present, as far as my experience goes, and is one of the last symptoms to disappear as the patient recovers. Its disappearance is a good sign, its reappearance is an indication of a recrudescence of the disease.

Unfortunately the disease is very treacherous, and recrudescences or relapses are very liable to occur.

The rashes are very useful aids to diagnosis.

1. The pink spots are not unlike those of typhoid, but are not usually raised. They are more frequently found on the back and about the joints.

2. Pressure erythema is almost invariably present after the first few days, occurring on the part of the body exposed to pressure.

3. *Tache méningitique* is always present, usually well marked.

3A. Three of these cases had urticaria; Cases II and IV severely, and Case III only slightly.

4. Herpes occurred in Cases II and IV.

5. Haemorrhagic eruption occurred only in Case I. This is sometimes very evident.

Hyperaesthesia is sometimes very marked, at other times it is absent. In only two (Cases III and IV) was it present, and then only for a few days, and only well marked in Case IV.

Photophobia was also present in Cases III and IV, but only slightly for a short period.

The temperature in this disease is by no means constant; in fact, its irregularity is characteristic. A high temperature is generally found at the onset, but a fall is only a good sign if it remains below normal for several days.

The joint affection which occurred in Case IV is a fairly frequent complication of the disease, but the attack of nephritis which occurred in the same patient is an unusual one. Both these conditions are due to the diplococcus or its toxins.

Treatment.

As stated, these cases were treated by lumbar puncture together with injections of antimeningococcic serum. Previously I have had some cases recover with lumbar puncture alone, and I am confident that it is a most valuable aid to the patient's recovery. On this account on every occasion when a lumbar puncture has been performed as much fluid as possible has been withdrawn without applying suction, and even as much as 2 to 3 oz. has been withdrawn.

In the early summer of 1914 I had a lad of 19 in my wards at the Liverpool Stanley Hospital suffering from cerebro-spinal meningitis. He progressed most satisfactorily for about five weeks under the treatment of lumbar puncture alone; indeed, so well did he progress that, though the advisability of giving serum was considered, it was decided that it was unnecessary. Suddenly, however, a recrudescence occurred, his temperature rapidly rose, he became comatose, and died in a few hours. Having this case fixed in view, the treatment in these four cases has been that of lumbar puncture *plus* antimeningococcic serum, and the result has been eminently satisfactory. There is no doubt that the serum has been beneficial in its effects; the symptoms abated more rapidly and constantly. In nearly all instances the puncture has been made under local anaesthesia (ethyl chloride spray), and the injection given by an ordinary serum syringe, the serum being injected very gradually. It has been noticeable that patients invariably complain of pains in the legs if the injection is hastened. There is occasionally some numbness in the legs after injection, but this passes off in about half an hour.

The pulse throughout the injection was always good, and the necessity of taking blood pressure was never evident. At the first injection 20 to 30 c.cm. of serum are generally given, and daily doses of 15 to 20 c.cm. for the following three or four days. After an interval of about three days another injection is given, and further injections at intervals if the cerebro-spinal fluid still shows the diplococcus, and Kernig's sign still remains marked, or the temperature still shows a tendency to spiking. Daily injections appear necessary so long as the cerebro-spinal fluid remains turbid; and even when the fluid becomes clear and shows no diplococci, persistent Kernig and irregularity of temperature are, in my opinion, indications for further injections at intervals.

The importance of prophylaxis cannot be over-estimated. In all cases, disinfection of billets, and the isolation of

contacts, and the treatment of their naso-pharynx by an antiseptic spray, was rigorously carried out. Naso-pharyngeal swabs were taken and examined for the diplococcus in all contacts, and isolation of contacts was persisted in for twenty-two days, and it is gratifying to report that no case of the infection has been reported from these four cases.

Since this paper was prepared for press Case II had a further recrudescence, and died on April 2nd; the other cases are convalescent.

FURTHER REMARKS ON THE MIXED TYPHOID + PARATYPHOID A + PARATYPHOID B VACCINE.

BY

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So many inquiries have recently reached me concerning the mixed typhoid + paratyphoid A + paratyphoid B vaccine—especially on its preparation—that a further note on the subject will perhaps be found useful.

First of all, as regards the amount of immunization induced, the technical method of preparation of typhoid vaccines is—within limits, of course—not, in my experience, of paramount importance: vaccines killed by heat or by various chemicals may be used; or live attenuated vaccines, sensitized vaccines, etc., with almost equally satisfactory results. The important point is that, whatever the method of preparation, the antienteric vaccine should not be a simple typhoid vaccine, but should contain the three species of germs—typhoid, paratyphoid A, and paratyphoid B.

The simplest and most practical types of the mixed typhoid-paratyphoid vaccine, are, according to my researches, the following two:

1. Dead mixed vaccine, with germs killed by heat.
2. Dead mixed vaccine, with germs killed by carbolic acid.

I have described in detail the technique of preparing them in previous papers,¹ but it may be here again briefly summarized.

