Vaccinal immunity in relation to the serum treatment of small-pox, with a record of cases / by R.S. Thomson and Ernest L. Marsh.

VACCINAL IMMUNITY IN RELATION TO THE SERUM TREATMENT OF SMALL-POX, WITH A RECORD OF CASES

BY

R. S. THOMSON, M.B., B.Sc.,

Visiting Physician, City of Glasgow Small-Pox Hospital, Belvidere;

AND

ERNEST L. MARSH, M.B., D.P.H. (Oxon.),

Late Resident Medical Officer, City of Glasgow Small-Pox Hospital, Belvidere.

Reprinted from the "Scottish Medical and Surgical Journal," August 1897.

EDINBURGH:

WILLIAM F. CLAY, 18 TEVIOT PLACE

1897

VACCINAL IMMUNITY IN
SERUM TREATMENT O
A RECORD OF CASES

By R. S. THOMSON, M.B., B.Sc., Visi
Small-Pox Hospital, Belvidere; a
ERNEST L. MARSH, M.B., D.P.H.
Officer, City of Glasgow Small-Po

BEFORE detailing our own obse
dictated by our experience, it m
briefly the experimental work whi
has gradually developed the hope
enable immune to cow-pox we hav
pestic agent which may enable u
with a disease which, in unvaccin
those who by lapse of time have
by early vaccination, has till now s
medical treatment.

In a series of experiments cond
(1), it was shown that vaccinal immu
the horse, ox, or child by subcutane
of dilute vaccine lymph, and th
cutaneous or other external manife

Raynaud, in 1877 and 1878, re
upon the *Influence of the blood in*
immunity (2), and upon *Vaccinal inf*
his earlier experiments this observ
children with blood derived from
negative results, neither vaccinatio
resulting. In a later experiment
blood—viz., from 250 to 500 gramm
heifer on the sixth day after vacci
of an unvaccinated heifer, with the n
day after the experiment the second
immunity to vaccinia. In response,
ments conducted by Chauveau (4) in
immunity in a young and healthy h
blood of 500 and 1000 grammes
horse with natural horse-pox, Rayna
but failed to reproduce the positive
case of transfusion, and admitted th
accidental vaccination in his former
been defective. He, therefore, came

VACCINAL IMMUNITY IN RELATION TO THE SERUM TREATMENT OF SMALL-POX, WITH A RECORD OF CASES

By R. S. THOMSON, M.B., B.Sc., Visiting Physician, City of Glasgow Small-Pox Hospital, Belvidere; and
ERNEST L. MARSH, M.B., D.P.H. (Oxon.), Late Resident Medical Officer, City of Glasgow Small-Pox Hospital, Belvidere

BEFORE detailing our own observations and any remarks dictated by our experience, it may be interesting to review briefly the experimental work which, begun thirty years ago, has gradually developed the hope that in serum of animals made immune to cow-pox we have an immunising and therapeutic agent which may enable us to deal more successfully with a disease which, in unvaccinated subjects as well as in those who by lapse of time have lost the immunity conferred by early vaccination, has till now shown itself uninfluenced by medical treatment.

In a series of experiments conducted in 1866 by Chauveau (1), it was shown that vaccinal immunity might be conferred upon the horse, ox, or child by subcutaneous or intravenous injection of dilute vaccine lymph, and this without producing any cutaneous or other external manifestations of the disease.

Raynaud, in 1877 and 1878, recorded certain experiments upon the *Influence of the blood in the transmission of vaccinal immunity* (2), and upon *Vaccinal infection and immunity* (3). In his earlier experiments this observer inoculated unvaccinated children with blood derived from an immune animal with negative results, neither vaccination nor consequent immunity resulting. In a later experiment a much larger quantity of blood—viz., from 250 to 500 grammes—was transfused from a heifer on the sixth day after vaccination into the jugular vein of an unvaccinated heifer, with the result that on the fourteenth day after the experiment the second animal possessed complete immunity to vaccinia. In response, however, to certain experiments conducted by Chauveau (4) in 1877, who failed to obtain immunity in a young and healthy horse by two transfusions of blood of 500 and 1000 grammes respectively, taken from a horse with natural horse-pox, Raynaud repeated his observation, but failed to reproduce the positive result obtained in his first case of transfusion, and admitted that the precautions against accidental vaccination in his former experiment might have been defective. He, therefore, came to the general conclusion

that from 250 to 500 grammes of blood might be transfused from a vaccinated into an unvaccinated animal without producing either a specific vaccinal eruption or immunity, but that it was not impossible that exceptionally there might be conditions of potency associated with the transfusion of a very great quantity of blood which might confer immunity upon the animal receiving it. Chauveau came to a somewhat more definite conclusion —viz., that the blood of an animal having a fully developed and natural vaccinal eruption is not necessarily free from virus; but this is so deficient that one may administer from 500 to 1000 grammes of the blood without there being present virulent matter in quantity sufficient to immunise a susceptible subject by transfusion.

Following up Raynaud's observations, Pfeiffer (5) in 1884, by using small quantities of blood, obtained results which he himself apparently considered positive and conclusive. He injected 30 grammes of defibrinated blood taken from a calf on the eighth day after vaccination into another calf assumed to be susceptible to vaccinia: vaccination performed on the sixth day after the injection proved negative. A similar experiment was carried out upon a third calf with the same result. In a further observation he injected only about a teaspoonful of blood taken from a calf four days after vaccination into a presumably susceptible animal, and thereby claimed to have produced immunity to vaccination. But Straus, Chambon and Ménard (6), working in concert, showed in 1889 that the quantities of blood employed by these last experimenters were much too small to produce immunity, and that only much larger quantities—viz., 4, 5, or even 6 kilogrammes—transfused from a calf on the seventh day of a well-developed vaccinal eruption were capable of conferring it. The conclusion they drew from their observations was that the blood of a vaccinated animal contained a hypothetical specific micro-organism during the eruptive period, though in very small amount. Still, they were inclined to admit the possibility that, instead of the microbes themselves, soluble substances secreted by them in the eruption and absorbed into the circulation might confer vaccinal immunising properties upon the blood. Reasoning from the fact that vaccination in the horse produces a generalised eruption, the former hypothesis seemed to them the more likely. In a concluding experiment made by these observers with the object of deciding whether the immunising power of the serum persisted after complete disappearance of the vaccinal eruption, 5·5 kilogrammes, practically all the blood of a calf which had been vaccinated seven weeks previously, were transfused into the veins of an unvaccinated calf, but without producing immunity in this animal.

