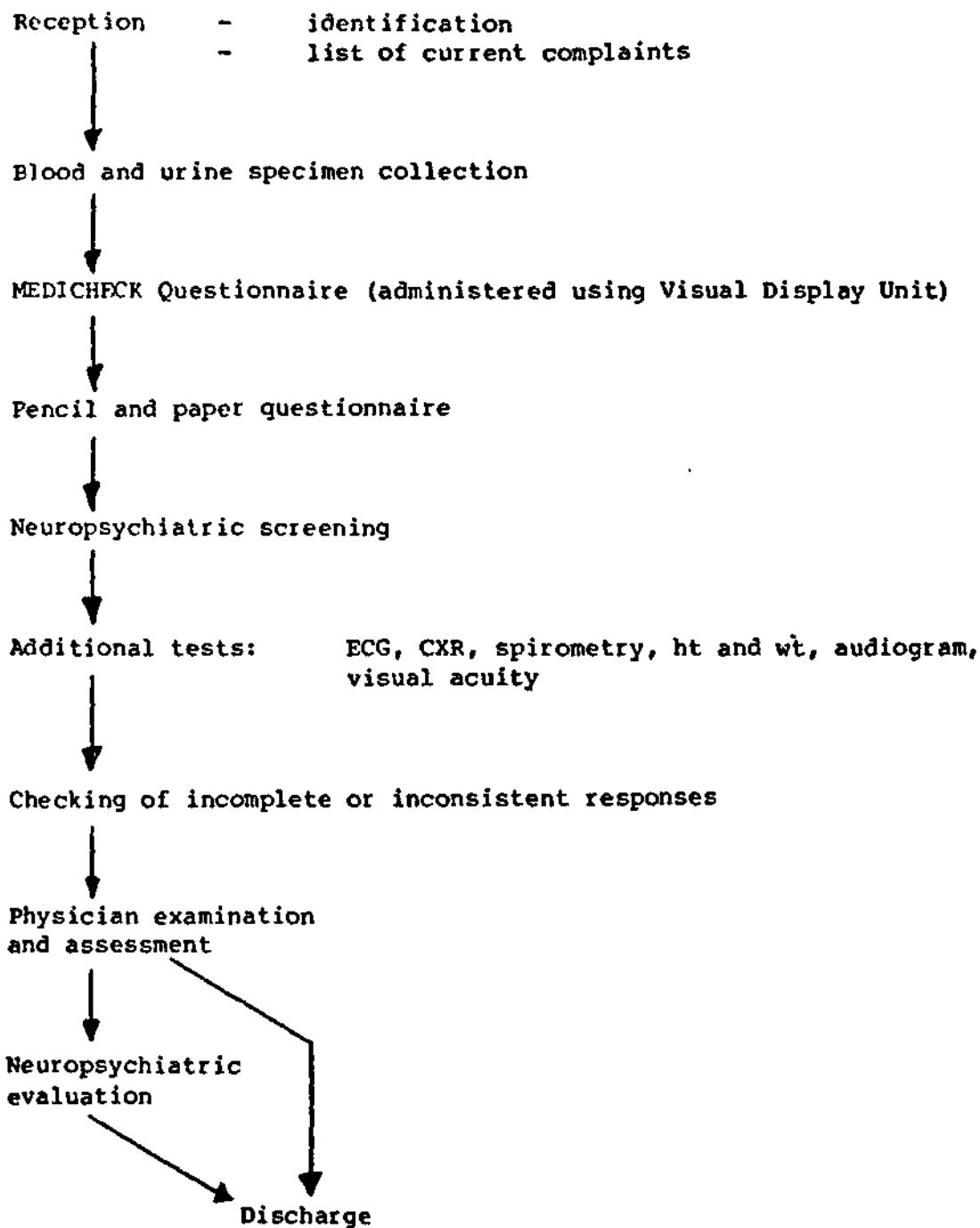
Electrocardiogram, lung function test, chest x-ray, hearing and vision test, height and weight measurement

Physical examination and evaluation by a doctor

See Figure 4 for plan for medical examination.

Figure 4

Plan For Medical Examination



High scorers on the neuropsychiatric screen plus a 10% random sample will undergo detailed neuropsychiatric testing.

Under option A subjects with suspected undiagnosed gastroenterologic, dermatologic or neurologic conditions will be referred to appropriate co-operative specialists for full clinical evaluation. Under option B, any referrals for specialist opinion for research purposes will depend upon the results of initial analyses of the morbidity profiles of veterans and controls (see 4.5.11).

The current and previous wives/female partners will be interviewed by telephone, and failing that will be interviewed at home or sent a pencil and paper questionnaire, to be returned by mail.

Subjects who are located but do not present for examination will be asked to complete as much of the questionnaire (all pencil and paper) as possible, and give a blood and urine sample.

Subjects will be referred to their local doctors for management, where indicated on clinical grounds.

4.5	<u>Design of Examination Procedure for Subjects</u>	MEDICHECK
4.5.1	<u>Reception</u>	component
	Name taken and identified on subject list.	yes
	Given written request to answer all questions as honestly and completely as possible.	no
	Given form to describe (unprompted) all current complaints, with severity and duration.	no

4.5.2 Blood and Urine

Samples taken yes

Blood tests:

Biochemistry

Glucose, lipids, electrolytes, urea, creatinine yes

Liver enzymes, serum protein yes

Drug screen* - benzodiazepines, salicylate no

Alcohol* no

Microbiology

VDRL Screen* no

Melioidosis and strongyloides serology* no

Hepatitis B serology* no

1. Core antibody - indicator of past infection.
2. Surface antigen if core antibody (+)
- indicator of current infection.
3. Be antigen if surface antigen (+)
- indicator of infectiousness.
4. Surface antibody if surface antigen (-)
- indicator of resolved infection.

* Contractual arrangements with additional laboratories will be required for these tests.

MEDICHECK
component

Hematology

Hb, MCV, MCHC yes

WCC, ESR yes

Platelet count yes

Urine tests

Culture yes

'Dipstix' chemical testing - Hb, protein,
glucose, bilirubin, pH yes

Additional serum for storage no

4.5.3 MEDICHECK Questionnaire yes

Questions in Yes or No format, will cover the following
areas:

Marital status

Job satisfaction block

Financial status/problems

Sleep/worry

Depression and state of mind

Drinking habits

Smoking habits

Exercise

Tablets

Bereavements and family history

Coronary symptoms

Leg pain symptoms

Heart beat/hypertension

Breathlessness, numbness, varicose veins

Ankle oedema symptoms

Lung problems and diseases

Abdominal diseases and history

Sexual problems

VD and U/G history, infections, operations

Joint & muscle pains/arthritis

Neurological symptoms

Skin disease and allergies

Vision and eye problems

Ear, nose and throat problems

Tropical diseases

Infections and miscellaneous diseases

The questionnaire will take up to 40 minutes to complete.

4.5.4 AVHS Questionnaire

no

Pencil and Paper Questionnaire:

Occupation, employment

Education

Marital and offspring history

Wife/partner identification

Reasons for Vietnam/non-Vietnam service

Combat experience

Combat injuries

Alcohol and tobacco consumption - diary

Chemical exposure in Vietnam

Exposure to noxious substances

Other drug consumption including tea and coffee

Medical and hospital consultations

- reasons, when, duration, name and address.

Medical record release

Herbicide exposure in Australia

4.5.5 Neuro-Psychiatric Screen

Interview by clinical psychologist, assessing psychiatric pathology using the Present State Examination (PSE), assessing post traumatic stress disorder, interpersonal relationships, and psychological well-being. no

Tests of psychological functioning, given to all subjects:

AVHS schedule of life events

Eysenck Personality Inventory

Army Self Description Inventory

Symbol-Digit Modalities Test

Supra-Span Digit Learning Test

Trail Making Test

Nelson Adult Reading Test

Army Speed and Accuracy Test.

4.5.6 Additional Tests

Electrocardiogram yes

Chest x-ray yes

Spirometry yes

Audiogram yes

Visual acuity yes

Height and weight yes

While these tests are being performed, the AVHS questionnaire and neuropsychiatric screen will be checked for completeness and consistency of answers, and the neuropsychiatric tests will be scored, to determine whether the subject needs further psychiatric or neuropsychological testing as a 'high scorer'.

If incomplete or inconsistent answers are detected, the interviewer will ask the subject to correct his answers at the end of the 'Additional Tests' section.

4.5.7 Doctors Examination and Evaluation

The examining doctor will have the results of the MEDICHECK questionnaire and the AVHS questionnaire, and will seek further information from the subject to guide his/her clinical formulation of the subject's morbidity.

