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THE SERUM PROPHYLAXIS OF MEASLES.

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WITH AN INTRODUCTORY NOTE BY

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(With 6 Figures.)

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INTRODUCTORY NOTE

MALAYA, or at least the part of it with which I am well acquainted—the coast districts of Selangor—was free from measles until 1910. In that year infection was probably imported from India by immigrant coolies, and the disease spread rapidly through the rubber estates on which there was a considerable non-immune population of locally born Indians. Since then measles has been constantly present, causing deaths among the children and loss of efficiency in the labour forces. During the year 1916 it was particularly rife, and the resulting economic loss may be gauged by the fact that on Estate No. 3 of Dr Kingsbury's series there were 100 cases which involved a total of 1180 days' hospital treatment.

When Indian coolies arrive in Malaya a very large percentage is infected with Ankylostomes and Ascarides. The passage of the embryos through the lungs is the probable cause of the bronchitis so frequently seen in children in this very equable climate and this pulmonary irritation doubtless tends to make measles more serious than it would otherwise be.

Isolation and disinfection are of little value in controlling spread, and in the face of previous failure I naturally welcomed the suggestion of the prophylactic use of convalescent serum. On Estates Nos. 3 and 6 the proportion of

immune cases may be gathered from the following table showing the incidence of measles over the preceding six years, though it is but fair to add that a considerable influx of coolies from India occurred in 1925.

Cases of Measles.

Year	1919	1920	1921	1922	1923	1924
Estate No. 3	92	9	5	2	0	1
Estate No. 6	2	4	—	0	25	2

Dr Kingsbury gives figures which speak for themselves, and I can only add that the prophylactic effect of serum was very definite. It would appear that we now have a method for controlling measles epidemics, and it is to be hoped that subsequent experience will confirm these very promising results.

MALCOLM WATSON.

I. ENDEMIC AND EPIDEMIC MEASLES.

In Europe and America, measles is so widely endemic that it is generally regarded as one of the necessary ills of childhood and a malady of no serious import. Statistics, however, indicate that it is in reality a very formidable agent in infantile mortality. The annual death roll in European countries alone is not far short of 100,000, and case mortality is falling more slowly than for such diseases as scarlet fever and whooping cough. The heaviest toll is taken during the first few years of life, for, although in endemic areas a fleeting immunity is present at birth, it tends to disappear after the first few months of life and about 80 per cent. of the deaths occur in infants under five years of age.

When infection is introduced into a community which has been free for a long period of years, the disease is extremely fatal to both children and adults. Its appearance in Fiji and the Faroe islands was followed by devastating epidemics, and a less known illustration may be cited in the widespread outbreak in the Central Provinces of India which resulted in upwards of 100,000 deaths during 1902–3.

The position in the Federated Malay States is an intermediate one. Measles is one of the less common diseases, but small epidemics have occurred during the past two decades. Only a minority of the population is however infected in childhood and an outbreak which shows signs of spreading over a wide area must therefore be viewed with concern.

II. THE PROPHYLAXIS OF MEASLES.

Isolation, *per se*, has been pronounced a complete failure by Pfaundler when applied to young children immediately after the first appearance of symptoms in a member of the same family, but Milne has claimed some measure of success by the employment of eucalyptus oil for inunction and application to the clothing of contacts, combined with repeated swabbing of the throat with 10 per cent. carbolic oil.

