

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

AD HOC COMMITTEE ON STUDIES OF VETERAN TWINS

Minutes of First Meeting - 21 February 1957
Munitions Building and Academy-Research Council Building
Washington, D. C.

ATTENDANCE:

Committee:

Dr. James V. Neel, Chairman.
Drs. Halbert L. Dunn, Thomas H. Hunter,
Abraham M. Lilienfeld, Norma Ford Walker,
and William B. Wartman.

(Absent): Dr. Robert F. Loeb.

Liaison Representatives:

Veterans Administration:

Dr. Charles C. Chapple, Research and
Education.

National Academy of Sciences -
National Research Council:

Drs. Gilbert W. Beebe and Bernard M. Cohen;
Mr. Seymour Jablon, Follow-up Agency.
Dr. Robert W. Miller, Division of Medical
Sciences.

The meeting was called to order at 9:30 a.m. by the Chairman, Dr. Neel.

Dr. Neel, in the absence of Dr. Cannan, welcomed the Committee, and stated that the interest of the Division of Medical Sciences in veteran twin studies went back to as early as 1946, to his knowledge. He asked Dr. Beebe and Dr. Wartman to outline the background of the considerations leading to the present meeting.

Dr. Beebe extended the Council's greetings to the Committee. The early exploration to which Dr. Neel referred was a casual one but sufficient to show that there was nothing in routine military or veteran records which would facilitate the preparation of a twin roster. Interest on the part of the NRC Follow-up Agency then languished for lack of investigative stimulus until 1953 when it was reawakened by a paper by Macfarlane Burnet in The Lancet. In a presentation before the annual VA Medical Research Conference in 1953, Dr. Beebe had drawn the attention of VA investigators to the veteran population as a great resource for twin studies. In 1955 Dr. Wartman was referred to the Follow-up Agency by Dr. Martin Cummings of the VA and indicated his interest in clinical-pathological studies of twins. Discussions with Dr. Wartman stimulated Dr. Cohen and Mr. Jablon to examine the feasibility of screening a large group of veterans to find the twins among them, of determining zygosity, and of mapping out in a gross way the morbidity of twins in a large roster as a prelude to more refined studies. In 1955 and 1956 the Follow-up Agency tested the possibility of finding veteran twins by systematic searching of the central alphabetic files of separated military personnel. This proved to be feasible, and a number of pairs of twins were found in a small-scale test, but the method seemed expensive. In 1956 the FBI agreed to make available the induction fingerprints of twins who entered service. Using the fingerprints of the

twins who had been identified, together with their height, weight, and eye color, Mr. Jablon found that a modified discriminant analysis of these factors had promise as a method of differentiating monozygotic and dizygotic pairs. These preliminary findings were encouraging and led to further consultation with Dr. Wartman, and it was decided to seek Dr. Neel's opinions on the matter. Dr. Neel emphasized the importance of diagnosing zygoty accurately and the limitations of a veteran group from the point of view of age and sex. Nevertheless, he encouraged further development of the proposal, provided that more attention be given to the problem of diagnosing zygoty. Dr. Wartman later presented a plan to Dr. Cannan, who indicated substantial interest and advocated moving slowly and in the direction of long-term support. In June 1956 the Committee on Veterans Medical Problems reviewed Dr. Wartman's proposal and the preliminary findings of the Follow-up Agency. The Committee expressed enthusiasm for the program, provided long-term support could be found. Meanwhile, another method of finding twins among veterans, based on birth certificates, was tested and found workable at less cost than the laborious search through military files. With Dr. Dunn's encouragement and substantial assistance, Dr. Cohen canvassed the 52 vital statistics offices of the United States to determine the feasibility of searching local birth records and obtaining copies of those of white male twins born in the years for which there was the greatest likelihood of entering military service in World War II. The response answered the question of feasibility unequivocally, provided a realistic estimate of costs, and justified the preparation of the current draft of the protocol for which Dr. Cohen was responsible. In 1957 Dr. Cannan appointed this Committee to advise him on the merit of the proposal and on its implementation if this seemed indicated to the Committee.

Dr. Wartman added that he had discussed his earlier ideas about twin studies with Dr. Burnet and, in later correspondence with him about the proposal now under consideration, found him most encouraging. Dr. Wartman said his own initial interest had been in establishing a clinical center for direct study of selected pairs of veteran twins, but that he had come to see the value of starting with the kind of record approach under discussion.

