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AGENDA TO REVIEW
VETS II
August 30, 1984

TIME	SUBJECT	SPEAKER OR PARTICIPANTS
8:00 a.m. - 8:30 a.m.	Welcome and Charge to Committee	Dr. Greene
8:30 a.m. - 9:15 a.m.	Ranch Hand Study (U.S. Air Force)	Dr. Wolfe
9:15 a.m. - 10:00 a.m.	a) Epidemiological Study of the Health of Vietnam Veterans	Dr. Erickson
	b) Agent Orange Birth Defects Study (Centers for Disease Control)	
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10:45 a.m. - 11:00 a.m.	National Needs Assessment of Vietnam Era Veterans (Veterans Administration's RFP 101-9-84)	Dr. Greene
11:00 a.m. - 3:00 p.m.	Review of VETS II and Working Lunch	Review Committee
3:00 p.m. - 5:00 p.m.	Meeting with Principal Investigator and Staff of VETS II	Review Committee
5:00 p.m. - 8:00 p.m.	Discussion, Recommendations, and Preparation of Summary Statement	Review Committee

Attachment A

Participants

"Vietnam Experience Twin Study"

August 30, 1984

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	(Veterans Administration's RFP 101-9-84)	Dr. Denny
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Attachment B

VIETNAM EXPERIENCE TWIN STUDY
PROTOCOL NO. 2
CSP #256

RESUME

The Cooperative Study Protocol (CSP) under review is designed to investigate the impact of military service on the Vietnam veterans' medical, psychological and overall social adjustment. This study has one primary purpose and two ancillary purposes: the primary purpose is to further examine the nature and degree of relationship between characteristics of Vietnam service and a range of medical, psychiatric, psychological, and psychosocial aspects of the veteran's health. Secondary purposes include the investigation of possible relationships between exposure to Agent Orange and the health of the veteran and his offspring, and efforts to define and measure Post Traumatic Stress Disorder.

One of the unique features of this approximately 10 million dollar investigation is the inclusion of monozygotic co-twin pairs. It is proposed to locate and intensively study 600 male monozygotic twin pairs born during 1939-1953 who served in the military between 1965-1971. It is anticipated that of this sample about 360 will be discordant for service in Vietnam and 240 will be concordant, i.e., 120 co-twin pairs in which neither member had any Vietnam service and 120 co-twin pairs in which each member had some period of Vietnam service. The investigation will test whether there is reliable evidence of differential post-service medical, psychological or social well-being changes associated with different service experiences. The plan is to bring subjects to St. Louis for a week of extensive examinations.

The feasibility of the proposed study is, of course, contingent on the prior successful completion of the Vietnam era Twin Registry. The preparation of such a registry was approved (Protocol #1) and is being undertaken by the National Research Council Commission on Life Sciences--Medical Follow-up Agency of the National Academy of Sciences. The application for review (Protocol #2) does not, however, include a report indicating the successful completion of this Registry or its readiness for use in Protocol #2.

Also to be completed prior to initiating the study are such instruments as the DIS III, Current Behavioral Indices, the Life History and Medical History Questionnaires.

CRITIQUE - General criticisms of project design and concepts.

The overall impression of the proposed study is that it is fundamentally overambitious, with not enough serious, scientific rationale provided for the work described. The hypotheses for performing the numerous laboratory procedures outlined in the proposal are not based on solid scientific data. This is basically

a "fishing expedition" among cohorts of twins, in which the focus will be on clinical, laboratory, and behavioral parameters of disease, or of disease indicators. The General Medical Assessment, as outlined in this protocol, represents a cosmic approach to clinical assessment, which may also be said for the extensive battery of laboratory tests proposed. Instead of a proposal consisting of a series of well-defined questions for which research studies are to be done, the veterans will be subjected to all manner of tests, clinical and other, on basically flimsy scientific evidence, to see what emerges. Even the more specialized tests have insufficient justification and weak scientific rationale.

The only independent variable in this proposed study is service in Vietnam. A reasonable hypothesis might be generated that links Vietnam service to psychiatric sequelae, however, other studies directed to this goal are already being undertaken.

