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Minutes, Committee on Epidemiology
and Veterans Follow-up Studies,
No. 3 - 27 April 1967 - p. 1

SUBJECT TO APPROVAL AT NEXT MEETING

NATIONAL ACADEMY OF SCIENCES - NATIONAL RESEARCH COUNCIL
Division of Medical Sciences

COMMITTEE ON EPIDEMIOLOGY AND VETERANS FOLLOW-UP STUDIES

Minutes of Third Meeting - 27 April 1967
Academy Building
Washington, D. C.

ATTENDANCE

Committee on Epidemiology and Veterans Follow-up Studies

MacMahon, Dr. Brian, Harvard University, School of Public Health, Chairman
Chalmers, Dr. Thomas C., Tufts University, Department of Medicine
DeBakey, Dr. Michael E., Baylor University, Department of Surgery
Epstein, Dr. Frederick H., University of Michigan, School of Public Health
Jordan, Dr. William S., University of Virginia, Department of Preventive Medicine
Lemkau, Dr. Paul V., Johns Hopkins University, School of Hygiene and Public Health
Moriyama, Dr. I. M., HEW, National Center for Health Statistics
Neel, Dr. James V., University of Michigan, Department of Human Genetics

Absent:

Clark, Dr. Duncan W., State University of New York, Downstate Medical Center
Remington, Dr. Richard D., University of Michigan, School of Public Health
Zeldis, Dr. Louis J., University of California, School of Medicine

Liaison Representatives

Veterans Administration, Department of Medicine and Surgery

Rosenberg, Dr. C. A.
Shaw, Mr. Lawrence
Wolcott, Dr. Mark W.

National Institutes of Health, National Heart Institute

Feinleib, Dr. Manning

U. S. Atomic Energy Commission, Division of Biology and Medicine

Burr, Dr. W. W., Jr.
Sagan, Dr. Leonard A.

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National Academy of Sciences - National Research Council

Division of Medical Sciences

Cannan, Dr. R. Keith, Chairman
Hrubec, Dr. Zdenek
Jablon, Mr. Seymour
Nefzger, Dr. M. Dean
Simon, Mr. A. Hiram

Dr. MacMahon opened the meeting at 10:00 a.m. and welcomed Dr. DeBakey, who had been unable to attend the previous meetings, and the guests.

The minutes of the meeting of 28 March 1966 were approved.

Report on Studies Considered at Second Meeting

There was a brief review of the status of the proposals considered by the Committee at its previous meeting. With respect to parkinsonism, Dr. Hrubec reported that a number of discussions with various interested investigators had failed to delineate a feasible study. Evaluation of the possible etiologic role of encephalitis lethargica was an attractive possibility, but was hampered by the fact that overt infections were infrequent, and there was no known way to sample sub-clinical infections. It seemed impractical to attempt a study of familial associations by considering cases in World War I veteran fathers and World War II veteran sons because of difficulties in record linkage. Review of a sample of World War II Army cases had shown, moreover, that for these cases neurologic consultation was infrequent at the time of original diagnosis, and the diagnoses were often contradicted at subsequent VA medical examinations. The only proposal, therefore, which still had possible life was for a follow-up study of men admitted with this disease to VA hospitals in 1950 or thereabouts, for whom the subsequent course could be studied. However, there were problems in obtaining samples of VA admissions in 1950 and unless these can be solved, this study, too, will be impractical. At the moment, therefore, nothing was underway in the area of parkinsonism.

Dr. Hrubec further reported the inauguration of the study of the epidemiology of lumbar disc lesions, which had been approved at the previous meeting. In accordance with the recommendation of the Committee attention was being given to the specialty of the surgeon who made the original diagnosis (whether neurosurgeon or orthopedic surgeon) and to the severity of the disease, and an attempt was being made to assess the possible importance of the psychiatric component.

Two other studies which had been considered at the previous meeting -- Regional Differences In Mortality from Cerebrovascular Disease and Mortality in Veterans with Psychiatric Diagnoses -- were not brought up under this heading since they were each to be discussed under later items on the agenda.