Dr. Neel outlined the Committee's concern in four parts: First, the merit of the proposed project; second, its feasibility; third, the availability of study material to investigators with special interests; and fourth, the matter of costs.

Dr. Hunter said he had also been stimulated by Burnet's paper, and asked whether the project could be expanded to include females and earlier ages, and what medical data would be taken. He felt that much thought needed to be given to the types of studies which could be undertaken, and to establishing the criteria governing the making of observations.

Dr. Wartman and others spoke of the special advantages of the veteran population: the completeness of their medical histories during service, the ease of following them, and the completeness of their mortality records.

Dr. Lilienfeld pointed out the special advantages of using the restricted population to work out certain methodological questions, to study intensively such things as constitutional and physiological differences in twins of both types, and to contribute information of wider usefulness in human genetic studies generally.

Dr. Dunn believed that the selectivity of the sample would not be a severe limitation; there was no reason why the project could not later be expanded to include other groups, but the veteran studies would provide a testing ground for methodological problems. In 1940 he had proposed twin studies to the NRC Committee on Human Heredity and had been strongly supported by Dr. Vannevar Bush. He referred to a proposal by Howard B. Newcombe, head of the Biology Branch of Atomic Energy of Canada, Ltd., to develop an elaborate system of identifying cousin marriages from official records of family and marriage relationships, as a means of detecting changes in gene mutation rates. Consanguineous marriages have an even broader usefulness as study materials in human genetics, and the Canadian proposal, insofar as its methodology would be based on records, presented an interesting parallel with the project under discussion. Dr. Dunn foresaw the usefulness of twin studies in relation to what he characterized as a future new axis in medical and public health interest: the concept of "wellness," of freedom from ill health and from stress and tensions in human populations.

Dr. Neel remarked that he was not known as a strong advocate of human twin studies. The method provides a potentially powerful tool, but the actual studies so far done on twins had in many instances been accepted uncritically. He stated that Dr. Walker was one of the most active workers in a field of special importance to twin studies - that of zygosity diagnosis - and asked her to discuss this aspect of the problem.

Dr. Walker felt that the problem of zygosity, which had become her major interest, is of critical importance in twin studies, and that one cannot rest on assumptions in its diagnosis, e.g., by depending on characteristics whose inheritance is not well understood. She pointed out that, even if one assumes that morphologic factors are useful indicators, unsubstantiated statements with respect to, say, eye color, cannot be trusted. The diagnosis of zygosity must be as nearly certain as possible, and the only way to achieve this is by comparison of blood types and serum proteins in all twin pairs. Dr. Walker said she now had under way studies of twins in whom zygosity had been determined with the aid of examination of fetal membranes, and felt that her results might eventually throw some light on the value of morphologic characteristics in the diagnosis problem. She asked how fingerprints, eye color, etc., were to be used in the proposed study.

Mr. Jablon described his scoring approach, emphasizing that he had had at hand information on only 14 pairs of twins with which to work, and had not attempted a comprehensive analysis, but only a rough trial with a few factors to see if a method would emerge. He first scored the fingerprints on an arbitrary numerical scale of similarity in print type between homologous digits, taking into account whorls, loops, ridge counts, or combinations thereof, as the particular digit might require. A value was assigned independently to each of the 10 digits, so that the summed score for each twin pair varied directly with increasing similarity of print types. When the pairs were ranked by this score, it was found that those pairs of twins who did not differ either in eye color, or in height by more than two inches, or in weight by more than five pounds, all fell toward the high end of the scale. With so few pairs of twins and with a small number of gross characteristics, this seemed to be a surprisingly sharp differentiation, and indicated that a more comprehensive analysis with a large sample of twins might distinguish a high proportion of monozygotes and dizygotes, leaving not too large a proportion with indeterminate zygosity.

Dr. Neel felt that the indeterminate group would be at least 10 per cent, and would constitute the group of greatest interest to geneticists: the most dissimilar monozygotes and the most similar dizygotes. He felt that these had to be differentiated if any concordance studies were to be valid, and that such studies would be the target of criticisms unless the best diagnostic methods were used.

Dr. Hunter pointed out that there is some uncertainty in every investigation, and that it is always possible to measure the degree of uncertainty. He asked why the presence of an undiagnosed 10 per cent would destroy the validity of studies confined to the remaining well-differentiated pairs. This might be a limitation in some problems, but surely not all other problems have been solved.

