

ON SOME RECENTLY DEVELOPED METHODS FOR MEASLES PROPHYLAXIS.

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PART I.

A. INFECTIVITY OF, AND MORTALITY DUE TO, MEASLES.

THAT the human race is extremely susceptible to the ravages of measles is well known, Brownlee not being guilty of much exaggeration when he states that, in the presence of infection, the only way to avoid this disease is to have had it. MacNalty (1918) states in his report on the subject to the Local Government Board that "the disease is so universal in this country that few children escape it," this being particularly true in reference to the poorer urban classes. Butler (1913) found as a result of the study of the statistics for the public elementary schools of Willesden that among persons who had attained the age of 15 and upwards, only 2·7 per cent. had escaped measles. Zingher states that amongst children who have not previously suffered from the disease, and who are exposed to it, between 96 and 98 per cent. will develop it.

That measles is, moreover, a very serious disease is now generally admitted, particularly, as pointed out by MacNalty in the report already referred to, when it breaks out in an institution where children are aggregated; in these cases, as Comby says, the fatality is generally much above the average. MacNalty adds that, from a study of the Registrar-General's figures, over 21 per cent. of the total deaths in infancy, and nearly 33 per cent. of the total deaths in the first five years of life are due to infectious diseases, amongst which, in order of magnitude for all ages under 5, measles ranks first. From 1911 to 1913 the deaths due to measles in the British Isles numbered 36,627 whilst the number of deaths from all other notifiable infectious diseases together reached 31,641; the measles mortality from birth to one year being 0·5 per cent. of the total number of deaths at all ages; from birth to five years being 2·3 per cent. of the total number of deaths at all ages. Nobécourt (1922) states that the hospital mortality in France exceeds 13 per cent., whilst Pfaundler estimates that more than 30,000 deaths occur annually from this cause in Germany. According to Rosenau, during the period 1900-11 more than 100,000 deaths due to measles occurred in the United States. It is in the group under 5 years of age, moreover, that 90 per cent. of this mortality occurs (Zingher); if the disease could be prevented during this period of childhood many lives could evidently be saved. With this end in view it would appear that an efficient method of prophylaxis against measles is much

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to be desired, since methods which may be effective in the case of other infectious diseases have not the same efficiency when applied to measles, owing to its long period of incubation, and its four days' period of invasion during which the patient is in his period of maximum infectivity, but during which the disease frequently remains unrecognised.

B. PRESENT METHODS OF PROPHYLAXIS.

The only method of measles prophylaxis which, in the presence of an epidemic, is at all generally carried out in this country at the present time is that of isolating all suspected or confirmed cases for two to three weeks, and of closing the class or school attended by the original case nine days after the sickening of the first child, for 5 days, during which time all others who have been infected will develop the disease at home. Wheaton and MacNalty further recommend:

(1) Compulsory notification.

(2) Early visit to patient's home by Health visitor.

(3) Provision of adequate nursing and medical attendance in patient's own home.

The high mortality from measles, particularly amongst children under 5 years of age, who live under conditions of poverty and overcrowding, render it desirable to see other and more effective methods of prophylaxis against this disease. Such a method has been worked out during the last few years and reported by many observers to have been of value. It consists in its original form of the administration of small doses of serum obtained from a patient convalescent after measles, as soon as possible following exposure to infection. The application of this method of prophylaxis to measles was a logical adaptation of the system already employed with some degree of success in the prevention and cure of several other diseases, such as scarlet fever and poliomyelitis, whose causative agents, as in the case of measles itself, have not as yet been identified and isolated.

It has been found that antibodies are also present in the serum of adults who have had measles at any period of their life. As would be expected, however, they are generally present in considerably smaller quantities than is the case with persons convalescent from the disease. These antibodies are transmitted from mother to child through the medium of the placenta, and this results in a temporary immunity of the new-born infant against measles, which lasts from 5 to 7 months. This immunity was recognised by Bécclere, in France, as long ago as 1882, and has lately been studied by Herrman in New York and Débré in Paris.

