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SERUM DISEASE AFTER INTRATHECAL INJECTIONS OF SERUM.

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THE clinical aspect of serum disease is so familiar that some apology is necessary for raising the subject again, and this perhaps may be offered in a brief comparison between its manifestations after the intrathecal and after the more usual hypodermic method of serum injection. It might naturally be anticipated that intrathecal injection would make a difference, inasmuch as any local reaction in the meninges comparable to the rash sometimes seen to start from the neighbourhood of a hypodermic injection of serum might, from the proximity of the spinal cord and brain, cause special nervous symptoms. The following statements are based on analysis of the clinical notes of cases of cerebrospinal fever in the Royal Navy.

Meningism due to serum disease.—During the third year of the war out of 96 bacteriologically proved cases of cerebrospinal fever treated by serums and surviving for ten days or more, 58, or 60 per cent., had a serum reaction, as judged by the appearance of a rash. Among these 58 cases there were 9, or 15.5 per cent., in which the rash was preceded or accompanied by a more or less definite recrudescence of meningitic manifestations, thus, especially when preceding the rash, suggesting a relapse of the disease. These symptoms are relieved by lumbar puncture, and under the assumption that they point to a relapse a fresh injection of serum may be given, as was done in 6 out of the 9 cases. The 3 cases not so injected recovered, and of the 6 cases injected intrathecally with serum 5 were probably made worse, 4 eventually proving fatal, though it is not suggested that death was thus induced. The effect of intrathecal injection of serum presents some peculiar features. Whereas, as is well known, injection into a healthy intrathecal space sets up an aseptic chemical meningitis, injection of anti-meningococcic serum in cerebrospinal fever—as is shown by the clearing of the cerebrospinal fluid—reduces the inflam-

matory process, presumably by destroying the meningococci. In discussing the injection of immune serum in acute poliomyelitis, Neal, Abramson, and others¹ point out that injection of serum into slightly inflamed meninges sets up in most cases an acute aseptic meningitis shown clinically by fever, rigidity of the neck, and other signs of meningeal irritation. It seems probable that at the time of the serotoxic meningeal reaction the meninges are slightly inflamed, and that, as this is not due to meningococci, a fresh injection of serum aggravates the symptoms and possibly does harm rather than good.

It is therefore desirable to have some means of determining whether there is a genuine relapse which will be benefited by serum or whether the condition is one of meningeal irritation or meningism and a manifestation of serum disease which may be intensified by a further injection of serum. This diagnosis can be made by examination of the cerebrospinal fluid for the presence of meningococci, and also for the normal reducing agent (glucose) which is absent in relapses of meningitis and present in the meningism due to serum disease (Reveillelet, Nové-Josserand, and Langeron²). This test, which takes a few minutes only, and so enables a decision to be made on the question whether to withhold or inject serum at once, has been employed by Staff-Surgeon L. Warren, R.N., and by Dr. C. Ker at the City Hospital, Edinburgh, where some naval ratings were treated.

This meningeal manifestation of serum disease is peculiar to intrathecal injection of serum, and though it occurs in a small proportion of cases should be more widely recognised in this country in view of the war-time increase of cerebrospinal fever. It has not, however, passed unnoticed. Netter and Debré³ in 1911 gave a good account of it, and regarded it as a result of serotoxic oedema of the meninges. It may also be added that, as the mucous membranes originally attacked by diphtheria are liable to swell at the time of the serum reaction, an analogous sequence may be suggested in the case of meningococcic infection of the meninges.

If the meningism is part of the serum disease to be expected after intrathecal injection, the question arises why it is not noted more often. It does not appear to result from large quantities of serum given, for out of the 9 cases among the 58 naval cases with a serum reaction, 8 had less than 100 c.c., and 4 of these 8 less than 50 c.c.; nor can it be explained as due to an intrathecal injection within a very few days of the appearance of the serum rash. That it is connected with some hypersensitiveness of the meninges is probable enough, but it is impossible to go beyond this vague statement.

¹ Arch. Int. Med., Chicago, 1917, xx., 341.

² Reveillelet, Nové-Josserand, et Langeron: Jour. de Physiol. et Path. Gén., Paris, 1914-15, xvi., 1080.

