RECENT RESULTS IN THE SERUM TREATMENT OF CEREBRO-SPINAL FEVER.*

BY

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RECENTLY published records of the results obtained in the treatment of cerebro-spinal fever during the year 1916 show very marked improvement in the mortality rates when compared with those of 1914 and 1915. In the sudden and widespread outbreak of the disease in the British Isles in the winter of 1914-1915 death-rates of 50 or 60 per cent. and even higher were common. Various explanations were then suggested to account for the failure in many places to obtain as satisfactory results as had been the usual experience after the introduction of the intrathecal injection of antimeningitis serum by Flexner in 1907.

In the large epidemics in New York and elsewhere in America in 1904-1906 the death-rate seldom fell below 75 per cent. in any series of cases, and was frequently much higher. Similar terrible mortality was experienced in the extensive outbreaks in Scotland and Ireland in 1906 and the early part of 1907.

In the spring of 1907 Flexner introduced the intraspinal injection of serum. Its adoption led to the immediate reduction of the death-rate to about one-third of what it had been. Thereafter, mortality rates of 25 to 30 per cent. were the rule, and in some outbreaks even better results were obtained, notably by Netter in Paris and Christomanos in Athens.

My own experience was that in nearly 300 cases in the Belfast Fever Hospitals in the first seven months of 1907, and before the use of intraspinal injections of serum, the mortality was 72 per cent.; then, while the epidemic was still going on, Flexner's method was adopted, with serum supplied by him, and the death-rate immediately fell to under 30 per cent. In the total of over 270 cases which I have now treated by this method the death-rate works out at just over 26 per cent. Similar rates were obtained with the serum treatment in the extensive epidemic in Texas in 1912; Sophian, in 180 cases treated by him in that epidemic, had a mortality of 25 per cent.

But in the winter of 1914-1915, when cases were numerous in Britain, though the majority were treated by spinal puncture and the injection of serum, the results were in many places very far from satisfactory.

Two main theories were put forward to explain this: (1) That the cases then met with were infected by strains of the meningococcus differing from those employed in the preparation of the serum. (2) That the serum available was not of the same high standard of quality. I think it is now becoming generally accepted that the second of these affords the true explanation, and that, in the words of one of our greatest authorities, "much of the serum then available was of very poor quality, and some of it quite worthless." This has all been changed, and abundance of serum is now obtainable from many different sources, and has recently been giving good results. This is shown by the very interesting reports by Surgeon-General Rolleston, giving the results in the navy for the year August, 1915, to July, 1916; by Captain Charles Gray on military cases in the London area; by the reports on cases in Australia, and also by the results in Canada reported by Fitzgerald and others. Rolleston reports 95 cases in the navy with a mortality of 31.6 per cent., and Gray 46 cases with a mortality of 21.7.

Serum from several different sources was employed in the treatment of the cases recorded in these reports—from the Rockefeller Institute, the Pasteur Institute, Paris, the Lister Institute, that made from Colonel Gordon's strains, Burroughs and Wellcome's serums, and those from the laboratories of Melbourne University and of Toronto University. Good results were obtained with all.

Since Dr. Flexner again took up the preparation of serum at the Rockefeller Institute all my cases have been treated with this serum. Since that time I have had 48 cases of all ages, from 3 months to 55 years. Of these, 13 died, a mortality of 27 per cent. An analysis of the figures shows that, apart from the severity of the type of

attack, the most important points are the early commencement of treatment and the greater gravity of the outlook in the older subjects. All recent records afford additional evidence of the enormous importance of early diagnosis.

<i>Navy: 95 Cases (Rolleston).</i>			
In 74 cases treated on the first to third day the death-rate was	...	...	24.7 per cent.
In 15 cases treated on the fourth to seventh day the death-rate was	...	...	33.3 "
In 6 cases treated later than the seventh day the death-rate was	...	...	50.0 "
<i>Soldiers in the London Area: 43 Cases (Gray).</i>			
In 33 cases treated on or before the third day the death-rate was	...	...	9.09 per cent.
In 10 cases treated later than the third day the death-rate was	...	...	50.0 "
<i>Belfast: 48 Cases (latest Series).</i>			
In 36 cases treated within the first five days the death-rate was	...	...	22.2 per cent.
In 12 cases treated later than the fifth day the death-rate was	...	...	41.6 "

The great importance of early treatment cannot be fully shown by statistics, because in every considerable number of cases there must occur some of very fulminant type, dying within a day or two, or even within a few hours. The following case I had some years ago is an example:

A man of 28 years, of splendid physique and a noted athlete, first complained at 8 a.m.; by 10 a.m. he was wildly delirious. He was then removed to hospital; before noon he was comatose and he died at 1 p.m.: total duration five hours.