C. HISTORICAL.

Whilst repeating the experiments of Nicolle on the monkey, Anderson and Golderberger in America noticed that a first inoculation assured immunity against future inoculations, showing that antibodies were formed. This gave

Nicolle and Conseil the idea of employing serum from cases convalescent from measles for the purpose of prophylaxis. This idea they first put into practice during a small epidemic in Tunis in 1916. In a family of four children, the first contracted measles on the 2nd July, the second on the 3rd July and the third on the 5th July. The youngest child was well on the 12th July and should, therefore, have contracted measles on the 16th July, if not previously infected. She received 4 c.c. of serum from the eldest child, who was then in the 7th day of convalescence, and the same amount again on the 13th. She remained in contact with the others, but did not contract the disease. In the same year Park and Zingher injected 48 exposed children with convalescent measles serum at Metropolitan Hospital on Welfare Island. Twenty-eight of these children received doses varying from 1.5 to 4 c.c., and 20 received 8 c.c. In the first group six children developed measles—one, 2 days; one, 7 days; one, 8 days; one, 15 days; one, 17 days; and one, 25 days after the serum injection. In the second group there were no cases of measles. These results were not, however, published.

In 1919 Richardson and Connor of Boston, U.S.A., reported the successful use of convalescent serum in a small group of exposed children. They took blood from patients 25 days after appearance of eruption, mixed the different sera, and preserved it with small amounts of tricresol (0.25 per cent.). Further successful work combined vaccination with serum treatment. Fifteen c.c. convalescent serum were injected at the same time as an inoculation with nasopharyngeal secretion; 12 days later an abortive subcutaneous measles eruption appeared.

In June 1919 Degkwitz, working in Pfaundler's clinic in Munich, began his interesting series of observations with convalescent serum in the prophylaxis of measles. Until this time the mortality for children under 2½ years of age, in this clinic, had been 29 per cent. He, however, gave 700 injections of varying doses, all of which were successful. He has now injected over 1700 children and the work has been organised on a considerably wider scale. He was followed by various observers in Germany, Hungary, Italy, Spain, South America and the U.S.A. Amongst these authors may be cited Torres and Pacheco in South America, who in 1920 used serum in all exposed children with good results, Zschau (1921), Glaser and Müller (1921), Kütter, who adopted the Degkwitz routine and reported great success, stating that isolation during his epidemic proved to be unnecessary as it was stamped out after 4 days. Kundralitz in 1923 reported failure in a certain number of cases, whilst Maggiore at Palermo in 1921 reported 113 successful cases. Other contributions to the literature were made by Nobécourt and Paraf (1922), Manchot and Reiche (1921), P.-L. Marie, Zimmermann (1922), de Stefano (1923), Blackfan, Peterson and Conroy (1923), Ratnoff (1923), McNeal (1922), de Jong and Bernard (1923), and Weaver and Crooks (1924). De Castro during an epidemic sealed the dried residue of 5 c.c. of convalescent serum in ampules. This, he stated, kept indefinitely. Débré and Ravina (1923)

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emphasised the greater value of conferring an *active* immunity by modifying the disease by the use of convalescent serum so as to obtain a modified mild form of measles rather than completely to prevent its development. Hiraishi and Okamoto also endeavoured to produce an active immunity by means of inoculation with minute quantities of citrated blood from a patient in the infective stage of measles. They used doses of between 0.001 and 0.002 c.c. or in smaller repeated doses from 0.0001 to 0.0002 c.c. Further references to active immunisation will be made later.

A great deal of work is being done at the moment on the subject in France and America, notably by Débré, Bernard, Joannon, and Bonnet in the former country, and by Park, Zingher and Herrman in America. I have been unable to find references to any literature on the subject of the sero-prophylaxis of measles published in England.

D. PRACTICE.

(a) *Collecting and Preserving the Serum.*

The practitioner cannot in most cases prepare the serum for this purpose for himself; this constitutes one of the difficulties which attend a general adoption of this method of prophylaxis. The question of the necessity for establishing centres at which the serum can be collected and prepared is raised later. The essential points to be observed in the collection and preservation of serum, according to Débré, whose technique is simpler than that of Zingher, are as follows:

1. The donor should be an adult or a child over the age of 10 years (cf. Degkwitz), who must have had a typical and unmistakeable attack of measles; this attack being primary, and not a second case, the occurrence of which points to a deficiency in the production of antibodies. Up to 500–600 c.c. may be taken from adults (Zingher).

2. The convalescence should be uncomplicated, and the defervescence be complete.

3. The donor must be free from tuberculosis, syphilis and malaria, the blood being tested for these in each case.

4. He should be observed for several days after the blood has been taken, to make sure that he was not in the invasion period of some disease due to a blood-borne virus—typhoid, for example.