Physical examination will be directed toward arriving at a conclusion about problems suggested by the questionnaires and the history. In addition, examination will be directed toward detecting abnormalities in the following areas:

Skin

Hepatosplenomegaly

Neurological screening examination

Thoracic auscultation

Legs - vascular, reflexes, sensation

Blood pressure

Auditory canals and tympanic membranes (to facilitate interpretation of audiogram)

Blood pressure measurement and ear examination could be performed by technicians.

The doctor will then record all physical signs found and his clinical impression in the form of differential diagnoses, with confidence ratings. Three days later, when the results of pathology tests are available, he will have an opportunity to reassess and modify or add to his list of possible conditions.

4.5.8 Detailed Neuro-psychiatric Assessment.

Subjects who are 'high scorers' on the neuropsychiatric screen plus a 10% random sample will undergo detailed neuropsychiatric assessment consisting of both pencil and paper tests:

Hostility Questionnaire

Spielberger Anxiety Scale

Depression Questionnaire.

4.5.9 Specialist Referral

Two options have been identified with respect to specialist referral:

Option A: If, in the opinion of the examining doctor, a neurological or gastroenterological condition is suspected, he will be referred to specialists who have agreed to co-operate with AVHS. The specialist will carry out a full evaluation as warranted by the subject's symptoms and signs.

If, in the opinion of the examining doctor, a subject has an unusual skin condition, or if any doubt exists about the diagnosis of a skin

condition, the subject will be referred to a dermatologist for consultation.

Option B: At the stage of data analysis the frequencies of disabilities will be compared for veterans and controls. If, after adjusting for the relevant confounding variables (e.g. alcohol consumption in the case of liver disease), an apparent excess in veterans is evident, the affected veterans and controls will be identified on the subject file. Within this group, samples of veterans and controls with no obvious clinical explanation for their examination findings will be referred to the appropriate specialist for full clinical evaluation.

The arrangement between AVHS and specialists will provide for a full report to be sent to AVHS with regard to every subject referred.

4.5.10 Local Doctor Referral

If, in the opinion of the examining doctor a subject has a condition requiring treatment he will be advised to consult his local doctor immediately.

With the prior approval of each subject, his medical report (including specialist reports, if applicable) will be sent to his local doctor.

4.6 Information From Wife/Female Partner

4.6.1 Definition

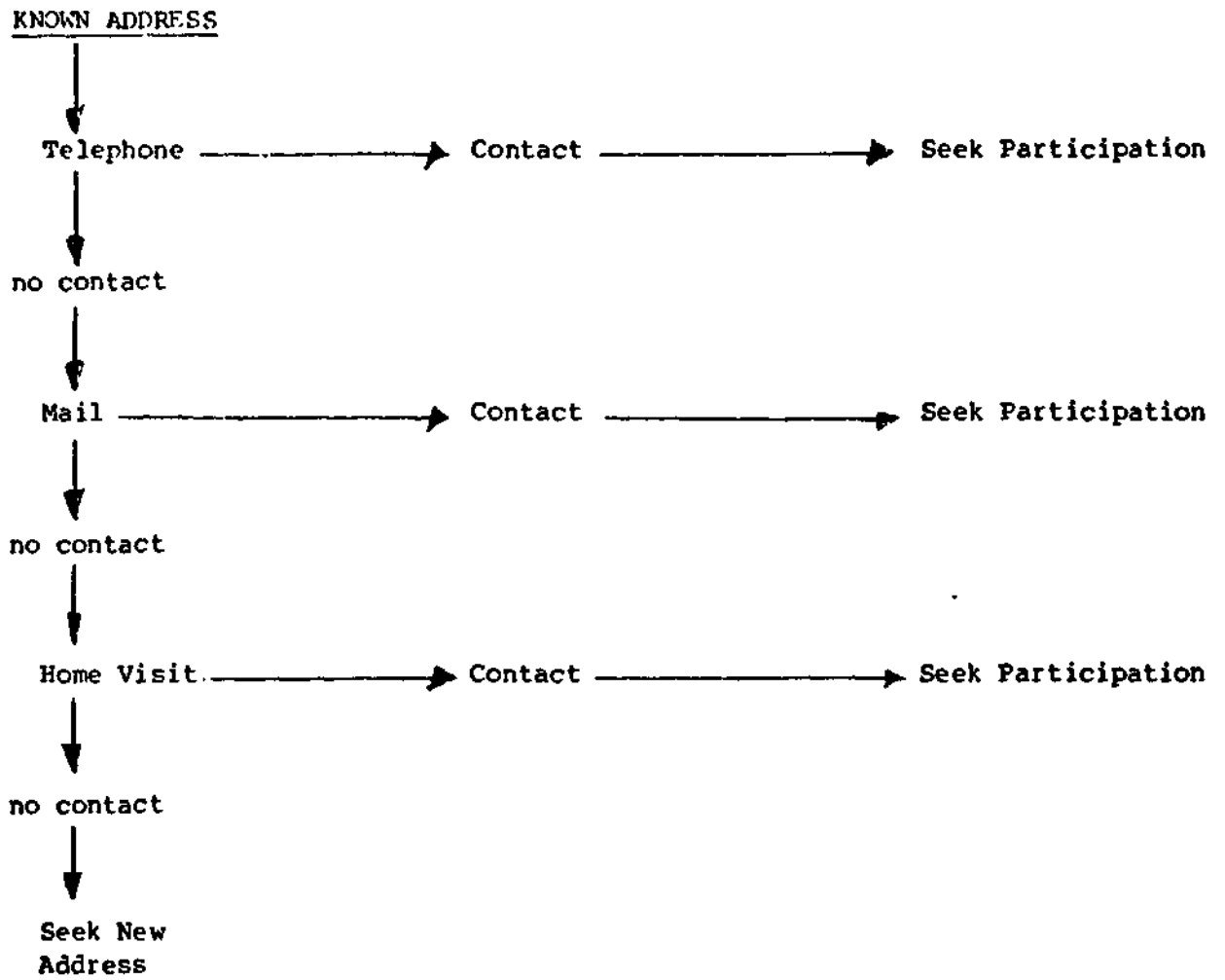
A partner will be any woman who has cohabited with the subject for at least 12 months, or who became pregnant while cohabiting for a lesser period. Thus each subject could have more than one partner.

4.6.2 Verification of Address

All subjects will be asked to provide the full names, dates of birth, telephone numbers and current addresses of their partners, if known. For partners where the address is unknown, it will be sought on the Electoral Register microfiche, and then telephone number sought in telephone directories (see Figure 5).

4.6.3 Figure 5

Plan for Partner Follow-up



4.6.4 Questionnaire

A structured telephone interview will seek the following information, for the most recent pregnancy and then for any other pregnancies going back in time:

Mothers date of birth.

Outcome of pregnancy

Difficulties with the pregnancy. (If yes, year and name of treating doctor or hospital).

Miscarriages leading to curettage in hospital. (If yes, year and name of treating doctor).

For each child biologically fathered by the subject:

sex and birthdate

Congenital anomalies or death (If yes, year and name of treating doctor).