In 1892, Sternberg (7), in association with Griffiths, made

some observations upon the neutralising power of serum from an immune animal when mixed in small quantity with active vaccine lymph taken from a calf, or with crushed vaccinal crust from the arm of a child. The result of vaccinating a susceptible calf with this mixture was in every instance negative, while the same calf thereafter was readily vaccinated with the production of characteristic and typical vesicles when inoculated with unmixed lymph.

In the same year Reute and Enoch (8), while carrying out investigations on vaccine culture, succeeded in isolating a toxin which in their hands gave in the case of calves and pigs somewhat conflicting results. Their experiments are, however, inconclusive and open to many serious objections; but the general evidence brought forward by these observers is in favour of the immunising power of the so-called "vaccine toxin."

An attempt to produce an antitoxic serum by repeatedly revaccinating a monkey was recorded by Copeman (9) in 1893. His results, however, were not encouraging.

Centanni (10), working at the subject of vaccine immunity about this time, concluded as the result of his observations that there was no constant relation between existing immunity and the presence of a protective substance in the blood-serum of a vaccinated animal, and that a high degree of immunity might exist in the absence of any such protecting substance. Kramer and Boyce's (11) experiments, published in 1893, gave further effect to this opinion. These observers carried out a series of six experiments in which serum from immune calves was injected in quantities varying from 415 to 2500 grammes into other calves, these quantities corresponding to from 3·04 to 18·94 grammes per kilo. of body-weight. The serum was given at intervals in doses varying from 100 to 300 c.c. In five of the experimental calves vaccination performed within forty-eight hours after cessation of the injections ran a normal course; but in the sixth, which received a total of 1240 grammes of serum, attempts at vaccination proved unsuccessful.

Landmann's (12) observations published in 1894 also point in the same direction as those of Centanni. His experiments were made upon children; in eight cases with serum taken from immunised calves a considerable time—viz., from twenty-eight to eighty-three days after vaccination, while in two cases the serum wasd erived from human subjects, also at a late period. In such serum he was unable to demonstrate the existence of any immunising power, and concluded that, while possibly a protective material might be present in the blood for a short time after vaccination, yet that this rapidly disappears from the circulation and combines with the solid tissue-elements. In this way he

sought to explain the high degree of immunity enjoyed by the tissues of vaccinated animals in the absence of any distinct immunising power in the blood.

Further researches on the subject were separately conducted by Gundobin (13) and Hanover (14). The former took 28 c.c. of the serum of a calf which had been vaccinated with animal and humanised lymph twenty-six days previously, and injected this quantity into another calf. Five days later, this calf was vaccinated, with the result that a few characteristic papules were produced locally which ran an abortive course. He believed, however, that this single experiment did not conclusively prove that the blood contained protective matter. Hanover's experiment was almost a repetition of the latter. He injected 100 c.c. of serum taken from a calf thirty-one days after vaccination, into another calf, with the result that on vaccinating this second calf twenty-six hours later, normal vesicles developed at all parts of the inoculated surface.

Rembold (15) varied the method of immunisation. He submitted goats to three or four revaccinations at intervals of one or more weeks, and this even though the first attempt to revaccinate proved negative. He further supplemented this treatment by the injection of vaccine matter subcutaneously. Serum from these animals was injected twenty-four hours before vaccination, under the skin of three calves and a goat, in doses varying from $\frac{1}{4500}$th to $\frac{1}{1200}$th of the body-weight, without producing any definite immunising effect.

Further experiments upon the immunising power of serum transferred from a vaccinifer to an animal supposed to be susceptible to vaccinia were commenced in June 1895 by Beumer and Peiper (16). Calves mostly formed the subjects of a series of five experiments. In each of the first three of these, 100 c.c. of *serum*, in the fourth 30 c.c. of *defibrinated blood*, and in the fifth 60 c.c. of similar blood taken from immunised calves were injected into susceptible animals. In every case, subsequent vaccination ran a normal course. These observers concluded that the blood-serum taken from vaccinated calves either contains no protective material capable of conferring immunity when transferred to susceptible calves, or that it exists in such small quantity as to render it apparently useless for practical purposes.

The experiments of Hlava and Houl (17) in 1895 yielded more hopeful results than those just described, and immunity to vaccination is stated to have been conferred by the injection of immunised serum into a susceptible calf, to the extent of from 0·6 to 1·0 c.c. per kilo. of body-weight, the injection having been made four days before vaccine inoculation.

Lastly, from a long series of interesting experiments recorded

in 1896 by Béclère, Chambon and Ménard, (18), and undertaken with the object of deciding—

1. *The immunising power of the serum of vaccinated heifers,*
2. *Whether the immunising power of serum is due to some chemical substance in solution or to active microbic elements,*
3. *The prophylactic and therapeutic properties of the serum of vaccinated heifers,*
4. *Whether the immunising power of such serum could be increased by a succession of vaccinal inoculations repeated at short intervals:*

these observers came to the following conclusions:—

1. That serum of a vaccinated heifer collected during the most active period of the eruption, *i.e.*, five to six days after vaccine inoculation, possesses properties conferring immunity against subsequent vaccination.