5. The blood should be taken between the 7th and 9th day (6th to 10th, Degkwitz) after defervescence, as this is found experimentally to be the period during which the blood is richest in antibodies, although Nobécourt and Paraf, and Marie report successful results with serum collected on the 10th, 11th, and 12th day after defervescence.

6. The blood should be allowed to coagulate at room temperature; later the serum can be aseptically decanted, tested for sterility, pooled with the sera from at least two other subjects and placed in ampules of 3 to 5 c.c. ready for use.

7. The serum should be kept in the ice chest for at least 4 to 5 days before use; a sufficient time to allow for the death of certain micro-organisms such as the *Spirochaeta pallida*, which might, in spite of negative tests, theoretically be contained in it.

8. The serum, if kept in the ice chest, retains its activity for several months.

9. If any doubt as to its complete sterility exists, it may be heated to 56° twice, at 24 hourly intervals (Nobécourt and Paraf). Degkwitz adds one drop of 5 per cent. carbolic solution for each 10 c.c. of serum.

(b) *Methods of Employing Serum.*

Serum from convalescent measles cases, or, to a lesser extent, the serum of adults who have had measles previously, can be employed in several different ways, leading in each case to a different end result.

(i) It may be injected into the normal person: passive immunity being established which lasts about one month; or it may be injected soon after infection. If injected during the first five days of the incubation period, a complete passive immunity will be established, and the patient will not develop measles. The dose will have to be increased, however, the later the period to which the injection is delayed, whilst after the 5th or 6th day no amount of injected serum will do more than modify the case. For a child of 3 years Degkwitz gives the following table:

1st to 4th day	2.5 c.c. will prevent measles.
4th to 5th day	5 to 6 c.c. will prevent measles.
7th day	Uncertain even with very large doses.
8th day	Even 40-50 c.c. serum will not prevent measles developing.

(ii) It may be injected later, whilst the patient is still in the incubation period, but after the 6th day. In this case measles will develop, but in a modified form, the characteristics of which will be dealt with later. In this case, of course, an active immunity will result.

(iii) It may be injected even later—at the commencement of the period of invasion. In this case only a local inhibition of the eruption at the site of the injection will result (phenomenon of Débré), the course of the disease itself being unaffected.

(iv) It may be injected still later, when the symptoms of the disease have already declared themselves. In this case it will generally have no action, the disease developing normally.

(v) Serum may be injected into a healthy subject, who is later inoculated with the virus of measles. In this case an active immunity will be established.

In cases of emergency, whole blood from a convalescent may be injected in lieu of serum.

Before considering each of these methods in more detail, however, it may not be out of place to say a few words with reference to the dose of serum to be employed. Different authors recommend different doses which from my

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experience I consider to be generally rather too small. It is, granted the difficulty of collecting convalescent serum, obviously desirable to give as little as is consistent with the desired result, but most of the failures recorded, such as those described by Aviragnet and Kundralitz in 1923, can probably be attributed in large degree to insufficient dosage. Débré recommends:

Large children and adults	...	6-8 c.c.
Children, 3 to 10 years	...	3-6 c.c.
Children under 3 years	...	3 c.c.

These doses are somewhat larger than those recommended by Degkwitz. In the cases where ordinary adult serum (not convalescent) from a subject who has in the past had measles, is employed, these doses must be multiplied by 4.

We can now consider each of the above methods of employing serum in more detail.

(i) Injection into the uninfected individual, or one who has been infected less than 6 days, to establish a passive and temporary immunity. This is the method employed originally by Nicolle and Conseil in 1916 (Sero-prevention); as mentioned previously, in cases of urgency the parents' or relation's whole blood, citrated or non-citrated, may be injected intramuscularly in the same way as the serum; the dose in this case should, however, be double or quadruple that employed when the serum alone is used, as it also should be in cases where non-convalescent adult serum is employed, and is the one generally employed where it is important for any reason to defer the attack of measles until later in life, as for instance in the case of infants under 3 years of age, or in institutions. It is also indicated in the case of weakly, tubercular, or rachitic children, especially if they have recently been convalescent from any other disease; another indication, according to Débré, is in the case of pregnant women who, not having had the disease, have been exposed to infection. The immunity appears to last about a month, after which a similar injection can be repeated. The later in the incubation period at which the patient receives the injection, the larger will the dose have to be to produce complete "prevention."