Because the "n" (sample size) is small the study has only a low statistical power to detect modestly increased risks for medical or psychiatric illnesses. The small "n" may also invalidate the meaning of a negative result. While it may be true, as the investigators argue, that the "n" is large enough to detect subclinical differences in continuous variables such as laboratory values, such differences would have no clinical significance and are of insufficient importance to argue for implementing such a massive study. What are the implications of finding small deviations from normality in the co-twin pairs?

Two problems with the data analysis presentation deserve some comment. First, information on data analysis is scattered throughout the proposal. Although each of these subsections is clearly presented, the relationships between the various types of analyses is not fully discussed. The second problem is relevant to the issue of multiple comparisons and spurious effects. This would be less of a problem if the data anaylses were divided into confirmatory and exploratory analyses. The confirmatory analyses should test a prior hypotheses which are explicitly specified by the investigators. These hypotheses could be based on either past empirical findings or theoretical developments. Since this group of tests will be less than the number of tests discussed in the proposal, it would be reasonable to apply a higher alpha level to them than to the exploratory analyses.

The medical illnesses of Vietnam servicemen, were for the most part self-limiting and will likely have long ago disappeared. Although acute and/or chronic exposure to drugs or chemicals might yield some abnormal test results initially, 14 or 20 years have now elapsed since active Vietnam service and any relationship of cause and effect will be compromised.

A basic problem is that health differences between twins may be unrelated to Vietnam service, and may have developed in the 14 to 20 years post-Vietnam.

Since it will not be possible to obtain accurate data on which servicemen were exposed to Agent Orange this study has essentially no relevance to the problem of Agent Orange effects on health. Thus, the hypothesis that the numerous psychological and biochemical tests are for purposes of evaluation of Agent Orange effects are invalid because, 1) of uncertainty of Agent Orange exposure, 2) the long period of time that has elapsed after a possible exposure to this herbicide and 3) the small number (65) of twins to be studied, who might have been exposed to Agent Orange.

A basic concern is possible sample bias. The twins to be studied appear to be coming from only 4 or 5 states, however, this is a problem that is disregarded by the investigators. The individuals picked at random, who are invited to participate in the study cannot be assumed to be neutral with regard to the outcome of this study. Some may be recipients of medical care for service connected or service aggravated disabilities or may be receiving pensions. As a consequence there may be a problem in gaining full and objective cooperation from those veterans who fear that they may be jeopardizing their future or present VA claims. Some subjects may be selected out because of illness or their job commitment, and are unable to travel to St. Louis. Others, because of an affluent life-style or professional commitments may not wish to volunteer for the extensive studies and trip to St. Louis. This may then result in the study assembling a group of volunteers who are unrepresentative of the population of Vietnam veterans.

Another general problem of concern to the reviewers was the feasibility of assuring quality of medical, psychological and laboratory examinations via competitively bid contracts. What input will the investigators have on the letting of the contract and sub- contracts, and how will they monitor the competence of these contractors.

SPECIFIC CRITICIMS OF EXAMINATION ELEMENTS

Mental Health Examinations:

Psychiatric assessment is to be made using the Diagnostic Interview Schedule (DIS), medical records, and interview with spouse or equivalent.

The preferred diagnostic instrument is to be the DIS III. This may strike the psychiatric community as an odd choice. The major value of the DIS, to date, is as an epidemiological survey instrument

that can be administered by non-clinicians; however,in the contemplated study expert clinicians could more appropriately be used. The potential contribution of this instrument for clarifying PTSD is not self-evident. It is ironic that the protocol involves transporting 1,200 person to St. Louis, but ignores the opportunity for expert clinical examination in favor of a survey instrument.

A more serious and certainly more pragmatic concern is that at the time this protocol was prepared the DIS III had not yet become available for inclusion in this study.

The Psychological assessment is to use a wide array of psychological instruments: 1) four self report measures of psychological distress, 2) three measures of cognitive deficit, 3) one measure of psychological constriction, 4) three coping measures, 5) two measures of cognitive measures, 6) life events, and 7) a measure yet to be developed (Current Behavioral Indices).

