cases of ovarian tumour required section before the ovarian cyst could be disimpacted and removed. Tapping such a tumour by the vagina does not commend itself owing to doubt as to its exact nature. It was quite out of the question to push the tumour past the presenting part.

Cervical and Vaginal Stenosis.—A patient with cervical stenosis showed signs of obstructed labour, the os was closed, rigid, and difficult to reach. She had been twice curetted. A number of these cases met with have responded to incision of the fibrous ring, but this was not possible here. The vaginal stenosis could not be explained. An elderly multipara with a ring of contraction below the cervix was watched carefully in the later months of pregnancy and early in labour, but as the ring showed no relaxation a Caesarean section was performed.

Eclampsia (two cases).—Both cases had in addition marked pelvic contraction, and obstructed labour. One died later from sloughing of the lower uterine segment; the baby was dead. The other had a fit on the table and was operated on while unconscious; an anaesthetic was given when stitching up. Both she and the baby survived.

THE BACTERIOPHAGE IN THE TREATMENT OF TYPHOID FEVER.

BY

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THE value of the administration of bacteriophage in the treatment of organismal infections in man has not yet been definitely established. *In vitro* the bacteriolytic principle, whether it be due to an ultramicroscopic living virus or some other property associated with organismal life, has a very marked effect on susceptible bacteria.

The extensive work of d'Herelle (1922)¹ has shown that the spread of avian typhoid and paratyphoid can be controlled and actual cases may, in some instances, be cured by the subcutaneous injection of a small dose of bacteriophage active for *B. gallinarum* and *B. pullorum*. In human beings affected with typhoid and dysentery d'Herelle (1922)² has demonstrated repeatedly that a very active bacteriophage can be isolated from the faeces when convalescence commences. He has also treated seven cases of dysentery by giving 2 c.cm. of bacteriophage by mouth, and apparently obtained good results. Bruynoghe and Maisin (1921)³ have treated with success infections due to the staphylococcus and *B. anthracis* by subcutaneous injection of suitable bacteriophage. Beckerich and Hauduroy (1922)⁴ have treated seven cases of typhoid fever and two cases infected with *B. paratyphosus* B by giving 1 c.cm. of a culture of active bacteriophage subcutaneously and 2 to 5 c.cm. by mouth. From all these cases the infecting organisms were isolated from the blood forty-eight hours previous to the administration of bacteriophage. In every case defervescence took place within forty-eight hours.

Methods.

The bacteriophage employed in the treatment of cases of typhoid fever was isolated from the faeces of a normal individual who never had an intestinal infection. It was obtained by the technique devised by d'Herelle.

Five grams of faeces were added to 50 c.cm. of broth (pH 8.0) and incubated overnight. The broth was centrifuged to remove all coarse material, and the supernatant fluid was afterwards passed through an L₁ Chamberland candle; 2 c.cm. of the filtrate were then added to tubes containing 10 c.cm. of broth. Young agar cultures of strains of the coli-typhoid-dysentery group were now suspended in broth. Sufficient of each suspension was added to the broth tubes to give a turbidity corresponding to that in a standard tube containing 250 million bacilli per cubic centimetre. After a further period of incubation various degrees of turbidity were noted in the tubes. The broth tubes were now subcultured on to agar slopes, and after incubation the presence of plaques definitely indicated the activity of the bacteriophage culture for a particular strain.

A bacteriophage showing some power to cause lysis of *B. typhosus* having been obtained, its virulence was enhanced by filtering the broth culture through a bacterial filter and adding five drops of the filtrate to another broth tube along with a suspension of *B. typhosus*. The second

broth culture was then incubated and afterwards filtered. By repeating this process fifteen times a bacteriophage of such virulence was obtained that it produced lysis in a broth culture of *B. typhosus* in from three to four hours.