(ii) Injection during the second half of the incubation period, after the 6th day until the 8th or even 9th day (Sero-attenuation). In this case, as has already been mentioned, the attack of measles is not *prevented*, but is modified, being of a very mild type which confers active immunity on the patient for the future. The signs and symptoms of this *modified* form of measles (which must be distinguished from ordinary mild measles) are as follows. In the majority of cases the incubation period is not altered, although in some cases mentioned by Débré it was extended to 17 or 18 days. The invasion period is, however, modified; the catarrh of the mucous membranes, so prominent a feature of typical measles, is generally entirely absent, or minimal. Koplik's spots are nearly always absent, and the temperature seldom rises above 100.4° F., for one or two days, sometimes not exceeding

the normal at any time. It can therefore be said that in the majority of cases, the period of invasion is, for all practical purposes, wanting, the disease starting straight away with the period of eruption. The eruption, which is scattered over the face and body and hardly at all on the arms and legs, scarcely resembles ordinary measles at all, being more discrete, the individual macules appearing about the size of a pin's head and occasionally being surmounted by a tiny vesicle. Prodromal rashes are said to be of more frequent occurrence (Torday). Sometimes large macules alternate with the smaller ones, and in certain cases the eruption is typical, or even purpuric, a condition which need not give rise to anxiety. Complications are never encountered. According to Degkwitz this type of measles is not very infectious, possibly owing to the lack of nasal secretion. The patient's general condition is usually very little removed from the normal. Treatment by this method is indicated in the normal case where a healthy subject of more than 2 or 3 years of age, who has never had measles, has been infected with the disease. Butterweisser considers that this immunity only lasts 3 to 4 months; most authorities, however, seem to consider that this is an under-estimate. Débré and Joannon claim three advantages for this method: (1) owing to the clinical manifestations which are observed one can be sure whether the child has had measles or not; (2) it confers an immunity which they consider to be more durable, if not permanent; whilst "sero-prevention" may be considered merely to postpone the attack; (3) it is economical, since with a small dose of serum one can obtain a lasting result. One can, moreover, recoup oneself for the small outlay of serum by removing some blood from the patient after his modified attack, since it is equally efficacious with that of an ordinary convalescent patient.

(iii) Injection at commencement of period of invasion—10th day. Débré and Ravina have shown that intradermal or subcutaneous injections of convalescent serum will not modify an eruption which has once established itself; nothing comparable with the Schultz-Charlton phenomenon being observed in measles. If, however, from 1–5 c.c. of convalescent serum be injected at this period (when Koplik's spots are visible and first signs of catarrh are manifest), it will be found that the eruption will not appear round the site of the injection, the line of junction between the pale area and the rash being, if the injection has been made at the right moment, extremely sharp. This reaction ("Phenomenon of Débré") is specific for measles, and can therefore be used to test the richness of any given serum in antibodies, and thus its value for therapeutic use.

(iv) "Serum therapy"—The injection of convalescent serum into a patient suffering from measles has, in the hands of some observers, notably Ribadeau-Dumas, Et. Brissand, Terrier, Méry and Girard, and Débré, given good results. These results are, however, too variable and inconsistent to lead us to suppose that the method can have any constant therapeutic value. Favourable results, it has been suggested, are equally likely to have been due

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to some form of protein shock as to any specificity of action of the serum at this stage. This would appear to emphasise still further the need for sound *prophylactic* measures.

(v) Injection of serum prior to inoculation of the patient with the virus of the disease, producing an active immunity. This is a method advocated in certain cases by Nicolle and Conseil, and of which there are several variations described by other authors. Nicolle and Conseil recommend injecting the child it is desired to protect with 10 c.c. of convalescent serum and 24 hours later with 1 c.c. of blood from an early case of measles. Measles does not develop, and the immunity is of considerable duration. No ill results of this method have been reported. These authors consider that a permanent immunity is produced by a repetition of the injection of blood. This method is probably reproduced to some extent naturally when an injection of serum is administered to a patient who shortly after becomes infected with measles.

(c) *Active and passive Immunity.*

From what has already been said, it is seen that of the various methods of employing serum in the prophylaxis of measles, the resulting immunity is in some cases active, in some passive. These methods must not be considered to be alternative, to any great extent, as each method has its own indications for use, and is therefore the method of choice in certain circumstances. It may not be out of place before proceeding, to recapitulate briefly the methods described and note the type of immunity produced by each.

(i) "Sero-prevention" (injection before 6th day)—passive immunity lasting about a month.

(ii) "Sero-attenuation" (injection 6th to 9th day)—active immunity established.