This, of course, is an extreme example, but it is these exceedingly fulminant cases, in which there is practically no hope, which are most likely to be diagnosed at once and early sent in for treatment. The statistics of cases treated on the first day of illness include many such.

In the 48 cases which I now report the average duration of illness when first injected with serum was 5.5 days; but two of these cases were sent in very late, one on the twenty-first day and one already over fifty days ill. Excluding these two exceptionally late cases, the average duration in the remaining 46 was 4.1 days. I believe that were it possible to cut that average duration down, to say one half, the death-rate would be proportionately reduced.

Age.

It has invariably been found that the older subjects and the young infants give much higher mortality-rates than the older children and the young adults.

Belfast Cases (48). Deaths in Age Periods.

Ages.	Cases.	Deaths.	Mortality.
			Per Cent.
Under 1 year	9	3	33.3
1 to 2 years	3	1	33.3
2 to 5 "	3	0	0.0
6 to 10 "	4	1	25.0
11 to 20 "	16	2	12.5
21 to 30 "	8	2	25.0
31 to 40 "	2	1	50.0
41 to 50 "	2	2	100.0
Over 50 "	1	1	100.0
All ages	48	13	27.0

From this table it will be seen that, of the 15 cases under 5 years, 4 died—a mortality of 26.6 per cent.; of the 28 cases between the ages of 11 and 30, 4 died—a mortality of 16.6 per cent.; of the 5 cases over 30 years, 4 died—a mortality of 80 per cent. This mortality in age periods compares very closely with my former statistics.

All three cases over 40 years (43, 47, and 55) ended fatally. I have had cases of more advanced years than any in this series make quite complete recovery after severe attack, but such good results are the exception. These older subjects seem much more prone to develop grave complications, such as pneumonia and serious albuminuria, and they have a much greater tendency to pass into a state of general septicæmia.

* Synopsis of a paper read before the Ulster Medical Society on March 4th, 1917.

In mortality tables the young infants show nearly always a comparatively high death-rate. I believe that this is largely, if not entirely, due to the greater difficulty in making the diagnosis in the infant, and the consequent longer average duration of the illness when they come under treatment. The diagnosis in an infant of a few months old is, of course, most difficult; also there is greater opposition to the sending of young infants into hospital. Of the 15 cases in this series under 5 years of age 9 were treated within five days of the onset. Amongst these 9 there was only one death; mortality 11.1 per cent. Whereas of the 6 first treated later than the fifth day 3 died; mortality 50 per cent. When the serum treatment is commenced early, my experience is that these very young children do very well.

Included in this series were 12 military cases. Ten of these made good recoveries and rejoined their units, one admitted on the sixth day of illness died on the sixteenth day, and one, who also had pulmonary phthisis, recovered so far as to show sterile cerebro-spinal fluid and to be allowed up, but he then developed very rapidly progressive tuberculosis in both lungs, and he died two months later.

The average number of injections given in these 48 cases was 4, and the average amount of serum injected was 90 c.cm. The largest amount in any one case was 280 c.cm.

One infant of six months, which lived, admitted to hospital on the fifth day of illness, was punctured thirty times, had 250 c.cm. of serum, and had 1,948 c.cm. of cerebro-spinal fluid drained off from the canal.

Another infant of five months was admitted on the eighth day of disease. Lumbar puncture on admission gave only a few drops of fluid. There was considerable bulging of the fontanelle, puncture was therefore made through the fontanelle, and the serum given by this route. The puncture was repeated five times, and 72 c.cm. of serum given. The infant made slow progress at first but completely recovered, and was discharged after nine weeks. It left hospital last September, and I have recently heard from Dr. Currie of Ballymena, who sent the case in, that the child has remained well since, and appeared to be developing quite normally.

This case is of interest, as the number of cases so far recorded of recovery after treatment by injections given through the fontanelle, rendered necessary by the failure to obtain drainage by lumbar tapping, is very small. I have only been able to find three.

Two years ago, when the results of the serum treatment were in many instances disappointing, other methods of treatment were advocated as follows:

Simple Puncture and Drainage.

