

Both these fractions consist of nucleoprotein. Fraction E. is relatively stable, but Fraction D. is very easily broken down into simpler substances, and even slight increases in the pH of the solutions are capable of bringing this change about. It was found almost impossible to maintain the exact pH of the neutralised sodium bicarbonate solution owing to loss of CO₂ with slight rises of temperature or even rough handling. This is the cause of the varying potency of the D. fragment. In regard to the bacterial fragments it would seem that the less the protein complex is broken up, the greater is its antigenic power. This is also shown by the larger moleculised globulin fraction having a greater antigenic power than the smaller moleculised albumin fraction.

PREPARATION OF ALBUMIN AND GLOBULIN FRACTIONS (GOUGH, 1933)

Twenty litres of a 24-hour culture of hæmolytic streptococci, grown in glucose phosphate broth, was centrifuged and the deposit desiccated over concentrated sulphuric acid in vacuo for two days. The dried organisms were then transferred to a ball mill and ground until no intact organisms could be seen in a stained smear.

The contents of the ball mill were then extracted with 500 c.cm. of distilled water by shaking for 2-3 hours and then centrifuged and the supernatant fluid removed. The deposit was again shaken with 200 c.cm. of water and recentrifuged, and the supernatant fluid removed and added to the first fluid. This was repeated until only a little insoluble material was left. The supernatant fluids were then saturated with ammonium sulphate. After a short time a curd appeared, consisting of the precipitated proteins. The whole was filtered and the curd saved. This greyish curd was washed into about 100 c.cm. of distilled water, shaken vigorously, and refiltered. This process was again repeated, and the filtrate was then half saturated with ammonium sulphate. A white flocky precipitate formed; the whole was centrifuged and the precipitate, the globulin fraction, was dissolved in a minimal amount of water. The supernatant fluid was completely saturated with ammonium sulphate, and the precipitate, the albumin fraction, was redissolved in a minimal amount of water. Both the globulin and albumin fractions were dialysed in collodion sacs until no more ammonium sulphate was present.

We are indebted to Dr. D. N. Nabarro, director of the pathological department at the Hospital for Sick Children, for his help and encouragement in these researches. Our thanks are also due to Dr. C. R. G. Barrington and the nursing staff at West Wickham for their valuable assistance, and to Mr. G. W. Cecil for his technical aid.

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BIRMINGHAM GENERAL HOSPITAL.—A further financial improvement is to be noted in the report of this hospital. The contributory association has increased, and not only has ordinary expenditure been met out of ordinary income, but a large proportion of extraordinary expenditure has also been provided from the same source. Substantial legacies have made it possible further to increase the reserves. The income was £86,482, as against £82,026 in the previous year, and the number of in-patients was 8369 (an increase of 63 on last year). The total number of new out-patients was 59,400, as against 56,459 in 1933.

CLINICAL TRIALS WITH A NEW ANTITYPHOID SERUM

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In September, 1934, a new antityphoid serum was obtained from Dr. Felix, of the Lister Institute, London, for experimental purposes. The serum was unconcentrated and contained antibodies to both the "O" and the "Vi" antigens to a titre of 1 in 40,000 and 1 in 400, respectively. It was decided to give this serum to every other case admitted, alternate cases receiving equivalent amounts of normal horse serum. This plan was adhered to for the first 8 cases, but when the beneficial effects of antityphoid serum were observed, it became difficult to withhold it from subsequent severe cases. Consequently the experimental group, to date, comprises 8 cases, whereas the control group numbers only 4. Of the 8 patients receiving antityphoid serum all except one recovered, the exception being a case who perforated some days after receiving 10 c.cm., a dose we now know to have been far too small. One of the 4 controls also died, another developed a carditis which prolonged convalescence, and two children who had mild illness pursued a normal course towards recovery, though one continued to have liquid motions for six weeks from onset.