In general, the theoretical and conceptual specification of the diagnostic outcomes of primary interest is adequate; however, there are several points of concern. First, regarding diagnostic outcome of primary interest, there is no DIS algorithm for the schizotypal borderline or narcissistic personality disorders which current research suggests overlaps with PTSD. Secondly, the specification of four distinct groups of veterans is not well conceputalized, either theoretically or operationally.

The delineation of construct areas is a useful procedure, however, the proposed scales to measure the construct area do not always represent the best possible measures, i.e., CPT to assess psychological constriction, or the resurrection of the out-moded California F scale as an index of cognition.

A more detailed operational definition of hypotheses is necessary. What is it about war stress that contributes differentially to PTSD, primary diagnostic outcomes and psychosocial measures? What independent validations are being employed to cross-check pre-service risk factor variables? There is a need to interview significant others and obtain documentation for the occurrence of a self-reported risk factor.

Of great concern is the need to establish the feasibility of subjecting individuals to the onerous chore of completing the time-consuming battery of tests. Could there be a serious sample biasing effect toward compliance and perhaps "health" for those subjects who fully cooperate in this heavy assessment program? What will be the rate of subject attrition? Consider the likelihood of a movie-version PTSD patient holding still for these evaluations.

Overall, the measures will generate a plethora of data which ultimately may have to be factored into empirically derived rather than rationally predetermined dimensions suggested. The limits of the study, include such factors as: 1) inability to match within twin pairs for post military experience, 2) possible relevant aspects of military service, e.g., duration of service, rank, time of service, branch, etc., and 3) the limits of the cross-sectional design involving measurement of "effects" taken 15-20 years after the putatively critical service experiences. It is difficult to be reassured by the argument that a "longitudinal" view will be constructed.

Medical and Laboratory Examinations.

It is proposed to perform a multitude of liver function tests. This combination of tests, if abnormal, may indicate that the subject has hepatic dysfunction, however, it will not define the type liver disease. The primary usefulness of assays of gamma-glutamyl transpeptidase (GGT) as a diagnostic test is limited to confirmation of elevated alkaline phosphatase of bony origin, since GGT is not found in bone and should be low in isolated disease of the bone. A finding of elevated GGT has limited usefulness, because the enzyme is ubiquitous and elevation of GGT in no way specifies hepatic disease. Of concern in this study is the fact that this is an inducible enzyme. Numerous enzyme-inducing drugs, most notably alcohol, elevate the serum level of the enzyme in the absence of other evidence of hepatic disorder. In reading their protocol it would appear that the PI's will depend solely on the subject's concepts of his drinking habits. On the other hand if all of the other liver associated tests are within normal limits, an elevated GGT may be an indication of recent and/or continous alcohol intake.

In summary, results will be obtained from the performance of a battery of liver associated tests. The interpretation of these results will be difficult unless those with abnormalities undergo liver biopsy to determine the morphologic changes associated with liver diseases. It will be difficult to interpret whether Agent Orange is responsible for any of the biochemical changes that may be found.

The section on porphyria is weak. The authors have failed to delineate the modern day concepts of hepatic porphyrias. The latent and manifest forms of acute intermittent porphyria and porphyria cutanea tarda (PCT) differ in the excretion of porphobilinogen, delta-aminolevulinic acid, uroporphyrin and coproporphyrin. They do not specify which of these intermediates of heme synthesis they will measure. Most cases of PCT are sporadic, although there is a inherited enzymatic defect (deficient

activity of uroporphyrinogen decarboxylase) that predisposes to development of PCT.

