February 5, 1954

TO: Members of National Advisory Committee and Participants in Atlanta Meeting of January 27-29.

FROM: Chairman

SUBJECT: Draft of Summary Report

Enclosed is a copy of the draft of the Summary Report that Dr. Eichenwald and I have prepared from the reports of the Subcommittees. We have endeavored to keep the editorial changes to a minimum and to maintain the "Sense of the Committee."]

We have been informed that the Editor of the JAMA would be interested in reviewing the manuscript and that a publication dead line of four to five weeks would be possible if the manuscript is accepted. The delay may require the issuance of a news release prior to publication of the report. Decision in this regard resides in Washington. We will endeavor to get a copy of the final news release in your hands as well as to all State Health Officers before the release date.

On sober second thought and considering the three dissenting votes at the meeting, it has been decided to omit the "policy paragraph" submitted by the Subcommittee on Administrative Aspects.

There is considerable urgency in securing final approval of this Summary. We want to submit it to the JAMA as early in the week beginning February 8, as possible. All of you should receive this by Monday morning, February 8. We are establishing Tuesday evening, February 9, as a dead line for the receipt of approval or corrections, so that the final clearance through the Surgeon General's Office can begin on February 10.

Therefore, would you kindly review this draft and reply by telegram collect at once. Telephone calls collect either to me or Dr. Eichenwald would be entirely appropriate.

Chairman

Thank you for the antibody titration data, which we plan to incorporate in the final version of the report.

Sincerely,

Chairman
AN EVALUATION OF THE EFFICACY OF GAMMA GLOBULIN IN THE PROPHYLAXIS OF PARALYTIC POLIOMYELITIS AS USED IN THE UNITED STATES DURING 1953

A Summary of the Report of the National Advisory Committee for the Evaluation of Gamma Globulin

A study, sponsored by the U.S. Department of Health, Education, and Welfare, Public Health Service, Communicable Disease Center, Atlanta, Georgia, in collaboration with the Association of State and Territorial Health Officers, the American Physical Therapy Association, and the D. T. Watson School of Physiatrics, affiliated with the University of Pittsburgh School of Medicine.

1/ Aided by a grant from the National Foundation for Infantile Paralysis, Inc.
THE NATIONAL ADVISORY COMMITTEE FOR THE EVALUATION OF GAMMA GLOBULIN

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During the summer of 1953, the Communicable Disease Center of the U. S. Public Health Service sponsored a national program for the evaluation of the efficacy of gamma globulin in the prophylaxis of paralytic poliomyelitis. Health departments in 41 states and 4 cities actively collaborated in the study. The program was planned and executed in accord with recommendations of a National Advisory Committee. The present report consists of a brief outline of the organization and plan of the study, a summary of the major findings, and the conclusions of the Advisory Committee. A full report of the study will be published elsewhere.

Organization and Plan of Study:

The National Advisory Committee was constituted of authorities in poliomyelitis research, state health officers, epidemiologists from states and large cities, and a physical therapist. While the members served as individuals, most of them had participated in various capacities during the planning of the procedures for the national allocation of gamma globulin during the spring of 1953. Similarly, all were active either in the field, in the laboratory, or in the clinic in the study of poliomyelitis and the effects of gamma globulin during the summer of 1953.

In considering its mission the Committee recognized that a practical objective was the collection of sufficient quantitative data to determine, if possible, the relative advantages and disadvantages of the administration of gamma globulin to an entire age segment in an epidemic area, and its use in household associates of cases of poliomyelitis. The Committee was aware that during the winter and spring of 1953, considerable difficulty was encountered by the committees working on the allocation problem in arriving at a rational basis of apportioning the supply between mass use and contact use.

The direct scientific evidence obtained during the field trials of 1951 and 1952 (1,2,3,4), suggested the value of mass use, at least when administered
at a suitable time prior to expected illness, in specified communities experiencing intense epidemics. It was clear, however, that the successful measurement of any mass effect, in terms of paralytic cases prevented or modified, would depend directly upon the degree of efficacy of gamma globulin, the intensity of the epidemic and the time when inoculations were given in relation to the rise and fall in incidence of cases. There was some doubt whether the number of severe epidemics that would occur in the country would utilize effectively more than a small proportion of the anticipated supply. Furthermore, it was problematic whether the subsequent course of an epidemic in a threatened community could be predicted with sufficient accuracy and in sufficient time to permit the necessary community organization to inoculate the children at risk before the epidemic waned.

Answers to such questions could only be obtained from practical field experience. Therefore, one of the approaches considered for the evaluation program was to plan detailed epidemiological descriptions of each of the epidemics in areas where there was mass use.