Before summarising the main points of interest in the individual cases comprising this small series, it should be mentioned that every case of proved infection with *B. typhosus* admitted to hospital since last September was either given antityphoid serum or used as a control. The intramuscular route was used except in Case 9, when some of the serum was given intrathecally. None of the 12 patients had received T.A.B. vaccine or had suffered from a previous enteric infection. The controls were actually alternate cases and were not selected. The cases here referred to were treated independently of the Palestine experiment,¹ Dr. Felix deliberately withholding his findings so that the serum might be investigated without any preconceived ideas as to its effects.

In the following notes the expression "clinically definite" means that the patient had many or all of the classical symptoms and signs of enteric infection—viz., insidious onset; steadily rising temperature in the first week, remaining remittent later, and subsiding by lysis; disproportionately slow pulse; headache (giving way later to delirium); epistaxis; bronchitis; tumid and perhaps tender abdomen; some abnormality of the digestive system, usually diarrhoea; enlargement of the spleen; rose spots; and the appearance of the diazo reaction in the urine between the 8th and 12th day of the fever. Toxæmia was graded according to severity by a system of pluses. Toxæmia graded "+" corresponds to that met with towards the end of the first week of the disease in an average case, the grading "++" indicates a degree similar to that experienced during the "stage of advance" in the average case, whereas "+++" connotes a degree equivalent to that found quite early in the very severe cases, or more commonly, in the "typhoid state" into which the average case may drift towards the end of the third week.

It is unfortunate that there is no precise method of

assessing, and of graphing, toxæmia, for the effect of the serum in reducing it was much more striking than is apparent from a study of the temperature charts, some of which are reproduced below.

CASE RECORDS

CASE 1.—John A., aged 17½ years, admitted on 8th day of disease. Clinically a definite enteric infection; Widal

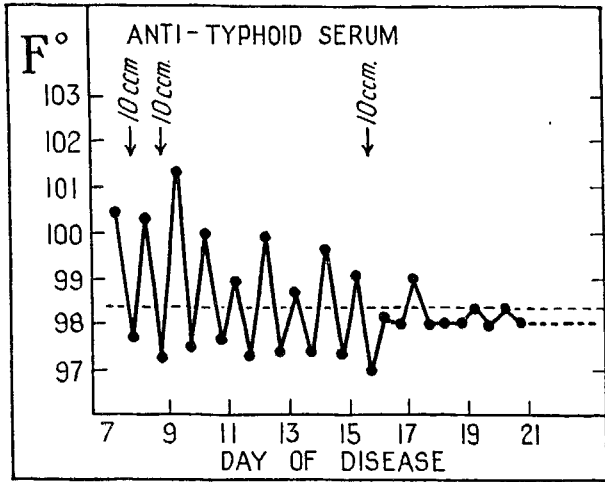


FIG. 1 (Case 3).

on which day motions were normal. Toxæmia was noted as absent before horse serum given. Pulse-rate kept over 100 until 32nd day of disease.

CASE 3.—Mrs. A., aged 45, mother of the two previous patients, admitted on 7th day of disease. Clinically an enteric infection. *B. typhosus* grown from the blood. Toxæmia on admission graded “++.” After two doses of serum (each 10 c.cm.) given on 8th and 9th day, pyrexia at a lower level, and toxæmia “+” (Fig. 1). Final dose of 10 c.cm. of antityphoid serum on 16th day seemed to abort the disease, toxæmia being noted as absent within next 24 hours. Motions normal on 23rd day.

Comment.—This woman was quite as ill on admission as her son who died after perforation.

CASE 4.—A control. Bridget B., aged 25, admitted on 8th day of disease. Clinically definite. Widal, at first negative, was positive on 13th day for *B. typhosus*. Given 10 c.cm. of normal horse serum on 14th day. Temperature seemed to settle 48 hours later (16th day of disease) but convalescence was slow, and a carditis supervened which persisted for six weeks, the sedimentation-rate of the red cells being still slightly above normal at this late date. Motions were normal 13 days after the injection of horse serum (27th day of disease).

Comment.—This was a mild case of enteric and toxæmia was noted as absent before the patient received horse serum.