³ Netter et Debré: La Méningite Cérébrospinale, p. 264, Paris, 1911.

The frequency of serum reactions after intrathecal injections.

—Flexner⁴ remarks that possibly the manifestations of serum disease are more frequent after the intrathecal than after the subcutaneous injection of serum, and at first some of the figures relating to the naval cases appear to confirm this; thus, out of 61 cases of cerebro-spinal fever which received Flexner's serum intrathecally only and recovered or (if fatal) survived more than 10 days, 43, or 70 per cent., had a serum rash. Whereas out of Currie's⁵ 50 cases of cerebro-spinal fever treated mainly by subcutaneous injection (36 by subcutaneous injection only, 13 by one intrathecal and the other injections subcutaneously, and 1 case by one intrathecal, one intravenous, and the remaining injections subcutaneously), 29, or 58 per cent., had rashes. The incidence of serum rashes after ordinary hypodermic injections is given by Goodall⁶ from analysis of a large number of cases, as about a third, so that the percentage of 70 is in excess of Currie's and Goodall's figures. But the naval cases, besides being rather few, were all injected with Flexner's serum, which seems to be specially effective in inducing a serum reaction. Out of 241 naval cases given various brands of serum (in some instances hypodermically as well) during the first three years of the war, and surviving for ten days or more, rashes occurred in 99, or 41 per cent. This is indeed lower than the incidence (44 per cent.) of serum rashes among 37,277 cases of diphtheria treated by serum during the years 1898–1903 in the hospitals of the Metropolitan Asylums Board, and very much lower than in some other series where serum rashes were specially looked for and found in from 67 to 81 per cent. of the cases (J. D. Rolleston⁷). It does not therefore appear to be proved that the incidence of serum disease is higher after intrathecal than after the hypodermic method of injection.

Bad effects from increased intracranial pressure caused by intrathecal injection of serum are so well known and the precautions necessary to avoid this accident so well recognised that they do not require further discussion.

Intrathecal injections of serum in rare instances are followed by *secondary infections* through the wound, especially after a large number of lumbar punctures. Secondary infection may also occur through the blood-stream, and it has been thought that this may be favoured by the injection of serum. Netter and Salanier⁸ refer to 22 cases of

⁴ Flexner: *Mode of Infection, Means of Prevention, and Specific Treatment of Epidemic Meningitis*, The Rockefeller Institute, N.Y., p. 42, 1917.

⁵ Currie: *Jour. Hyg.*, Cambridge, 1908, viii., 457.

⁶ Goodall, E. W.: *System of Medicine* (Allbutt and Rolleston), 1911, ix., 113.

⁷ J. D. Rolleston: *Practitioner*, 1905, lxxiv., 660.

⁸ Netter and Salanier: *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, 1917, 3e sér., xli., 789.

secondary pneumococcic infection of meningococcic meningitis treated by intrathecal injections of serum during the first four months of 1917, when from the increased incidence of primary pneumococcic meningitis since December, 1916, the virulence of the pneumococcus was presumably intensified. These authors suggest that the injection of serum into the subarachnoid space, especially when large quantities of serum not corresponding to the type of the meningococcus present are given, may provide a better culture medium and so favour pneumococcic infection. But since a mixed meningococcic and pneumococcic infection of the meninges may occur before lumbar puncture, as was found in a naval case, it is clear that secondary pneumococcic infection does not necessarily depend on intrathecal injection of serum. Further, the secondary pneumococcic infection would appear to depend mainly on the virulence of the pneumococcus, for in a previous series of 300 cases of meningococcic meningitis Netter and Salanier⁹ found 4 cases only of secondary pneumococcic infection.

To sum up: (1) Symptoms of meningeal irritation may precede or accompany the appearance of the serum rash. (2) Though serum disease is frequent after intrathecal injection of serum, especially after Flexner's antimeningitis serum, it is not clear that it is more frequent than after hypodermic injection of serum. (3) Intrathecal injection of serum necessarily involves risk of inducing increased intracranial pressure and may introduce a secondary infection; but it is not proved that the volume of serum injection favours a secondary infection of the meninges from the blood-stream.

⁹ Idem : Ibid., p. 394.