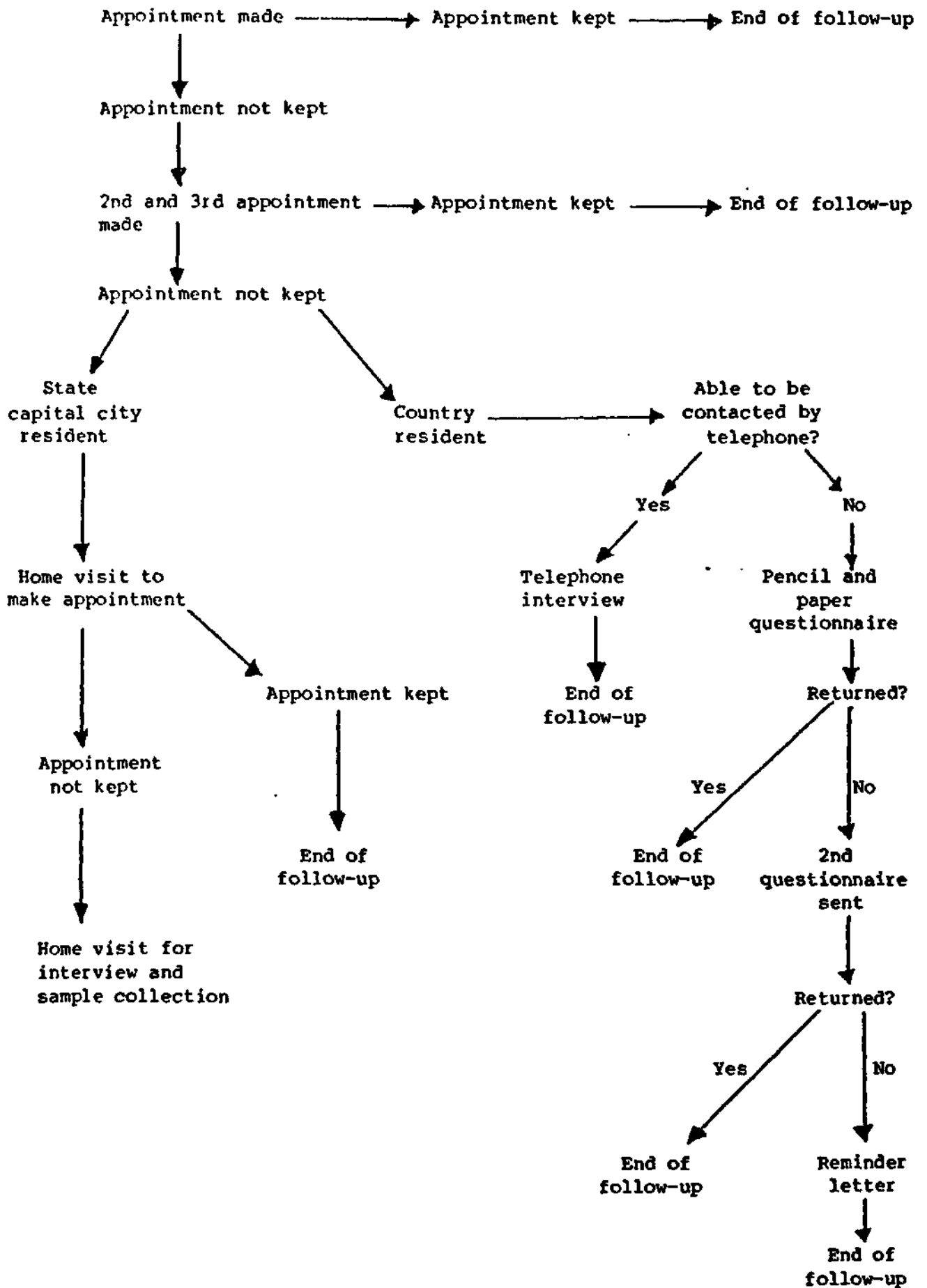
A medical record release will be sent to participating partners for signature and return by mail.

4.7 Follow-Up of Non-Complying Subjects

4.7.1 Additional Strategies for Obtaining Compliance.

If a subject fails to present for examination after 3 appointments have been made, or, if at an earlier stage he expresses a desire not to present for examination, he will be contacted at home and a modified health evaluation performed. This contact will be by telephone if the subject lives in the country or personal visit (initially) if the subject lives in Sydney, or the capital city of another State.

Figure 6 Follow-up of Non-Complying Subjects



4.7.2 Health Evaluation Modified for Home Administration.

List of current complaints

VDU questionnaire in pencil and paper format

AVHS questionnaire

Neuropsychiatric screen

Reasons for reluctance to co-operate

If nurse available:

Blood samples

Urine sample

Blood pressure measurement

4.7.3 Hierarchy of Data to be Sought

Data will be elicited in a particular order so that if the subject becomes reluctant to continue at any point the most critical data will have been gathered. A suggested sequence is given below but this will be modified in the light of experience with initial home interviews.

Order of precedence:

Blood pressure measurement

List of current complaints

Combat exposure (veterans only)

Reasons for Vietnam/non-Vietnam service

Sleep/worry

Depression and state of mind

Drinking habits

Smoking habits

Tablets

Marital status

Job satisfaction
Medical and hospital consultations
Medical record release
Neuropsychiatric screening
Social adaptation
Family coherence
Behavioural
Education
Occupation, employment
Neurological symptoms
Abdominal diseases and history
Skin diseases and allergies
The remainder of the MEDICHECK questionnaire
The remainder of the AVHS questionnaire
Blood samples
Urine sample

4.8 Follow-up of Non-Complying Wives/Female Partners

4.8.1 Additional Strategies for Obtaining Compliance

Partners not able to be contacted by telephone will be visited at home if residents of a State capital city, and failing that, will be sent a pencil and paper questionnaire. Partners failing to return a questionnaire will be sent another, and then a reminder letter.

4.8.2 Suggested Hierarchy of Data to be Sought

Order of precedence:

Sex and birthdate of all children
Death of children

Miscarriages leading to curettage in hospital

Difficulties with pregnancies

Mother's date of birth

For each occurrence:

when

name and address of institution or treating doctor

Medical record release

4.8.3 Data Not Able to be Obtained

All data not obtained due to poor compliance will be coded to indicate this.

4.9 Pilot Testing of Medical Examination

The components of the routine MEDICHECK evaluation that are being retained will not require specific pilot testing. The AVHS questionnaires for subjects and wives/partners will be tested on a small sample of men and women (not study subjects) prior to the commencement of the medical examinations to detect and overcome any ambiguities or problems which might arise during questionnaire administration. The sources of men and women for pilot testing have not yet been determined.

The physician assessment will be pilot tested by MEDICHECK doctors prior to commencement of AVHS medical examinations, and the comments provided by the doctors used to modify both the physical examination protocol and the documents used to record clinical findings and judgments.

Following this, it is intended to operate the examination centre for a 1 or 2 week period initially, to determine how long the various components of the examination take, how many subjects will keep a first appointment and to

discover any logistic or organizational problems. This examination period will be followed by a 1 or 2 week break, while solutions are found to the problems revealed by the initial run. Following this, the examination centre will commence full scale operation.

4.10 Verifying Data in Medical Records

All medical data volunteered by subjects or partners that is accompanied by the name of a treating doctor or hospital and signed release form will be verified.

A letter giving the reported complaint and time of occurrence will be sent to the relevant doctor or hospital with a request for substantiation of the condition and for the provision of more accurate or clarifying information.

The verified data will not be used to replace data volunteered by the subject, but will be retained for complementary analyses.

5. ADDITIONAL DATA FROM ARMY SOURCES

5.1 Caro Dossier

Verification of:

Dates of birth, enlistment, discharge

Veteran/control status

Corps

Civil education

Vietnam postings data

Obtain:

Australian posting data

Special courses completed

Disciplinary offences

Promotions

Volunteer/ballotee

5.2 Central Medical Record

Verify:

Enlistment and discharge PULHEEMS (Army health rating APPENDIX 2)

Obtain:

From enlistment medical examination:

Weight, height

Significant past medical history

PULHEEMS

Hospital admissions:

site (e.g. Vietnam, Australia)

type of pathology (trauma - combat/non combat, sexually
transmitted disease, other infection, drug induced,
psychiatric, other stress-related,)
duration of admission

From discharge medical examination:

PULHEMS

5.3 Psychology Record Cards

Obtain:

All test results

Corps preferences - 1st, 2nd, 3rd.

Referrals - reason (application for course or promotion, disciplinary
problem, psychological problem).

- date.

6. DATA ASSESSMENT AND ANALYSIS

6.1 Data Acquisition and Verification

Baseline information from the MRCC tape has been checked for logical inconsistencies, and where possible, for inconsistencies with the CARO tape. As error emerged, they have been checked against original dossiers in CARO.

Follow-up information, including last known address will be stored on computer disc file and verified against the original source documents. This information will be used as a basis for a master file which will be used to record the appointment and compliance history of each subject. A parallel file will be developed for the corresponding information on wives and female partners.

Combat exposure information will be derived from manual searching of army records, and the reliability of coding, punching and verification will be established during pilot studies and spot checks of the final data set.

Verification of veteran/control status is essential. For some individuals on the MRCC tape there were logical inconsistencies - eg "veterans" with periods of service which were far too short for them to have served in Vietnam. This suggested that there are errors on the tape, either in relation to veteran status and/or in relation to duration of army service. All inconsistent records have been checked manually and manual spot checks will be made of other "self-consistent" computer records to assess the accuracy of the remaining information on the MRCC tape.

Furthermore, if at the time of interview there is a conflict between the reports of the subject ("I went to Vietnam") and the computer record ("he is a control"), the details will be returned to CARO for clarification. Final data will be coded according to the correct (CARO) classification.

Interview information will be obtained from computerised MEDICHECK records, from AVHS pencil and paper questionnaire, from psychiatric questionnaires, neuropsychology assessments and physician assessments. The reliability of coding, punching and verification will be established during pilot studies and spot checks of the final data set.