Review of Mail Ballot Regarding Regional Differences in Mortality From Cerebrovascular Disease in U. S. Veterans

Dr. MacMahon introduced the study which had already been approved by the Committee on a mail ballot but which nevertheless deserved discussion in open meeting.

Dr. Nefzger reported that the National Institute of Neurological Diseases and Blindness had indicated that the study would be supported by contract, and work was expected to begin in two or three weeks.

The objective was to assess the meaning of the difference in reported death rates from stroke as between Georgia on the one hand and five Rocky Mountain states on the other. The rate in Georgia was about twice that in the other region. The method proposed was to examine critically the documentary evidence

regarding death for all veteran deaths in which cerebrovascular disease was mentioned on the certificate and for a sample of deaths in which it was not mentioned. One of the problems was that of obtaining adequate documentation and it was planned to use only recent deaths as one way of coping with this.

During an animated discussion, members of the Committee made a variety of points regarding the study, which was considered to be of great interest. It was thought that classification of "sudden" deaths occurring at home as due to ASHD or CVA might well depend on custom of individual physicians. Often such deaths, called coronaries, proved on investigation not to be so sudden after all.

There were a number of problems to which complete answers could not now be given: How to deal with men who had previously had strokes which were actually unconnected with the death; how to decide, finally, what was the probable cause of death in each instance; whether deaths of veterans are representative of all deaths in the communities. If it were to turn out that the distributions of veterans' deaths by cause were similar to those of the general male population of the same ages in the communities there would be no problem, but a serious question would be raised if they were different. It had been planned that Dr. Heyman would classify the deaths by cause on the basis of the accumulated information, but perhaps a panel of physicians could be used instead. It was expected that autopsy reports would be available for about 25 percent of the deaths, but in any case it was necessary to have definite rules to govern the decisions. The problem of old strokes was troublesome, and it was hoped to be able to ascertain those which occurred within the year preceding death, but it would probably not be possible to go back further than that.

Dr. Epstein pointed out that the study was in many ways exploratory. It might be possible, with the lessons learned, to devise a good prospective study.

The opinion was expressed that the problem of diagnostic errors on death certificates was important in many other disease areas and that the methodology developed in this study of cerebrovascular disease may prove useful in other studies.

Requests for Access to Twin Registry

The Committee then turned to a consideration of requests for access to the Twins Registry. Mr. Jablon explained that the Twins Registry had been under development for several years and had finally been brought to such condition as to make it feasible to employ the Registry in actual studies. Three requests had been received and were before the Committee today. The first, by Drs. Friberg and Cederlöf, was the most extensive. The activities of the Agency in relation to the Twins Registry were supported, on contract, by NIH, and it was expected that the costs of the Agency in providing access to investigators would ordinarily be allocated to these funds. However, Dr. Friberg proposed a questionnaire directed at smoking patterns, residential histories and other items, and these costly activities would require separate funding. Application for such funds had been made by Dr. Friberg to the A.M.A. Committee for Research on Tobacco and Health. Additional support from U.S.P.H.S. National Center for Air Pollution Control was also in prospect.

Dr. Neel drew the attention of the Committee to the need for developing general rules of procedure for such applications. The first paper on the Twins

Panel had now appeared, calling the attention of investigators to its existence. Next year there might be many more applications. It was necessary to develop criteria for the applications themselves - the first application on the agenda seemed complete, but the other two did not give sufficient information. Further, it was necessary for the Committee to decide what its own procedures would be in considering applications. He believed that the Committee should be quite discriminating in its judgments. If so many as 12 to 15 really good studies are done the whole effort of creating the Panel will have been worthwhile, but these may come out of a much larger number of applications.

There were other, general questions, to be considered in relation to the Registry. One is how to analyze the material. Traditionally, the concordance for a disease is measured, leading to an estimate of what is called "heritability." However, as time passes and more men develop various diseases, concordances will change and so will the heritability estimates based on them. It would be necessary, therefore, to update the file periodically.