The "andrology" studies, as proposed, have little intellectual basis, with the literature briefly summarized instead of critically reviewed. The studies of spontaneous abortion are seriously undersold in their complexity. The cytogenetic testing for sister chromatid exchanges and chromosomal aberrations has several specific flaws, but the allusion that somatic cell chromosome alterations may reflect alterations in haploid cells which, in turn, bear on sterility, fetal wastage, teratogenesis, etc., is especially troublesome in its conceptualization, even more so than in its implementation. The mechanism of communication of cytogenetic test results is left, pretty much as it was at the Love Canel, unexplained. The semen analysis is unfortunately open to serious question for several reasons. It is stated that only a single semen sample will be collected. This is inadequate because of the variability in ejaculate volume, sperm numbers and sperm motility in human semen samples. A minimum of two and optimally three semen samples collected at 1-2 month intervals should be obtained. The qualitative assessment of sperm motility is inaccurate and unacceptable. A quantitative estimate of sperm motility is essential. There is a question about the wisdom of freezing semen for assessment of sperm numbers and morphology since there is no description of the method of freezing semen and no assurance that it will be done properly.

Recent large, independent investigations of Australian Vietnam veterans (NEJM 308:719, 1983) and American Vietnam veterans (JAMA 252:903, 1984) concluded that there was no evidence that service in Vietnam was related to the risk of fathering a child with a birth defect, and thus there is little reason for further evaluation of this topic with such a small number of subjects.

A wide range of immunological assays, particularly of T cell function are proposed, again with little evidence of a rationale for the studies. No review of Agent Orange effects on this immune system is provided, in humans or in experimental systems, and there is no specific reason to believe that being in Vietnam per se alters immune function. Immunotoxicology is a developing science, and is not yet applicable for definitive studies of humans exposed to toxins. What are normative values in the population? What would small alterations of suppressor T cells mean for these subjects?

In summary, it is felt that the many specific laboratory tests proposed would be of little value. More troublesome is the weak or absent rationale for including many of the laboratory procedures.

BUDGET

Since the prospects of generating objective, scientifically sound data from this project are slim, the total costs of approximately 10 million dollars is highly cost ineffective. The request for 100 percent support for so many principal investigators is surprising. The budget justification indicates that the staff members are to work on other projects and conduct clinical duties in addition to work on this proposal.

INVESTIGATORS

The reviewers expressed considerable concern about the competence of most of the investigators, who have never before directed a project of this magnitude. The physician PI, Dr. Eisen has no significant research experience and no scientific publication for the past 8 years, except for a case report in 1982. He has one active VA supported research project through HSR&D, but has demonstrated no expertise in any of the areas of this proposal. Dr. Levitt, Ph.D., psychologist has no publication as a primary author and no research support. Dr. True, Ph.D., anthrophology and MPH in epidemiology has no publications in refereed journals and no research support. Dr. Goldberg, Ph.D. in epidemiology has 12 refereed publications in health service research and is senior author of five of these. He lists no research funding. Susan Fisher has a BS in Nursing and an MS in Biostatistics. She is the primary or coauthor of eight publications in the field of nursing. Dr. Henderson, Ph.D. in biostatistics is Associate Professor, Department of Pharmacology, Loyola University and Chief, Hines VA Cooperative Prograrm, Hines, Illinois. He has an impressive list of publications, mostly in field of Clinical Trials and is considered to be a global authority in this area.

RECOMMENDATIONS

Disapproval of Twin Protocol #2, CSP #256 (by a vote of 13 to 1). Protocol #1 should continue to develop the registry of Vietnam twins and increase the scope of the mortality and morbidity questionnaire for all of the approximately 10,000 male twin pairs born between 1939-1953 with military service from 1965-1975. If necessary additional funds should be provided to expand the questionnaire and/or sample size in order to provide an improved data base for a possible future implementation of a clinical study on a subset of twins. The questionnaire for the morbidity study might be expanded to include selected behavioral questions, family and social history and other confounding variables such as drug and alcohol abuse.

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CRITIQUE - General criticisms of project design and concepts.

The overall impression of the proposed study is that it is fundamentally overambitious, with not enough serious, scientific rationale provided for the work described. The hypotheses for performing the numerous laboratory procedures outlined in the proposal are not based on solid scientific data. This is basically

a "fishing expedition" among cohorts of twins, in which the focus will be on clinical, laboratory, and behavioral parameters of disease, or of disease indicators. The General Medical Assessment, as outlined in this protocol, represents a cosmic approach to clinical assessment, which may also be said for the extensive battery of laboratory tests proposed. Instead of a proposal consisting of a series of well-defined questions for which research studies are to be done, the veterans will be subjected to all manner of tests, clinical and other, on basically flimsy scientific evidence, to see what emerges. Even the more specialized tests have insufficient justification and weak scientific rationale.