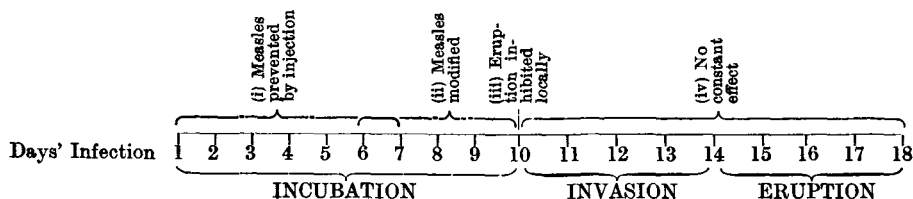
(iii) Local inhibition of eruption (injection 10th day)—no general immunity established.

(iv) "Sero-therapy" (injection after eruption)—no constant effect observed.

(v) "Sero-vaccination" (injection of virus and serum in normal subject)—active immunity.

According to Zingher, if injection of serum on the 6th day or later does not result in a modified attack of measles (too large a dose given), a "mixed" immunity lasting from 2 to 3 months will be produced.

The time relationship of the first four of these methods may be expressed simply, in graphic form, as follows:



Other Methods of Inducing Active Immunity.

Besides the method already described (Nicolle and Conseil) one or two other methods for producing an active immunity have from time to time been put forward by various observers, notably by Herrman in America, Degkwitz in Germany, and Hiraishi and Okamoto in Japan.

Herrman in 1915 noted that children who were exposed to measles before the age of 5 months would not only enjoy immunity at the time of exposure, but that this immunity appeared to last for several months, and even in one or two cases for several years. As a result of this observation, he suggested and practised a method of active immunisation by applying a swab taken from the nasal mucous membrane of an early case of measles to the nasal mucous membrane of children of 5 months and under. Since there is some risk, however, of the child developing a typical attack of measles should the immunity be abnormally poor, the difficulty was surmounted by adopting a combination of his method and passive immunisation by convalescent serum. Children of any age could thus be immunised. Herrman's method has not been practised by other observers, since there are obvious practical difficulties in the way of its widespread adoption.

Degkwitz (1921) reported on the use of a measles virus which had been enriched in cultures containing human albuminous fluids. No further observations or details have, however, been published by the author on this method.

Hiraishi and Okamoto, as mentioned previously, endeavoured, with varying success, to produce an active immunity by the subcutaneous injection of minute quantities of citrated blood obtained from early measles cases. They recommend the injection of 0.0001 c.c. of blood, to be followed 2 weeks later by a second injection of 0.001 c.c. in children under 5 years of age and 0.002 in children over 5 years of age. More work is needed on this method before its value can be gauged.

RESULTS.

(i) The results obtained by the majority of the authors already quoted have been extremely favourable, and tend to show that the method has a very considerably prophylactic value. Degkwitz and his assistants have practised over 1700 successful injections in Pfaundler's clinic at Munich. Zingher in his paper read before the Section on Pediatrics of the New York Academy of Medicine in January 1924 summarises some results as follows:

Of the 102 children injected, 10 developed measles. These 10 had all been injected after the 7th day; the attacks being modified and the incubation periods prolonged. Of the five control cases, four developed the disease.

From this he concludes that "Convalescent measles serum, plasma or whole blood has a definite value in the prophylaxis of measles."

Débré and Joannon (August 1923) report the case of an asylum for ailing

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children at Médan (France), where the death-rate from measles was 70 per cent. of the infants attacked. In the summer of 1922, to the surprise of the staff, two commencing epidemics were entirely wiped out, without death, by means of the method of sero-prevention. They further report, as do also Méry, Gastinel and Joannon (*Acad. de Médecine*, 6th February 1923), that by the adoption of this method measles patients may be nursed in a common ward. My personal experience also tends to confirm the truth of this statement. Aviragnet (1923), as previously mentioned, reported a 25 per cent. failure of the method, including two deaths, in a small series; his doses were, however, very small, as were those administered by Kundralitz (1923), who reports some failure, the doses mentioned varying between 1 and 2 c.c.

Success must depend on (a) quality of the serum, (b) sufficient dose, (c) time of injection. Of the quality of any given serum we have no method of judging other than the rough method suggested by Débré of injecting it into a patient who is in the catarrhal period of measles, and observing the degree of the resulting local inhibition of the eruption. Since no method of standardisation of serum has yet been arrived at, the difficulty is overcome to some extent by "pooling" the sera from various subjects and injecting the resulting mixture. The other two factors on which successful inoculation must depend have been dealt with in some detail previously.