Dr. Neel continued that another general problem concerned the availability of fingerprints for the purpose of diagnosing the twin pairs as monozygotic or dizygotic. It was true that the twins' statements had proved to be fairly accurate, but they were far from perfect, and it would be very advantageous to have another independent method of diagnosing zygosity.

Mr. Jablon explained that the fingerprints had been furnished by the FBI for about one-third of the Panel, but in recent years no more had been made available. In conversations with the Chief of the Identification Division, it had been explained to us that the problem was simply that the greatly increased

workload of the Division made it impossible to undertake any but absolutely essential file searches. The Agency had offered to supply funds so that extra, temporary employees could be hired, or to permit overtime, but the answer was that funds were not the problem -- the Division had difficulty in hiring properly qualified people. However, the Division Chief was very sympathetic to the need, and offered to raise the question once more with his superiors. Later we were informed that his proposal had been denied by the Chief of the Bureau. The Agency staff felt they had exhausted the possibilities open to them for obtaining the prints.

A general discussion of the problem followed. Dr. Cannan expressed the opinion that the most useful new approach might be through the President's Scientific Advisory Committee.

Study of Twins in Relation to Effects of Smoking and Air Pollution on Health

The Committee then turned its attention to the proposal by Drs. Friberg and Cederlöf. Dr. Hrubec summarized the details of the proposal. There was general agreement that the study seemed worthwhile, and that it would be valuable to have available for other uses, too, the smoking histories that it was planned to obtain. However, several members found problems with the questionnaire: The thought was expressed that the questionnaire seemed much broader than was strictly required by the objectives of the study, yet did not give overall coverage; perhaps it would be desirable to use something even broader like the Cornell Medical Index which might have application to many future studies. It was observed, on the other hand, that some of the areas covered were almost sure to return information of doubtful validity, notably the questions directed at the presence of

angina pectoris. No one could foretell what further applications for access to the Registry might be made in the next few months, and it would be undesirable to wear thin the patience of the twins when it might be necessary to return to them again soon. After considerable discussion the consensus was that it would be impossible to resolve all of the questions in a meeting, and that the Agency staff should be charged with drafting a set of ground rules and procedures over the next few months. The Chairman asked members of the Committee to send their suggestions directly to Mr. Jablon.

The present application would be considered on its own merits without regard to what applications the future might bring. However, it should be understood clearly that the questionnaire to be used was the responsibility of the Academy, and the resulting information would become part of the central files, available to future investigators. Further, attention should be given to suitable wording of a cover letter for the questionnaire, in which an attempt should be made to attract the interest of the twins in the ongoing study, so that they would not be unpleasantly surprised by another questionnaire in a year's time if that should prove desirable.

With respect to the present proposal, the point was made that, while objections might be raised to some of the questions, one of the objectives was to replicate the study already reported on the Swedish Twin Registry, and it was important not to disturb the comparability of the two sets of data. The Chairman asked the members of the Committee to send their specific comments on the questionnaire to the staff for discussion with Drs. Friberg and Cederlöf.

Several members of the Committee expressed the opinion that the proposed budget was too low, and urged that it be increased.

It was moved and seconded that the request by Drs. Friberg and Cederlof for access to the Registry of Veteran Twins be approved. The motion was voted unanimously.

Study of Twins Discordant for Schizophrenia and Comparison With Affected and Normal Concordant Pairs

The Committee then directed its attention to the proposal by Dr. Hoffer for a study of twins discordant for schizophrenia. Dr. Hrubec reported that he had only recently been able to get a count of the number of pairs in the Registry that met Dr. Hoffer's criteria and it turned out that there were just six pairs. Nevertheless, Dr. Hoffer was much interested in obtaining access to these six pairs. (After the meeting it was discovered that an error in tabulation had occurred, and the correct number was 72 pairs where both were alive and had answered the questionnaire.)