2. That the immunising action of serum from a vaccinated heifer is very rapid, a single subcutaneous injection of such serum in sufficient quantity, made immediately before free vaccination, being sufficient to modify the development of the subsequent vaccinal eruption to such an extent as almost to completely abort it; while, on the other hand, the immunity following on the introduction of *vaccine* under the skin shows itself but slowly—a subcutaneous injection of vaccine lymph made immediately before free vaccination with the same lymph did not modify in the slightest the development of the subsequent eruption. Still further, when the subcutaneous injection of vaccine lymph was given one, two and even three days before vaccination, it manifested no preventive power by any alteration in the external appearance of the vaccinal eruption. After the third day, the immunity gradually attains its full development, but does not seem complete until the eighth day, at which time at the earliest it is sufficiently developed to render sterile all fresh inoculations made under the epidermis.

3. That the rapidity of the immunising action of the serum of a vaccinated heifer, when contrasted with the slowly-developed immunity which follows upon the subcutaneous injection of vaccine, is sufficient to demonstrate that the serum owes its immunising power to certain substances in solution, and not to the presence of the microbes (hypothetical) of vaccinia.

4. That the progressively increasing immunity which follows from four to eight days after *subcutaneous vaccination* manifests itself in animals tested by vaccination during this period in three ways—(1) some of the inoculations prove completely sterile; (2) others give rise to vesicles more or less rudimentary and aborted, the gradual maturation of the immunity being indicated by the daily increased proportion of sterile inoculations; (3) the

activity of the lymph of these eruptive elements is gradually attenuated up to the point of being inert, as demonstrated by inoculation of the fluid upon unvaccinated children and heifers.

5. That the immunising action of the *serum* of a vaccinated heifer, injected under the skin of an animal of the same species, shows itself also in three ways when tested by vaccination—(1) by the complete failure of many of the inoculations; (2) by the rudimentary and abortive appearance of the eruptive elements; (3) by the attenuation of the virulence of the contents of these elements.

6. That the immunising power of the serum of a vaccinated heifer, when injected under the skin of a susceptible animal of the same species, depends on the relation between the weight of the animal and the amount of the dose. The minimal dose necessary to produce manifestations of the immunising property of the serum being relatively considerable. Thus a dose $\frac{1}{100}$th of the weight of an animal vaccinated shortly afterwards, does not confer complete immunity, but only sufficient to cause a marked modification of the eruption and render sterile a great proportion of the inoculations.

7. That the immunising action of the serum of a vaccinated heifer also shows itself by the three characteristic signs already referred to, even when the subcutaneous injection of the serum does not precede the vaccination, but is given *after* an interval of twenty-four or even forty-eight hours. The serum, therefore, of a vaccinated heifer possesses not only a prophylactic action against vaccinia, but also a therapeutic activity, although this is rather feeble if the administration be long delayed after the inoculation.

8. That the immunising action of the serum of a vaccinated heifer does not seem to be increased to an appreciable degree by the daily injection, for forty-two consecutive days, of vaccine virus under the skin of the animal furnishing the serum.

Passing from this, the more experimental part of the subject, to those clinical observations which seek to establish the therapeutic value of immunised serum in the treatment of variola, we find the first record in two cases published by Kinyon (19) in the "Abstract of Sanitary Reports," U.S. Marine Hospital Service, 1894. Somewhat later these observations were extended by Wilson (20) with a record of three cases, and by Elliot (21) with a record of five cases. The doses of immunised serum used in following out this treatment were small and given at varying intervals, *e.g.*, among the cases recorded by Wilson the maximal total dose amounted to only 13 c.c. administered to a child aged three years. Each of these observers claims that the treatment was followed by definite results, that the course of the eruption was modified and in

some cases even aborted, that convalescence was hastened and sequelæ such as abscesses and "pitting" prevented.

Our own observations on this subject, of which the following cases form a record, were commenced in the City of Glasgow Small-Pox Hospital on October 23rd, 1895, with serum prepared and kindly supplied by the Health Department, Brooklyn, N.Y. This serum, though named "variola antitoxic serum," was derived from calves rendered immune to cow-pox by inoculation with vaccine lymph, not with the virus derived directly from a variolous patient.

CASE I.—William H., æt. twenty-two, clerk, was admitted into the Small-Pox Hospital on October 23rd, 1895, on the fifth day of his illness. *He had been vaccinated in infancy and presented one well-defined, foveated vaccine cicatrix having an area of* 0·86 *square inch.* The attack of small-pox in this case commenced during the third week of convalescence from scarlet fever and while the patient was under medical observation, so that a record of the consecutive phenomena from the first commencement of the symptoms was obtained, the following representing the temperature during this time—*first day of illness*, 99·6° F. A.M.; 101·8° F. P.M.: *second day of illness*, 101° F. A.M.; 103.2° F. P.M.: *third day of illness*, 101·8 F. A.M.; 103·4° F. P.M. Early on the third day of the attack a punctiform eruption, which disappeared on pressure, was observed over the flanks and groins. There was likewise marked injection of the fauces and pharynx. The general symptoms during this period were those of moderate fever, which was maintained until the evening of the fourth day when the temperature reached 104·2° F. In the course of the night, however, the temperature fell to 100·8° F., this defervescence being associated with the appearance of a papular eruption on the forehead and arms.

On admission, patient was found to present on the face, scalp, sides of the neck and over the forearms, a copious variola eruption in the initial stage of papulation. Elsewhere a few scattered papules were present. On the trunk, especially over the back, there was a fading morbilliform rash, the remains of the prevariolar eruption noted above. The fauces were injected and on the palate a sparse eruption was noticeable. The patient's general symptoms at this stage were trifling, and a careful physical examination gave negative results. The pulse was regular and of good tension.