Surer methods than these are required for prevention, and a very promising one has arisen from Anderson and Goldberger's attempts to transmit measles to monkeys, when they noted that a successful inoculation rendered the animal immune in subsequent experiments. From these results Nicolle and Conseil conceived in 1916 the idea of using serum from convalescent measles cases for the protection of contacts, and by this means succeeded in preventing measles in a young child, although she was in contact with cases in her own family. In the same year Park and Zingher independently essayed this method of protection but did not publish their work until 1924. Richardson and Connor (1918) obtained successful results with a small group of contacts, and in 1920, Degkwitz, while working with Pfaundler in Munich, published a record of 172 inoculations. He later organised a supply of serum so that it could be employed on an extensive scale. In the same year Torres and Pacheco recorded some results and in 1921 the method attracted the attention of Glaser and Müller, v. Torday, Kütter, Zschau, Maggiore, and Manchot and Reiche. In 1922 McNeal, Marie, Nobécourt and Paraf, de Castro, Galli, and Zimmermann reported on their investigations and more recently de Stefano (1923), Blackfan, Peterson and Conroy (1923), Ratnoff (1923), Kundralitz (1923), Aviragnet (1923), de Jong and Bernard (1923), Weaver and Crooks (1924), Zingher (1924), Park (1925) and Copeman (1925) have employed the method for prophylactic purposes. Rather varying figures have been obtained by these workers, but a summary of 2000 reported cases showed failure in less than 3 per cent.

In view of the comparative rarity of second attacks, Rietschel concluded that the antibodies produced during infection in childhood were of a lasting nature. He therefore employed adult serum or citrated whole blood when no convalescent cases were available, obtaining excellent results which have since been confirmed by Salomon.

The objection to Nicolle and Conseil's procedure is that only a transient immunity is conferred, the duration of which has been variously estimated at from one to three months. McNeal reported one infection after an interval of two months, and v. Torday, three cases between the 72nd and 75th day after inoculation. The duration of the passive immunity will vary with the quantity and potency of the serum and although the present writer has recorded evidence of residual immunity as long as five months after treatment, it would be unsafe to rely on such protection for a longer period than two months.

Attempts have been made to stimulate the production of active immunity. Thus Herrmann (1923) claimed to have protected a number of children by swabbing the nasal mucosa with mucus from a case in the late stages of incubation, but this procedure is unlikely to find general application owing to its uncertainty and possible dangers. Hiraishi and Okamoto (1921) approached the problem by injecting at intervals increasing doses of blood from acute measles cases, and Nicolle and Conseil (1923) suggested the injection

of convalescent serum, followed 24 hours later by 1 c.c. of blood from an acute measles case.

Débré and Ravina (1923) have introduced a modification of Nicolle and Conseil's method for passive protection which promises to be a marked advance. They inject convalescent serum towards the end of incubation. A mild form of measles ensues which is unlikely to be followed by dangerous complications. It is claimed that the attack is thus rendered innocuous and yet a lasting immunity is produced. Débré and Joannon, and Regan have also reported favourably on this method.

Tunnicliffe and Moody (1922) have described an anaerobic diplococcus as the causative agent of measles, and it has been suggested that vaccination could be carried out with killed emulsions of this organism. Caronia (1923) has also claimed etiological significance for an anaerobic micrococcus. The claims of these workers, however, do not find general acceptance at the present time.

III. Conditions on Malayan Rubber Estates.

The Tamil (Southern Indian) rubber estate cooly lives in a self-contained community on the plantation with its provision shop and school. Strangers are not welcomed, particularly in times of labour shortage as they may be recruiters from other estates. The coolies themselves seldom wander further than the nearest toddy shop to indulge in their favourite drink which is prepared by fermenting the juice of the cocoanut palm. There is a certain influx of recruits from India when additional labour is required, and a few coolies may abscond to other estates on which higher rates of pay are offered; but on healthy well-managed estates such movement is negligible, and, unless the plantation is near a town or village, the coolies have little intercourse with the outside world.

A visiting medical officer is responsible for the health on plantations. Hospitals are usually provided, either by each estate, or on the group system by which a number of plantations co-operate in the building and staffing of a larger establishment. Children are often accompanied to hospital by their mothers and thus infant sickness results in the loss of the mother's work to the estate.

IV. An Outbreak of Measles.

During the latter half of 1925 measles occurred on a number of estates in Selangor, Perak, Negri Sembilan and Johore. Though the death rate was not heavy, broncho-pneumonia and colitis were troublesome complications in some districts. The epidemic occurred at a time of labour shortage consequent upon the gradual lifting of rubber restrictions and with a rising market in the commodity, so that, apart from the risk to life, the heavy sick returns were a matter of anxiety to estate managers.