In reply to a question, Dr. Lemkau expressed the opinion that the diagnoses of schizophrenia found in the records were probably pretty good. In subsequent active discussion two general issues emerged: First, the question of the design of the study, and secondly the question whether it was proper to violate the confidentiality of the information available to the Agency by disclosing to a third party the fact that a veteran had been diagnosed as schizophrenic. With regard to the question of confidentiality the consensus was that before disclosing any names, the Academy staff should first make contact with the twins and solicit their agreement to having their names made available. On the question of design, there was difference of opinion whether it was part of

the Committee's function to advise investigators with respect to design or merely to consider the merit or lack of merit of what the investigator put before them. Dr. Cannan expressed the opinion that it would be unwise for the Committee to go on record as suggesting any changes in the investigator's proposed design, all the more since there had been no opportunity to discuss the questions with him.

It was moved, seconded, and voted that Dr. Hoffer be given access to the Registry of Veteran Twins, on the condition that the Agency make the initial contact with each veteran or his responsible guardian and obtain permission to disclose the name and address. Dr. Lemkau would telephone Dr. Hoffer and discuss with him the design problems that were raised during the Committee discussion.

Ophthalmologic Studies on Twins Regarding Glaucoma, Diabetic Retinopathy, and Ophthalmic Screening Examinations Emphasizing Changes Associated With Aging

Dr. Hrubec then introduced the application of Dr. Schwartz who proposed to examine twins living in the area of Washington, D. C., for the purposes of studying glaucoma, diabetic retinopathy, and age-related ophthalmic changes. The proposal had not been worked out definitively, and was better considered an idea rather than a protocol. Dr. Neel thought that Dr. Schwartz was an able investigator. He further suggested that it would be valuable if, at the examination, Dr. Schwartz were to arrange to obtain blood samples for serologic study in order to improve the zygosity diagnoses in the pairs studied.

In a general discussion it was pointed out that some of the same issues appeared that had been discussed in connection with Dr. Hoffer's application,

namely, the propriety of releasing information to outside investigators without the consent of the veterans and the problem of possibly exhausting the good will of the twins with the proposed examination so that other investigators in the Washington area might be debarred from useful access for some years. With respect to the problem of confidentiality, although some members felt that the issue was not so important here since the defining characteristic in the present instance was merely residence in an area rather than a diagnosis such as schizophrenia, the consensus was that the initial contact should be made by the Agency and only the names of those men who consented should be provided to the investigator. However, the other issue, that of exhausting the patience of the twins, was less easy to resolve. It was pointed out that because of the concentration of medical investigators in the Washington area, many groups might wish to have access to the veterans who live there. On the one hand, one would not wish to debar other investigators for a period of years merely because Dr. Schwartz had been first to apply, nor on the other hand did one wish to obstruct useful investigations merely in the hope that someday something else might turn up.

The issue was resolved by the observation that Dr. Schwartz's proposal was not sufficiently specific and required to be re-submitted in the form of a protocol. Such a protocol could be considered by the Committee by mail. Meanwhile there would be opportunity for others, particularly at NIH, to consider the desirability and feasibility of joining forces in a study of the Washington area twins directed at wider objectives. A motion was made, seconded, and approved that consideration of Dr. Schwartz's proposal be deferred, and re-submitted to a mail vote when ready.

Mortality Patterns in Veterans With Psychiatric Diagnoses in World War II

The next item to be brought up was the proposal by Mr. Keehn for a study of Mortality Patterns in Veterans with Psychiatric Diagnoses in World War II. Mr. Jablon explained that, if approved by this Committee, the proposal would be submitted to the National Institute of Mental Health. Mr. Keehn had consulted with Dr. Lemkau while drawing up the proposal. Dr. Lemkau explained that the objective was to determine whether psychiatric tension shortens life - it was in effect a test of the psychosomatic hypothesis. In reply to a question by Dr. DeBakey he asserted his opinion that the diagnoses of psychoneurosis made during World War II were probably pretty good. After some further discussion it was moved, seconded, and voted that the proposal be approved.

