

CHEMICAL, CLINICAL, AND IMMUNOLOGICAL STUDIES ON THE PRODUCTS OF HUMAN PLASMA FRACTIONATION.

XII. THE USE OF CONCENTRATED NORMAL HUMAN SERUM GAMMA GLOBULIN (HUMAN IMMUNE SERUM GLOBULIN) IN THE PREVENTION AND ATTENUATION OF MEASLES^{1,2}

By C. W. ORDMAN, C. G. JENNINGS, JR., AND C. A. JANEWAY

(From the Departments of Bacteriology and Immunology, and Pediatrics, Harvard Medical School and School of Public Health, and the Children's and the Infants' Hospitals, Boston)

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The prevention or modification of measles by means of passive transfer of human antibodies is a well-established procedure. Convalescent measles serum, pooled adult serum, and globulin derived from human placentas have all proved effective. Convalescent serum has probably given the best results, whereas pooled adult serum has been the least satisfactory. The following data, compiled from the literature by McKhann (1), indicate the comparative value of these preparations:

Preparation	Number of Cases	Protec- tion	Attenua- tion	Failure
		<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Convalescent serum	1627	75	17	8
Adult serum	584	56	24	20
Placental extract	2740	64.3	30.4	5.3

This material was unselected, no adjustment being made for dosage, exposure-injection interval, age, or degree of exposure.

The following communication presents the results of studies on the value of Fraction II (Human Immune Serum Globulin) as a prophylactic agent against measles. Fraction II is a serum gamma globulin concentrate derived from pooled normal human plasma by the methods of Cohn, Oncley, Strong, Hughes, and Armstrong (2).

¹ This work has been carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

² This paper is Number 19 in the series "Studies on Plasma Proteins" from the Harvard Medical School, Boston, Massachusetts, on products developed by the Department of Physical Chemistry from blood collected by the American Red Cross.

Since, as has been demonstrated by Enders (3), the antibodies against certain viruses, such as those of mumps and influenza A, are concentrated many times in this fraction, it was felt that it should constitute an effective prophylactic agent against measles, as originally suggested by Robinson.³ These studies were begun somewhat later, but carried on at the same time as those of Stokes, Maris, and Gellis (4), reported in the preceding paper.

During the winter and spring of 1942-43, a limited epidemic of measles occurred in and around Boston. This was complicated by a contemporaneous and much more extensive epidemic of German measles. Those cases alone have been included in the survey in which the diagnosis of true measles was unequivocal. Four groups of persons served as subjects during the course of the study: children of families under the care of city physicians, students at several private schools, cases encountered in private practice, and individuals exposed in the wards of a hospital.

CONTROLLED FAMILY STUDY

Most of the primary cases occurred in families in the lower income groups living in crowded quarters, and, accordingly, the exposure of the other children of the family was, in all but a few instances, intimate.⁴ Each primary case was

³ See J.A.C.S., 1940, 62, footnote on page 3398.

⁴ We wish to acknowledge our indebtedness to the late Dr. Harry Goldman, Deputy Health Commissioner, City of Boston, and his office associates, and to Dr. Joseph Rosenthal and his associates of the District Medical Service, Boston Dispensary, for their invaluable assistance in reporting to us cases of measles with home contacts.

investigated as soon as possible after it was reported to us. If the patient was found to have true measles, those siblings who had no history of measles were used in the study, provided the time relations were appropriate.

The first part of the work comprised an attempt to ascertain, under carefully controlled conditions, the capacity of Fraction II to prevent measles. A single preparation (A66) was used. The dosage was arbitrarily selected as 5.0 cc. for children over 5 years, and 2.5 cc. for children under this age, with the exception of infants between 6 months and 1 year, who were given 2.0 cc. Those under 6 months were presumed to be immune and were not inoculated.

When there were 2 or more susceptible contacts in a family, they were divided into 2 groups composed of persons as nearly alike as possible with respect to age and degree of exposure. Children over 15 years of age were placed in the control group in order to minimize the effects of the greater immunity which has been found to characterize older persons. The globulin was injected intramuscularly in the gluteal region into the members of one group. The other group received no injection and served as a control of the validity of the exposure. The globulin was administered as early as possible after exposure,

usually on the fourth or fifth day. The family was visited by one of us at 2- and 3-week intervals after inoculation, or when we had been informed by the family of the first sign of illness in any of the children. At each visit, all children were examined for coryza, Koplik spots, rash, and fever, and inquiries were made of parents and children concerning symptoms and signs which meanwhile might have occurred in any of the contacts.