Dr. Neel said it was a question of whether the trait under study is continuous or discrete. For a quantitative variable the detection of a difference could well depend on the missing 10 per cent. Where a factor was simply present or absent, as, e.g., a tumor, the middle group would be less important.

Dr. Lilienfeld agreed that in many studies the results would depend in certain ways on the missing group of indeterminate zygosity.

Dr. Walker stated that some of the major twin studies of the past were inadequate as to validity of zygosity diagnosis.

Dr. Neel agreed that on this point there was a profound dissatisfaction with many prior studies on human twins.

Dr. Hunter suggested that these considerations pointed to the central importance, in the proposed study of veteran twins, of the plan to undertake an intensive exploration of diagnostic methods among the twins who were in the Detroit area and accessible to Dr. Neel's laboratory.

Dr. Walker agreed that a methodological study of the diagnostic significance of morphologic characteristics in twins of confirmed zygosity would be useful. She felt that fingerprints had not been used properly in past studies.

Dr. Neel said his group was completing a comparative study of morphological and serological data by the double-blind method; he believed this would throw some light on the matter.

Dr. Dunn emphasized the necessity of "calibrating the scale" (i.e., Mr. Jablon's scoring method) in the special study in the Detroit area, and the other members of the Committee concurred.

Dr. Neel felt that when the pilot study had been completed and the results were in hand, a committee would have to meet to discuss their implications and consider the next steps.

Dr. Lilienfeld suggested that in connection with the pilot study a great deal of other pertinent information could be obtained directly from the twins under study. He said that MZ and DZ twins differ not only in degree of similarity of environment, but also in frequency of prematurity and stillbirths, in

family size, in birth order, etc. There is a general interest in constitutional factors, but many factors other than zygosity may influence constitution. He recommended collecting socioeconomic and physiological data for the twins, and felt this was important to do even at the stage of exploring methodology.

Dr. Neel cautioned that much which was essential to the immediate problem might be lost if the men were pushed too far. He was particularly interested in the results of testing the middle group of Mr. Jablon's scale, and visualized the possibility of finding scoring areas on either side of a middle group where the statistical diagnoses were perfect.

Mr. Jablon pointed out that the scale was a probability continuum throughout, and that at no point would there be an expectation of 100 per cent certainty. He felt that many morphologic characteristics would be useful, and would want to rework the fingerprint data and other traits into a better scoring system.

Dr. Lilienfeld suggested that the middle group could be made useful even without undertaking their precise diagnostic differentiation, if concordance ratios as determined throughout the scale were treated in regression fashion.

Mr. Jablon agreed that this would be consistent with his view of his scoring system as a probability distribution.

Dr. Walker expressed some misgivings as regards the probability approach, feeling that there was no real substitute for accuracy of diagnosis, particularly now that a high degree of accuracy was attainable by serological methods.

Dr. Dunn pointed out that no method reached perfection, and that the question was rather at what point short of certainty one wished to operate. He illustrated his point with the problem of measuring the diameter of a steel sphere, where the error could never be eliminated but could be reduced to any stated magnitude, providing one were willing to pay the cost.

Dr. Hunter strongly advocated a step-by-step approach, first building the roster, next exploring the diagnosis problem, and then taking stock to plan the subsequent steps.

Dr. Chapple discussed the intra-uterine environment, citing evidence that localized pressure on the fetus may be responsible for some types of congenital deformities. He suggested that such pressures, being presumably greater in twins, may result in considerable structural dissimilarities in MZ twins.

Dr. Neel agreed that the intra-uterine environment was important but thought that MZ and DZ twins would, in general, be subjected to the same kinds of pressures. He suggested that the nature or extent of fetal response to such forces might have a genetic basis.

Dr. Neel agreed with Dr. Hunter that the first step was to establish the roster and proceed with studies of diagnostic methods.

Dr. Dunn asked if nonveteran twins in the Detroit area might be sought, using other means of finding them.

Dr. Wartman said there are twin societies which might be helpful in this. He knew of one twin club in Chicago.

Dr. Lilienfeld referred to the importance of environmental factors, many of which are not really rigidly controlled in twin studies.

Dr. Neel agreed, and suggested that it might be well to consider a control group of nontwins or nontwin siblings of twins.

Dr. Dunn thought that the Detroit pilot study would provide an opportunity to define such a group.

Dr. Neel, reflecting on what had been brought out in the discussion so far, posed some general questions on the project as a whole: What conditions would be studied and what conclusions could be derived? What are the implications of a gradient of concordances? Is the study justified by its potential yield? Total costs could be visualized in millions of dollars.