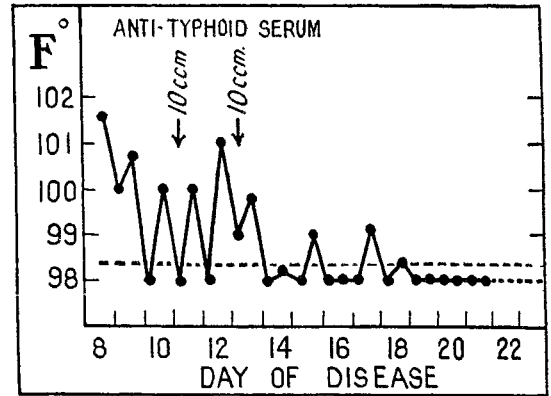


FIG. 2 (Case 5).

CASE 5. Mrs. C., aged 29, admitted on 8th day of her disease. Clinically a definite enteric, the rose spots being particularly profuse. Widal positive for *B. typhosus*, a blood culture being negative earlier. Given two injections (each 10 c.cm.) of antityphoid serum on 11th and 13th day, after which the disease seemed to abort (Fig. 2), although the motions were not normal until 31st day. On admission toxæmia graded as “+,” but within 48 hours after second dose of serum the note was “toxæmia absent.”

CASE 6.—A control. Elizabeth D., aged 23, admitted on 25th day of disease. Clinically an enteric infection. Widal positive for *B. typhosus* in very high titre. Given two doses (each 10 c.cm.) normal horse serum on 26th

positive on 9th day. One of three members of the same family treated. Was first case in series to receive antityphoid serum, a single dose of 10 c.cm. being given on 17th day. Toxæmia graded “++” before serum administered. Noted as “brighter, toxæmia less” on succeeding days, but perforation suddenly occurred on 20th day. Laparotomy immediately performed revealed a large rent in the distal end of his small intestine which was sutured. Several other impending perforations in adjacent bowel noted. Patient died seven hours after operation.

Comment.—Dosage of serum far too low. This was due to Dr. Felix’s absence in Palestine, his advice as to dosage not being received until some weeks later, by which time we had ourselves increased it. If such a case had come under treatment in November, three doses, each of 50 c.cm., would have been given, and in the event of perforation supervening 80–100 c.cm. would have been injected into the peritoneum before closure of the laparotomy wound. This was the only fatality among the cases receiving antityphoid serum.

CASE 2.—A control. Michael A., aged 5 years, brother of John A. (Case 1), admitted in 12th day of disease. Clinically definite but, as is usual with children, a mild case. Widal positive for *B. typhosus* 14th day. Given one injection of normal horse serum (10 c.cm.) on 22nd day,

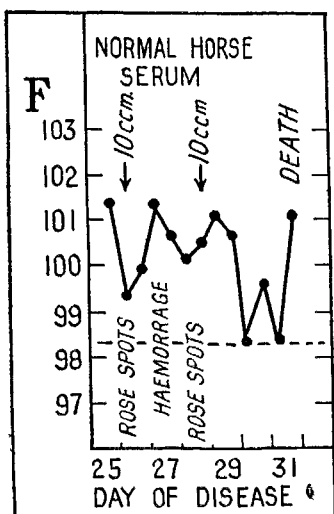


FIG. 3 (Case 6).—Control.