The second part of the family study consisted of an attempt to attenuate the disease rather than completely to prevent it. The same dosage was used as in the first phase of the study, but the injection of Fraction II was withheld until about the 9th day after exposure. A different preparation (D26) was used in all but 3 cases, in which A35 was used. Return visits were made every 2 days until 3 weeks after injection. The same examinations were carried out and history obtained as in the previous series.

The results of the study are shown in Table I and Figure 1. Table I includes all cases. In 3 families, the adequacy of exposure of the contacts was questioned at the time they were first seen. The fact that subsequently no additional cases developed in the controls or in the inoculated children indicates that either exposure was

TABLE I

Results in controlled family study
(Crude figures)

Aim	Total no. cases	Inoculated	Results			Uninoculated controls	Results		
			No measles	Mild measles	Typical measles		No measles	Mild measles	Typical measles
Protection	74	45	40 (89 per cent)	5 (11 per cent)	0	29	7 (24 per cent)	2 (7 per cent)	20 (69 per cent)
Attenuation	65	40	27 (67.5 per cent)	12 (30 per cent)	1 (2.5 per cent)	25	4 (16 per cent)	0	21 (84 per cent)
Total	139	85	67 (78.5 per cent)	17 (20 per cent)	1 (1.5 per cent)	54	11 (20 per cent)	2 (4 per cent)	41 (76 per cent)
(Corrected figures)									
Protection	54	31	26 (84 per cent)	5 (16 per cent)	0	23	1 (4 per cent)	2 (8 per cent)	20 (88 per cent)
Attenuation	54	31	18 (58 per cent)	12 (39 per cent)	1 (3 per cent)	23	2 (9 per cent)	0	21 (91 per cent)
Total	108	62	44 (71 per cent)	17 (27 per cent)	1 (2 per cent)	46	3 (7 per cent)	2 (4 per cent)	41 (89 per cent)