This mode of treatment was, before the introduction by Flexner of the intrathecal injection of serum, extensively tried in America and elsewhere, and although it was recognized as useful the results were very far from satisfactory. I have watched the published records of treatment in this disease, and, so far as I know, no one has ever by this method obtained in any considerable number of cases a mortality under 40 per cent., and often it was only practised in more or less selected cases.

Subcutaneous Injections of Antiserum.

At that time also attempts were made, here and elsewhere, to obtain better results by subcutaneous injections of antiserum with at the same time drainage by lumbar puncture, in the hope that the serum would thus more effectually reach the seat of infection, but without any noteworthy success.

It has never been claimed, I think, by those who doubt the value of the intrathecal injections of serum that the serum reduced the patient's chances, but it has been claimed that the results obtained are due to the drainage and not to the serum. If that were so, the method just referred to should have effected as good results. Also the brand or quality of the serum should be of no importance, and the results two years ago should have been as good as those at other times obtained by puncture and the injection of serum.

Puncture and the Injection of Disinfecting Solutions.

Fifteen years ago treatment by puncture and the injection of 1 per cent. lysol was advocated and practised in Lisbon during an extensive outbreak. This method was followed in America, but the results were disappointing, and it was abandoned. Later Wolff recommended the

injection of 0.2 per cent. protargol into the canal, and more recently several other disinfectants have been recommended—dilute solutions of carbolic acid, of chloramine-T, of eusol, etc.

Last year Flexner and Amoss carried out at the Rockefeller Institute an elaborate series of experiments to determine the power of lysol and protargol to counteract the effects of meningococcal infection artificially produced in monkeys and young guinea-pigs. They found that:

"Neither protargol nor lysol proved to have any curative action on the experimental infection thus produced in these animals. On the contrary, both lysol and protargol exert antileucocytic and antiphagocytic effects, and are also potent protoplasmic poisons, and the leucocytes with which they come in contact are injured and made to degenerate. According to the extent to which these harmful properties are exerted these chemicals promote the advance, rather than restrain the progress, of meningococcal infection.

"Recovery from meningococcal infection in man and animals is accomplished chiefly through the process of phagocytosis. . . . Any means which interfere with and reduce these essential processes retard or prevent recovery. Both lysol and protargol interfere with and diminish the emigration of leucocytes and the phagocytosis of meningococci, and neither possesses antitoxic power. It follows, therefore, that whatever theoretical advantages might accrue from a bactericidal activity exerted by these chemicals independently of the type of meningococcus causing epidemic meningitis is more than offset by the harmful effects which they cause."

These experiments of Flexner and Amoss prove that the use of lysol and of protargol in guinea-pigs and monkeys infected with meningococcal meningitis do harm and not good. There is no reason to believe that their use in man would be more beneficial than in the monkey. They also raise grave doubts as to the justification for the employment of similar chemical agents, at least until much further experimental research has been done.

All the recent work on cerebro-spinal fever goes further to prove that the most hopeful line of treatment is by lumbar puncture, drainage, and the intrathecal injection of carefully prepared polyvalent antimeningitis serum; and that the most important factors which make for success are early treatment and sufficient dosage.

NOTES ON THE ETIOLOGY OF DYSENTERY.

I.—*Types of Dysentery Bacilli Isolated at No. 3 Australian General Hospital, Cairo, March–August, 1916, with Observations on the Variability of the Mannite-fermenting Group.*

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(Abstract.)

ATTEMPTS to isolate dysentery bacilli from 217 cases in which the stools contained mucus with or without blood were made. In many cases the amount of mucus in the stool was very small.

B. dysenteriae Shiga was recovered on forty-seven and mannite-fermenting dysentery bacilli on seventy-six occasions. *Amoebae histolyticae* or their cysts were present in 63 cases and in 36 no causative organism was discovered.

The method employed was to wash the mucus, break it up in sterile broth, and plate out some drops on the surface of a MacConkey plate. Next day likely colonies were picked off, sown into warm broth, and incubated for a few hours. They were examined for motility, and, if motile, discarded. The non-motile broth cultures were sown into glucose and mannite peptone water, and on to an agar slope. If glucose or both glucose and mannite were fermented with the formation of acid only, an emulsion was made from the agar slope and tested as regards agglutinability against a Shiga or Y serum respectively. Macroscopical methods were employed.

In about fifty instances the further biochemical characteristics of the strains were investigated immediately.

The Shiga strains of dysentery bacilli isolated were all true to type.

The organisms of the mannite-fermenting group were, on the contrary, very variable, both as regards their