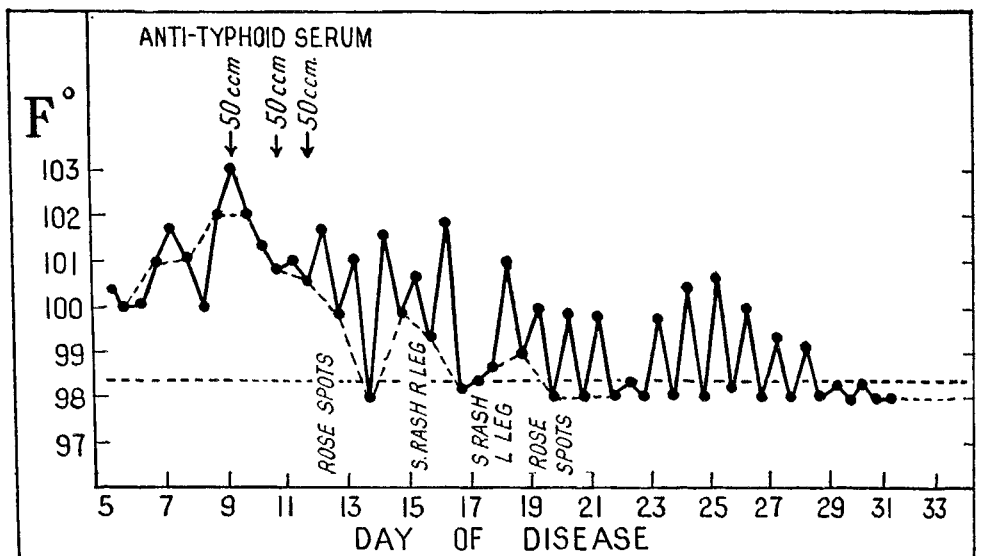


FIG. 4 (Case 7).—S. rash = serum rash. An interrupted line shows the course of the morning temperatures up to the time when they became consistently subnormal.

and 28th day. Hæmorrhage from the bowel occurred on 27th day. This was checked but patient gradually drifted into the typhoid state and died on 31st day (Fig. 3). Toxæmia on admission “++” became “+++” 48 hours after first dose of normal horse serum.

CASE 7.—Josephine D., aged 21 years, sister of Case 6. Admitted on 5th day of disease. Clinically definite. *B. typhosus* grown from blood during first week. Temperature steadily ingravescent from 100–103° F. for first five days after admission (Fig. 4), pulse-rate varying from 80–90. Toxæmia “+” on admission, “++” on 9th day of illness, when patient received first dose of antityphoid serum (50 c.cm.). Temperature curve immediately became defervescent, the morning temperature being progressively lower on next four days, reaching 98° on 14th day of disease. Same dose (50 c.cm.) serum repeated on 11th and 12th day of illness. With the exception of two pyrexial “mounds” occurring between the 14th and 20th day of disease, the morning temperature remained normal thereafter, the pulse-rate meanwhile fluctuating between 72 and 80. The two mounds in the morning temperature curve (indicated by interrupted line on chart) were definitely related to serum rashes, which—after 150 c.cm. of unconcentrated serum—were to be expected. Motions normal on 23rd day. Toxæmia graded as “+” on day serum treatment started, as “++” on days when second and third doses administered, and as “absent” two days after the last dose given (14th day of disease). The pyrexia occurring during serum rashes was unassociated with anything other than local discomfort. Rose spots continued to appear until the day before the morning temperature finally settled (19th day).

Comment.—In this case antityphoid serum seemed to cancel the toxæmia, and to bring the disease to a premature conclusion when the “stage of advance” should normally have occurred.

CASE 8.—A control. Annie D., aged 9 (sister of Cases 6

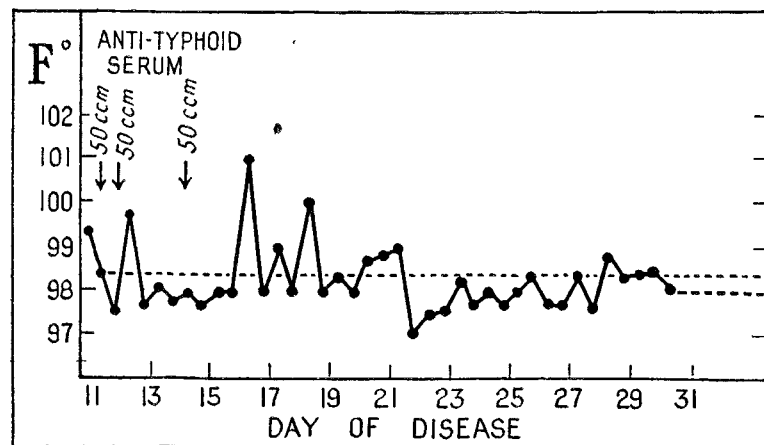


FIG. 7 (Case 11).