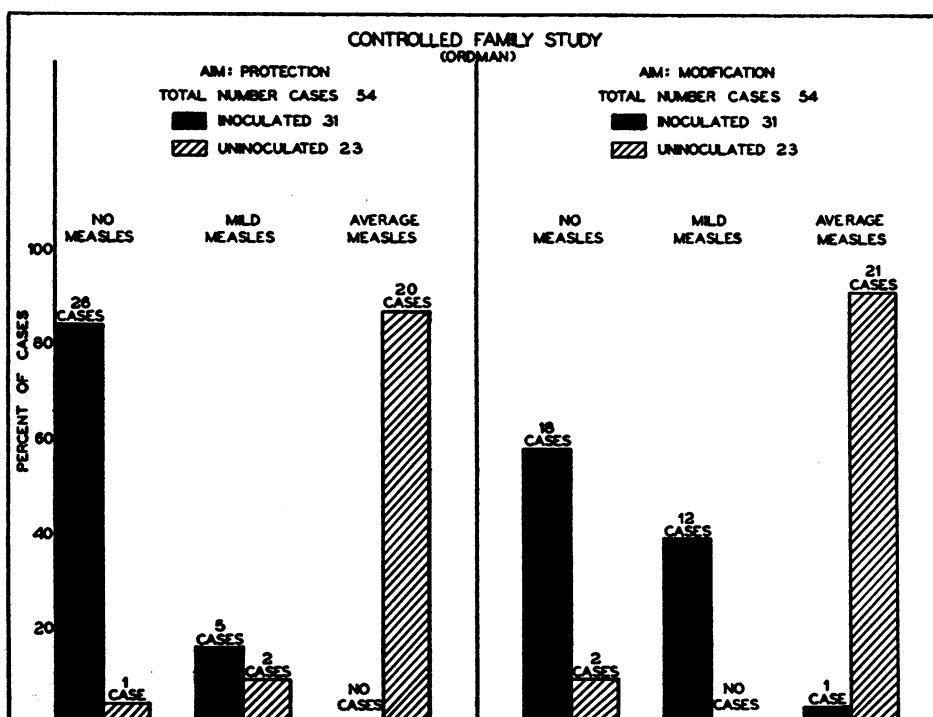


FIG. 1. CONTROLLED FAMILY STUDY

inadequate or immunity was present. In Table I and Figure 1 are presented the data obtained only in those families in which one or more controls developed measles, or in which one of the inoculated children developed modified or typical measles. It should be emphasized, however, that among 85 susceptibles inoculated with Fraction II, only 1 case of typical measles developed, and, in this instance, the child was accidentally given only 1.5 cc. of preparation D26 on the tenth day after exposure. Of 54 controls, 41 developed typical measles which was of average or severe intensity. Moreover, no complications were observed among the 17 children who contracted measles in a markedly attenuated form after inoculation, whereas, of the controls who got measles, 4 subsequently developed otitis media and 2 developed pneumonia.

EPIDEMICS IN PRIVATE SCHOOLS

An opportunity to observe small or potential epidemics of measles in 3 private schools was afforded us through the courtesy of the school physicians, Dr. J. R. Gallagher of Phillips Academy, Andover, Mass., and Dr. R. K. Byers of

Milton Academy (Boy's and Girl's Boarding Schools), Milton, Mass. We are indebted to both of these men for their assistance in following the subsequent course of the patients in these groups.

In the Andover epidemic, 70 presumably susceptible boys, ranging from 13 to 18 years of age, were exposed to 19 cases of measles between January 15, 1943, and February 9, 1943. On February 10, 28 of these boys were inoculated intragluteally, each with 5.0 cc. of A66. Also, on February 10, 7 additional susceptibles, who were already patients in the Infirmary with the questionable diagnosis of measles in the pre-eruptive stage, were given similar inoculations of the globulin. Thirty-five of the boys who denied having had measles were not inoculated, and thus served as controls. The degree of exposure in each case was virtually impossible to ascertain and the exposure-injection interval equally difficult to determine because of the widespread and irregular distribution of the disease throughout the school.

The sudden cessation of this epidemic makes the results hard to interpret. Of the 35 students

inoculated, 9 developed measles within 3 days of injection, suggesting that exposure had occurred some 10 days before inoculation. Five boys developed measles more than 3 days after inoculation, but all these cases were extremely mild in character. Of the 35 controls, 11 developed measles within the first 3 days of our study. Four only came down 3 or more days later, all with disease of at least average severity. Thus, some 21 inoculated students and 20 controls, all of whom were presumably susceptible, failed to develop measles. It was the impression of the school physician that the disease among the inoculated students, even those who developed measles shortly after injection, was less severe in general than among the controls, and that the incidence of complications was less. Only 1 case of otitis media developed in the former group in contrast to 6 cases in the latter group. Moreover, 2 susceptible students, who had been admitted to the Infirmary for illnesses other than measles and had been inadvertently placed in measles wards in close contact with active cases, were inoculated and failed to develop the disease.

In Milton Academy Boy's Boarding School, the study began on February 25, 1943. Two of the students had come down with measles on February 16 and 17, respectively, and a third had developed the disease on February 23. All of them were at large in the school for a day or two, carrying on their normal activities, before the rash was noticed. There were, in the boarding school, 26 presumably susceptible students ranging from 12 to 19 years of age. Twenty-four of these were inoculated intragluteally, each with 5.0 cc. of A66, on February 25, 1943. Two boys, one of whom failed to appear for inoculation and another, who supposedly had had measles previously, became, inadvertently, controls.

Of the 24 inoculated students, 20 did not come down with measles, and 3 developed definitely modified measles. One inoculated boy and both uninoculated controls developed measles of average severity. It is of interest that 7 inoculated students developed symptoms of upper respiratory infection about 2 weeks after injection, but had no other signs of measles. An opportunity to determine, in part, the length of immunity conferred by the globulin was afforded when one of the group who had been inoculated on Febru-

ary 25, developed a typical measles rash on April 16. Subsequently, 11 of the previously inoculated group developed measles within the next month. Of these, 4 exhibited a very mild form of the disease, whereas the remaining 7 had measles of average severity. Six of these were boys who had had symptoms of upper respiratory infection 2 weeks after their original exposure, indicating that they either had had no measles at that time or else the attack was so mild as to have induced no immunity.