At 4 P.M. on this day, the fifth of his illness, 5 c.c. of "variola antitoxic serum" were injected under the skin of the abdomen, the temperature shortly before the injection being 101·6° F. One hour later the temperature registered 101·8° F., and this level was maintained till midnight, when it fell to 100·4° F.

A sample of urine passed at this time was free from albumen and otherwise normal.

At the visiting hour, on the morning of the sixth day of illness, the temperature had fallen to 99° F., and the patient, who had passed a comfortable night, expressed himself as feeling very well. His eruption showed the usual progression from papulation to vesiculation, the latter being, however, nowhere advanced. The elements were of a small type with narrow well-defined areolæ. The fauces continued acutely injected and patient complained of a sense of soreness in the throat. The pulse was 72, regular, and of good tension. There was slight tenderness on pressure over the seat of injection, but no redness or swelling. At 1 P.M. a further injection of 5 c.c. of serum was administered, the temperature at this time being 99·2° F., but it rose gradually towards evening, reaching a maximum of 100·2° at 8 o'clock. The 45 oz. of urine passed during the previous twenty-four hours showed nothing abnormal.

On the morning of the seventh day the nurse reported that patient had again had a comfortable night. The temperature was now 99·2° F., and the pulse 80, regular, and of good tension. The throat was, if anything, more uncomfortable than before, and inspection showed the whole guttural fossa to be injected and closely set with white-capped vesicles, especially numerous over the pharynx. As regards the skin eruption, vesiculation was now general, that on the face and forearms developing in association with concurrent œdema of the superficial tissues in the manner of typical small-pox. The seats of injection presented nothing noteworthy. At 4 P.M. on this day, when the temperature was 99·6° F., a further injection of 10 c.c. of serum was given. Thereafter the temperature rose to 100·8° F., which point was reached at 8 P.M. The urine passed during the previous twenty-four hours amounted to 39 oz. and continued normal.

On the morning of the eighth day patient was declared to have again enjoyed a quiet night, and this in spite of the steady evolution of the eruption. The swelling of the face had now become more pronounced, the nose being considerably broadened and the eyes closed. The elements of the eruption on the face were everywhere becoming pustular, and a similar development was noticeable on the forearms and elsewhere. On the throat the eruption was flattened and yellowish, while the tongue continued thickly coated. The pulse was 100, regular and of good tension. Temperature, 101° F. At 1 P.M. a further injection of 10 c.c. of serum was given, the temperature being 101° F. at the time. Subsequently the temperature rose to 102° F., and patient was noticed to perspire freely. Urine passed amounted to 49 oz., was neutral in reaction and free from albumen.

On the ninth day the patient still felt comfortable, although the face presented the œdematous appearance already described. Some of the pustules on the face and scalp now showed signs of commencing desiccation, but elsewhere they presented an almost fully developed appearance and a bright yellow colour resembling drops of hardened yellow wax. Traces of the eruption were still visible on the fauces and pharynx. Temperature, 99·8° F. A.M.; 98·4° F. P.M. The urine for the day amounted to 63 oz., and was still neutral in reaction and normal in character.

At the morning visit on the tenth day the temperature was normal, and patient reported himself as feeling very well. The œdema of the face was much less, and desiccation was advancing rapidly. The throat was almost well. Tongue clean and moist. Pulse 70, regular and of good tension. Urine 48 oz., acid and normal. Evening temperature, 99° F.

From this date onwards the case followed the usual course of a somewhat sharp uncomplicated attack of variola, the crusts separating and the skin desquamating in quite a normal manner. Except for some "pitting," the patient was dismissed well on the 27th of November, forty days from the commencement of his illness. The only interesting feature during early convalescence was the occurrence of an urticaria on the twelfth day of illness. This was especially well-marked around the sites of the injections, but for two days was also diffused over the whole abdomen.

CASE II.—David C., æt. twenty, plumber, admitted on October 25th, 1895. *His vaccination dated from infancy, and the scar, which was well defined and foveated, measured* 1·6 *square inches.* This patient, like the previous case, contracted small-pox in the third week of his convalescence from an attack of scarlet fever, and entered the Small-Pox Hospital on the fifth day of his illness. He was under medical observation from the commencement of the attack, and the records of his temperature during the initial illness are as follows :—*first day of illness*, 99° F. A.M.; 102·6° F. P.M. : *second day*, 101° F. A.M.; 104° F. P.M. : *third day*, 102·2° F. A.M.; 101·8° F. P.M. : *fourth day*, 101·8° F. A.M.; 101·6° F. P.M. On the third day of the attack an erythematous eruption was observed over the abdomen, and was accompanied next day by several papules suggesting small-pox. A sparse eruption of similar papules appearing coincidently with a fall of the temperature to 99·2° F. on the morning of the fifth day confirmed the suspicion of variola. On admission he presented a sparse eruption of papules most abundant and typical on the face, where they showed signs of already commencing puriform change. This eruption was evidently as greatly modified in its course of development as in the number of its elements, for on the rest of the body only a few scattered

and ill-defined pocks were to be found. Inspection of the throat showed some slight injection of the fauces, with here and there a spot of eruption. Otherwise patient appeared to be healthy.

At 4.15 P.M. on this day, 10 c.c. of serum were injected under the skin of the abdomen, the temperature being 99° F. at the time. In the evening the thermometer registered 99·6° F., and no symptoms or changes attributable to the injection were observed.

On visiting the patient on the morning of the sixth day the elements of the eruption showed, if anything, more marked puriform change. The temperature, however, was normal (98·4° F.), and throughout the day rose no higher than 99° F. The urine passed during the previous twenty-four hours amounted to 30 oz., and was in every way normal.

On the morning of the seventh day the patient expressed himself as feeling very well. The eruption on the face was now beginning to dry; the pulse was of good tension; the temperature perfectly normal.