Mixed Vaccine (Heated).

This is a mixture of the three vaccines—typhoid, paratyphoid A, and paratyphoid B—each of which is prepared according to the technique used by Wright and Leishman in the preparation of their simple typhoid vaccine.

1. Prepare broth cultures of *B. typhosus*, broth cultures of *B. paratyphosus* A, and broth cultures of *B. paratyphosus* B, from recent agar cultures, inoculating two normal loopfuls per tube, into tubes containing 10 c.cm. of broth.

2. Incubate at 37° C. for eighteen hours.

3. *Standardization*.—Count the number of bacilli by using a Thomas-Zeiss blood counter, and, by dilution, bring the number down to approximately 1,000 millions per cubic centimetre.

4. If the germs are very motile they are immobilized, as done by Leishman, by adding a trace of formalin. Keep the standardized cultures at 53° C. for an hour in a water bath. Leishman has shown that 53° C. is the minimal thermal death point for typhoid bacteria, and that the lower the temperature at which the germs are killed the greater is the immunizing power of the vaccine.

5. Mix in the following proportions:

Typhoid	...	...	...	2 parts
Paratyphoid A	...	...	...	1 part
Paratyphoid B	...	...	...	1 "

To this mixture, when cooled, add 0.25 per cent. lysol, and shake thoroughly. Twelve hours later inoculate some agar slopes to test for sterility. The mixed vaccine will contain per cubic centimetre:

Typhoid	...	...	...	500 million
Paratyphoid A	...	...	...	250 "
Paratyphoid B	...	...	...	250 "

Of this vaccine 0.5 to 0.6 c.cm. is inoculated subcutaneously in the arm the first time, and the second time,

a week later, 1 to 1.2 c.cm. If a third inoculation be possible the same dose as the second may be given two weeks after the first.

Carbolized Mixed Vaccine (Not Heated).

Agar cultures twenty-four hours old are used. The growth of the typhoid agar cultures is washed off with sterile 0.85 per cent. salt solution, to which 0.5 per cent. carbolic acid has been added; the emulsion so obtained is stored at room temperature (18° to 20° C.) for twenty-four hours and then tested for sterility* and standardized. To standardize it the germs are counted by using a Thomas-Zeiss apparatus, and sufficient carbolic salt solution is added to bring the number of germs down to 1,000 millions per cubic centimetre. The standardized emulsion is again tested for sterility. The same procedure is carried out with paratyphoid A and paratyphoid B cultures, these two emulsions being also standardized to contain 1,000 million germs per cubic centimetre. The three standardized emulsions, when found sterile, are mixed together in the following proportions:

Typhoid	...	...	...	2 parts
Paratyphoid A	...	...	...	1 part
Paratyphoid B	...	...	...	1 "

The mixed vaccine will therefore contain per cubic centimetre:

Typhoid	...	...	...	500 million
Paratyphoid A	...	...	...	250 "
Paratyphoid B	...	...	...	250 "

Of this mixed vaccine 0.5 to 0.6 c.cm. is given under the skin of the arm the first time, and 1 to 1.2 c.cm. the second time, a week later. It produces, perhaps, a slightly less severe reaction than the heated broth vaccines.†

Experimental Work on which the Preparation of Mixed Vaccines is Based.

The preparation of the typhoid + paratyphoid A + paratyphoid B vaccine, as well as other combined vaccines, is based on the experimental work I carried out in 1901-1902 in Professor Kruse's laboratory,² when I was able to demonstrate that if an animal (rabbit) were inoculated with two or three species of bacteria agglutinins and immune bodies for all the germs were elaborated, provided a sufficient minimum quantity was given, the amount of agglutinins and immune bodies elaborated for each germ being nearly the same as in control animals inoculated with only one species. I demonstrated also that when immunization is obtained by a single inoculation the amount of agglutinins and immune bodies elaborated is not in proportion to the amount of cultures injected, provided a sufficient minimum dose be used. A series of rabbits inoculated with 2 c.cm. of typhoid culture will give the same average agglutination limit and the same amount of immune bodies as a series of rabbits inoculated with 4 c.cm. In rabbits no good results are obtained, as a rule, by inoculating more than three species of bacteria; in man, however, certain vaccines containing four species of germs (tetravaccines)—as, for instance, typhoid + paratyphoid A + paratyphoid B + cholera—may give good results.³ In fact, I have used with good results a vaccine containing five species of germs: Typhoid + paratyphoid A + paratyphoid B + cholera + plague.⁴ In most cases, however, when more than four species are used, protective substances are apparently developed for three or four species only, and may suddenly disappear.

Objections Made to the Use of the Mixed Vaccine.