With regard to the alternate method of use of gamma globulin, namely contact use, no direct scientific evidence based on field observations was available to support its value. However, because household associates have an increased risk of developing poliomyelitis, it seemed likely that the administration of gamma globulin to these associates would equal, if not exceed, the benefits of mass use in terms of cases prevented or modified. The basis for these estimates, however, rested strongly on the assumption that gamma globulin administered within one week of onset would modify the severity of paralysis. This conclusion was reported by Hammon and associates, but the evidence was based on only 12 cases in his gamma globulin-inoculated group, compared with
16 cases in the gelatin-inoculated control group. Although the differences were statistically significant, conclusions based on such small numbers are hazardous in a disease as complex as poliomyelitis. There was a great need, therefore, to collect much more extensive data on the possible modifying effect of gamma globulin.

The Committee recognized that it would be very difficult to conduct rigidly controlled studies in the United States during 1953. The Committee recommended therefore, that the effort be concentrated on the collection of a maximum amount of well-defined descriptive epidemiological data for careful analysis and comparison with the wealth of past epidemiological experience in this country. It was believed that a marked preventive effect of gamma globulin in the recommended dosages when given at the right time might be observed in large epidemics, even in the absence of rigid controls, in the form of consistent and repeated deviations from classical epidemiological patterns normally observed in the age group inoculated. If it had a marked modifying effect, this should be evident in the mildness of the paralysis among patients coming down with poliomyelitis after receiving gamma globulin. While recognizing certain difficulties in this plan of investigation, the Committee nevertheless agreed that efforts should be made to collect the best possible data and to analyze them for valid conclusions.

Specifically, the Committee recommended four approaches to the problem:

1. Descriptive epidemiological studies for each of the areas where mass use of gamma globulin was employed.

2. A comparison of the severity of paralysis of patients developing the disease immediately before mass use with the severity of those acquiring the disease after receiving gamma globulin.
3. Study of the severity of paralysis among multiple case households, namely, those households in which two or more cases of poliomyelitis were reported.

4. The documentation of administrative aspects of the distribution of gamma globulin.

The program followed the general plans and objectives established by the Committee. In June an outline of the plans was sent to all State Health Officers with an invitation that they join in the national undertaking. The response was immediate and enthusiastic. The population of the 41 states and 4 cities participating in the study constituted about 90 per cent of the whole country. Thus, the program was truly national in scope.

A National Evaluation Center with headquarters in Atlanta was organized as a special task force for the program. A group of 20 Epidemic Intelligence Service Officers, 3 Nurse Officer Epidemiologists and 6 Statisticians was assigned by the Communicable Disease Center for essentially full time duty in the Program. A group of 38 physical therapists was mobilized by the American Physical Therapy Association.

Detailed epidemiological descriptions were collected in each of the 23 areas where mass inoculations of gamma globulin were given. In 5 of these areas the incidence of poliomyelitis after the gamma globulin administration was sufficiently great to warrant assigning a physical therapist for special studies to measure the possible modifying effect of gamma globulin.

The most extensive aspect of the program was the study of households from which more than one case of poliomyelitis was reported. In all participating states and cities record systems for matching case reports were organized either at the local or state level to identify multiple case households. As soon as
possible after the identification, field visits were made to the hospital or the home to collect uniform data. A standard form was provided. The main purpose of this visit was to verify the diagnosis, and to secure dates of onset that were as accurate as possible. Many different sources of data of varying completeness and accuracy were used. Special effort was made, however, to determine the status of paralysis during the period from 7 to 14 days after onset.

A special abridged system of muscle grading was employed that permitted an estimate of the extent of paralysis on the basis of muscle bulk involved. An index could be calculated and expressed in terms of per cent of muscle damage. Multiple case household data were included in this study if dates of onset fell within the interval from approximately June 1 to October 31. Reports of 830 multiple case households comprising 1,828 reported cases of poliomyelitis were forwarded to the National Evaluation Center in the study.

Data on the administrative aspects of gamma globulin distribution and uses in the field were collected.

Evaluation of Mass Use:

During 1953 gamma globulin was given by mass inoculation in 23 communities in 13 separate states. In all but two areas, entire county units were included. In one instance mass immunization was limited to a city and in another, only portions of two adjacent counties were selected. The populations of these areas ranged from 6,800 to 139,000 with a majority falling in the 25,000 to 50,000 population group. The total number of children inoculated in these areas was close to 235,000.