At Milton Academy Girl's Boarding School, 2 cases of measles developed on May 2, 1943. Fourteen girls, ranging in age from 15 to 18 years, were presumably susceptible. All of this group had had intimate contact with the primary cases and were injected intragluteally with D26, 5 days after exposure. Seven girls were each inoculated with 5.0 cc. and 7 were given 1.5 cc.

Of the 7 girls who had received 5.0 cc. of globulin each, 1 developed no disease, 5 had very mild measles, and 1 had an average case. Of the 7 who received 1.5 cc. of globulin, 4 were apparently protected, 1 developed mild measles, and the other 2 had average severe cases. The higher incidence of disease among those who received the larger dose can probably be accounted for by the small number of cases in each group and the apparent inadequate selection of cases for each group.

Table II includes the total uncorrected figures for all schools, and shows the results obtained when correction is made for the sudden cessation of the Andover epidemic by eliminating that group of cases.

CASES ENCOUNTERED IN PRIVATE PRACTICE

A number of physicians in Boston and its vicinity were given certain of the preparations for use in their private practices. Their cooperation, interest, and careful observation of their patients have been very helpful in this study. Most of these physicians had had considerable previous experience with the use of placental extract. One hundred and ninety-six supposedly susceptible individuals were inoculated with one or another preparation of Fraction II. The dosage and exposure-injection interval were left to the discretion of the individual physician, so that these factors, as well as degree of exposure, age

TABLE II
Results in school epidemics
(Crude figures)

Total no. cases	Inoculated	Results						Uninoculated controls	Results				
		No measles	Per cent	Mild measles	Per cent	Typical measles	Per cent		No measles	Per cent	Mild measles	Typical measles	Per cent
110	73	46	65	14	19	13	16	37	24	65	0	13	35
(Corrected figures)													
40	38	25	66	9	23	4	11	2	0		0	2	100

of contact, and use of controls varied considerably. A standard report form was returned by the physician after a period of from 3 to 4 weeks. Only 8 uninoculated controls were noted in this group of reports.

TABLE III
Results in cases in private practice
(Crude figures)

No. cases inoculated	No measles	Per cent	Mild measles	Per cent	Typical measles	Per cent
196	99	51	87	45	10	4
(Corrected figures)						
164	71	43	83	50	10	7

The data presented in Table III show that the percentage of individuals protected was smaller than in the controlled family group. The total number of cases, however, in which it can be fairly stated that the globulin exerted a modifying effect on the disease represents 96 per cent of the whole number of the presumably susceptible children who were inoculated within 11 days after their initial exposure. When those with less than intimate exposure, those who might in all probability have been immune before injection, those on whom data was inadequate, or those who were inoculated after the ninth post-exposure day are excluded, 93 per cent of the presumably susceptible children either did not contract measles or had the disease in a mild form.

INDIVIDUALS EXPOSED IN A HOSPITAL

During the course of our study, a number of cases of measles developed among patients on the

wards of a hospital. In each case, most of the presumably susceptible children on the ward where the disease occurred, regardless of intimacy of contact with the primary case, were inoculated intragluteally with one of the preparations of Fraction II, the dosage being set at 2.5 cc. for children under 5 years and at 5.0 cc. for those over that age. The exposure-injection interval varied from 0 to 11 days, although in most cases globulin was given within 5 days of exposure.

Of the 82 children inoculated, 77 appeared to be protected and 5 had definitely modified measles. However, among 18 presumably susceptible uninoculated children, only 2 known cases of measles developed. Thus, it is apparent that the degree of exposure encountered in a well-run hospital ward is minimal and evaluation of the efficacy of an anti-measles preparation of this sort under these conditions is impossible without adequate controls and a satisfactorily high morbidity rate in the control group.⁴

DISCUSSION AND SUMMARY

The evidence derived from the controlled study in families indicates that Fraction II is a good source of measles antibody. Moreover, this evidence is supported by the results of the trials of the material which were carried out under other conditions. From the standpoint of protection, the product appears to be at least as effective as convalescent serum or placental extract, and probably superior to normal human serum in