6.2 Adequacy and Utility of Morbidity Study Data

6.2.1 Comparability of Follow-up of Veterans and Controls

As shown in Table 3.3, there is suggestive evidence that the proportion of NSW veterans found on the Electoral Register (78%) is less than the proportion of controls (81%); furthermore, of those found on the register, the proportion of veterans presently living outside NSW, (12%) was greater than the proportion of controls (9%). These differences may reflect differences between veterans and controls in relation to socio-economic factors, employment and social mobility.

It should be noted that the men who will be most difficult to trace (namely those men who are single, divorced, separated, itinerant, unemployed, or alcoholic) are most likely to be at greatest risk of disability. Thus in order to minimise any bias between veteran and control families arising from incomplete follow-up, it will be

important to reduce the number of untraced men in both groups to an absolute minimum.

Some idea of the magnitude of bias arising from incomplete follow-up could be obtained by looking to see how the morbidity of each veteran and control subject varies with the amount of follow-up required to trace him (i.e. was his address found in a primary, secondary or other source).

6.2.2. Compliance Rates for Veteran and Control Subjects

Even if the follow-up is adequate for both veteran and control subjects (e.g. 95% or more followed to their most recent address), the results of the morbidity assessments could still be biased if there were a difference between veteran and control rates of compliance with the interview. The most likely bias would be for veteran subjects with a disability to be more compliant than control subjects with a disability.

After maximising the compliance rate, the magnitude of any residual bias could be assessed by comparing the morbidity profiles of veteran and control subjects according to whether they attended the first, second or third appointment. These data can also be compared with the (incomplete) data obtained from non-compliers at a home interview. If the morbidity patterns do vary according to level of compliance (appointment) then this can be adjusted for (at least in part) during the analysis of the results.

6.2.3 Subjectivity of Self Reported Information

A major source of potential "bias" is that self reports from veterans are likely to be influenced by an expectation of disability which is greater than that of non-veterans. This tendency, whether it is conscious or sub-conscious, could be so general that it could lead to quite marked differences between veterans and controls in the prevalence of symptoms related to many different disabilities.

The potential for such bias will lead to major problems in the interpretation of all subjective information collected in the course of this morbidity study. Similar problems of interpretation have been encountered in assessing the symptoms of "effort syndrome" and "combat syndrome" in servicemen from previous wars, and in assessing symptoms associated with "compensation neurosis" after injury at work or in road accidents.

There are several approaches to this problem of interpretation. It may be appropriate to accept the reality of the symptoms, as such, and to explain them as being consequent on the psychogenic stimulus (of the war). This interpretation is, of course, more plausible if the symptoms can be identified as components of a depressive syndrome, an anxiety reaction or if they can plausibly be identified as somatic equivalents of psychogenic origin. In some circumstances the physical findings may support a functional diagnosis (eg tachycardia, sweating and hyperventilation if otherwise unexplained), and in other circumstances the functional origin of symptoms is supported by their

pleomorphic or protean nature, and by their failure to fit an organic syndrome. However, the functional or psychogenic origin of symptoms should only be accepted after steps have been taken to exclude an organic or biologic basis for the symptoms.

An organic basis can be suggested by the pattern of symptoms: thus if a veteran complains of chronic productive cough, shortness of breath on exertion and give a history of heavy smoking, we would be justified in suspecting the presence of chronic obstructive airways disease. This could be confirmed by physical examination or by objective testing.

The presence of dissimulation or malingering might be suspected if there were a constellation of plausible symptoms, together with an absence of supportive objective signs. In some subjects it may be possible to suspect dissimulation if there is a high score on the social desirability scale administered as part of the psychological assessment.

However, in general it will be necessary to assume that all symptoms are real, to analyse the contexts in which the symptoms are found, and to look to the epidemiological data, the physical examination and objective tests to provide clues about the physical disabilities which may underlie the symptoms.

In the context of this study, the analysis of subjective information is made easier by the fact that we are not necessarily required to make judgments about the physical bases of symptoms in individual veterans; it will suffice to show that in veterans as a group, such

and such a symptom complex is associated with objective signs of disease significantly more often than in similar groups of control subjects.

For those symptom complexes which are not supported by objective measures, the symptoms might be provisionally identified as being of functional or psychogenic origin. However, if these symptoms are found to be more frequent in veterans, and specifically if they are correlated with measures of combat exposure or herbicide exposure, then they can plausibly be regarded as real effects of war service. Certainly, if any functional syndrome is associated (see 6.5) with a measurable outcome which is more frequently observed in veterans (e.g. more frequent divorce) then it should probably be counted as one of the real hazards of army service.

6.2.4 Objective Measures

Several objective measures are available. For example, lung function testing will provide an objective test for chronic obstructive airways disease, biochemical tests on plasma will provide objective evidence of abnormalities of liver function and help to detect heavy drinkers. Objective tests are also available for the detection of past hepatitis B infection and for the detection of past syphilitic infection. Neuropsychological tests for the detection of brain damage and neurophysiological test of nerve function can also be regarded as objective.

The importance of these objective tests is not that they will provide a definitive medical diagnosis in their own right, but rather that they can provide independent support for disabilities which might be

suspected from the pattern of symptoms and from signs reported by the examining physician. As argued in the previous section, although this objective support might not be evident in every case with symptoms, it should be sufficient to show whether, as a group, veterans symptoms are significantly associated with objective measures more often than in similar groups of control subjects.

Because of the importance of objective measures, and because of the need to make inferences about the whole population of veterans and controls, we have argued that objective measures should be included either:

- (i) for all veterans and controls, or
- (ii) for randomly selected veterans and controls, plus those who have a clinical indication or those who fail a screening test.

6.2.5 Face Validity of Medical Diagnosis Made by a Physician

Medical diagnoses made by a physician must be accorded face validity, because the practice of diagnosis is defined in terms of the judgment of the physician. This is not to say that a judgment of a physician is necessarily reliable and objective, but as it is based on a contextual analysis of symptoms, physical signs and the results of special tests (gestalt), it provides an assessment of the meaning of the data which can be obtained in no other way.

Nevertheless, because a physician's judgments are subject to error, it is important to consider the possibility that there may be a systematic bias in diagnostic accuracy between veteran and control subjects. Such a bias could invalidate any conclusions which were

based on physician judgments. To minimise this bias in the pilot study, a decision was made to "blind" the physician carrying out the physical examination to the veteran status of each subject and to the results of the medical history (and vice versa). As a result, the judgments made by the physicians were out of context, and they were less helpful than might otherwise have been expected. It would be unwise to separate the assessments of symptoms and physical signs in the proposed morbidity study, although it would be desirable to try to maintain "blinding" of the physician to the veteran status of each subject during the examination.

However, regardless of the precautions taken, it is unreasonable to suppose that the physician will always remain ignorant of the veteran status of each subject; accordingly it will be impossible to always exclude physician bias as an explanation for (minor) differences in the frequency of certain diagnoses in veteran and control groups.

This conclusion is not as gloomy as it sounds, in that it will be possible to test some of the medical diagnoses made by the physician against objective data which are free from bias. For example, suppose that on the basis of physicians' diagnoses, the frequency of alcoholic liver disease appears to be higher in veteran than in control subjects. This difference could be real, or it could be a result of a systematic bias in the physicians assessments. However, if the objective tests of liver function show more abnormalities in veterans than controls, this would suggest that the difference in diagnostic frequency reflected a real difference in disease frequency, and not just a diagnostic artefact.

On the basis of this example, it might be argued that it would be wise to discard the physicians' judgments and to rely on objective tests alone. Such a policy would be misguided, for several reasons:

- (i) Objective tests are not available for all organ systems.
- (ii) Although objective tests can identify the organ system involved (eg liver), additional information is usually needed before an aetiological diagnosis can be made.
- (iii) Physician judgments are based on contextual clues, and on an "intuitive" synthesis of the available information. It is not possible to automate this synthetic function of the physician, if only because of the difficulty of capturing and codifying all the observations upon which his judgments are based. Any attempt to use the physician merely as an "observer" would be misguided, because it is impossible to separate "observation" from "theory" (contextual analysis and selective acquisition of data to test provisional diagnoses) in the course of medical diagnosis.
- (iv) The face validity of physicians judgments is widely accepted, both in the medical and in the lay mind. Thus a study which ignored the opinions of physicians could lack credibility in the eyes of the community.