From this point the patient continued to improve, the pustules desiccating and the crusts separating in the usual manner. The patient was dismissed well on 27th November, thirty-eight days from the commencement of his illness. No eruption or other condition which could be associated with the serum treatment was observed.

CASE III.—Mrs M'E., æt. fifty-five, housewife, admitted on October 25th, 1895, the sixth day of her illness. *Patient's left arm showed two ill-defined, non-foveated vaccine cicatrices dating from infancy, and measuring* 0·32 *square inch.* The initial symptoms had been followed by an eruption which appeared on the face and hands the day before admission. The patient was of stout build and florid complexion, and her body, especially over the face, back, and forearms, presented a copious eruption of papules, having the shotty feel characteristic of small-pox at this stage. There was no evidence of vesiculation anywhere. The throat was dry and covered with tough mucus, but no eruption could be seen. A careful physical examination of the internal organs gave a negative result. Pulse regular, 88, and of good tension. Temperature on admission at 1 P.M., 102·4° F.

At 5 P.M., 10 c.c. of serum were injected under the skin of the abdomen, the temperature being 102° F. At 10 P.M., five hours after the injection, the thermometer registered 101·6° F. Patient was restless throughout the night, but at the morning visit (seventh day of illness) declared that she was much as before, and was definite in the assertion that she felt no worse. The eruption was now more abundant on the lower extremities, while on the parts mentioned above, the papules showed signs

of commencing vesiculation, and the throat a characteristic eruption on the soft palate, fauces, and pharynx. The tongue was fairly clean. The pulse was regular, 68, but of poor tension. There was some faint redness over the site of the injection. Temperature, 100·6° F.

At 2 P.M. on this day a further injection of 10 c.c. of serum was administered, the temperature being 99·2° F. In the evening the temperature registered 98·4° F. During the preceding twenty-four hours 44 oz. of urine were passed. This had an acid reaction, and contained a distinct amount of albumen, which, however, had been present before the administration of the serum.

Patient was again seen on the morning of the eighth day, when she stated that, notwithstanding a restless night, she felt tolerably well. There was no change observed in the eruption from the previous day, the impression being that there had been no advance in its development on any part of the body. Inspection of the throat showed a clearing-up of the mucous membrane, the remains of only one or two vesicles being visible. Pulse 64, regular, and of better tension than formerly. The seat of the first injection showed a faint redness, and was slightly tender on pressure. Morning temperature, 97° F.

At 1 P.M. a third dose of 10 c.c. of serum was injected, the temperature being still 97° F. Later it again registered 97° F., and this level was maintained throughout the day. The urine, which contained much less albumen than before, amounted to 64 oz. for the day.

On the ninth day of the attack there were further signs of improvement, and the elements of the eruption on the face showed no advance in their development, while elsewhere, where formerly slightly vesicular, they were observed to be rapidly drying up with the formation of thin superficial crusts. The throat and tongue were clean and moist. Temperature normal. Urine passed amounted to 52 oz., and contained a trace of albumen with some uric acid crystals.

From this time onwards the process of desiccation became generally established and the patient progressed rapidly towards recovery, the albumen disappearing from the urine before dismissal from hospital on the 22nd November, thirty-four days from the commencement of her illness. It is worthy of note in this case that by far the larger portion of the eruption, which was a very abundant one, disappeared in most cases without the papules showing the least tendency to become vesicular.

CASE IV.—Samuel C., æt. twenty-one, carter, admitted on October 26th, 1895, the sixth day of illness. *He had two well-defined foveated vaccine cicatrices on the left arm dating from infancy, and measuring 2·7 square inches.* The initial symptoms

were followed by the characteristic rash, which was first noticed on the third day after sickening. On admission the eruption on the face was found to be copious and in the early stage of vesiculation, while elsewhere it was less abundant and not so far advanced. Temperature, 102·6° F. The throat was deeply injected, and presented an abundant eruption. The lungs yielded a good deal of râle, especially towards the bases behind. Heart-sounds normal. Pulse regular, 100, and of good tension.

At the evening visit 10 c.c. of serum were injected under the skin of the abdomen, the temperature at the time being 103° F.

Next morning, the seventh day of illness, the nurse reported that the patient had spent a restless night, complaining of pain in the throat and abdomen. On examination the former was found to be congested, and the eruptive elements much in the same condition as on admission. There was no evidence of localised irritation at the seat of injection. On the face and forearms the eruption was advancing in quite a typical manner, the vesicles being well-formed, characteristic, and associated with a certain amount of swelling on the face. The patient expressed himself as ill at ease with regard to his general condition and cough. Temperature, 100·2° F. Pulse regular, 98, and of fair tension.

At 1.30 P.M. a further injection of 10 c.c. of serum was administered, the temperature being 100·8° F. Towards evening the temperature rose to 101·8° F., but the pulse continued at 98 and of good tension. The urine passed during the twenty-four hours amounted to 26 oz., had an acid reaction, and contained a trace of albumen.

On the morning of the eighth day the nurse reported that the patient had passed a very restless night and had perspired freely: this latter might have been caused by a dose of Battley's solution administered on account of his restlessness. Pain was still complained of in the throat, which continued injected and studded with eruptive elements. On the face the pocks had a yellow colour, and showed here and there signs of commencing desiccation associated with a moderate amount of œdema and redness. A similar condition of the eruption was present on the forearms and hands. The temperature was 99·4° F.; pulse 92, regular, and of good tension. There was no redness at the seat of the injections. The evening temperature reached 101° F. The urine passed amounted to 47 oz. for the day, was acid in reaction, and still contained a trace of albumen.

The general condition on the ninth day was similar to that noted on the eighth, but desiccation was more advanced. Temperature, 98·4° F. A.M.; 100° F. P.M. The urine (34 oz.) passed on this day contained only a minute trace of albumen.