In investigating the following cases, the faeces of the patient were examined for bacteriophage previous to the administration of the bacteriophage culture, and again twenty-four hours after administration. Thereafter the faeces were examined every second day, so far as was possible, for bacteriophage. The activity of the bacteriophage isolated from the cases was tested against the stock strain, and in the charts the degrees of virulence are thus expressed:

- 0 = No bacteriophage obtained.
- + = Bacteriophage of slight virulence as shown by a few plaques on the agar slope.
- ++ = More numerous plaques.
- +++ = Still more numerous plaques of bacteriophage.
- ++++ = No growth on agar slope or only a few discrete colonies of *B. typhosus*.

CASE I.

A female, aged 58 years, was admitted to hospital eighteen days after falling ill. On admission she had no acute symptoms. The bacteriological examination showed that the blood serum agglutinated *B. typhosus* in a dilution of 1 in 240. No typhoid bacilli were obtained from the blood and urine, but the faeces contained

FIG. 1.—Case I.

B. typhosus. No bacteriophage was found in the faeces active for the stock strain or the patient's own strain. Six days after admission the patient was given 0.5 c.cm. of bacteriophage culture subcutaneously and 2 c.cm. by mouth. The temperature then subsided, and twelve further examinations of the faeces and urine were made, with negative results for *B. typhosus*.

CASE II.

A. W., a male aged 38 years, was admitted after being ill for three weeks. *B. typhosus* was not obtained from the blood or urine, but the faeces showed numerous colonies on McConkey plates. The blood serum agglutinated *B. typhosus* in a dilution of 1 in 120. There was no bacteriophage in the faeces active for the stock strain

FIG. 2.—Case II.

or the patient's own strain of *B. typhosus*. On the day after admission 2 c.cm. of bacteriophage culture were given subcutaneously and 15 c.cm. by mouth. Thereafter the temperature became normal, and nine further examinations of the faeces and urine did not show *B. typhosus*.

CASE III.

A. D., a female aged 11 years, was admitted in a moderately ill condition after having been confined to bed at home for two weeks. The blood serum agglutinated *B. typhosus* in a dilution of 1 in 120. *B. typhosus* was not found in the blood, urine, or faeces,

FIG. 3.—Case III.

and the faeces did not contain bacteriophage. Twenty-four hours after admission the patient received 2 c.cm. of bacteriophage culture subcutaneously and 15 c.cm. by mouth. Convalescence was uneventful. The faeces were examined twelve times and the urine ten times, with negative results for *B. typhosus*.

CASE IV.

E. S., a female aged 8 years, had been ill for two weeks before admission. *B. typhosus* was found in the faeces, but not in the blood or urine. The Widal reaction was negative. The patient's faeces showed the presence of bacteriophage which was only slightly bacteriolytic for the stock strain and the patient's own strain. Bacteriophage culture was given subcutaneously and by mouth, and

FIG. 4.—Case IV.

the patient became afebrile. Seven days later, however, there occurred a slight rise above normal in the temperature. A blood culture remained sterile and thereafter the patient made excellent progress. Subsequent to the administration of bacteriophage the faeces were examined eighteen times and the urine nineteen times, but typhoid bacilli were not found.

CASE V.

A. W., a female aged 20 years, was admitted after having been ill for ten days. The bacteriological examination showed that

FIG. 5.—Case v.

B. typhosus was present in the blood, the urine, and the faeces. The faeces did not yield a bacteriophage active for *B. typhosus*.

The day after admission the patient received 2 c.cm. of bacteriophage culture subcutaneously and 15 c.cm. by mouth. No immediate lysis occurred, but the patient made an uneventful recovery. The faeces were found to contain typhoid bacilli forty-eight hours after the administration of bacteriophage, but fifteen further examinations of the faeces and urine gave negative results for *B. typhosus*.

CASE VI.

J. S., a male aged 20 years, was admitted after being ill for ten days. The Widal reaction was negative and *B. typhosus* was only found in the blood. No bacteriophage active for *B. typhosus*

FIG. 6.—Case vi.

was obtained from the faeces. The patient received 2 c.cm. of bacteriophage culture subcutaneously and 15 c.cm. by mouth. Nineteen subsequent examinations of the faeces and urine proved negative for *B. typhosus*.