Dr. Hunter emphasized that if the study were done properly it must be worth millions.

Dr. Dunn referred to the ever-growing problems of old age and the question of fitness in the aged. He believed that the future prospects of the twin study promised to throw important light on some of the aspects of these problems.

Dr. Lilienfeld pointed out the value of a prospective study. Genetic inferences based on retrospective data must be qualified.

Dr. Hunter remarked that so far there had never been a prospective twin study.

Dr. Lilienfeld restated his belief that a good deal of special pertinent information could be obtained from the men examined in the pilot study.

Dr. Neel referred to the guinea-pig aspect of the pilot study, and felt that much planning would be required before it was undertaken.

Dr. Dunn suggested actively seeking the cooperation of the twins to be examined and, in a sense, making them and their interests part of the planning.

Dr. Beebe asked Dr. Chapple if he believed veterans could be motivated toward voluntary continuous participation in such a study, and if the VA would have any objections to such an effort.

Dr. Chapple replied that the only restriction he was aware of was that the VA could not call back veterans for research purposes.

Dr. Neel suggested contacting them at their homes, if this was not inconsistent with VA policy.

AFTERNOON SESSION

Dr. Neel discussed in general terms the function of the Committee and how it could best discharge the obligation it undertook to review critically the proposed study of veteran twins and make specific recommendations to the Council as to (a) the value of the study, (b) whether in the Committee's opinion the study should be actively undertaken, and (c) such details of procedure as the Committee felt were in its province to suggest. He pointed out that this was an ad hoc committee, called together for a single meeting, and would cease to exist as a committee when the business of the day had been completed.

The members of the Committee discussed at some length a variety of details, in part reviewing the facts and opinions expressed during the morning session, but concerned largely with the general nature and specific details of such recommendations as the Committee was prepared to formulate. Two ideas were of special prominence in this discussion:

1. If the project is activated, a group of qualified persons should constitute a continuing body to guide the conduct of the study.
2. In view of the overriding importance of the question of zygosity diagnosis, special emphasis needed to be placed on the importance of a pilot study to "calibrate" the statistical method of diagnosis based on morphologic characteristics.

With respect to the second point, Dr. Lilienfeld reiterated his belief that advantage should be taken of the opportunity presented by the pilot study to obtain a variety of facts concerned with the biological, physiological, social, and economic factors which characterize the twins under study.

Dr. Hunter agreed in principle, but insisted that these details could not be prescribed by the present Committee. He felt that Dr. Lilienfeld's proposal constituted a specialized study, and its precise formulation, to which much time and thought would need to be devoted, must be left to the investigators directly concerned in planning and conducting the investigation and to the permanent body which would be appointed to guide the study on a continuing basis. There was general agreement with Dr. Hunter's view.

The results of the day's deliberations are embodied in the following recommendations, in which the membership of the Committee unanimously concurred:

1. The Committee believes that a singular opportunity for studies on twins is afforded by the record systems of the Armed Forces and the Veterans Administration, and that this opportunity should be seized upon. The Committee heartily endorses the initiation of a study along the lines described in the draft protocol of 14 December 1956, entitled "The Role of Heredity in Disease as Determined by Studies on Veteran Twins." Specifically, it recommends that steps be taken to establish a roster of twin veterans as soon as feasible.

2. The Committee recommends that adequate provision be made for the continuity of the study, and suggests the creation of a special group as one such mechanism.
3. In view of the critical importance of accurate diagnosis of zygosity to the validity of the inferences to be drawn from the data, the Committee recommends, as soon as the full roster has been established, a pilot study to compare the relative effectiveness of various diagnostic methods.
4. Consideration should be given to the feasibility of obtaining, at the time of the pilot study on zygosity determination, relevant socioeconomic and other data concerning the two types of twins, provided the collection of these data does not jeopardize the primary objective of establishing accurate zygosity diagnosis.
5. The Committee recommends that the pilot study include an exploration of the practicability of establishing a roster of siblings of the twins as a control group, or of establishing a roster of pairs of nontwin siblings, as an additional control, designed to detect certain types of bias.
6. The pilot study should include a careful consideration of the best means of enlisting the cooperative participation of veterans in what will be a long-term research project.
7. The inferences which may be drawn from a study of veteran twins may be limited by the operation of the Selective Service System, and such limitations should be explored.

The meeting was then adjourned.