The only independent variable in this proposed study is service in Vietnam. A reasonable hypothesis might be generated that links Vietnam service to psychiatric sequelae, however, other studies directed to this goal are already being undertaken.

Because the "n" (sample size) is small the study has only a low statistical power to detect modestly increased risks for medical or psychiatric illnesses. The small "n" may also invalidate the meaning of a negative result. While it may be true, as the investigators argue, that the "n" is large enough to detect subclinical differences in continuous variables such as laboratory values, such differences would have no clinical significance and are of insufficient importance to argue for implementing such a massive study. What are the implications of finding small deviations from normality in the co-twin pairs?

Two problems with the data analysis presentation deserve some comment. First, information on data analysis is scattered throughout the proposal. Although each of these subsections is clearly presented, the relationships between the various types of analyses is not fully discussed. The second problem is relevant to the issue of multiple comparisons and spurious effects. This would be less of a problem if the data anaylses were divided into confirmatory and exploratory analyses. The confirmatory analyses should test a prior hypotheses which are explicitly specified by the investigators. These hypotheses could be based on either past empirical findings or theoretical developments. Since this group of tests will be less than the number of tests discussed in the proposal, it would be reasonable to apply a higher alpha level to them than to the exploratory analyses.

The medical illnesses of Vietnam servicemen, were for the most part self-limiting and will likely have long ago disappeared. Although acute and/or chronic exposure to drugs or chemicals might yield some abnormal test results initially, 14 or 20 years have now elapsed since active Vietnam service and any relationship of cause and effect will be compromised.

A basic problem is that health differences between twins may be unrelated to Vietnam service, and may have developed in the 14 to 20 years post-Vietnam.

Since it will not be possible to obtain accurate data on which servicemen were exposed to Agent Orange this study has essentially no relevance to the problem of Agent Orange effects on health. Thus, the hypothesis that the numerous psychological and biochemical tests are for purposes of evaluation of Agent Orange effects are invalid because, 1) of uncertainty of Agent Orange exposure, 2) the long period of time that has elapsed after a possible exposure to this herbicide and 3) the small number (65) of twins to be studied, who might have been exposed to Agent Orange.

A basic concern is possible sample bias. The twins to be studied appear to be coming from only 4 or 5 states, however, this is a problem that is disregarded by the investigators. The individuals picked at random, who are invited to participate in the study cannot be assumed to be neutral with regard to the outcome of this study. Some may be recipients of medical care for service connected or service aggravated disabilities or may be receiving pensions. As a consequence there may be a problem in gaining full and objective cooperation from those veterans who fear that they may be jeopardizing their future or present VA claims. Some subjects may be selected out because of illness or their job commitment, and are unable to travel to St. Louis. Others, because of an affluent life-style or professional commitments may not wish to volunteer for the extensive studies and trip to St. Louis. This may then result in the study assembling a group of volunteers who are unrepresentative of the population of Vietnam veterans.

Another general problem of concern to the reviewers was the feasibility of assuring quality of medical, psychological and laboratory examinations via competitively bid contracts. What input will the investigators have on the letting of the contract and sub- contracts, and how will they monitor the competence of these contractors.

SPECIFIC CRITICIMS OF EXAMINATION ELEMENTS

Mental Health Examinations:

Psychiatric assessment is to be made using the Diagnostic Interview Schedule (DIS), medical records, and interview with spouse or equivalent.

The preferred diagnostic instrument is to be the DIS III. This may strike the psychiatric community as an odd choice. The major value of the DIS, to date, is as an epidemiological survey instrument

that can be administered by non-clinicians; however,in the contemplated study expert clinicians could more appropriately be used. The potential contribution of this instrument for clarifying PTSD is not self-evident. It is ironic that the protocol involves transporting 1,200 person to St. Louis, but ignores the opportunity for expert clinical examination in favor of a survey instrument.