Towards the end of October 1925 Dr Bernard Day, who visits a number

of estates around Kuala Lumpur, approached the writer as to whether something could not be done to check these plantation outbreaks. A number of convalescent adults were then available, and it was decided to inject children who had not developed measles with serum from these cases.

V. TECHNIQUE OF SERUM PROPHYLAXIS.

Blood was taken 4 to 10 days after defervescence from the convalescent adults. Patients were placed on a plank bed, and a serum needle, sterilised in boiling oil, inserted into a vein in the cubital fossa of each arm, after the loose application of a tourniquet. The blood was received into sterile 100 c.c. flasks so that 200 c.c. were obtained from each case. If clotting occurred, the needle was cleared by applying a syringe and withdrawing a few c.c. of blood. After collection the flasks were taken to the laboratory where they were placed on ice until the following morning, when the serum was pipetted off and filtered through a Berkefeld candle. A Wassermann reaction was carried out on each batch, and 0·5 per cent. of phenol added, after which the serum was allowed to stand at room temperature for two days. At least three batches were then pooled, refiltered, and stored on ice, after the usual aerobic and anaerobic tests for sterility. Double filtration, combined with the addition of phenol, was considered sufficient precaution against the possible transfer of malarial infection to the children, and no ill effects followed any of the inoculations.

The time of exposure in any particular instance was quite unknown when injections were given so that the attempted protection of individual contacts, by employing larger doses for those in the later stages of incubation, was not feasible. The children were therefore treated *en masse*, and it was decided to try the effect of 2, 2½, 3 and 3½ c.c. of serum on different groups. In some instances only three-quarters of the children were treated on an estate, the rationale being that a large reduction in the number of susceptibles will bring an epidemic to a close.

For inoculation, the children were mustered in the shade outside the estate hospital or school, and admitted one by one. They were placed on a plank bed and the skin on both sides of the umbilicus painted with tincture of iodine. For some of the babies two inoculations were necessary, as injections were made subcutaneously and the actual serum content of the inoculum had been reduced to about 87 per cent. by the addition of the phenol in 4 per cent. solution.

Serum was poured into a sterile conical glass and covered by one-half of a Petri dish. Syringes were sterilised in boiling oil, and needles by immersing in undiluted lysol for 5 minutes, after which they were washed through and placed in saline until required. When an inoculation was completed the needle was removed from the syringe, and again washed in saline before being returned to the lysol bath. The required quantity of serum was then drawn into the syringe, and another sterilised needle applied. By this

technique it was possible to inoculate one child every two minutes, with the aid of two assistants.

VI. Results of Prophylaxis.

Estate No. 1 (*Fig.* 1). Plasma instead of serum was employed on this estate in doses of 2 c.c. Defibrination was accomplished by shaking the blood with glass beads, but in all other details the technique already described for the preparation of serum was followed. On the 3rd and 7th November, 27 and 66 children respectively were inoculated, and of the 93 cases treated 14 (15 per cent.) later developed measles. Ten children, including two who

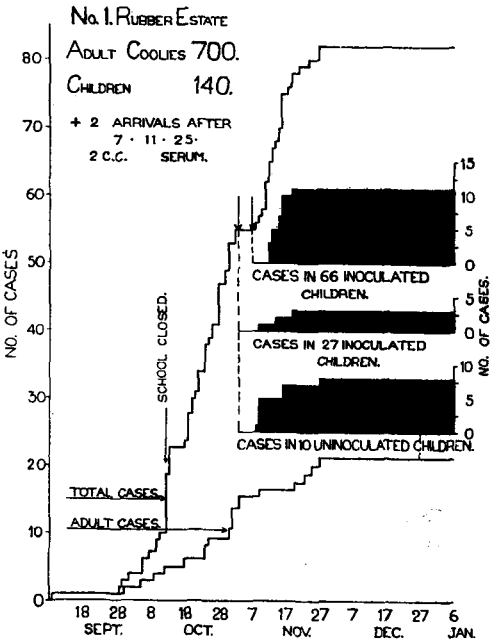

Fig. 1.

arrived from India after the 7th November, were not inoculated and 8 (80 per cent.) later became infected. The last case in the inoculated group occurred on the 19th November, but cases continued among adults and uninoculated children until the 27th November.