By the morning of the tenth day the swelling of the face had disappeared, and desiccation of the pocks over the whole body was well advanced and in some parts complete. The throat was much improved. Temperature, 99° F. A.M.; 99·8° F. P.M. Pulse regular, 92, and of good tension. Urine (45 oz.) free from albumen.

From this point the patient progressed steadily towards recovery and was dismissed well, except for some "pitting," on the 4th December, forty-five days from the commencement of his illness.

CASE V.—Mary F., æt. twenty-five, millworker, admitted November 10th, 1895, on the sixth day of illness. *In this patient three or four attempts had been made to vaccinate in infancy but without success, and no cicatricial evidence of vaccination could be discovered.* The prodromata in this case had been severe, the patient complaining specially of pain across the vertex and in the loins. There had been constant sickness and vomiting. The eruption noticed on the second day of the attack appeared first on the face and subsequently became general. The patient was admitted during the night, and on examination presented a copious and somewhat livid eruption of papules on the face, while the extremities and trunk showed a less abundant eruption in different stages of papulation and commencing vesiculation. Everywhere the rash presented hæmorrhagic characters, and in addition to the palpable eruption there were present numerous petechiæ, some bright red and others of a purple colour. The ocular conjunctivæ were the seat of hæmorrhage almost completely surrounding the corneæ, and the mucous membrane of the lips and buccal cavity also presented patches of a hæmorrhagic character. The soft palate showed a somewhat abundant eruption. There was a bloody discharge from the vagina, and the urine was tinged with blood possibly from this source. The temperature on admission was 101·8° F. The heart and lungs were normal.

At the visit on the morning of this day, the sixth of illness, the nurse reported that patient had dozed occasionally, but had had no sound sleep. She had been very sick and had vomited at intervals, the vomited matter containing minute clots of blood. Temperature, 102° F.; pulse regular, 90, but unduly compressible.

At 12 noon, 10 c.c. of serum were injected under the skin of the abdomen, the temperature at the time being 102° F. Towards evening the vomiting ceased, the pulse improved in tension and registered 84 beats per minute, and the temperature fell to 101·2° F. This improvement, however, may have been due to stimulants which were administered freely during the day.

At 11 P.M. a further injection of 10 c.c. of serum was given, and it was noticed that the hæmorrhage from the skin-puncture was more difficult to control than usual. Temperature was now 102° F., pulse, 92. In the course of the day 42 oz. of blood-stained acid urine were passed.

During the succeeding night the patient was restless, but in the morning (seventh day) her general condition presented no marked change. At many points the elements of the eruption seemed to have taken on a more healthy character, the vesicles filling up with clear fluid, though in parts the skin now showed a dark mottling probably due to deep-seated hæmorrhages. The lungs continued free from râle and the heart-sounds were regular and of fair intensity. The buccal mucous membrane and tongue were covered with sordes. Temperature, 100·2 F.; pulse 90, regular, and of moderately good tension.

At 2 P.M. a third injection of 10 c.c. of serum was administered, the temperature being 102° F. Later (6 P.M.) the temperature was 101·2° F., and the pulse-rate 94 per minute. The urine for the day amounted to 38 oz., and was blood-stained.

On the morning of the eighth day the night nurse reported that the patient had been very restless and sleepless in spite of 15 minims of Battley's solution administered overnight. There was also muttering delirium. A cough, evidently due to the throat condition, caused a good deal of disturbance, and fluids showed a tendency to return through the nostrils. The patient expressed herself as feeling weaker. The majority of the elements on the face and elsewhere presented varying degrees of vesiculation, and besides the swelling associated with this, there was an ill-developed papular and petechial rash, giving to the eruption altogether a most unsatisfactory character. The tongue continued foul, and the mucous membrane of the throat closely set with eruption. The ocular conjunctivæ were now elevated above the level of the corneæ as the result of extensive hæmorrhage, and there was a yellow serous discharge from between the lids. Temperature, 103° F.; pulse 108, regular, and of fair tension.

At 12 noon a fourth injection of 10 c.c. serum was given (temp. 102·2° F.). The skin on puncturing had now a more elastic and healthy feeling than on admission, and the last two punctures were not succeeded by the bleeding or subcutaneous ecchymoses which followed upon the first two. During the afternoon and evening of this day the patient was restless, but expressed herself as feeling easy. The temperature was 102·4° F. The urine passed during the day amounted to 75 oz. It contained a little albumen, but was now free from blood.

At the visit on the morning of the ninth day, the nurse again reported a restless night, and stated that the patient had been

mildly delirious and had several times attempted to get out of bed. Her condition was found to be very grave, the pulse being 134, small, and of very low tension; the breathing was rapid, though nothing could be detected in the chest on physical examination; while the eruption and skin generally had the dusky appearance suggestive of a failing circulation. From this time the patient gradually sank and died in the course of the afternoon.

Post-mortem examination made on November 14th, 1895.—The most obvious external appearance presented by the body was a profuse eruption of pocks and petechiæ, the elements of the eruption being overshadowed by the hæmorrhages. The sites of the various injections were marked off on the front of the abdomen by ecchymosed stains. Section of these showed extravasation into the subcutaneous and muscular tissues. The *lungs* were congested, and section of the lower lobes discovered numerous small areas of consolidation, evidently related to the small bronchi. The *heart*, *liver*, *spleen*, *kidneys*, *adrenals* and *ureters* appeared to be normal. Liver weighed 75 oz., spleen, 4¼ oz. The mucous membrane of the *stomach* at its pyloric orifice was markedly injected and showed numerous small patches of submucous hæmorrhage. Elsewhere, except for several congested areas in the large intestine, the intestinal portion of the alimentary tract looked healthy. The contents of the pelvis were normal. A thickly set eruption in the guttural fossa extended into the larynx and trachea, in which latter situations it was associated with a certain amount of superficial necrosis.