In attempting to evaluate the efficacy of the mass use of gamma globulin, the descriptive epidemiological data collected in each of these areas were
examined to see if consistent deviations from classical epidemic patterns were discernible. According to the data of Hammon and associates, the preventive effect of gamma globulin should begin about one week after its administration and should persist at a significant level until about the fifth week. Since large scale poliomyelitis epidemics tend to occur in symmetrical form, mass inoculations, if administered at or before the peaks of epidemics, might be expected to produce consistent and observable drops in the epidemic curve beginning about one week later. An asymmetry in the epidemic curve should become apparent. This should be most marked in the epidemic curve limited to the inoculated age group.

Corollary effects should be observed. For example, a marked shift in the incidence of cases to older uninoculated age groups should occur beginning after the mass inoculations. Similarly, the duration of epidemics in the inoculated group should be modified. Furthermore, differences should be observed in paralytic attack rates within the inoculated age group according to whether or not gamma globulin had been given.

These effects are postulated on the assumptions 1) that the gamma globulin available in 1953 was effective, 2) that the mass administration was given at or before the peak of the epidemics and 3) that the epidemics were sufficiently large scale. If, however, mass inoculations were given using less potent gamma globulin, or when the epidemics were already rapidly diminishing, or in small scale epidemics, then it would be difficult if not impossible to detect any effect attributable to gamma globulin.

A careful study of the 23 epidemics where mass use of gamma globulin was employed in 1953, revealed that in 13 instances the epidemics were too small, or the inoculations were given too late to permit further analysis. In the remaining
10 epidemics, however, comparisons were made for deviations from the classical epidemic patterns. A wide variety of asymmetrical epidemic curves was found and a comparison of these curves with those observed in epidemic areas this year where no gamma globulin had been employed revealed no consistent differences.

It was, therefore, concluded that asymmetry of epidemic curves could not be attributed with assurance to a gamma globulin effect, and thus, could not be utilized as a measure of the preventive action of gamma globulin on poliomyelitis at least for the size of outbreaks studied in 1953.

A study of the age incidence following mass administration of gamma globulin revealed a shift to older uninoculated groups in many of the epidemics. An examination of available data based on present and past experience, however, revealed that these age shifts are quite variable and that similar shifts frequently occur in areas where gamma globulin had not been used. The duration of the epidemics in mass inoculation areas was also compared with concurrent and past experience. Consistent differences were not found. Therefore, it was concluded that a study of neither the age shift nor the duration of the epidemic permitted valid conclusions regarding the effectiveness of mass use of gamma globulin in 1953.

Consideration was given to the possibility of comparing the paralytic rates before, during, and after the significant protection period described by Hammon and associates in the inoculated and uninoculated children. It was noteworthy that many paralytic cases appeared in uninoculated children, considering the relatively small number of such children thought to exist. It was necessary, however, to question the validity of this comparison because of the presumably disparate composition and unknown size of the two groups. It was conceivable that factors existed which would make the uninoculated groups a biased selection.
It was therefore impossible to apply this method of analysis to the experience in counties where mass injections were given.

In the 5 counties where physical therapy examinations were made 50 to 70 days after onset, 43 cases occurred in the eligible age group during the week immediately preceding the mass inoculations. A total of 48 cases developed after receiving gamma globulin, 32 occurring from 1 to 7 days later and 16, 8 to 31 days after. The severity of paralysis in these groups was compared. A modifying effect of gamma globulin was not statistically demonstrated.

Thus, while extensive and varied approaches were followed in the attempt to evaluate the efficacy of gamma globulin as used on a community inoculation basis in 1953, no valid basis was found for drawing confident conclusions as to its effect.

Evaluation of Contact Use:

The primary purpose of the extensive study of multiple case households was to evaluate contact use of gamma globulin. Multiple cases of clinically diagnosed poliomyelitis occur in 3 to 5 per cent of households. The interval between the first and subsequent cases has followed a rather characteristic pattern in many different epidemics. On the average, 60 per cent of subsequent cases occur within 5 days after the first case, 30 per cent 6 to 12 days, and approximately 10 per cent 13 to 30 days. Gamma globulin was administered to familial associates of patients on the assumption that the resulting paralysis might be in much milder form in those who would ordinarily develop it within 7 days of inoculation, while in a considerable proportion of the remainder, paralysis might be completely prevented.