⁴ By the time of publication, Fraction II had been given to 350 susceptible children exposed in 35 separate outbreaks of measles on the wards of various hospitals. Of these, 95 were not followed, 241 did not develop measles, 13 developed mild measles, and 1 typical measles.

amounts usually administered (1, 5, 6). In view of the finding of Enders (3), that the concentrations of antibodies in Fraction II reacting with certain viruses, bacteria, and bacterial toxins are from 10 to 40 times as great as those in the plasma from which the particular preparation was derived, it is not surprising that measles antibodies should be present in adequate concentration. This concentration of antibody is made apparent by the dose apparently necessary for protection. Although no set figures can be arbitrarily stated, the consensus of most authors appears to be that from 5 cc. to 20 cc. of convalescent serum, from 10 cc. to 80 cc. of pooled adult serum, and from 1 cc. to 4 cc. of placental extract are necessary to afford complete protection in the large majority of cases.

Dosage. Although we have not accurately determined the minimum effective dose of Fraction II, it is apparent that 5 cc. was adequate for protection in most of our cases, and in the smaller children, 2.5 cc. gave equally good results. It is also apparent that the exposure-injection interval plays a rôle in determining whether protection or attenuation is to result from treatment. Approximately the same proportion of individuals was protected if the injection was given in any one of the first 5 days, but from the sixth day onward, the percentage of attenuated cases and failures increased. In Figure 2 are plotted the doses per pound of body weight as ordinates, and as abscissae, the days which elapsed between first exposure and injection. This chart includes data from all of our groups of cases, but no cases

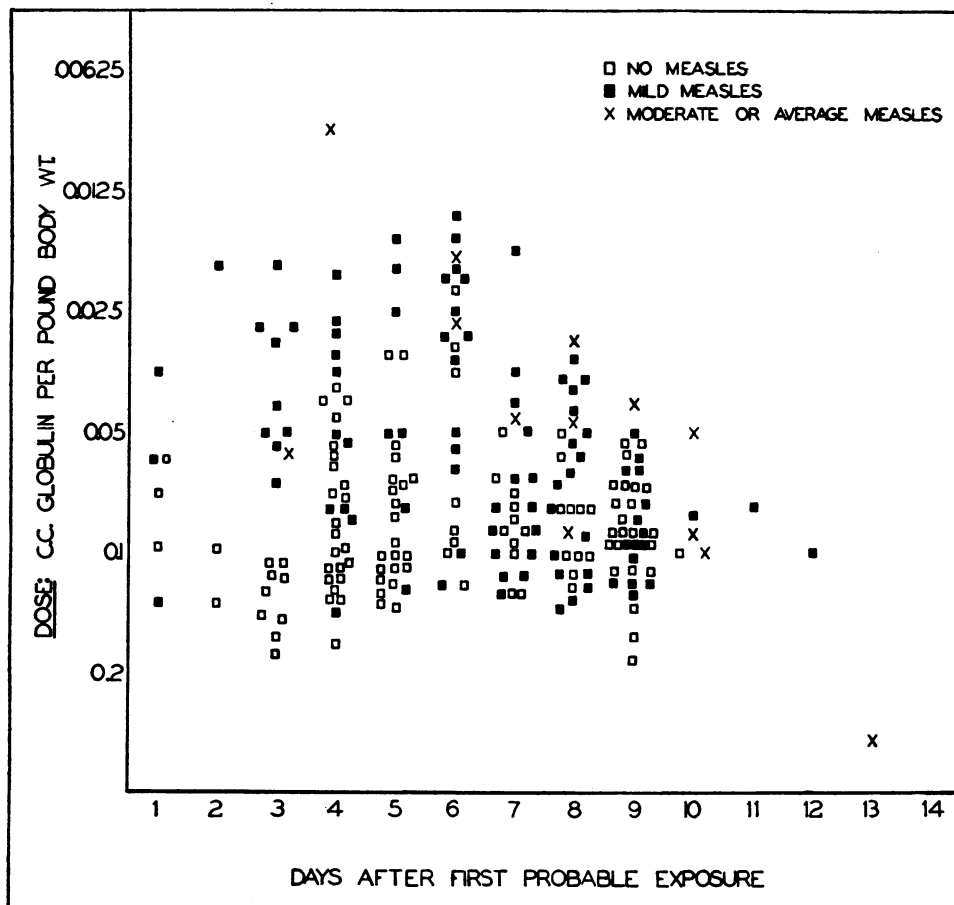


FIG. 2. RELATION OF RESULTS OBTAINED FOLLOWING INJECTION OF NORMAL HUMAN SERUM GAMMA GLOBULIN TO DOSAGE ON A WEIGHT BASIS AND TO EXPOSURE-INJECTION INTERVAL.