6.2.6 Data From Wives and Female Partners

Data from wives and female partners will be obtained via telephone, face-to-face interview or written questionnaire to assess pregnancy outcomes, birth defects and children's health. The data will suffer from subjective bias and selective recall, and even if there is no

real difference, these results could suggest that there is a greater frequency of disability in the families of veterans than in the families of control subjects.

Several strategies can be used to assess the validity of these subjective responses. The first is to verify the reported medical condition or event (eg stillbirth, birth defect, curettage for miscarriage) with the medical attendant or hospital authorities. This procedure is adequate as far as it goes, but it suffers from the defect that it is not possible to verify an event which has been forgotten or not reported in the first place. Thus, even using an outcome criterion such as hospital admission for miscarriage, it will not be possible to exclude the possibility of selective bias in recall between veteran and control wives. The potential for biased will be even greater for those (early) miscarriages which did not result in a hospital admission.

Hospital admissions occurring after 1978 are also likely to be subject to bias because of the publicity, from 1979 onwards, surrounding the alleged effects of herbicides. There is less likely to be bias for hospital admissions occurring before 1979.

For those outcome conditions which leave a more or less permanent trace (eg surviving children with birth defects or spasticity) the validity of the wife's responses could be assessed, in part, by arranging for a follow-up medical examination of the children affected. This could undoubtedly confirm the diagnoses in the (most severely) affected children, but it would not exclude the possibility

of bias in the initial reporting. For example, it is plausible that there would be less incentive for the wife of a control subject to report the presence of a disability in one of her children, and such a child, if unreported, would be missed from the follow-up study.

6.3 Hypotheses to be Tested

6.3.1 Descriptive Hypotheses

The null hypothesis is that there are no differences in the frequency of disabilities between Vietnam veterans and controls (national servicemen who did not go to Vietnam). This null hypotheses will be tested against each of the following alternative hypotheses:

- (i) That social and behavioural disabilities (unemployment, separation, divorce, motor accidents, alcohol abuse) are more frequent in veterans than in controls.
- (ii) That anxiety, depression and other psychiatric disabilities are more frequent in veterans than in controls.
- (iii) That disorders of the nervous system (including neuropsychological disorders) are more frequent in veterans than controls.
- (iv) That liver disorders are more frequent in veterans than controls.
- (v) That gastro-intestinal disorders are more frequent in veterans than controls.
- (vi) That skin disorders are more frequent in veterans than controls.
- (vii) That infertility, miscarriage or childhood disability or death have been more frequent in the families of veterans than in the families of controls.

6.3.2 Actiological Hypotheses

In the event that one (or more) of these disabilities is more frequently observed in veterans (or their wives and offspring), it will be necessary to explore the causal basis of the difference(s) observed. The following hypotheses need to be considered:

- (i) That for self-reported symptoms or disabilities, an apparent excess in veterans (or their wives) might be caused by bias between the subjective responses of veteran and control subjects.
- (ii) That an excess of some disabilities in veterans might be caused by non-comparability of the original groups of veterans and controls (eg in age, education, socio-economic status, and predisposition to subsequent disability).
- (iii) That an excess of some disabilities in veterans might be caused by the physical and psychosocial sequelae of war service and combat stress.
- (iv) That an excess of alcohol abuse in veteran, itself attributable to war service, might contribute to any observed excess of social, behavioural and physical disabilities.
- (v) That an excess of some disabilities might be caused by herbicide exposure in Vietnam.
- (vi) That an excess of other disabilities (e.g. tuberculosis, strongyloides, VD) might be caused by other aspects of Vietnam service.

6.4 Outcome Measures to be Used

6.4.1 Need for Simplicity

As the protocol calls for the collection of a large amount of information, it is essential to specify, a priori, a simple set of outcome measures which can be easily used to test the principal hypotheses of interest. --

Such a scheme is outlined in Table 6. It can be seen that most emphasis is placed on those outcome measures which are valid and unambiguous, potentially relevant and reliably measured.

Consequently, at the primary stage of analysis most attention will be paid to objective measures, to physician assessments and to subjective self-reports using psychiatric scales which have been well validated.

Table 6 Major Outcome Measures and Covariates To Be Used In Testing Principal Alternative Hypothesis

ALTERNATIVE HYPOTHESES Veterans will show an increased frequency of:	MAJOR OUTCOME MEASURES	MOST IMPORTANT CONFOUNDING FACTORS AND COVARIATES (in additions to age, Vietnam exposures to combat, herbicides, etc.)
1. Social disability	Employment/unemployment Level (status) of employment	Pre-enlistment education level, Pre-enlistment psychological assessment
Marital disability	Ever married/single Divorced, separated/Presently married Frequency of marital disputes	Number of children Religion S.E.S.
Substance use and abuse	Alcohol use (GGT, urate, MCV) Cigarette use Teas and coffee use Other drug use	Marital status S.E.S.
Behavioural disability	Uncontrollable rages Motor accidents Fighting at hotel/football etc Sexual problems	Marital Status S.E.S.
2. Psychiatric disability	SDI score Depression (Hamilton scale) Anxiety (Spielberger) Present state examination Prevalence of psychoactive drug use	Alcohol consumption S.E.S.
3. Neuropsychologic disability	Symbol digit substitution Trail making tests Supra-span digit learning Nelson adult reading test	Scores and components S.E.S Alcohol consumption
4. Neurological disability	Physician assessment of - peripheral neuritis & nerve conditions studies - other neurological disability Nerve conduction deafness	Alcohol Occupation history (Patency of external ear)
5. Liver disease	Liver enzymes Physician assessment of liver disease	Alcohol consumption Hepatitis B

6. Cardio-vascular disability	Blood pressure ECG abnormalities - individual items and components Physician assessment - angina - myocardial infarction - stroke - palpitations Plasma cholesterol	Cigarettes Alcohol
7. Infectious disease	Hepatitis B virus serology Tuberculosis - CXR report Melioidosis antibody titre Strongyloides antibody titre Venereal disease - VDRL	
8. Gastro-intestinal disease	Physicians assessment - irritable bowel syndrome - diarrhoea - ulcerative colitis	Alcohol consumption
9. Skin disorders	Physicians assessment	
10. Other symptoms	A. Symptom complexes, specified <u>a priori</u> , which are potentially relevant to particular outcomes (above) B. component or factor analyses of symptoms to define their latent structure. These components can then be used as outcome measures to look for differences between veterans and controls.	

Veteran wives partners have an increased frequency of:

1. Infertility	Complaints of inability to conceive No. of pregnancies No. of live-born children
2. Miscarriage	Verified miscarriage resulting in hospitalization prior to 1979.
3. Birth defects spasticity	Verified birth defect and/or spasticity in child born prior to 1979
4. Stillbirth	Verified still birth
5. Health disability in surviving children	Verified hospitalisation of child prior to 1979

6.4.2 Need for Data Reduction

Some of the outcome measures are simple and unambiguous (eg marital status). Others, such as the psychiatric scales contain numerous items which measure several different components, are relevant to psychiatric disability. The dimensions of these more complex outcome measures can be reduced by calculating, for each individual studied, a score on each of the known components. These component scores (e.g. for depression, anxiety and somatic symptoms) can then be used as measures to test for any differences in outcome between veteran and control subjects.

In other situations (e.g. with the neuropsychology tests) it may be more appropriate to use the data obtained in the study (from pooled cases and controls to avoid bias) to define the components of interest. Component scores in the reduced number of dimensions can then be used to test for any differences between veterans and controls.

6.4.3 Approach to the Analysis of Subjective Self Reports

Interpretation of subjective information presents many problems, and in sec. 6.2.3 some guidelines are given which should be helpful. In particular, it will often be wise to discount any disabilities for which the symptoms are not supported by objective data or physician assessments.

In some circumstances (Table 6) it will be possible to define, a priori, those self-reported symptoms which are deemed to be relevant to particular outcomes (e.g. the questions defining coronary heart

disease). Scores on these symptom patterns can then be used as outcome measures which should be complementary to those based on objective measures or physician assessments.

Another approach is to use the self-reported information itself to explore the factors or components giving rise to the observed variation. Thus it should be appropriate to subject the entire response matrix to factor and/or component analysis. If "expectation of disability" or "response bias" is an important cause of variation in response pattern (i.e. if many people tend to say yes to many symptoms) then this would be reflected in the identification of a "disability factor" which loads for most of the questions. The residual factors or components would then help to identify patterns of symptoms which are not simply due to "general disability" or "response bias" but which are likely to be more useful as potential outcome measures.