The usual objection raised against the use of the mixed vaccine (typhoid + paratyphoid A + paratyphoid B) is that it will probably give a much smaller amount of immunization than simple typhoid vaccine, and that paratyphoid A and B, being diseases of less importance than true typhoid, it would be a mistake to run such a risk. This belief is

* In some rare cases, when the emulsion is very thick, this period of time (twenty-four hours) may not be sufficient for the small amount of carbolic present to sterilize it completely; the germs, however, will be non-motile, easily counted, and the addition of the amount of carbolic salt solution necessary to standardize the vaccine to 1,000 millions per cubic centimetre will quickly kill all the germs.

† The mixed vaccine (both types) is prepared according to my instructions at the Serum Institute of Berne (Switzerland) since 1913. It is also prepared now at the Instituto di Patologia Generale of the Royal University of Naples.

not supported by the experiments quoted above. I would also call attention to the tables I published in the *BRITISH MEDICAL JOURNAL*, 1913, vol. ii, p. 1577,⁵ in which I collected, with the assistance of Mr. E. Burgess, the results—as regards agglutinins—of the examination of the blood, carried out regularly for many weeks, of individuals inoculated with simple typhoid vaccine, simple paratyphoid A vaccine, and simple paratyphoid B vaccine, in comparison with individuals inoculated with the mixed typhoid + paratyphoid A + paratyphoid B vaccine.

The individuals inoculated with simple typhoid vaccine, those with simple paratyphoid A vaccine, and those with simple paratyphoid B vaccine had two injections at one week's interval—0.5 to 0.6 c.cm. the first time and 1 to 1.2 c.cm. the second time, the vaccines containing 1,000 millions per cubic centimetre. The individuals inoculated with the mixed vaccine had two injections at one week's interval—0.5 to 0.6 c.cm. the first time and 1 to 1.2 c.cm. the second time. The mixed vaccine contained per cubic centimetre—

Typhoid	...	...	...	500 million
Paratyphoid A	...	...	...	250 "
Paratyphoid B	...	...	...	250 "

These individuals, therefore, had only half the amount of the typhoid germs and a quarter the amount of the paratyphoid germs inoculated in the control individuals injected with simple "one disease" vaccine. Still, the figures collected in the tables clearly show that in individuals inoculated with mixed vaccine the amount of agglutinins developed for each germ was nearly the same as in the control individuals inoculated with typhoid vaccine only, paratyphoid A vaccine only, and paratyphoid B vaccine only.

Conclusion.

The mixed typhoid + paratyphoid A + paratyphoid B vaccine may be prepared according to various methods. The simplest mixed vaccine consists of an emulsion of typhoid + paratyphoid A and B bacilli killed by heat, or by adding $\frac{1}{2}$ per cent. carbolic without heating, and standardized so that 1 c.cm. contains approximately 500 million of typhoid bacilli and 250 million each of paratyphoid A and B. Of this vaccine, 0.5 to 0.6 c.cm. is given the first time, and 1 to 1.2 c.cm. the second time, a week later. The mixed vaccine is harmless, does not give a severer reaction than simple typhoid vaccine, and the inoculated persons develop protective substances for the three diseases.

In my opinion, as I have stated in all my previous publications on the subject,⁶ in countries where in addition to typhoid, paratyphoid A and B occur, the mixed vaccine should be used as a matter of routine instead of the simple typhoid vaccine. This has been done in Ceylon since 1905 with good results.

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- 4 *Journal Ceylon Branch British Medical Association*, October, 1914.
- 5 Also in the *Indian Medical Gazette*, 1913, and the *Cent. für Bakt.*, 1914, Bd. 72, p. 536.
- 6 See *BRITISH MEDICAL JOURNAL*, 1913, vol. ii, p. 1577, etc.
- Castellani: *Zeit. für Hygiene*, 1902, p. 1; *Ceylon Med. Reports*, 1904 and 1905; *Cent. für Bakt.*, 1900; *Transactions Bombay Medical Congress*, 1909; *BRITISH MEDICAL JOURNAL*, 1913, vol. ii, p. 1577; 1914, vol. ii, p. 814; 1915, vol. i, p. 446; *Indian Medical Gazette*, 1913; *Cent. für Bakt.*, 1914, Bd. 72, p. 536; *Journal Ceylon Branch, British Medical Association*, 1914; *Sperimentale*, 1915.
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DR. E. BALLERINI, President of the Order of Medical Practitioners of Rome, in transmitting to Professor Jacobs a sum of money subscribed by them in aid of their Belgian brethren, apologizes for the smallness of the amount, which is explained by the demands on the doctors of Rome by the sufferers from the recent earthquake. He asks that it may be accepted as a sign of their affection for their colleagues in Belgium; as a proof of sympathy with them in the misfortunes which have fallen upon them; and as an expression of their fervent hopes for the resurrection of their heroic country. Professor Jacobs in acknowledging the gift says: "The hope of seeing ourselves one day free again remains fixed in our hearts. We shall fight to the death, but never as long as there remains a Belgian alive shall the hateful invader be able to boast that he has annihilated us. Robbed, yes! murdered, yes! burnt and pillaged, yes! conquered, never!"