Data obtained from 222 cases with intimate exposure and adequate follow-up.

have been included in which there was not intimate exposure for a reasonable period of time, reasonable evidence of susceptibility, or adequate data upon the results of injection. The great majority of the 222 cases recorded in Figure 2 were children under 10 years of age. Whether results obtained in this age group may be carried over to adolescents and adults by calculating the dose on a weight basis is not definitely known. It is apparent from the figure that, with 3 exceptions, all those individuals receiving 0.1 cc. per pound of body weight or more within the first 5 days after exposure were protected. When the dose was less than 0.1 cc. per pound of body weight or the interval after exposure longer than 5 days, there was a decrease in the number of cases protected and an increase in the number of cases developing mild (modified) measles. A dose of approximately 0.025 cc. per pound in the first 5 days resulted in the development of mild measles in most cases, but the numbers are too small for definitive conclusions. Finally, when very small doses were employed or the exposure-injection interval prolonged beyond 9 days, no effect on the disease was usually obtained. Further investigation is planned which, it is hoped, will more accurately establish the relationship between time and dosage.⁵

Duration of immunity. The family study yielded some information on the duration of the passive immunity produced by Fraction II, since in all families where the controls came down with measles, the inoculated children were thus subjected to a new and intimate exposure within 5 to 14 days after injection. In no case did the inoculated and re-exposed children develop recognizable measles. This suggests that an effective immunity lasts for at least 2 weeks after the injection of a dose of the size used. It is of interest that one nephrotic boy, who received what should have been a protective dose, developed typical measles, suggesting that the antibody may have been rapidly lost due to the proteinuria. The results in the Milton Academy Boy's School sug-

gest that the immunity produced by the injection of 5 cc. does not last for 7 to 10 weeks, since the majority of previously inoculated boys, re-exposed at this time, developed average measles. McKhann (1) has emphasized the prolongation of the incubation period in cases of modified measles, but in most of our modified cases, the rash appeared 10 to 15 days after that of the primary case. In a few patients, symptoms were observed only during the third week, so that a 3-week period of observation for inoculated cases is probably advisable.

Reactions. In spite of the established value of convalescent serum, placental extract, and adult serum, certain disadvantages are associated with each preparation. Convalescent serum is available in relatively limited quantities. Normal pooled adult serum is readily available, but its low potency necessitates the injection of large volumes, which is undesirable, particularly in small children. However, 2- to 4-fold concentration of serum has been achieved by the process of desiccation from the frozen state, the resulting dried powder being reconstituted with a smaller volume of water than was present in the original material. Such concentrated serum has proved both safe and effective for the prophylaxis of measles (7). Placental extract, although available in quantities and requiring only a small inoculum, causes local and systemic reactions of varying severity in a considerable number of inoculated individuals.

Fraction II, in contrast, offers definite advantages. It is readily produced from an abundant source of supply. In small doses, it has proved to be as effective as the best of the standard preparations. No severe reactions have been observed in the several hundred individuals inoculated with it. In less than 5 per cent of these, mild reactions occurred. With a single exception, the reactions consisted of a slight feeling of stiffness in the muscle injected or a little local erythema and induration. In one case, the individual had a rise in temperature to 102° F. 2 days after inoculation but no other systemic or local manifestation. Whether or not this febrile reaction was due to the globulin cannot be stated.