Estate No. 2 (*Fig.* 2). The disease appeared in a virulent form on this estate, three deaths occurring in the first five cases. Five days after its first appearance, $2\frac{1}{2}$ c.c. of serum were administered to the 50 children, who showed no signs of measles. Only one further case, which occurred on the day following treatment, was reported.

Estate No. 3 (*Fig.* 2). This estate is divided into "A" and "B" divisions, the two cooly lines being a mile or more apart. Measles spread on division "A" during October and the first half of November, but it was not until the latter month that the returns from division "B" began to rise rapidly. On the

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14th November 62 of the 78 presumably susceptible children living on this division were inoculated with 2½ c.c. of serum, and 5 later became infected. Of the 16 uninoculated children, three later developed measles. Cases in the

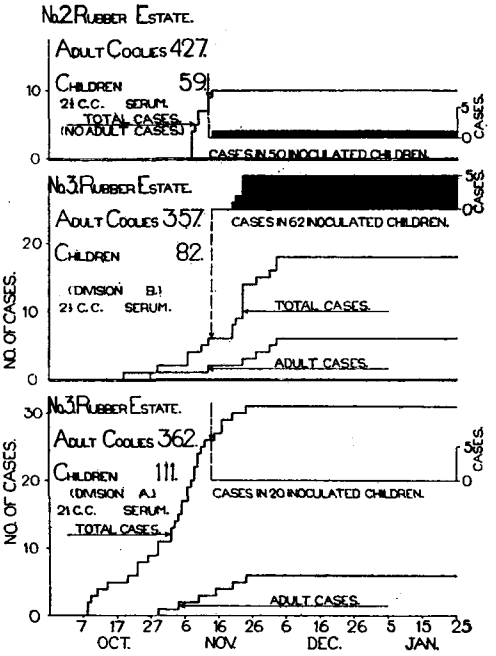

Fig. 2.

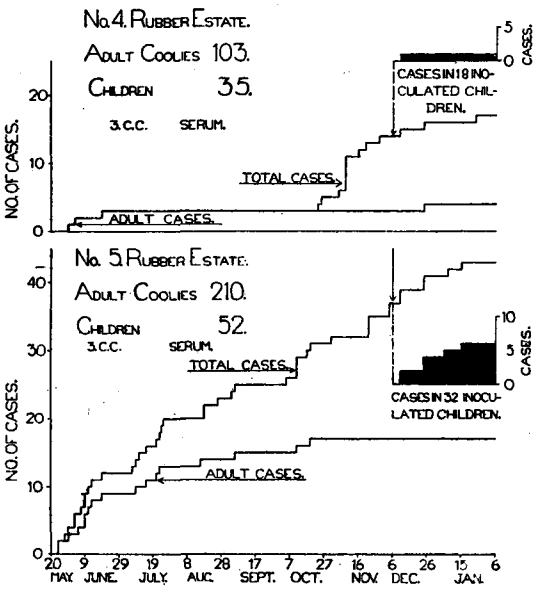

Fig. 3.

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protected group ceased on the 23rd November, but continued in the other children and adults until the 3rd December. Twenty children of division "A" were also given 2½ c.c. of serum on the 14th November. All these remained healthy although two further cases occurred in adults and three in the 69 non-protected children.

Estate No. 4 (*Fig.* 3). This was a small estate contiguous with Estate No. 5. Eighteen of the 24 presumably susceptible children were injected with 3 c.c. of serum on the 7th December, and two days later a case occurred in the inoculated group. On the 25th December an adult, and on the 23rd January one of the unprotected children, developed measles.