In 749 multiple case households, 1,654 individual patients with poliomyelitis were studied. Of this number, 749 were index cases, 8 were prior cases,
80 were co-index cases, and 817 became ill one or more days after the index case. For various reasons, depending mostly on the time required for recognition of the index case and the large proportion of secondary cases which develop simultaneously with or very shortly after the index case, only 278 (34 per cent) of the 817 subsequent cases received gamma globulin before onset of their illness. To determine whether or not gamma globulin modified the severity of paralysis in these patients, the extent of muscle involvement in this group as well as in other groups of subsequent cases who either received no gamma globulin or received it on or after onset was carefully measured by specially trained physical therapists. For various reasons, fully outlined in the complete report, the comparison was limited to 415 patients who exhibited paralysis 50 to 70 days after onset of their illness. Of these 415 patients, 158 received gamma globulin before onset, 184 received no gamma globulin, and 73 received it on or after onset. The analysis based on the 50 to 70-day evaluation was regarded as more valid because it was found that only 8.6 per cent of 338 patients, who were diagnosed as having paralytic poliomyelitis at 7 to 14 days after onset, had insufficient paralysis at 50 to 70 days to warrant their inclusion, while 57 per cent of 328 patients who at 7 to 14 days were classified as nonparalytic or were only suspected of having nonparalytic poliomyelitis, were found to be paralytic at 50 to 70 days. A statistical analysis showed no significant difference in the extent of muscle involvement in those who received gamma globulin before onset, as compared with those who received none or received it on the day of or after onset.

Another question investigated was whether the proportion of patients classified as nonparalytic at 50 to 70 days in the group which received gamma globulin before onset was different from the proportion in the other groups mentioned above. No significant difference was found.
An analysis of the familial aggregation of all subsequent cases was made in order to obtain an indication as to whether or not the administration of gamma globulin may have prevented a considerable proportion of the cases that are expected to occur 13 to 30 days after the first case in the family. To permit comparison with the established pattern of previous years, it was necessary to include all the data obtained from multiple case households regardless of whether gamma globulin was given to any member of the family. When this was done, the pattern turned out to be similar to that observed in previous years when no gamma globulin was used. The distribution of the paralytic cases which received gamma globulin before onset was also analyzed in relation to the number of days which intervened between the onset of their illness and that of the first case in the family. These data obviously cannot be compared directly with the classical pattern of previous years because most of the cases which appeared within a few days after the index case received no gamma globulin, but it is noteworthy that 58 per cent of 155 such patients became ill 6 to 12 days after the index case, and another 12 per cent 13 to 30 days.

There may be several alternative explanations for the apparent lack of effectiveness of gamma globulin in familial associates of patients with poliomyelitis: 1) gamma globulin preparations may contain too little antibody to be effective in the dosage used, or 2) gamma globulin of adequate antibody content may be ineffective when it is given to patients after they have been infected, and the vast majority if not all familial associates of a case may already be infected by the time the first case is diagnosed or by the time inoculations can be given.

Administrative Aspects:

Administrative problems relating to the distribution of gamma globulin for inoculation of household associates within the states were few after the
material was received. The establishment, in advance, of definite criteria for its use relieved pressure on practicing physicians and health departments. The evidence indicates that once a request had been properly made, the globulin was provided promptly. The major delay centered around the interval between onset of the index cases and their diagnosis; nevertheless, in several states from which data are available, gamma globulin was given to the great majority of household associates within an average of five days from the onset of the index cases. If gamma globulin is to be given earlier, it is apparent that efforts must be made to obtain earlier recognition of the first cases.

On the other hand, the procedure for obtaining gamma globulin for mass use in epidemic areas was cumbersome. Because of the difficulty in making accurate predictions, the level of incidence required and the need for approval of a request, the time required to carry out the mass procedure was likely to cause sufficient delay as to prevent its being administered until the peak was well past.

**Discussion and Summary:**

The mass use of gamma globulin carried out on a large scale in 1953 as a method to prevent paralysis in poliomyelitis infection, was done in response to a widespread demand as a public health measure and not on an experimental basis. As such, attempts to draw conclusions regarding its efficacy have not been easy and in many instances impossible. In any event, the method of analysis of carefully compiled and extensive data on the use of gamma globulin in those epidemic areas and populations where it might have been expected to be effective did not yield statistically measurable results. Therefore, its effectiveness in community prophylaxis as practiced during 1953 has not been
demonstrated. Nevertheless, the Committee cannot say that the use of gamma globulin for this purpose produced no effect.

A serious difficulty encountered in arriving at conclusions about the results of mass use of gamma globulin in 1953, has been the lack of controls. If such controls had been available, the results would probably have been more clear cut, and their evaluation easier.

On the other hand, the data on the efficacy of gamma globulin in contact use that have been accumulated in 1953, are considered to be adequate for reliable conclusions. They indicate that, with the preparations involved and in the dosages used, the administration of gamma globulin to familial associates of patients with poliomyelitis, has had no significant influence on (1) the severity of paralysis developing in subsequent cases; (2) the proportion of nonparalytic poliomyelitis occurring in subsequent cases who received gamma globulin before onset; and (3) the classical pattern of familial aggregation of cases in the country at large.
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