CASE VII.

G. W., a female aged 36 years, was admitted after having been in bed at home for nine days. The bacteriological examination showed that the patient's blood serum agglutinated *B. typhosus* in a dilution of 1 in 240. The blood culture remained sterile and no organisms were present in the urine at the first examination.

FIG. 7.—Case VII.

B. typhosus was found in the faeces, but no active bacteriophage was present. The bacteriophage was given subcutaneously and per os, and the patient's temperature fell by lysis immediately, but the course of the disease was complicated by an infection of the urinary tract. The urine showed the presence of many pus cells and *B. typhosus*. On two more occasions 4 c.cm. of bacteriophage were given subcutaneously, but this had no apparent effect on the infection of the urinary tract. Eventually the urine became sterile a month after the date of admission.

Discussion of Results.

The results in these seven cases of typhoid fever treated with bacteriophage are of considerable interest. In five there occurred an immediate lysis after the administration of bacteriophage. The type of the disease, the stage of the illness, and the provision of hospital treatment may, however, be sufficient to explain this. It falls to be noted also that these five cases yielded sterile blood cultures. In the two remaining cases, in which the blood culture showed the presence of *B. typhosus*, the bacteriophage had apparently no effect in modifying the course of the disease. The strains of *B. typhosus* obtained from the blood, from the urine, and from the faeces of the various patients were equally susceptible to the bacteriophage *in vitro*.

In the faeces of only one case a bacteriophage of slight virulence for *B. typhosus* was isolated previous to the administration of bacteriophage. Within twenty-four hours of administration, however, an extremely virulent bacteriophage was obtained from all patients. Coincident with the presence of an active bacteriolytic agent in the faeces there occurred a rapid disappearance of *B. typhosus* from the faeces of six out of the seven patients. The course of one case (Case VII) was complicated by an infection of the urinary tract due to *B. typhosus*, and on several occasions when the faeces were obviously contaminated with urine *B. typhosus* was found. A sample of the urine obtained from this case within the first twenty-four hours after the administration of bacteriophage was examined for the presence of bacteriophage, but no active bacteriolytic agent could be demonstrated. The case had repeated subcutaneous injections of bacteriophage, but this did not apparently influence the typhoid bacilli present in the urinary tract. The disappearance of the bacteriophage from the faeces coincides very closely with defervescence except in Case VII, who had repeated doses of the lytic agent. The administration of bacteriophage subcutaneously and by mouth has so far proved to be a perfectly harmless procedure.

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THE PRECIPITATION OF CRISIS IN THE TREATMENT OF PNEUMONIA.*

BY

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THE hypothesis is accepted that pneumonia, either secondary to influenza or primary from so-called chill, is a manifestation of a suddenly lowered resistance to a germ or germs, normally present in the respiratory tract, which, in consequence of that lowered resistance, suddenly become pathogenic.

In 1922 I published with Dr. James Graham Willmore¹ a paper founded on observations made in the 17th General Hospital in Alexandria in 1918 and 1919 during the great pandemic of influenza and towards its close. We based our treatment on the fact that the white cell blood count of cases of influenza is low and remains low after the fever has ceased and for about five days after that, after which there is a sudden reactionary increase, usually about the tenth day of the disease and the fifth day of convalescence.

It is during this period of depression and lowered resistance, the result of or the cause of the leucopenia, that the danger of secondary infection exists, and we showed that an injection, either subcutaneously or intramuscularly, of sodium nucleinate in solution precipitates the reactionary increase of white cells in the peripheral circulation and so reinforces the patient's resistance. Sodium nucleinate, given in this way, greatly increases the white blood count whether the patient has a leucopenia or not, and in a normal individual it about doubles the white cell count in twenty-four hours. In cases of marked leucopenia in severe influenzal pneumonia counts have been seen to rise from 3,200 to 18,300 three days after a nuclein injection, with corresponding improvement in the patient's condition from a practically moribund state to one of convalescence in the same period. The toxic symptoms of many of the cases suggested an acidosis, and intensive doses of sodium bicarbonate were given either by mouth, bowel, or intravenous injection, together with glucose in the food or by bowel.