Estate No. 5 (*Fig.* 3). Thirty-two children who had not become infected were treated with 3 c.c. of serum, and six very mild cases occurred notwithstanding the attempted protection.

Estate No. 6 (*Fig.* 4). The writer was asked to apply serum prophylaxis on this estate at the commencement of the outbreak. Five days after the

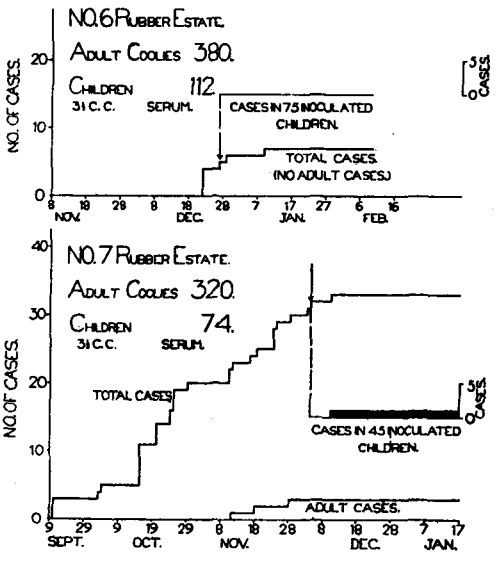

Fig. 4.

first cases, 75 of 107 children were treated with 3½ c.c. of serum. There were no failures, although 2 and 13 days later cases occurred in unprotected children.

Estate No. 7 (*Fig.* 4). Measles had been prevalent on this plantation for three months prior to treatment. All the children who had not had measles were given 3½ c.c. of serum, and after an interval of 6 days one further case occurred.

Fig. 5 depicts the incidence of measles on two plantations (Nos. 8 and 9) on which no prophylactic inoculations were made. Estate No. 8 was contiguous with No. 3 and near No. 7, while Estate No. 9 was close to No. 1.

Estate No. 8 had 35 cases among 210 children with 7 cases of broncho-pneumonia, 6 cases of colitis and 4 deaths. On Estate No. 9 there were 34 cases among 100 children, with 2 cases of broncho-pneumonia and 2 deaths. Two cases on No. 8 developed both broncho-pneumonia and colitis, so that of 69 cases in children, 13 (18·8 per cent.) had serious complications and 6 (8·7 per cent.) died.

On Fig. 6, the failures in the serum series are collected and graphed as percentages against the interval in days between inoculation and onset of measles.

Group A contains 93 children, all of whom received 2 c.c. of serum, and in about 15 per cent. the treatment failed. Group B consists of 132 children

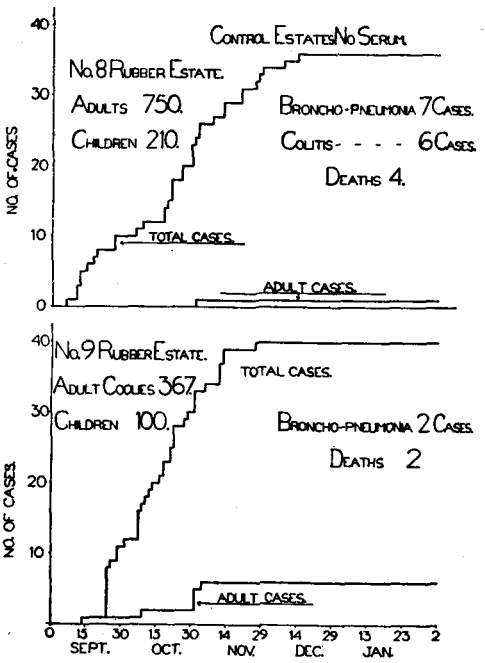

Fig. 5.

