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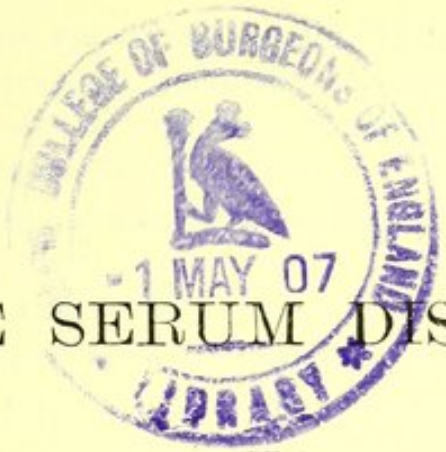

THE SERUM DISEASE.*

BY

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The phenomena designated *maladie de serum* in France, *serumkrankheit* in Germany, and *malattia di siero* in Italy, have until recently received but comparatively small attention in English-speaking countries.

In spite of the large number of serums that have been introduced for various diseases, the great majority of which are of doubtful value, none have received such universal employment as Behring's antitoxin for diphtheria. It is therefore for the most part from observations on patients suffering from diphtheria, and from experiments on animals that have been injected with this serum, that a knowledge of the serum disease is to be obtained. Though an enormous amount of laboratory work has been done, the pathology of the condition is still uncertain. The clinical phenomena, however, are very definite, and will alone be considered in the present paper, which is based on observations made on 1100 diphtheria patients that have come under my care in the course of the last four years. Of this number 1057 or 96·09 per cent. were

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injected with antitoxin. The serum in all cases was given subcutaneously. From comparative observations I have not been able to persuade myself that the intravenous method has sufficient advantages to counterbalance the greater risk of the operation and the length of time required to perform it.

The symptoms of the disease may be divided into (*a*) the early, (*b*) the late.

Among the earliest phenomena of the serum disease is the activity of the sweat glands. Within a few hours of injection the skin becomes moist, and in well-marked cases perspiration may be profuse. This phenomenon will usually be found to coincide with a rapid disappearance of membrane from the throat. In malignant cases of diphtheria, in which the action of serum is delayed, the skin remains dry. This dry state of the skin is not due to a febrile condition, for in such cases the temperature is often normal or subnormal. Associated with the activity of the skin is a condition of sleep or drowsiness to which adults and children are alike subject, which may last for some days after the injection. Diminution in the amount of urine passed is another early symptom, which is often accompanied by activity of the sweat glands. It must be distinguished from that due to the toxines of diphtheria. In the latter case the skin is dry, much albuminuria is usually present, and the general condition is characteristic of toxæmia. The most striking feature of the serum disease is the occurrence of rashes. The skin eruptions that follow the injection of antitoxin are of three kinds, (*a*) a scarlatiniform type, (*b*) urticaria, (*c*) circinate erythema. In addition to these must be mentioned an erythema localised to the site of injection that is liable to occur within the first few days, especially if the injection has been made into the dermis.

Scarlatiniform eruptions following the injection of serum are often the source of great difficulty. Some authorities

of considerable experience, such as Marfan, regard them as a modified form of scarlatina. Undoubtedly this is true in a certain number of cases, but that it is not always so, is shown by the fact that when such cases have been removed to a ward for patients suffering from concurrent diphtheria and scarlatina, they have shortly afterwards developed an undoubted attack of scarlet fever. Neither the tongue nor the throat may be typical, the pulse and temperature may remain normal, and there may be no subsequent desquamation. The case may, nevertheless, prove to be scarlet fever, either by the development of some characteristic complication such as nephritis, or by infecting other patients in the same ward. Drowsiness, activity of the sweat glands, local or generalised erythema, and diminution of the urinary secretion, may thus be regarded as the earliest symptoms of the serum disease. There is now a latent period varying in duration from 1 to 7 or 8 days during which no fresh phenomena are obvious.

The second stage is characterised by the development of urticaria. Almost always, it first appears at the injection site. It may be limited to this spot, or become generalised. It is often associated, especially on the face, hands, feet and prepuce, with considerable œdema. Œdema, however, is a symptom which is most marked when a second injection of antitoxin is given for a relapse or second attack of diphtheria when the primary injection has been given some weeks or months before. In such cases the latent period is suppressed. Within an hour of injection urticaria may develop at the injection site, and rapidly become generalised. Rigors, vomiting, and collapse may also occur. These alarming symptoms are most likely to arise after a large dose has been given, so that it is well, if possible, to employ small doses in cases of relapse. Apart from the pruritus, which in some cases may amount to a veritable torture, there is no constitutional disturbance at this time. The temperature is seldom raised. It is important to note that albuminuria may occur simul-

taneously with the eruption of the urticaria, or pre-existent albuminuria may be increased. The total amount of urine passed in the twenty-four hours may also be somewhat reduced. The duration of urticaria is usually about three or four days, but it is often much longer or much shorter. Sometimes only a single wheal develops, and is followed by no more; on the other hand, several fresh crops may come out every day, or, before the rash finally disappears, there may be an interval of one or more days in which no rash is noted. Urticaria is the most common of the skin eruptions following the injection of antitoxin. It occurred in 734, or 66·7 per cent. of the present series of cases.