The success which attended our efforts in the pandemic

period was so marked that when I returned to general practice I invariably treated all cases of pneumonia on the same lines, with what I believe is an equally satisfactory result—that is, in every case of definite lobar pneumonia so treated a crisis has occurred about forty-eight hours or so after the first dose of sodium nucleinate was given, no matter what day of the disease it was administered.

I have not made a regular practice of making blood counts in all my private patients, but in those cases in which I did I found the white count little more than normal with the patient seriously ill from pneumonia.

The Egyptian cases were 32 in number and cover a period of some six weeks only; they are not selected, but only one of us kept records, so that at least double that number were similarly treated within that period. The English cases consist of 21 consecutive cases over a period of three and a half years. Records of 53 cases in all have therefore been kept, all of which responded to treatment except 8. All the patients were seriously ill, all had pneumonia, all had definite lobar consolidation except 7 cases of bronchopneumonia, nearly all had blood-stained sputum; this often appeared after the so-called crisis, indicating that the severity of the disease was arrested early. Many showed signs of acid toxæmia. All were treated as above described with sodium nucleinate injections. Most of them had as much as half a drachm of sodium bicarbonate every four hours; some had a full drachm. Those who had purulent sputum had an emulsion of creosote and potassium iodide. Cardiac and respiratory stimulants were given if indicated.

Of the 8 fatal cases, 2 were of patients with bronchopneumonia; the other 6 were war-worn soldiers in the pandemic period; 4 had nephritis to a marked degree which was not recent. All were in a very toxic condition on admission to hospital. Two were proved to have white blood counts under 4,000; one was as low as 1,900. Four had no special alkaline treatment, as they occurred before we appreciated its value, and therefore really ought not to be included in this series. One had dysentery and two had malaria.

Three of the patients who suffered from lobar pneumonia relapsed, sustaining a fresh invasion of lung area, but in all the temperature fell again by crisis within forty-eight hours after a further injection of nuclein. All the English cases of lobar pneumonia responded to treatment and recovered.

It will be seen that the cases of bronchopneumonia did not respond so typically as did those of the lobar type. They fell by lysis rather than crisis. It will be seen also that, if we eliminate from the series all the cases of bronchopneumonia and also all the cases which did not receive intensive alkaline treatment, we also eliminate all the fatal cases but two, which were moribund on admission, and had chronic conditions of nephritis before contracting pneumonia.

I do not for one moment claim that all these cases would not have recovered with ordinary expectant treatment, but I think it is at least worthy of note that in all the cases here reported of lobar pneumonia, fully treated, the patient's condition began to improve at once after the nuclein injection, that all of them experienced a sense of well-being the next day, and that in every case the crisis occurred from forty-eight to sixty hours after the first injection of sodium nucleinate.

The preparation used for intramuscular injection is a solution of sodium nucleinate put up by the Clin Laboratories of Paris in ampoules of 2 c.cm., containing 0.05 gram per cubic centimetre. The British agents are F. H. Mertens, 64, Holborn Viaduct, London, E.C.1.

The accompanying diagram shows the length of fever of forty successful cases of lobar pneumonia. The vertical lines represent the duration of the pyrexia, and the horizontal lines the nuclein injection, showing that the effect of the treatment in precipitating devolution is independent of the duration of the illness. In the three charts the heavy black line represents the temperature, while the dotted line represents the white cell count, the normal count of about 7,000 corresponding with the line of normal temperature. The leucocytic increase will be seen to be coincident with

* A paper read before the Liverpool Medical Institution, April 3rd, 1924.