A more serious and certainly more pragmatic concern is that at the time this protocol was prepared the DIS III had not yet become available for inclusion in this study.

The Psychological assessment is to use a wide array of psychological instruments: 1) four self report measures of psychological distress, 2) three measures of cognitive deficit, 3) one measure of psychological constriction, 4) three coping measures, 5) two measures of cognitive measures, 6) life events, and 7) a measure yet to be developed (Current Behavioral Indices).

In general, the theoretical and conceptual specification of the diagnostic outcomes of primary interest is adequate; however, there are several points of concern. First, regarding diagnostic outcome of primary interest, there is no DIS algorithm for the schizotypal borderline or narcissistic personality disorders which current research suggests overlaps with PTSD. Secondly, the specification of four distinct groups of veterans is not well conceputalized, either theoretically or operationally.

The delineation of construct areas is a useful procedure, however, the proposed scales to measure the construct area do not always represent the best possible measures, i.e., CPT to assess psychological constriction, or the resurrection of the out-moded California F scale as an index of cognition.

A more detailed operational definition of hypotheses is necessary. What is it about war stress that contributes differentially to PTSD, primary diagnostic outcomes and psychosocial measures? What independent validations are being employed to cross-check pre-service risk factor variables? There is a need to interview significant others and obtain documentation for the occurrence of a self-reported risk factor.

Of great concern is the need to establish the feasibility of subjecting individuals to the onerous chore of completing the time-consuming battery of tests. Could there be a serious sample biasing effect toward compliance and perhaps "health" for those subjects who fully cooperate in this heavy assessment program? What will be the rate of subject attrition? Consider the likelihood of a movie-version PTSD patient holding still for these evaluations.

Overall, the measures will generate a plethora of data which ultimately may have to be factored into empirically derived rather than rationally predetermined dimensions suggested. The limits of the study, include such factors as: 1) inability to match within twin pairs for post military experience, 2) possible relevant aspects of military service, e.g., duration of service, rank, time of service, branch, etc., and 3) the limits of the cross-sectional design involving measurement of "effects" taken 15-20 years after the putatively critical service experiences. It is difficult to be reassured by the argument that a "longitudinal" view will be constructed.

Medical and Laboratory Examinations.

It is proposed to perform a multitude of liver function tests. This combination of tests, if abnormal, may indicate that the subject has hepatic dysfunction, however, it will not define the type liver disease. The primary usefulness of assays of gamma-glutamyl transpeptidase (GGT) as a diagnostic test is limited to confirmation of elevated alkaline phosphatase of bony origin, since GGT is not found in bone and should be low in isolated disease of the bone. A finding of elevated GGT has limited usefulness, because the enzyme is ubiquitous and elevation of GGT in no way specifies hepatic disease. Of concern in this study is the fact that this is an inducible enzyme. Numerous enzyme-inducing drugs, most notably alcohol, elevate the serum level of the enzyme in the absence of other evidence of hepatic disorder. In reading their protocol it would appear that the PI's will depend solely on the subject's concepts of his drinking habits. On the other hand if all of the other liver associated tests are within normal limits, an elevated GGT may be an indication of recent and/or continous alcohol intake.

In summary, results will be obtained from the performance of a battery of liver associated tests. The interpretation of these results will be difficult unless those with abnormalities undergo liver biopsy to determine the morphologic changes associated with liver diseases. It will be difficult to interpret whether Agent Orange is responsible for any of the biochemical changes that may be found.

The section on porphyria is weak. The authors have failed to delineate the modern day concepts of hepatic porphyrias. The latent and manifest forms of acute intermittent porphyria and porphyria cutanea tarda (PCT) differ in the excretion of porphobilinogen, delta-aminolevulinic acid, uroporphyrin and coproporphyrin. They do not specify which of these intermediates of heme synthesis they will measure. Most cases of PCT are sporadic, although there is a inherited enzymatic defect (deficient

activity of uroporphyrinogen decarboxylase) that predisposes to development of PCT.