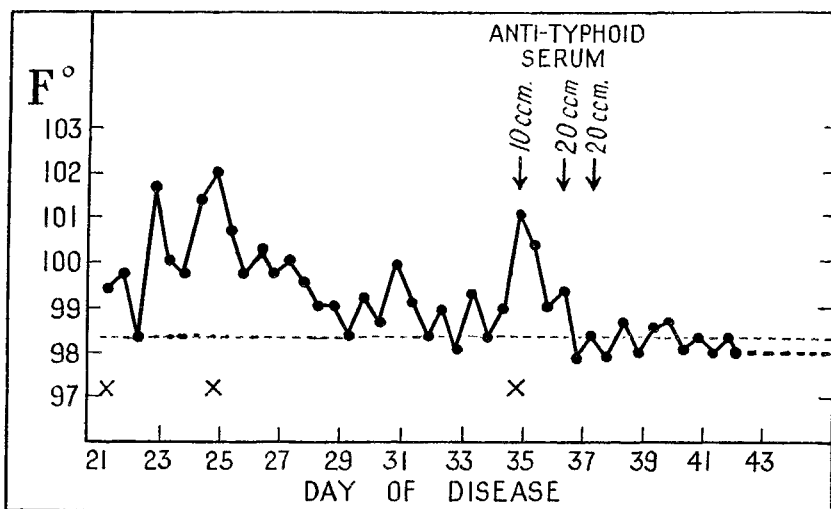


FIG. 5 (Case 9).— x = lumbar puncture.

and 7), admitted on 14th day of disease. Clinically a mild enteric, confirmed by positive blood culture for *B. typhosus* and, later, a Widal. Given three doses (each 50 c.cm.) of normal horse serum. Toxæmia graded as “+” before serum administered, and “absent” on the day on which the last dose was given (25th day). Motions not normal until 41st day of disease.

Comment.—In this mild case the morning temperature was normal only once in the third week of the disease, whereas in the case of her sister Josephine (whose ingravescent period had presaged a severe attack) the morning temperature was normal during the same period 4 days out of 7. The toxæmia in the case of the younger child

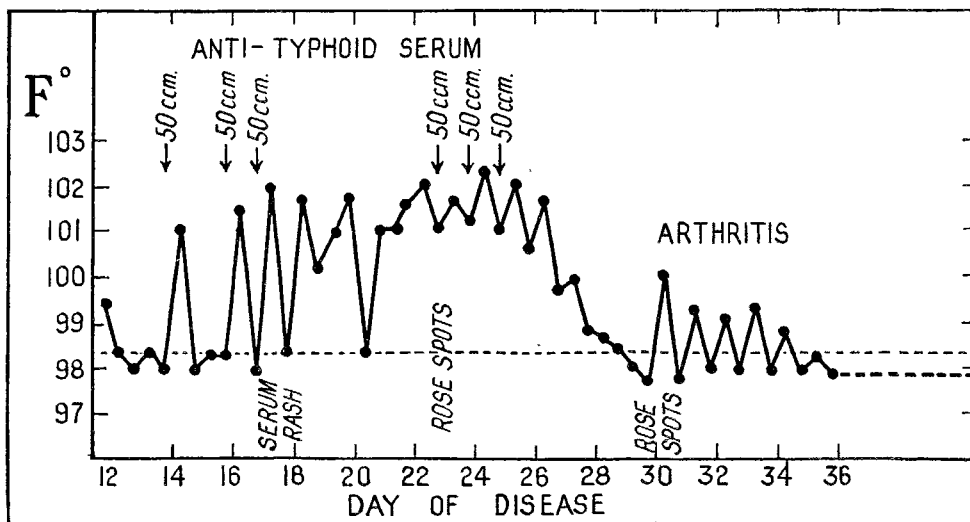


FIG. 6 (Case 10).

was graded as “+” during this period, whereas with Josephine it was noted as absent. The horse serum in the case of Annie did not seem to accelerate or retard the normal progress of her mild infection towards recovery.