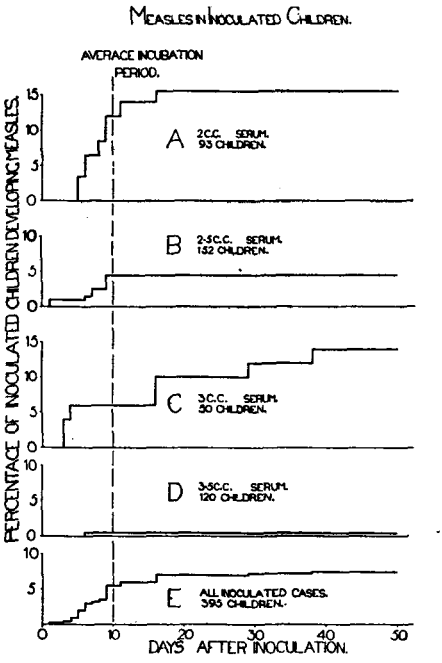

Fig. 6.

who were given 2½ c.c. of serum. The percentage of failures was 4·5. Group C contains the comparatively small number of 50 children, which may account for the anomalous results. Three c.c. of serum were injected and 14 per cent. later developed measles.

Group D consists of 120 children to whom 3½ c.c. of serum were given. The failures were less than 1 per cent.

Graph E of Fig. 6 shows the results of the combined groups. Of the 395 treated children about 7 per cent. developed measles. A vertical line, representing the average incubation period of the disease, is drawn at a point corresponding to an interval of 10 days after inoculation, and of the treated cases, less than 2 per cent. developed the measles eruption after this interval.

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Even some of these may have received serum some days after exposure; for when serum is administered during the incubation period, an extension of the usual interval between exposure and the onset of symptoms to 18 or 20 days has been observed in many instances.

Very erroneous conclusions may be drawn regarding the effect of a prophylactic measure on the course of an epidemic, if the waning of virulence and the exhaustion of the numbers of susceptible persons are ignored. In this epidemic, the virulence reached a maximum in November and gradually fell in December and January. On Estate No. 1 it would appear that the number of non-immunes was becoming exhausted when serum prophylaxis was introduced; yet after the date of inoculation 80 per cent. of the children, who were not protected, sickened. Measles had not occurred for many years on Estate No. 2, and thus a large number of the 59 children must have been susceptible, while at the time there was no indication of falling virulence. On Estate No. 3, "B" division came under observation soon after the commencement of the outbreak, though infection had already made considerable progress on "A" division. Of 78 presumably susceptible children 62 were treated, and the total incidence among the children on "B" division was 14·6 per cent., compared with 22·5 per cent. for "A" division. Virulence was falling when Estates Nos. 4 and 5 (Fig. 3) were visited, and it seemed that few non-immunes remained, yet, notwithstanding protection, occasional very mild cases occurred for four weeks following inoculation. The best results obtained were those shown for Estates No. 6 and 7 (Fig. 4). The virulence of the virus was certainly falling at this period, and on Estate No. 6 a number of children had had measles two years previously; but it is difficult to suppose that the outbreaks would have ceased so quickly but for active intervention.

Better protection would probably have been obtaining if serum from Europeans had been employed. The Tamil is notorious for lack of resistance to disease, and, among the adult cases, the writer met with two who claimed to have had measles in India less than 18 months previously. It is thus probable that the antibody content of the serum employed was relatively low.

VII. Attenuated Measles.

A very striking feature was the mildness of the disease in the 28 inoculated children. Among the group which had received 2 c.c. of serum, the eruption was mild and the maximum temperature varied between 101° and 104° F. for one or two days only. In one case, however, a child aged 3 years, the eruption developed 7 days after inoculation and the course was complicated by the onset of broncho-pneumonia. Recovery was, however, comparatively rapid, and discharge from hospital was possible 14 days after the appearance of the rash.

The cases which followed larger doses of serum were even milder. When the quantity had been 3 c.c., the eruption was much less severe and tem-

peratures ranged to 99°–99·5° F. for a day or two only. These children did not feel ill, and often objected to going to hospital.