The "andrology" studies, as proposed, have little intellectual basis, with the literature briefly summarized instead of critically reviewed. The studies of spontaneous abortion are seriously undersold in their complexity. The cytogenetic testing for sister chromatid exchanges and chromosomal aberrations has several specific flaws, but the allusion that somatic cell chromosome alterations may reflect alterations in haploid cells which, in turn, bear on sterility, fetal wastage, teratogenesis, etc., is especially troublesome in its conceptualization, even more so than in its implementation. The mechanism of communication of cytogenetic test results is left, pretty much as it was at the Love Canel, unexplained. The semen analysis is unfortunately open to serious question for several reasons. It is stated that only a single semen sample will be collected. This is inadequate because of the variability in ejaculate volume, sperm numbers and sperm motility in human semen samples. A minimum of two and optimally three semen samples collected at 1-2 month intervals should be obtained. The qualitative assessment of sperm motility is inaccurate and unacceptable. A quantitative estimate of sperm motility is essential. There is a question about the wisdom of freezing semen for assessment of sperm numbers and morphology since there is no description of the method of freezing semen and no assurance that it will be done properly.

Recent large, independent investigations of Australian Vietnam veterans (NEJM 308:719, 1983) and American Vietnam veterans (JAMA 252:903, 1984) concluded that there was no evidence that service in Vietnam was related to the risk of fathering a child with a birth defect, and thus there is little reason for further evaluation of this topic with such a small number of subjects.

A wide range of immunological assays, particularly of T cell function are proposed, again with little evidence of a rationale for the studies. No review of Agent Orange effects on this immune system is provided, in humans or in experimental systems, and there is no specific reason to believe that being in Vietnam per se alters immune function. Immunotoxicology is a developing science, and is not yet applicable for definitive studies of humans exposed to toxins. What are normative values in the population? What would small alterations of suppressor T cells mean for these subjects?

In summary, it is felt that the many specific laboratory tests proposed would be of little value. More troublesome is the weak or absent rationale for including many of the laboratory procedures.

BUDGET

Since the prospects of generating objective, scientifically sound data from this project are slim, the total costs of approximately 10 million dollars is highly cost ineffective. The request for 100 percent support for so many principal investigators is surprising. The budget justification indicates that the staff members are to work on other projects and conduct clinical duties in addition to work on this proposal.

INVESTIGATORS

The reviewers expressed considerable concern about the competence of most of the investigators, who have never before directed a project of this magnitude. The physician PI, Dr. Eisen has no significant research experience and no scientific publication for the past 8 years, except for a case report in 1982. He has one active VA supported research project through HSR&D, but has demonstrated no expertise in any of the areas of this proposal. Dr. Levitt, Ph.D., psychologist has no publication as a primary author and no research support. Dr. True, Ph.D., anthrophology and MPH in epidemiology has no publications in refereed journals and no research support. Dr. Goldberg, Ph.D. in epidemiology has 12 refereed publications in health service research and is senior author of five of these. He lists no research funding. Susan Fisher has a BS in Nursing and an MS in Biostatistics. She is the primary or coauthor of eight publications in the field of nursing. Dr. Henderson, Ph.D. in biostatistics is Associate Professor, Department of Pharmacology, Loyola University and Chief, Hines VA Cooperative Prograrm, Hines, Illinois. He has an impressive list of publications, mostly in field of Clinical Trials and is considered to be a global authority in this area.

RECOMMENDATIONS

Disapproval of Twin Protocol #2, CSP #256 (by a vote of 13 to 1). Protocol #1 should continue to develop the registry of Vietnam twins and increase the scope of the mortality and morbidity questionnaire for all of the approximately 10,000 male twin pairs born between 1939-1953 with military service from 1965-1975. If necessary additional funds should be provided to expand the questionnaire and/or sample size in order to provide an improved data base for a possible future implementation of a clinical study on a subset of twins. The questionnaire for the morbidity study might be expanded to include selected behavioral questions, family and social history and other confounding variables such as drug and alcohol abuse.