The third stage of the serum disease is not always realised. Usually separated by one or more days from the second, it may sometimes be continuous with it. The most striking feature of this third stage is the development of a rash, at first usually an amorphous erythema, but sometimes circinate from the first, and almost always becoming circinate subsequently. The temperature is usually raised. Malaise and anorexia are present, especially in older patients, who are more likely than younger ones to suffer at this time from pains in the joints and muscles. The sub-maxillary and cervical glands, and, to a less extent, the axillary and inguinal, become swollen and painful. Usually there are no phenomena within the throat to account for neck swelling, but occasionally specks may appear on the tonsils, or even a continuous deposit. This condition, which I have elsewhere designated "angina redux" (*British Medical Journal*, May 19th, 1906) may so closely simulate a relapse that those not familiar with the condition may re-inject the case, and thereby considerably aggravate the patient's condition. Much less common than *Angina redux* is a reappearance of laryngeal symptoms in cases that have been croupy at the beginning of the disease, but in which those symptoms have subsided. Personally I have only seen one case of

the kind. Sevestre and Aubertin, Marfan and Mya have reported cases in which the symptoms were severe enough to necessitate intubation.

The other mucous membranes, according to some authorities, may also be affected. Thus, Sevestre and Martin say that diffuse bronchitis and hæmorrhagic diarrhœa frequently occur. In none of my own cases, however, could bronchitis or enteritis be attributed to the use of serum.

The relative frequency of each of the symptoms of this late syndrome is shown in the following table:

	Cases.		Percentage.
1. Circinate erythema ...	207	or	19·5
2. Pyrexia	174	„	16·4
3. Pains in joints or muscles...	104	„	9·8
4. Adenitis	98	„	9·2
5. Angina redux	40	„	3·7

I have elsewhere dwelt on the dissociation of the elements of this late symptom-complex. "Joint pains may be the only manifestation of a serum reaction in the second week from injection. A circinate rash may appear and run its course without any pyrexia, or the temperature may be raised for a few days without anything to account for it. Adenitis at the angles of the jaw may also be met with as an isolated phenomenon."—*Practitioner*, May, 1905.

Abscesses at the injection site cannot be regarded as forming part of the serum disease, since they are less liable to develop after the injection of antitoxin than after the use of the ordinary hypodermic syringe.

Prognosis.—The prognosis of the serum disease is absolutely good. Though considerable distress may be caused by some of the symptoms, especially the pains in the joints and muscles, they all pass off, without leaving any trace, in a few days. The prognosis of diphtheria, so far from being aggravated by the supervention of the serum

disease, is, on the contrary, ameliorated thereby. I pointed out two years ago what my subsequent observations have confirmed—that the frequency and intensity of serum manifestations were directly proportionate to the size of the dose injected, and inversely proportionate to the character of the initial diphtherial attack. In other words, the larger the dose of antitoxin injected, the more likely a rash and the other symptoms were to occur, while the severer the attack of diphtheria, the less likely was such an occurrence. From this I concluded that the more marked the serum phenomena the better the prognosis, both as regards ultimate recovery and as regards escape from serious paralysis.

Treatment.—The treatment of the serum disease is both prophylactic and curative. Prophylaxis consists in the administration of calcium chloride in gr.-v doses thrice daily for the first few days. This treatment, which is advocated by Netter, of Paris, I have adopted chiefly in the mild cases, and found, with few exceptions, that either no rashes resulted, or that the rash was localised or discrete. As the serum disease is most likely to develop in mild cases of diphtheria, especially in adolescents and adults, this prophylactic treatment should be reserved for such cases. In young children, who rarely suffer much from the serum disease, it is unnecessary.

For the irritation produced by urticaria nothing excels the application of menthol ointment (menthol ʒj, Par. alb. moll. ℥j). For joint pains immobilisation of the joints by splints or the application of glycerine of belladonna fomentations is suitable. Aspirin or aceto-salicylic acid given in gr. viij doses two hourly acts better internally than do the salicylates. Cessation of the pains often coincides with hyperidrosis due to the drug.

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