Failure must depend on (a) insufficient dosage, (b) error in time of injection, (c) bad serum, (d) other unexplained causes. (a) and (b) have already been considered. In the case of (c), bad serum may result from three causes: (i) error in diagnosis in the case from which the serum was taken; (ii) donor being a bad antibody producer; failure to "pool" sera; and (iii) serum withdrawn too long after defervescence (*e.g.* 20th to 30th day). Other, unexplained, causes form a very small percentage of the total and are incidental to any biological method.

In considering the method of sero-attenuation, statistics are not needed, since all the authorities quoted on the subject appear to be agreed that the desired result, *i.e.* modification of the attack, is by this method attained, and should therefore be employed in all cases in which it is not contra-indicated, in preference to the method of passive immunisation.

E. CONCLUSIONS.

As the result of the work done by the numerous observers already quoted, the following conclusions appear to be legitimate:

(1) That the serum or whole blood of persons who are either convalescent from, or who have in the past suffered from, measles has a definite value in the prophylaxis of this disease.

(2) That if it be injected in sufficient dose during the first five or six days after infection, it can produce a complete passive immunity which lasts for about one to two months; whilst if it be injected in small doses after the

5th day, a modified form of the disease will result, leading to active immunity of uncertain duration, but which many observers consider to be permanent.

(3) That in the absence of the contra-indications mentioned, it is better to allow a modified form of the disease to develop (sero-attenuation) than to rely on renewing the patient's passive immunity constantly by means of serum, and that in cases modified in this way the complications proper to measles do not develop.

(4) That in certain cases passive immunity (sero-prevention) should be employed, but must be regarded as merely deferring the attack—in the absence of further injections; however, as P.-L. Marie stated, "Le but n'est pas tant de faire disparaître la maladie de la face du monde, que de réculer son apparition jusqu'à un âge où les risques qu'elle fait courir deviennent très minimes." This method should therefore generally be employed in children two or three years old, this being the most fatal period, and also in the case of children suffering from tuberculosis, rickets, diphtheria, whooping cough, and in feeble children, especially in very cold weather, and in institutés.

(5) With the increasing number of days of exposure, the doses of the serum have to be increased, Degkwitz's scale having being reproduced above.

(6) A simple emergency method, if prepared serum is not available, is to inject citrated or non-citrated whole blood (from the parents or a relation) intramuscularly into the patient in two or three times the amount recommended for serum.

(7) That since the supply of convalescent serum is ordinarily limited and needs preparation in a laboratory, to render the preceding methods possible of wide application, small collecting, preparing, testing and storing centres for serum should be established in connection with institutions where measles is treated, the supply being available to the outside practitioner. The personnel of these centres could also visit the scene of epidemics and deal with them in routine fashion.

(8) That since the demand for convalescent serum would generally be in excess of the supply, supplies of adult and recovered serum, which can be more readily obtained, be also collected at these centres, the doses having to be altered accordingly when these sera are employed.

(9) That the public might, with advantage, be instructed to some extent in the nature and scope of the method, by propaganda emanating from recognised health authorities, in order that donors might be forthcoming (who could be suitably compensated) and cases notified at the earliest possible moment.

(10) That careful notes should be kept of all cases in which these methods are employed, and used for future guidance.

(11) That it has been thought worth while to establish centres for collecting, preserving and distributing convalescent and adult measles serum in France, America and Germany. Owing to the small doses necessary for children under 3 years, for whom the *convalescent* serum is reserved, a comparatively

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small number of doses is required; at the Munich centre 300 donors being sufficient to protect 2000 to 3000 children. Older patients receive mixed adult serum.

PART II.

NOTES ON PERSONAL EXPERIENCE DURING THE EPIDEMIC OF MEASLES
IN PARIS (FEBRUARY-JULY) 1925.

The following results of 58 injections were obtained at the Hôpital des Enfants Malades, Paris. My thanks are due to Profs. Nobécourt and Débré, and Drs Pichon, Lévy, and Cros-Decam for their kindness in placing all facilities for the investigation at my disposal.

Ward 1. Koplik's spots discovered in child Ferdinand S.—14 days after admission—30. iii. 25 (typical measles eruption 2. iv. 25—died later).

Ten children in ward with no history of measles, all injected with mixed convalescent serum subcutaneously. 31. iii. 25.