Follow-up of Soldiers Assigned to Manhattan District Units

The proposal by Drs. Mancuso and Sanders for a mortality follow-up of soldiers formerly assigned to the Manhattan District at Oak Ridge and other atomic plants was considered next. Mr. Jablon explained that the proposal was one facet of a much larger study being supported by the Atomic Energy Commission, designed to learn whether workers in atomic energy plants suffered later ill effects as a result of occupational exposure to radiation. Although the exact numbers had not yet been determined, apparently there were between 1,500 and 2,500 men who had been assigned to Manhattan District units at Oak Ridge and other places during World War II. The proposal was to trace these men for subsequent mortality through the VA files and to compare mortality, by cause, with that in a suitably chosen comparison group to be selected from the Agency's sample file of men who took out National Service Life Insurance during World War II.

Dr. Sagan amplified this explanation, pointing out that the whole study would involve about 150,000 men. Mortality tracing of veterans through the VA files was very much easier than for men who were not veterans, and the proposal was in a certain sense, therefore, a kind of pilot study for the larger study.

During subsequent discussion the points were made that the veteran group was so small, and the probable average dose received so tiny (well under one rad) that one could not expect to demonstrate anything either positively or negatively about radiation effects on health. On the other hand, since the methodology involved in the follow-up of veterans was so different from that applicable to other workers, it was hard to see what the value of the proposed study could be even if considered only as a pilot venture. For these reasons, it was moved, seconded, and voted that the proposal by Dr. Mancuso not be approved.

Cooperative Survey of Amputations in VA

Mr. Jablon next reported to the Committee that the Agency had been asked by VA to serve as a central statistical unit for a cooperative survey of lower extremity amputations for ischemia, under the general direction of Dr. Richard Warren. The Agency had agreed to do this. The study was of limited duration. Dr. DeBakey remarked that he was glad to see the study being done. Dr. MacMahon observed that since the study was not a follow-up study of the kind in which the Committee had interest, the report would be considered merely as information for the Committee, and no action was needed.

Follow-up of Korean Head Wounds

Mr. Jablon then related the background of Dr. Caveness' proposal for a follow-up study of the Korean head injury cases. There was a roster of about

1,400 injuries, of which some 400 Navy and Marines had been studied by Dr. Caveness and colleagues, and about 1,000 Army cases had been worked up by Dr. Arnold Meirowsky. The initial work-ups were apparently quite good, and the proposal was to undertake a 15-year clinical follow-up. It was proposed to establish a group of clinical centers strategically located around the country. The program would be financed by the National Institute of Neurological Diseases and Blindness. The study would be expensive, but the Congress has given evidence, through a line item in the budget, of its interest in head wounds. The Advisory Council for NINDB had established a Subcommittee on Head Wounds which had considered the project at its last meeting but deferred action until a subsequent meeting to be held on 15 June.

After some discussion, the consensus was that the Committee inclined to approve the project in the event that the Advisory Council Subcommittee decided to approve it. A motion to this effect was made, seconded, and passed.

Retrospective Study of Relationship Between Service on Guam or Other Mariana Islands and Subsequent Amyotrophic Lateral Sclerosis

Mr. Jablon explained that there was no documentation before the Committee in relation to the last study on the Agenda, that concerning the possible relationship between military service on Guam or other Mariana Islands and subsequent ALS. The subject had been under discussion with Drs. Huber and Quadfasel of VA and with Dr. Brody of NINDB for nearly a year, but the practicability of a retrospective study depended on how many veteran deaths from ALS could be identified. Quite recently it had been learned that it would probably be possible to identify about 600 such deaths, and this made a retrospective

study of these deaths seem practicable. The staff therefore planned to go ahead with the more specific design of a definite proposal.

Dr. Jordan remarked that the problem was of interest from the point of view of the possible slow development of a virus. Dr. Neel mentioned the studies of the genetic aspects of the Guam syndrome which had involved the establishment of a panel which, to his regret, was later discontinued. The decision of the Committee was to approve the detailed planning for the study.

Establishment of Priorities

Having reviewed the various proposals placed before it, the Committee then turned to a consideration of the impact of the approved studies on the Agency's facilities. Consideration of the workloads that would accrue to each of the sections disclosed that no particular difficulties would be encountered.

It was agreed to leave open the date for the next meeting.

The meeting was adjourned at 4:00 p.m.