6.5 Principles of Statistical Analysis

6.5.1 The Problem

The major objective of the analysis is to examine the relationship of the several outcome measures to veteran status, to measures of exposure in Vietnam, and to those explanatory covariates which may be confounded with Vietnam service or with exposure while in Vietnam.

The interpretation of morbidity study results would be moderately straightforward if the allocation of national servicemen to Vietnam service had been completely at random (rather than being haphazardly selective, as was the case), if there had been no mortality while in Vietnam, and if there were no selective compliance with the proposed

interview schedules. If this were the case, then any observed differences between the veteran and control subjects could be interpreted, at least in a very general sense, as being caused by the Vietnam experience. On this view, even the most subjective of self reported symptoms (see Sec. 6.2.3) could be attributed to the Vietnam experience acting through functional or psychogenic processes or through a (conscious or subconscious) desire for compensation.

Unfortunately, because of non-random allocation to Vietnam, selective mortality and the likelihood of selective compliance, the veteran and control subjects studied will differ for reasons which may not be logically consequent on Vietnam service; therefore, much of the statistical analysis will be directed towards examining the effects of the variables which are confounded with Vietnam service. This will allow assessment of the effects of Vietnam service on outcome to be made which have been adjusted for the effects of confounding variables.

6.5.2 Basic Approaches to Analysis

Because of the non-experimental design, it will be most appropriate to fit regression models to the data, using the outcome measures as the dependent variable.

For those situations where the outcome variable is qualitative and binary, it would be appropriate to use a logistic regression model (Cox, 1970; Breslow and Day, 1980), and for those situations where the outcome variables is quantitative, the basic approach will be that of standard multiple regression (Draper and Smith, 1966).

The advantage of the regression approach is that it provides a flexible method for dealing with confounding and for estimating the main effects (and interactions) of explanatory variables. This is achieved at the cost of making assumptions about linear effects and about the distribution of residuals. As required, these assumptions can be tested or relaxed at a later stage of the analysis.

In some situations it may be appropriate to fit mixed models for the analysis of covariance to allow for the effects of factors which are related to outcome but which have random rather than fixed effects (Sokal and Rolf, 1972).

In other situations, with qualitative outcome data and qualitative explanatory variables, it would be appropriate to use log-linear models for the analysis of multidimensional contingency tables (Bishop et al, 1975; GLIM manual - Baker and Nelder, 1978).

For those outcome measures which are measured on random samples (because of the hierarchical design) the analyses will be modified accordingly. Special procedures will be developed to use data from the "random" samples and the "extreme value" samples to make efficient estimates about the distribution of the outcome measures over the entire population studied and to find the most efficient procedures for testing for differences in outcome related to veteran status.

6.5.3 Confounding variables can be regarded as (nuisance) variables which have (potential) effects on outcome, and which are "accidentally" correlated with the main factor of interest (veteran status) and logically independent or antecedent in the causal chain.

For example, age is likely to be confounded with veteran status in the present study.

Thus because morbidity will be higher in older men, there could, due to confounding, be an artefactual association between morbidity and veteran status. - The appropriate analysis is to first fit a model which includes only the confounding variable(s) (age) and then to fit the factor of interest (veteran status). The test for improvement in fit then provides a measure of the significance of the factor after allowing for the effect of the confounding variable. In practice, it will be necessary to allow for the effects of a number of confounding variables, although care is needed to ensure that variables which are secondary to veteran status are not treated as if they were confounding variables.

Effects of interactions can also be estimated. For example, consider the hypothesis that any effect of Vietnam service on subsequent morbidity was greater in men who were older at the time that they went to Vietnam. This hypothesis can be tested by first fitting the main effect of age at time of service (as a confounding variable) and then fitting the main effect of veteran status; the third term (age x veteran status interaction) will provide a test of the required hypothesis.

At least in principle, it is also possible to allow for non linear (quadratic) effects of covariates.

6.5.4 Strategy of Model Fitting

After the descriptive stage has been completed, it will be important to first fit a model which includes all necessary confounding terms (age, educational attainment, religion etc) without regard to veteran status, exposure indices etc. It also seems plausible to allow some degree of overfitting for these confounding variables.

Next it will be appropriate to fit (sequentially) the effects related to Vietnam service (veteran status, time in Vietnam, combat exposure) and to retain any significant effects in the model.

Thirdly it will be appropriate to look for interactions of these service related variables with the (confounding) explanatory variables (eg age x Vietnam service).

6.5.5 Incompleteness of Adjustments for Confounding Factors

If there is an apparent effect of Vietnam service on morbidity which is partly removed when confounding factors are fitted beforehand, it will be necessary to seriously consider the possibility that the Vietnam effect might have been removed completely if it had been possible to measure the confounding factor(s) more precisely (R. Peto, 1973). For example, if a pre-Vietnam measure (eg psychological assessment at induction) were found to be predictive of outcome and also to be confounded with veteran status, then it might be found to "explain away" a considerable proportion of any effect of Vietnam service. As there is always considerable error associated with the measurement of such psychological scales, it can be argued that a more precisely measured scale might have "explained away" a greater proportion of the observed effect. This qualitative argument could

be made somewhat more precise if data were available on scale reliability and validity.

6.5.6 Problems Arising from Non-orthogonality and Confounding

It is important to remember that there may be particular problems in elucidating the significance for outcome of factors which are confounded with Vietnam service. For example, national servicemen were selected for Vietnam service (either by the army or by themselves), so that veterans will differ from controls for a number of factors, only some of which will have been measured.

Consider a factor which is measurable and has been measured (e.g. psychological scale at army induction); furthermore, suppose that Vietnam service is selected partly on the basis of this factor ("they make good soldiers"). Given this state of affairs, how are we to interpret the relationships between Vietnam service, the "confounding" factor, and outcome? The problems arises, in part, because the measured factor is, in one sense, a cause of Vietnam service, and hence some of the outcome which might be attributable to Vietnam service would, in any conventional analysis, be partly attributed to the measured factor because it is a logically prior "confounding" factor and should be fitted first.

Thus if we simply adopt the policy of fitting only main effects and of fitting the confounding effect first, we could increase the risk of a Type II error (i.e. of missing a real effect of Vietnam service). To minimise the risk of such Type II errors it will be important to always examine the interaction terms between Vietnam service and each of the "confounding" factors which have a significant main effect on

outcome. For example, we would always be interested to know whether, after adjusting for main effects of Vietnam service and (say) the confounding (psychological) factor, there is a significant 2 way interaction effect on outcome. If there is such a significant interaction, then we are justified in concluding that both factors have real (causal) effects, even though the main effect of Vietnam-service may appear to be non-significant.

Thus by fitting such interaction terms it is possible to reduce the Type II error rate with respect to detection of effects related to Vietnam service.

It might be argued that an alternative strategy would be to fit the effect for Vietnam service before that for the confounding factor, or at the least to allow the effects to compete with each other at the same stage of model-fitting. Although these issues are complex, it is generally agreed that if the aim of the analysis is to make inferences about attributable (causal) risk, there is usually no justification for fitting first that factor which is logically (and/or causally) secondary. Thus in the context of the present example, we would not usually be justified in fitting the effect for Vietnam service before fitting an effect for a factor (e.g. psychological scale at induction) which is logically prior to Vietnam service.

In other words, although it is plausible to postulate that a psychological factor could influence the probability of Vietnam service, it is much less plausible to postulate that Vietnam service could influence psychological measures measured at army induction (i.e. well before the process of selection for Vietnam service began).

6.5.7 Approach to the Testing of Aetiological Hypotheses

Thus in developing statistical procedures for testing aetiological hypotheses, it is important firstly to impose a causal ordering on the explanatory variables, and secondly to see whether, after allowing for main effects of confounding variable and Vietnam service, the interaction terms also have significant effects on outcome. If the interaction terms are significant, this provides further evidence for rejecting the null hypothesis in relation to Vietnam service.