Case	Age	Dose in c.c.	Result
1 Lucienne B.	12	6.5	Protection
2 Denis R.	4½	5	Koplik 12. iv. 25. Eruption 13. iv. Very much modified; no coryza 14 days after exposure (13 days after injection)
3 Suzanne P.	3	3	Protection
*4 Yvette P.	6	6	Koplik 11. iv. 25. Eruption 13. iv. 25. Typical modified case. 13 days after exposure (12 days after injection)
5 Michael R.	5	5	Protection
6 Harriet R.	7	6	"
7 Martha C.	3	3	"
8 Marius N.	14	6	"
9 Pruche S.	3½	3	"
10 Simone L.	8½	6	"

This represents 80 per cent. success.

* Was at the time convalescent (15 days) from Varicella, fresh outburst of eruption superimposed on that of measles.

Ward 2. Child: Robert P.—removed with Koplik's spots 18. iii. 25 (subsequent measles confirmed. Eruption 21. iii. 25). Six children with no history of measles. All injected subcutaneously with mixed adult convalescent serum 19. iii. 25.

Case	Age	Dose in c.c.	Result
1 Germaine C.	2½	4	Protection
2 Simone R.	8½	6	"
3 Lucienne B.	17	8	Protection (patient is a cretin)
4 Leontine B.	15½	8	Protection
5 Félice L.	4	4	Koplik 1. iv. 25. Eruption 3. iv. 25. 14 days after exposure (13 days after injection)
6 Denise B.	3½	3	Rise in temperature for two days after the injection. Koplik 1. iv. 25. Eruption 3. iv. 25. 14 days after exposure (13 days after injection)

This represents 67 per cent. success.

Ward 3. Child developed Koplik's spots 21. v. 25. Eruption 23rd. Another case of measles came into ward for two days, later, 29th, and 30th, and was then removed to fever hospital.

Eight children aged from 5 months to 10 months in ward; no history of measles. All received on 25. v. 25 3 c.c. of mixed convalescent serum subcutaneously. Result—No case had appeared three weeks later among the eight cases inoculated. This represents 100 per cent. success, although, as one of the children was under the age of 5 months, this case should perhaps be eliminated in estimating the percentage success, on account of the natural immunity which children would appear to possess until about the age of 5 months.

Ward 4. Child: Le G. developed Koplik's spots 8 days after entrance, 2. iv. 25. Eruption 11 days after entrance, 5. iv. 25. All the children in the ward had had measles with the exception of:

1. Robert P., aged 5, who received 5 c.c. convalescent serum subcutaneously on the 4th day. Five days later, 9. iv. 25, Koplik's spots appeared and patient had a modified attack of measles (no coryza and little eruption, general cheerfulness unaffected, etc.). Patient had presumably been exposed to infection on the 31st of March (10 days before Kopliks appeared), his injection was therefore given on the 5th day of the incubation period; this being so, the result was all that could have been expected.

2. Yvonne B., who received *no* serum, and who developed a typical attack of measles on the 13th April (12 days after exposure).

Ward 5. Child removed for typical eruption of measles, June 12th 1925. Twenty children with no history of measles. All injected with mixed adult convalescent serum in doses recommended by Débré (see above) on the day after. No Koplik's spots had been observed, the injection was therefore probably made the 3rd day after exposure. Result: complete prevention—no cases of measles having occurred in the ward three weeks later. This represents 100 per cent. success.

Experiences 6. Child: Lucille M. caught measles at school. Typical measles eruption 17. iv. 25. Three other children in the family—all close contacts; injected 20. iv. 25.

1. Baby aged 1 year—3 c.c. mixed convalescent serum subcutaneously.

2. Germaine 26 months—18 c.c. mixed adult serum.

3. Pierre aged 7 years (slept in same bed as Lucille), 30–35 c.c. Whole blood from sister, intramuscularly; sister had had measles at 18 months, and is now aged 12 years. Result: One month later, although an epidemic rages in the tenement building where they live, all three have remained immune.

Experience 7. Child: Germaine P., aged 5½, in close contact with sister Jeanne who developed typical measles eruption 10. iii. 25. On 14. iii. 25 she was given 20 c.c. mixed adult's serum subcutaneously. Result: had not contracted the disease one month later (20. iv. 25).

Experience 8. Child: Yvonne D., aged 2½, developed typical measles eruption 9. iv. 25. The next day, 10. iv. 25 her sister Marie aged 4½, who slept in the same bed, received 20 c.c. of maternal blood intramuscularly and 5 c.c.

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mixed adult serum subcutaneously. Result: one month later 10. v. 25 child was still in perfect health.