CASE VI.—James P., æt. thirty-three, blacksmith, admitted November 11th, 1895, on the fifth day of illness. *He had been vaccinated in infancy, but now presented only one minute vaccine cicatrix too small to be measured.* The prodromal symptoms had been well marked and were followed by a rash on the third day of the attack. On admission a copious eruption consisting principally of papules, with here and there vesicles in an early stage of development, was present on the face, trunk, and extremities. The throat was considerably congested and presented an abundant eruption of pocks. Apart from the discomfort occasioned by the eruption in the throat, patient expressed himself as feeling well. Physical examination of the internal organs was negative. Temperature was 97·4° F.; pulse 88, regular and of good tension.

At 5 P.M. 10 c.c. of serum were injected under the skin of the abdomen (temp. 98·6° F.). Three hours later the temperature was 100° F. During the succeeding night patient slept well, and when seen on the morning of the sixth day of illness the temperature was 99° F., the pulse 98, regular, and of good tension.

There was some soreness of the throat, and inspection showed the tongue to be heavily coated, and the mucous membrane of the palate, fauces and pharynx to present a thickly set eruption. On the skin of the face and forearms the eruption had become vesicular, and a similar condition predominated on the trunk and lower extremities. There was no redness or swelling at the seat of injection.

At 1.30 P.M. a further injection of 10 c.c. of serum was given. Half an hour later the temperature rose 1° F., and remained at this level (100·2° F.) for the rest of the day. The urine passed amounted to 32 oz. for the twenty-four hours. It was acid in reaction and contained a distinct amount of albumen.

On the morning of the seventh day the nurse reported that the patient had spent a restless night. He was at this time slightly delirious but answered questions intelligently. The eruption on the face was now pustulating and there was considerable swelling, the eyes being completely closed, the nose broadened and the lips thickened by the œdema. On the rest of the body the eruption continued mainly vesicular. The throat condition was little changed. Temperature, 101° F.; pulse 108, regular, and of good tension. In the evening the temperature rose to 102·2° F. and the pulse to 124. There were 32 oz. of acid and slightly albuminous urine passed during the day.

When seen on the eighth day of the attack, the eruption was more or less pustular over the whole body, but most markedly so on the face. Temperature ranged about 100·8° F.; pulse (124) maintained a good tension. During this day 22 oz. of distinctly albuminous urine were passed. On the following day crusting commenced, and was accompanied by a decided subsidence of the swelling of the face. Here the pocks had apparently passed through all the phases in quite a typical manner, but elsewhere their development had not been so complete, the course of the eruption being apparently arrested before reaching maturation. There was still an abundant eruption on the throat. Temperature, 100·4° F. A.M.; 101·8° F. P.M. The pulse (124) was of good tension.

On the tenth day desiccation was well advanced on the face and arms, while on the lower limbs and trunk the elements of the eruption, though large, were flat, and not developed so fully as one might have expected. During the preceding twelve hours there had been some diarrhœa, and the motions contained a small amount of blood, and this in the absence of hæmorrhoids or other detectable local causes. The urine passed was small in amount, and contained blood and a considerable amount of albumen. Temperature, 101·6° F. A.M.; 103·4° F. P.M. Pulse continued about 128, and was of good tension. From this time patient's condition gradually improved, the convalescence being

interrupted, however, about the end of the third week by the formation of a few small boils and abscesses. He was dismissed well, except for some "pitting" of the skin of the face, forty-two days from the commencement of his attack.

CASE VII.—Hugh C., æt. 16, store-boy, admitted December 1st, 1895, on the fourth day of illness. *His left arm showed one ill-defined vaccine scar, dating from infancy, and having a superficial area of* 0·28 *square inch.* The prodromal symptoms had been mild, and were followed by an eruption which appeared on the face on the third day. When admitted, the face was studded with a moderately copious eruption of characteristic papules which likewise existed on other parts of the body, where, however, they were more sparsely distributed. The tongue was thickly coated with a white fur, and the fauces and pharynx, in addition to a copious eruption, showed marked congestion. Physical examination revealed nothing noteworthy. The pulse was regular, 80, and of good tension. Temperature 98·6° F.

Shortly after admission—viz., at 4.50 P.M.—10 c.c. of serum were administered subcutaneously. By 8 P.M. the temperature had risen to 102° F., but with this exception no change of any kind could be observed in patient's condition. Next morning he was reported to have had slight delirium in the earlier part of the night. On the face the eruption had advanced to the stage of early vesiculation, and there was redness, with œdema of the skin. A number of fresh papular elements existed on the extremities. There was an absence of any signs of irritation at the seat of the injection. Temperature, 100·6° F.; pulse 88 regular, and of good tension.

At 5 P.M. a second injection of serum (10 c.c.) was given (temp., 101° F.). Three hours later the temperature registered 101·8° F., but apart from this there was no indication of a reaction. During the day 32 oz. of normal urine were passed.

During the sixth day the eruption advanced in its development in quite a typical manner, and by the seventh day the pocks on the face and neck showed distinct evidence of pustulation, while those on the extremities were well advanced in vesiculation. The face was much swollen, the lips being nearly three times their natural thickness, and the eyes were closed. The throat condition was much as already noted. Temperature, 101·8° F. A.M.; 102° F. P.M. The pulse was 102, regular, and of good tension. Urine continued normal, 36 oz. being passed both on this and the preceding day.

The condition on the eighth day was much as noted on the preceding one, but the eruption continued to develop steadily. Temperature, 102·2° F. A.M.; 102·8° F. P.M. The urine passed on this day amounted to 45 oz. and was normal.