References

- Adams, I.M., Hehir, P.J., Byth, K., Charlesworth, N., Mears, A. Report on the Feasibility of Establishing an Index of Exposure to Herbicides for Vietnam Veterans. (Confidential document) Australian Veterans Herbicide Studies, November 1981.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder, ed. 3., Washington, D.C, 1980.
- Army Manning Review 1973-74, Department of Defence, Canberra.
- Axelsson, O. and Sundell, L. Herbicide exposure, mortality and tumour incidence. An epidemiological investigation on Swedish railroad workers. *Work Environment Health*, 11, 21-28 (1974).
- Baker, R.J. and Nelder J.A. The GLIM system release 3. Generalised linear interactive modelling. Numerical Algorithms Group, Oxford, (1978).
- Bishop, Y.M.M., Fienberg S.E., Holland, P.W. Discrete multivariate analysis: Theory and practice. MIT Press, Cambridge, (1975).
- Boman, B. Review: the Vietnam veteran ten years on. *Aust. N.Z. J. Psychiat.* 1982; 16:107-127.
- Breslow, N.E. and Day, N.E. Statistical methods in cancer research. I. The analysis of case-control studies. IARC Scientific Publications No. 33 (Lyon), (1980).
- Case-Control Study of Congenital Anomalies and Vietnam Service. (Confidential document) Australian Veterans Herbicide Studies, April, 1982.
- Cox, D.R. Analysis of binary data. Methuen, (1970).
- Draper, N.R. and Smith, H. Applied regression analysis. Wiley, N.Y., (1966).
- Fett, M.J. Retrospective Mortality Study of Vietnam Veterans and Controls. Revised Protocol. (Confidential document). Australian Veterans Health Studies, May, 1982.
- Figley, C.R. and Stretch, R.H. Vietnam Veterans Questionnaire. Unpublished manuscript. U.S. Veterans' Administration, (1980).
- Hardell, L. and Eriksson, M. Soft-tissue sarcomas, phenoxy herbicides and chlorinated phenols. *Lancet*, ii, 250, August 1, (1981).
- Hardell, L. and Sandstrom, A. Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br. J. Cancer*, 39, 711-717, (1979).
- Honchat, P.A. and Halperin, W.E. 2,4,5-T, trichlorophenol and soft tissue sarcoma. *Lancet*, i, 268-9, January 31, (1981).
- International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man: Some fumigants, the herbicides 2,4-D and 2,4,5-T, chlorinated dibenzodioxins and miscellaneous industrial chemicals. 15, 41-299, (1977).

- Mathews, J.D. Alcohol use as a possible explanation for socio-economic and occupational differentials in mortality from hypertension and coronary heart disease in England and Wales. *Aust. N.Z. J. Med.*, 6, 393-397, (1976).
- Mathews, J.D. Genetics and alcohol: Implications for human disease. *Aust. N.Z.J. Med.* 11, 109-114, (1981).
- National Service Act 1951-1971, The Commonwealth of Australia.
- Penk, W.E., Robinowitz, W.R., Roberts, E.T., Patterson, M.P., Dolan, M.P. and Atkins, H.G. Adjustment differences among male substance abusers varying in degree of combat experience in Vietnam. *J. Consult. Clin. Psychol.*, 49, 426-437, (1981).
- Peto, R. 1973, (Personal communication).
- Reggiani, G. Acute human exposure to TCDD in Seveso, Italy. *J. Toxicol. Environ. Health*, 6, 27-43, (1980).
- Riihimäki, V., Asp, S., Seppäläinen, A.M. and Heinberg, S., (1978) Mortality study of persons exposed to dioxin after an accident which occurred in the BASF on 13th November 1953. Working paper for the Workshop on Long-term Hazards of Polychlorinated Dibenzodioxins and Polychlorinated Dibenzofurans. International Agency for Research on Cancer, Lyons, January 10-12. Cited in Kimbrough, (1980).
- Scientific Advisory Committee Report. (Confidential document) Australian Veterans Herbicide Studies, February, 1981.
- Sokal and Rolf. *Biometry*. Freeman, San Francisco, 1972.
- The PULHEEMS System of Medical Classification. Medical Pamphlet. Department of Defence (Army Office), Canberra, 1978.
- U.S. Veterans' Administration. Review of literature on herbicides, including phenoxy herbicides and associated dioxins. Volume I, Washington D.C., 1981.

APPENDIX 1

SPECIFIC HYPOTHESES AND POWER CALCULATIONS

The null hypothesis is that there are no differences in the frequency of disabilities between Vietnam veterans and controls (national servicemen who did not go to Vietnam). These null hypotheses will be tested against the alternative hypotheses that each outcome listed in Table 1 is more frequent in veterans than controls.

In interpreting Table 1 the following points should be borne in mind:

- (1) Smaller numbers of study subjects (sample sizes) than those given have the consequence of increasing the minimum size of an effect (the relative risk) that can be detected, that is, of reducing the sensitivity of the study to detect veteran/control differences.
- (2) In the process of adjusting for pre-Vietnam and other differences in the veteran/control group (for example, differences in marital status at enlistment), the study becomes less sensitive than shown in Table 1. The data in Table 1 are therefore 'best possible case' data, where no adjustment for veteran/control differences is required.
- (3) Many of the putative effects of Vietnam service appear to be related to particular aspects of Vietnam service (e.g. combat). Since it is unlikely that all veterans would be exposed to the factor of importance (e.g. combat), the number of truly 'exposed' veteran subjects may be considerably below the total number of veteran

subjects. This further reduces the power of the study to detect veteran/control differences below those shown in Table 1. This consideration is the rationale for selecting veterans to controls in a 3 to 2 ratio, thereby permitting more powerful comparisons between veterans at different levels of exposure to possible causal variables for a given sample size, and at the same time reducing only slightly the sensitivity of veteran-control comparisons. It is not currently possible to perform power calculations within the veteran group, as the distribution of potentially causal variables among veterans is not yet known.

Outcome	Source	Estimated prevalence (limits)	2,500 subjects		5,000 subjects		18,000 subjects	
			Rel. risk detectable	Min VN-caused cases detectable/1000	Rel. risk detectable	Min VN-caused cases detectable/1000	Rel. risk detectable	Min VN-caused cases detectable/1000
<u>Cancer</u>	(i)	1%	2.23	8	1.83	5	1.63	4
<u>Musculoskeletal</u>								
Arthritis/rheumatism	(h)	3%	1.65	12	1.45	8	1.34	6
Muscular aches & pains	(a)	10-30%	1.16-1.32	19-28	1.11-1.23	14-20	1.09-1.18	11-16
<u>Infectious Disease</u>								
Syphilis (VDRL(+))	(a),(j)	0.5-1%	2.23-2.90	6-8	1.83-2.24	4-5	1.63-1.94	3-4
Melioidosis	(k),(l)	1-3%	1.65-2.23	8-12	1.45-1.83	5-8	1.34-1.63	4-6
Strongyloidiasis	(p)	1% in vets	2.23	8	1.83	5	1.63	4
<u>Medical Treatment</u>								
Hospitalised in last 12 months	(h)	14%	1.26	22	1.19	16	1.14	12
Medication taken in last 2 days	(h)	37%	1.14	30	1.10	21	1.08	17
<u>Reproductive</u>								
Relative infertility	(a)	5%	1.48	14	1.33	10	1.26	8
<u>Social and Behavioural</u>								
Never married	(h)	13%	1.28	22	1.19	15	1.15	12
Divorced	(h)	2.5%	1.74	11	1.50	8	1.39	6
Currently unemployed	(n)	4%	1.55	13	1.38	9	1.28	7
Recent accident	(b)	6%	1.43	16	1.30	11	1.23	8
<u>Psychiatric</u>								
Depression	(o)	3-16%	1.24-1.65	12-23	1.17-1.45	8-16	1.13-1.34	6-13
Anxiety	(o)	1-19%	1.22-2.23	8-25	1.15-1.83	5-17	1.12-1.63	4-14
Severe personality disorder	(a)	0.5%	2.90	6	2.24	4	1.94	3
Psychosis	(a),(p)	1-2%	1.83-2.23	8-10	1.53-1.83	5-7	1.43-1.63	4-5
Alcoholism (100gms+/d)	(g)	3-10%	1.32-1.65	12-19	1.23-1.45	8-14	1.18-1.34	6-11
Smoking: see Respiratory								

Table 1. Prevalence of Outcomes of Importance with Minimum Relative Risks Detectable as Statistically Significant and the Minimum Number of Vietnam-Caused Cases per 1,000 subjects that would be Detected with Power of 80% at P(1) 0.05 for Sample Sizes of 2,500, 5,000 and 18,000 subjects.