Experiences 9. Child: Marcel D., aged 3 years, developed a typical measles eruption 10. iii. 25. On 14. iii. 25 a mixed adult serum was administered to (a) her sister Germaine, aged $4\frac{1}{2}$, dose 12 c.c. subcutaneously, (b) child, a playmate, aged 4, who lived in the tenement and who had been in close contact until time of eruption; in this case the dose was 15 c.c. subcutaneously. Result: both children remained in perfect health, and were so one month later (20. iv. 25).

Experience 10. Child: Denis F., aged $2\frac{1}{2}$, in close contact with his sister Simone until 10. iii. 25, when she developed typical measles rash. Denis received on the same day (10. iii. 25) a subcutaneous injection of 3 c.c. of a mixed convalescent serum, and three weeks later (2. iv. 25) had developed no signs of measles.

Note. Most of the children over 6 years of age who recover from measles in the wards of this hospital have a small quantity of blood removed, 5–30 c.c. according to age, between the 7th and 9th day after defervescence. This is treated as described previously, in a laboratory which is devoted exclusively to the purpose, the Wasserman reaction and sterility tests being carefully applied in all cases. The sera are then pooled, and without addition of disinfectant, placed in 3 c.c. or 5 c.c. glass ampules, and kept in the ice chest for a minimum period of 4 days, until required. In all the cases cited above it is serum prepared in this fashion which is referred to as “mixed convalescent serum.”

The “mixed adult serum” was obtained from the centre which was recently established at the Hôpital Bretonneau for this purpose, and was prepared in a similar fashion.

REFERENCES.

- AVIRAGNET (20. iii. 1923). *Soc. de Ped.*
BLACKFAN, PETERSON and CONROY (1923). *Ohio State Med. Journ.* xix. 97.
BUTLER (28. ii. 1913). *Proc. Roy. Soc. Med.* (Epidemiol. Section).
BUTTERWEISSER (1924). *Deutsche med. Wochenschr.*
DÉBRÉ and JOANNON (viii. 1923). *Rev. d'Hygiène.*
DÉBRÉ and RAVINA (1923). *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, XLVII. 226.
DE CASTRO (1922). *Arch. Esp. de Ped.* vi. 517.
DEGKWITZ, R. (iv. 1920). *Zeitschr. f. Kinderheilk.* xxvii. 171; xxv. 134.
— (1921). *Monatschr. f. Kinderheilk.* xxii. 186.
DE JONG and BERNARD (1923). *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, XLVIII. 500.
DE STEFANO, S. (1923). *Pediatrics*, xxxi. 781.
GLASER and MÜLLER (1921). *Med. Klin.* xvii. 649.
HERRMAN, C. (1915). *Arch. Pediat.* xxxii. 503.
HIRAISHI and OKAMOTO (1921). *Jap. Med. World*, i. 10.
KUNDRALITZ, K. (1923). *Wien. med. Wochenschr.* lxxiii. 1200.
KÜTTER, P. (1921). *Zeitschr. f. Kinderheilk.* xxx. 90.
MACNALTY, A. S. and WHEATON, S. (1918). *Reports to the Local Govt. Board* (New Series, No. 115).

- MCNEAL, M. (1922). *Journ. Am. Med. Assn.* vii. 340.
MAGGIORE, S. (1921). *Pediatrics*, xxix. 873.
MANHOT and REICHE (1921). *Med. Klin.* xvii. 1230.
NICOLLE and CONSEIL (1918). *C. R. Acad. des Sc.*
—— — (1918). *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, xlii. 336.
—— — (1921). *Arch. Inst. Pasteur de l'Afrique du Nord*, i. 193.
NOBÉCOURT and PARAF (10. vi. 1922). *Presse Médicale*.
RATNOFF, H. L. (1923). *Arch. Ped.* xl. 683.
RICHARDSON and CONNOR (iv. 1919). *Journ. Am. Med. Assn.* lxxii.
TORRES and PACHECO (1920). *Arch. Lat. Am. de Ped.* xiv. 305.
WEAVER and CROOKES (1924). *Journ. Am. Med. Assn.* lxxxii. 240.
ZIMMERMANN, L. (1922). *Deutsche med. Wochenschr.* xlvi. 1701.
ZINGER, A. (1924). *Journ. Am. Med. Assn.* lxxxii. 1180.
ZSCHAU (1921). *München. med. Wochenschr.* lxviii. 1049.

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