CASE 9.—Mary E., aged 4 years, admitted on 21st day of disease. Child extremely emaciated and presented clinical signs of meningitis which was originally thought to be tuberculous, this suspicion being strengthened when a clear fluid under pressure was obtained by spinal puncture. No tubercle bacilli were isolated from the cerebro-spinal fluid. There were no intestinal symptoms at any time. Spinal puncture repeated 4 days later with similar result—viz., clear fluid under pressure, no tubercle bacilli isolated. Patient now in critical condition, extremely wasted, very irritable, semi-comatose with occasional screaming fits which rendered segregation in a cubicle necessary. A week after the second spinal puncture, the hospital pathologist (Dr. J. H. Pollock) succeeded in isolating an actively motile bacillus from the cerebro-spinal fluid. This “organism was strongly agglutinated by typhoid agglutinating serum, less strongly by Para B serum, and not at all by Para A.” The organism gave the typical black colonies on Blair and Wilson’s selective medium. A similar motile organism was isolated from an

otorrhœa which had developed subsequent to admission. Accordingly, on 35th day of disease, when the temperature was 101° F. and the child apparently moribund, a third spinal puncture was performed and, after clear fluid had been withdrawn, 10 c.cm. of antityphoid serum was administered intrathecally, a dose of 20 c.cm. of the same serum was given intramuscularly on the two succeeding days (Fig. 5). The result was more dramatic than would appear from a study of the temperature charts, although the speedy diminution in pyrexia was itself remarkable. The child became rational, quiet, and proceeded to put on weight rapidly. A week later the case note was "rational now—not irritable." The signs of meningitis cleared, and the patient left hospital men-

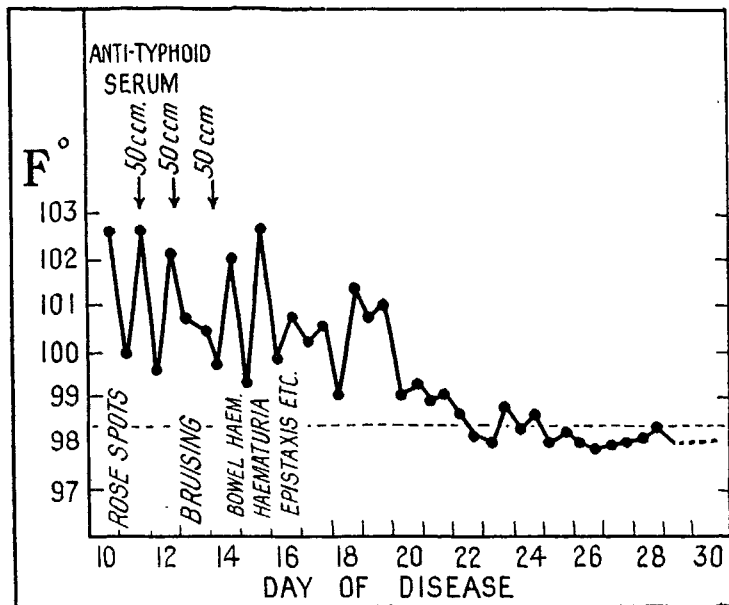


FIG. 8 (Case 12).—Hæm. = hæmorrhage.

tally and physically normal. Blood submitted for a Widal reaction on the day before serum therapy begun returned weakly positive for *B. typhosus* "O."

Comment.—This case appears to be an instance of primary typhoid meningitis, and a very remarkable amelioration of symptoms and signs, and of pyrexia, with a speedy and complete recovery followed the administration of antityphoid serum.