Outcome	Source	Estimated prevalence (limits)	2,500 subjects		5,000 subjects		8,000 subjects	
			Rel. risk detectable	Min VN-caused cases detectable/1000	Rel. risk detectable	Min VN-caused cases detectable/1000	Rel. risk detectable	Min VN-caused cases detectable/1000
<u>Nervous System</u>								
Clinical peripheral neuropathy	(2), (a)	0.5-1%	2.23-2.90	6-8	1.83-2.24	4-5	1.63-1.94	3-4
Neuropsychological abnormality	(3)	5%	1.48	14	1.33	10	1.26	8
Hearing abnormality	(3)	5%	1.48	14	1.33	10	1.26	8
Frequent headaches	(4), (b)	3-4%	1.55-1.65	12-13	1.38-1.45	8-9	1.28-1.34	6-7
<u>Skin</u>								
Severe acne	(a)	3%	1.65	12	1.45	8	1.34	6
Fungal infections	(a)	4%	1.55	13	1.38	9	1.28	7
<u>Liver</u>								
Cirrhosis	(a)	0.1-1%	2.23-6.3	3-8	1.83-4.3	2-5	1.63-3.5	2-4
Hepatitis B(+)serology	(c)	0.6%	2.70	6	2.11	4	1.85	3
Abnormal liver function tests	(3)	5%	1.48	14	1.33	10	1.26	8
<u>Gastrointestinal</u>								
Persistent vomiting	(a)	5%	1.48	14	1.33	10	1.26	8
Persistent diarrhoea	(a)	10%	1.32	19	1.23	14	1.18	11
Abdominal pain	(b)	1%	2.33	8	1.83	5	1.63	4
Peptic ulcer	(d)	1-2%	1.83-2.23	8-10	1.56-1.63	5-7	1.43-1.63	4-5
<u>Cardiovascular</u>								
Hypertension	(3)	5%	1.48	14	1.33	10	1.26	8
Receiving medication for hypertension	(e)	1-2%	1.83-2.23	8-10	1.56-1.83	5-7	1.43-1.63	4-5
Symptoms of ischemic heart disease	(b)	0.1%	6.3	3	4.3	2	3.5	2
ECG abnormality	(f)	0.6%	2.7	6	2.11	4	1.85	3
<u>Respiratory</u>								
Smoking currently	(g)	40-46%	1.11-1.13	30-31	1.08-1.09	22	1.06-1.07	17
Asthma	(h)	2-4%	1.55-1.83	10-13	1.38-1.56	7-9	1.28-1.43	5-7
Abnormal pulmonary function tests	(3)	5%	1.48	14	1.33	10	1.26	8

Notes

- (1) The power calculations have been performed using the following parameters:
 - o veteran to control ratio of 3 to 2
 - o the 'relative risk detectable' is the minimum relative risk that would be statistically significant at the level $P_{(1)} 0.05$, with power of 80%
 - o the excess cases in veterans are derived from the relative risk detectable and the veteran to control ratio of 3 to 2.
- (2) Pilot Study prevalence data have been used only where other data have not been obtainable, since the validity of Pilot Study data is limited. The prevalence rates cited are for veteran and control subjects combined.
- (3) For this measure an abnormal (positive) result is defined as that result above which only 5% of the normal population resides.
- (4) All data are for the appropriate age and sex group.

Sources of Prevalence Data

- (a) Pilot Study, Australian Veterans Health Studies.
- (b) Australian Health Survey 1977-78 Recent Illness. ABS.
- (c) Nelson (1975)
- (d) Health Care Surveys Gosford/Wyong/Illawara 1975. ABS, HC NSW.
- (e) Australian Health Survey 1977-78. ABS.
- (f) Personal Communication: Dr T. Ireland, Director of Research, Medichcek Centre.
- (g) Alcohol and Tobacco Consumption Patterns. February 1977. ABS.
- (h) Social Indicators. No. 3. 1980. ABS.
- (i) Cancer in NSW Incidence and Mortality 1977. NSW Cancer Registry.
- (j) Personal Communication: A. Lee, Serologist, NSW Red Cross Blood Transfusion Service.
- (k) Clayton et al (1973).
- (l) Kishimoto et al (1971).
- (m) Gilbert et al (1968).
- (n) Labour Statistics 1980 Australia. ABS.
- (o) Reynolds and Rizzo (1979).
- (p) Goldberg (1972).

References

Australian Bureau of Statistics. Alcohol and Tobacco Consumption Patterns.

February 1977. ABS Catalogue No. 4312.0, Canberra, 1978.

Australian Bureau of Statistics. Australian Health Survey 1977-1978. ABS

Catalogue No. 4311.0, Canberra, 1979.

Australian Bureau of Statistics. Labour Statistics 1980 Australia. ABS

Catalogue No. 6101.0, Canberra, 1980.

Australian Bureau of Statistics. Social Indicators. No. 3. 1980. ABS

Catalogue No. 4101.0, Canberra, 1980.

Australian Bureau of Statistics. Australian Health Survey 1977-1978. Recent

Illness. ABS Catalogue No. 4318.0, Canberra, 1981.

Australian Bureau of Statistics and Health Commission of New South Wales.

Health Care Surveys in Gosford-Wyong and Illawarra areas of NSW.

1975. ABS Catalogue No. 4305.1, Sydney, 1976.

Clayton, A.J., Lisella, R.S. and Martin, D.G. Melioidosis: A Serological

Survey in Military Personnel. *Milit. Med.* 38 : 24-26, (1973).

Gilbert, D.N., Moore, W.L., Hedberg, C.L. and Sanford, J.P. Potential Medical

Problems in Personnel Returning from Vietnam. *Review. Ann. Int. Med.*

68 : 662-678, (1968).

Goldberg, D.P. The Detection of Psychiatric Illness by Questionnaire.

Institute of Psychiatry Maudsley Monographs No. 21. Oxford University Press, London, 1972.

Kishimoto, R.A., Brown, G.L., Blair, E.B. and Wenkheimer, D. Melioidosis: Serologic Studies on US Army Personnel Returning from South East Asia. Milit. Med. 36 : 694-698, (1971).

Nelson, M. Immunology and Epidemiology of the Hepatitis B (Australia) Antigen. PhD thesis. Unilversity of New South Wales, 1975.

New South Wales Central Cancer Registry. Cancer in New South Wales Incidence and Mortality 1977. Health Commission of New South Wales, Sydney, 1981.

Reynolds, I. and Rizzo, C. Psychosocial Problems of Sydney Adults. Health Commission of NSW and Mediceck Referral Centre. 1979.

APPENDIX 2

PULHEEMS ARMY HEALTH RATINGS

The following tables outline the basis of the PULHEEMS ratings, and are extracts from 'The PULHEEMS System of Medical Classification', 1978.

NOTES ON THE PULHEEMS QUALITIES

15. a. P - Physical Capacity. This indicates general physical development, potential capacity to acquire a high level of physical stamina, capacity for hard work.
- b. U - Upper Limbs. This indicates the functional use of hands, arms, shoulder girdle and upper spine. Where there is a degree of incapacity which would limit general physical capacity the U assessment will also affect the P assessment.
- c. L - Lower Limbs. This indicates the functional efficiency of feet, legs, thighs, pelvis, lumbar spine, ankle, knee and hip joints. As with the U assessment the L assessment may also affect the P assessment.
- d. H - Hearing Acuity. This indicates hearing acuity only. Diseases of ear are to be assessed under the P quality.
- e. EE - Eyesight. This indicates visual acuity only. Diseases of the eyes are to be assessed under the P quality.
- f. M - Mental Capacity. This is difficult to assess on the basis of a single medical examination. Some guidance is given by:
- (1) Impression given on interview with regard to alertness and intelligence;
 - (2) School record and post-school occupational record;
 - (3) Selection test results.
- g. S - Emotional Stability
- This is also difficult to assess on the basis of a single examination. There are no tests of temperament or personality available to estimate emotional stability. Reliance must be placed on careful history taking, including family background and employment record, and physical examination.

DEGREES OF PULHEEMS QUALITIES

16. There are nine degrees of qualities but not all of these are in use. The following table shows the degrees used under each quality.

P	U	L	H	E	E	M	S
1	1	1	-	1	1	-	-
2	2	2	2	2	2	2	2
3	3	3	3	3	3	3	3
4	-	-	-	4	4	-	-
5	-	-	-	5	5	-	-
6	-	-	-	6	6	-	-
7	7	7	7	7	7	-	-
8	8	8	8	8	8	8	8
-	-	-	-	9	9	-	-

17. The broad correlation between degree of P, U, L, M, S, and functional capacity, combatant capacity, climatic restriction, is as follows:

Degree	Function Capacity	Combatant Capacity	Climatic Restriction
1	Above Average	Full	None
4	" "	"	Non tropical
2	Average	"	None
5	" "	"	Non tropical
3	Below Average	"	None
6	" "	"	Non tropical
7	Markedly Deminished	Restricted	Serve in Australia
<p>Note: The restriction "Service in Australia" applies only to P 7 and not to U7 or L7.</p>			
8	Under P, U, L, H, M, S = medically unfit for any form of service.		