So far no untoward sequelae have been observed, following the use of Fraction II intra-

⁵ Studies carried out in 1944 in a much larger series of cases and with a large number of preparations have confirmed the validity of these recommendations as to dosage. It is now clear that in order to achieve protection or attenuation the physician should vary the dose rather than the interval between exposure and injection.

muscularly, but the possibility that viruses present in the pooled plasma from which Fraction II is obtained might be carried over in the process of separation cannot be entirely neglected. Homologous serum jaundice, which has been described following the injection of human serum in yellow fever immunization (8) and in passive protection against measles and mumps (9), has an incubation period of 1 to 4 months. As many cases as could be followed were visited or questioned by letter 3 to 6 months after inoculation. Of 400 cases so followed, one case of typical catarrhal jaundice was noted just 3 months after an injection of 5 cc. of globulin. That this was pure coincidence is suggested by the fact that although 74 others are known to have received this preparation, no other cases of jaundice have been reported to us. It is hoped that answers to these and other problems will be forthcoming as a result of work now in progress.

The necessity for observing certain precautions in a survey of this sort is brought out very clearly in several of our studies. One must eliminate the possibilities, in so far as possible, of insufficient exposure, previous unrecognized clinical attacks, and unrecognized modified attacks at the time of investigation. In a number of infectious diseases, laboratory tests exist which can, with some certainty, eliminate various of these factors, while others may often be excluded by careful histories and physical examinations. In the case of measles, we are, as yet, entirely dependent on the latter methods and an evaluation of the results of a study must be carried out with the factors mentioned above clearly in mind.

The natural secondary attack rate of measles in an urban community has been established at about 75 per cent for all ages, rising to 85 to 90 per cent for children between 1 and 10 years of age and dropping sharply after 10 to between 15 and 40 per cent (10). In our investigation, by far the greatest number of inoculated individuals were in the 1- to 10-year age group.

In addition to age, intensity of exposure is of great importance in determining the secondary attack rate. In our hospital ward cases, for example, exposure was apparently entirely inadequate and no fair assumption may be made therefrom. It has been shown (6, 10) that prolongation or repetition of exposures is of no sig-

nificance, providing the original exposure is sufficiently intimate. One cannot assume that exposures in schools, hospitals, or on the playground are adequate. On the other hand, exposures within the family, of children within the same age group, are usually intimate. We have included in our corrected tables (excluding those in the school epidemics) only such cases, together with a few others where adequate proof of close exposure existed. Even under such conditions, there may be some doubt as to the adequacy of the exposure or about other factors such as pre-existing immunity. Accordingly, in order to obtain results of the greatest reliability possible, it is wise to have controls such as were demanded in our family study. The corrected tables in that study include data only from those cases in which one or more controls came down with measles or where the inoculated individual developed the disease.

Stillerman, Marks, and Thalhimer (5) have emphasized the necessity of careful observation of inoculated persons in order to detect the mildest cases of measles, which might escape any but trained and experienced observers. Undoubtedly, a number of individuals who might ordinarily be classified as having been completely protected exhibit, at one time or another, one or more of the stigmata of measles in very mild or bizarre form, and unless daily observations are made of each person, these might readily be missed. Their total of 77 per cent complete protection or very mild measles corresponds closely, as they note, with the figures given by most authors for complete protection alone with convalescent serum and with the 71 per cent protection obtained by us in our family survey. It is possible that the percentage of protection recorded by us may include some cases of very mild unrecognized measles.

CONCLUSIONS

1. The human serum gamma globulin (Fraction II), separated and concentrated by chemical fractionation of normal human blood, is a very satisfactory prophylactic agent against measles.

2. A controlled group of cases with exposure within the family afforded a rate of 71 per cent protection, 27 per cent modification and only 2 per cent failure, among 62 inoculated children.

Of 46 uninoculated controls, only 7 per cent failed to contract measles, while 4 per cent got mild measles, and 89 per cent developed measles of average severity.

3. In children, an intramuscular dose of 0.1 cc. per pound of body weight within the first 5 days after exposure appears to be adequate for complete protection in a large majority of cases, with the present methods of preparation. In order to produce attenuation of the disease, it would seem that about one quarter this dose should be administered during the first 5 days after exposure. After this, somewhat larger doses may be necessary.

4. No significant untoward reactions were observed in any of the inoculated cases.

5. The importance of adequate controls, intimate exposure, and careful observation of inoculated individuals in evaluating the efficacy of a prophylactic agent against measles is emphasized.

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