Among the 28 cases of measles which developed after the injection of serum the issue was complicated by broncho-pneumonia in one instance only (3·6 per cent.), and no deaths occurred, while on the control estates, 18·8 per cent. of the measles cases had serious complications, and 8·7 per cent. died. These figures are convincing evidence that when serum is given shortly before exposure or early in the incubation period the disease occurs in a mild form. The duration of the resulting immunity is at present unknown, and the success of the method for active immunisation depends on this factor. Repeated infection during childhood sometimes occurs and the writer has seen in the recent epidemic two cases which had a second attack within two months of the first. Attenuated measles may be less effective than the acute disease in the stimulation of antibody production, but it is probable that such protection would endure over the danger period of early childhood. Practical difficulties in exactly gauging the time of exposure will however detract from the usefulness of this means of attenuation.

VIII. Serum Administration in the Developed Disease.

Therapeutic use of convalescent serum has occasionally been tried, but the reports have been conflicting. The writer has employed this measure in two cases of measles, complicated by catarrhal colitis, with beneficial results in one instance. This complication has not been infrequent during the recent epidemic, and a dysenteric origin of the condition has been negatived by stools examinations for *Etamoeba histolytica* and cultural examination for *Bacillus dysenteriae*.

Case No. 1. A Tamil child, aged 12 years, was passing about 20 watery motions daily, containing a small quantity of mucus, but no blood. Twenty c.c. of serum were given intramuscularly on the 6th day after admission to hospital, but the patient was emaciated and somewhat collapsed. Death occurred on the following day.

Case No. 2. A Tamil child aged 8 years had had 12 to 20 motions daily, containing mucus and traces of blood, for seven days. Fifteen c.c. of serum were given intramuscularly, and on the following day the number of motions was reduced to eight, improvement being continuous.

IX. Establishment of Serum Depôts.

Although the taking of any quantity of blood from young children is to be deprecated, there can be little objection to obtaining 300 to 400 c.c. from a healthy adult during the convalescent period. This quantity would suffice for the prophylactic treatment of about 60 children. Collecting and storing stations have already been established in Germany, France and America, thereby making such serum available to the general practitioner. It would

appear that the emergency establishment of serum depôts during the serious epidemics which occasionally visit tropical areas would be a useful means of control.

X. Intracutaneous Serum Injections.

Schultz and Charlton (1918) found that the serum of convalescent scarlet fever cases, and of some adults, causes a local blanching if injected intradermally into a scarlet fever case with a bright rash. The fading of the rash commences about six hours later and is noticeable for several days over an area from one-half to a few inches in diameter. Such a reaction might be of interest as an auxiliary test in the diagnosis of morbilli, but Débré and Ravina found that blanching did not occur with convalescent measles serum, although the rash failed to develop in the locality of an injection made shortly before the appearance of the eruption.

An intradermal injection of 0·2 c.c. of convalescent measles serum, controlled by a similar saline injection, was made into a Chinese case with a well-marked rash. Apart from a transient paling, owing to the pressure of the inoculum, no local blanching was noted, although the patient was examined 6, 24 and 48 hours later.

XI. Conclusions.

1. A series of measles outbreaks on rubber plantations has been controlled by the use of convalescent serum.

2. Consideration of the virulence of the virus and the number of the non-immune cases on the estates indicate that the injection of convalescent serum was a prophylactic measure of very real value.

3. The most satisfactory dosage for *en masse* prophylactic treatment of children was 3·5 c.c. of serum.

4. Inoculated children who subsequently developed measles suffered from a very mild form of the disease.

5. The administration of the serum to two cases of measles colitis was followed by improvement in one instance.

6. The emergency establishment of serum depôts would be most useful for combating the serious epidemics which sometimes occur in the tropics.

7. Intradermal injection of convalescent serum is not followed by a blanching of the measles eruption.

The writer desires to express his appreciation of the courtesy of the visiting medical officers of the above estates, viz. Sir Malcolm Watson, Dr Bernard Day, Dr W. T. Quaife and Dr H. Meredith Harrison, in inviting his co-operation, and in kindly allowing him access to the records of the various estate hospitals.

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