On the ninth day the eruption on the face had become fully stustular, and here and there showed slight indications of drying while over the rest of the body the elements were in an earlier Pupular stage, the pocks being fully developed in point of size. patient continued restless and rather sleepless at night. Temperature, 102·2° F. A.M.; 103·2 F. P.M. The pulse was of fair tension. Urine to the amount of 30 oz. was passed.

From this point onwards the course was that of a well-marked case of variola, the eruption becoming mature and desiccating throughout in quite a typical manner, and on the thirteenth day of the attack the crusts commenced to separate from the face. Patient left the hospital on the fifty-sixth day from the commencement of his illness, his face showing some "pitting."

In forming our conclusions, based upon the results obtained in the foregoing cases, it must be borne in mind that, owing to the small number treated by means of "variola antitoxic serum," these are necessarily purely tentative; at the same time we have formed in our own minds, after careful consideration of each case in detail, the opinion that in no single instance did the treatment as employed by us modify the disease. The records of Cases III. and VI. certainly show a decided modification of symptoms, Case III. being especially striking in this respect, only a very few of the elements of the eruption, as already stated, becoming even vesicular; but the experience of every physician dealing largely with small-pox must recall many instances of cases in which an eruption, extremely abundant on every part of the body, has become similarly aborted in its early vesicular stage. While this result might be claimed for the treatment, we would point out that in both cases the course of the attack was presumably already modified by vaccination performed in infancy. In fact, vaccination, either alone or associated with comparative insusceptibility in the individual, would seem, under certain circumstances, to vary in its modifying influence upon the small-pox attack; sometimes, as in Case III., manifesting little tendency to reduce the number of eruptive elements, but cutting short their development at an early stage; while in others, as in Case II., the modifying influence is indicated by a great reduction in the number of pocks, which may either run only a short course or develop in a tolerably typical manner. Therefore, while not prepared to express any opinion as to what part is played by vaccination and what by

comparative insusceptibility in the individual, we have no doubt in our own minds that, judging from our past experience, the treatment had little to do with our results.

One of two explanations might be offered to account for the negative character of the results obtained by us, (1) that so-called "variola antitoxic serum" contains no substance antidotal to the toxin of small-pox, or (2) that it contains its active principle in such small amount that the doses administered were much too small to exert any appreciable influence on the course of the disease. The experiments on animals, quoted in the earlier part of this paper, would seem to indicate that the second of these is the more likely explanation. As our observations were carried out on the lines followed by the American physicians referred to, the average dose of serum administered did not exceed 10 c.c., repeated at varying intervals, and in no instance did a patient receive a total of more than 40 c.c., nor was the initial dose given earlier than the fifth day of the attack.

The important communication [1] by Béclère and his colleagues (18) appeared after the completion of our own observations, and the evidence furnished by their experiments would seem to prove conclusively that to get any important modifying influence exercised upon small-pox by serum taken from an animal immune to vaccinia, we must administer the serum in relatively large doses, possibly in an adult to the extent of 25 or 30 oz. at least. In marked contrast to the dose employed by ourselves and the American observers already quoted, was that given to a variolous patient cited in the paper just referred to. In this case more than 1·5 litres of serum were given hypodermically on the third day of the eruption without causing any local or general inconvenience. The patient made a rapid recovery.

Judging from the results obtained by recent observers in their experiments upon bovine animals, it seems reasonable to entertain the hope that in the serum of animals rendered immune to vaccinia we may have a new prophylactic as well as a therapeutic agent available for use in the case of persons exposed to small-pox infection but coming under the notice of the sanitary authorities at too late a period after exposure, say

[1] Entitled "Études sur l'immunité vaccinale et le pouvoir immunisant du serum de génisse vaccinée."

after the fifth or sixth day, for vaccination to be carried out with any likelihood of its modifying the course of a subsequent attack of small-pox. The rapidity with which immunity is conferred by the subcutaneous injection of immunised serum of calves and heifers would render this highly probable.

Further and careful experiments as to the prophylactic and therapeutic value in small-pox of the serum of animals immune to vaccinia is urgently required, and it is matter for regret that opportunities for the furtherance of observations on the lower animals in such an important matter as this are not afforded by those who have under their charge the health of our great communities.

REFERENCES.

1. *Bull. de l'Acad. de méd.*, 1866. 2. *Comptes rendus de l'Acad. des Sciences*, 1877, tome lxxxiv., p. 453. 3. *Bull. de l'Acad. de méd.*, 1878, p. 878. 4. *Revue de méd. et de chirurgie*, April 1877. 5. *Die Vaccination*, 1884, p. 13. 6. *Société de biologie*, December 20, 1890. 7. Trans. Assoc. Amer. Phys., 1892, p. 98, and see also "Immunity and Serum-Therapy," p. 228. 8. *Deutsche med. Wochenschr.*, 1893, p. 547. 9. Trans. Epidem. Soc., vol. xii., 1893. 10. *Deutsche med. Wochenschr.*, 1893, p. 1061. 11. *Brit. Med. Jour.*, 1893, vol. ii., p. 989. 12. *Zeitschrift f. Hygiene*, Bd. 18, 1894, pp. 318-326. 13. *Jahrb. f. Kinderheilk.*, Bd. xxxvii., 1894. 14. Quoted by Rembold, and by Béclère, Chambon and Ménard. 15. *Centralbl. f. Bacteriolog. u. Parasitenkunde*, xviii., p. 119. 16. *Berlin. klin. Wochenschr.*, 1895, p. 735. 17. *Wien Klien. Rundschau*, October 6-13, 1895. 18. *Annal. de l'institut Pasteur*, 1896, tome x., p. 1. 19. Abst. of Sanitary Reports, Marine Hospital Service, 1894, vol. x., p. 31, and see also *Philadelphia Med. News*, Feb. 2, 1895. 20. *Brooklyn Med. Jour.*, 1895, vol. ix., p. 425. 21. *Med. News*, June 29, 1895.