CASE 10.—Nurse F., aged 26, admitted from another hospital on 12th day of disease. Clinically a definite enteric. Blood culture negative for *B. typhosus* on 12th and 21st day but Widal strongly positive for that organism on 14th day. *B. typhosus* later isolated from urine. Received three doses (each 50 c.cm.) of antityphoid serum on 14th, 16th, and 17th day of disease. Temperature did not settle thereafter, a generalised urticarial serum rash appearing on 18th day (Fig. 6). The return of liquid motions, increase in size of spleen, the appearance of rose spots, return of the diazo reaction in the urine, and a rising temperature after the serum rash had faded suggested the onset of a relapse. Serum was repeated on 23rd, 24th, and 25th day of disease, 50 c.cm. being given on each occasion. Two days after the first dose of the second series of injections the temperature will be noted to have taken a downward trend and, apart from a mild attack of arthritis causing local discomfort, convalescence was speedy and complete. This patient never complained after her first serum treatment except about her serum rash and arthritis. The latter was undoubtedly a serum phenomenon, as the patient had in all 300 c.cm. of natural serum, double the maximum dose given to any other case. Motions were normal on 33rd day. Rose spots continued to appear until 30th day.

Toxæmia in this case graded as "++" on admission and "absent" immediately after first series of injections had been completed.

CASE 11.—Frank G., aged 54, a bedridden paralytic, admitted on 11th day of disease, much wasted and with

extensive bedsores. Clinically a definite enteric, blood culture positive for *B. typhosus*, also Widal and later fæces. On admission toxæmia "++." Given antityphoid serum (3 doses, each 50 c.cm.) on 11th, 12th, and 15th day of disease (Fig. 7). Subsequent toxæmia difficult to assess because of concurrent paralytic and mental condition. Appeared much better from 18th day, temperature remaining settled after 22nd day though motions not normal until 37th day.

Comment.—The clinical impression is that had this man not been given antityphoid serum, he would not, in his lowered state of vitality, have survived his attack of enteric.

CASE 12.—Kathleen H., aged 17. Admitted on 10th day of her disease. Clinically a definite enteric. Blood culture and Widal positive for *B. typhosus*. Toxæmia "++" on admission, quickly becoming "+++ " on development of hæmorrhages from mucous membranes of nose, mouth, intestine, and bladder. Large areas of subcutaneous hæmorrhage with petechiæ, hæmorrhage into rose spots, and discrete subconjunctival hæmorrhages also occurred. In addition, extravasation took place into the skin of the abdomen, which had been blistered by poulticing before admission. Patient's condition was now very critical and the typhoid state seemed imminent. Antityphoid serum was given in 3 doses of 50 c.cm. on 11th, 12th, and 13th days respectively (Fig. 8). Within 4 days of the last dose her condition showed a remarkable improvement. Toxæmia was definitely less (++) , the patient was again rational, hearing less blunted, and all restlessness gone. The urine which had contained a large quantity of blood for several days was clear on 19th day of disease, on which day the toxæmia was noted as absent. Stools were free of blood on 18th day. The temperature was normal on 22nd day, and remained so thereafter. Motions were formed on 26th day.

Comment.—The beneficial effects following serum therapy in this case were the most striking observed in the series of cases under review. Hæmorrhagic typhoid is a very rare disease (E. W. Goodall² says he saw only one in his extensive experience, while the late C. B. Kerr³ refers to it as "fortunately most uncommon" and "very fatal").

CONCLUSION

It is, of course, not claimed that any sweeping assertions can be made for the efficacy of this new antityphoid serum on so small a series of observations. This is more especially the case as the controls were, on the whole, not good. It is however possible to say that out of 8 cases receiving antityphoid serum, 7 ceased to cause anxiety within a few days of the last dose, and the only failure was the case receiving a very inadequate single dose who died from a local complication—viz., perforation.

I have to acknowledge the great kindness of Prof. J. W. Bigger who elected to carry out the bacteriological work in connexion with this investigation. I must also express my indebtedness to Dr. F. N. Elcock (senior resident medical officer at Cork-street Hospital) for his careful day-to-day notes on the series of cases here reviewed.

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HOSPITAL TREATMENT FOR UNEMPLOYED.—Lord Derby, as president of the Merseyside Hospitals Committee, has given his support to a new scheme for the provision of voluntary hospital care for unemployed families. This scheme is known as the Friends of the Sick Poor, and a condition of membership is an undertaking to adopt an unemployed family for voluntary hospital care at an annual cost of 10s. per family. It is hoped that this scheme will attract support from people who do not come within the penny-in-the-pound fund for Merseyside hospitals.