

A Clinical Address

ON

SERUM SICKNESS.*

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FOR many years before the introduction of the serum treatment of disease the occasional practice of transfusion had made it known that the intravenous or subcutaneous injection of the blood of certain animals into a human being might be followed by results which were not only unpleasant but even at times dangerous. In consequence, the use of animals' blood for transfusion fell into disuse, and on the rare occasions on which the operation was practised human blood was employed.

Soon after the introduction and universal acceptance of the serum treatment of diphtheria in 1894, a method of treatment which was speedily extended to other bacterial diseases, it was noticed that in a considerable number of cases certain symptoms, of which the most obvious was a cutaneous eruption, followed the injection of the serum. A considerable body of facts concerning these symptoms was quickly collected. The frequency with which they occurred, the almost constant presence of a latent period, the details of the symptoms, and so forth, were ascertained and recorded. But no special significance was attached to them until, in 1905, it was pointed out by von Pirquet and Schick.²³ What that is and what it has led to it will be part of my purpose to explain later. At present I will only remind you that to these writers we owe the name "Serum sickness" (*die Serumkrankheit*), a term which is very convenient to indicate the group of symptoms which reveal the disease.

Before I proceed to discuss any of the questions which are raised by a consideration of the facts of serum sickness, it will be necessary for me to say something about these facts. The observations I present are the outcome of a 22 years' familiarity with the disease as it occurs in the course of the serum treatment of diphtheria, and more particularly from a study of 3502 consecutive cases during the period January, 1898, to June, 1908. I need hardly do more than state that it is the serum which is the primary cause of the disease and not the specific antitoxic principle it contains.

It will be convenient to deal with serum sickness under three heads: as it occurs, first, in the vast majority of persons who undergo an attack after a primary injection of serum, or a series of injections given within a week or so; secondly, in persons who have been re-injected after a lapse of a period of at least 10 days from the primary injection; and, thirdly, in a few persons after a primary injection.

I. SERUM SICKNESS AFTER PRIMARY INJECTIONS.

In the first class of cases the most common symptom is a rash, with or without a rise of temperature. Usually these two symptoms are synchronous; but occasionally the one precedes the other by a few hours.

The Rash.

In the vast majority of cases the rash is one of two kinds, or a combination of the two, urticaria, and a variety of hyperæmic erythema, especially the marginate or circinate. Next in frequency is a papular and macular rash, something like that of measles. Occasionally it consists of large but ill-defined blotches. A scarlatiniform erythema is unusual. Very exceptionally the erythema, which is then usually blotchy, becomes petechial or purpuric; very rarely indeed does it become vesicular or bullous. I have seen ten or a dozen instances of a hæmorrhagic but only one of a bullous serum rash.

The proportions of the two most common forms of rash, urticaria and erythema marginatum, vary in different series of cases.

Thus, Rolleston,²⁶ in 1905, referring to a paper by Stanley³² on anti-toxin rashes, published in 1902 (and both these writers dealt with serum-sickness as they saw it in the hospitals of the Metropolitan

* Founded upon the annual oration delivered before the Hunterian Society.

Asylums Board), writes: "At that time a circinate erythema, associated with pyrexia and constitutional disturbance, was more common than any other eruption; next most frequently urticaria was met with. Now, exactly the reverse holds good."

At the present time (1917) I should say that for some years past there has not been so marked a difference in the proportions of the two rashes as Rolleston found; and that urticaria slightly preponderated.

The fact that the rash is so often urticarial or of the form of erythema marginatum is not without significance, as will appear later. The rash sometimes, but by no means always, appears first at the seat of injection, and after a few hours comes out on other parts or universally. It has a special liking for the extremities, and particularly their extensor surfaces. It may be limited to the skin round the injection puncture. The duration of the rash is very variable, from a few hours to a few days. Commonly it lasts three or four days. I have known it to continue for over a fortnight, even for 17 days.

I have said that the rash is usually one of two kinds, or a combination of the two. Concerning the combination a curious fact may be mentioned. It is not at all uncommon to see two separate rashes, parted by an interval during which the skin is quite free from eruption. Both the rashes may be urticarial or some form of erythema; or one rash may be urticaria and the other erythema; the last is the most frequent combination. But if one of them is urticaria and the other erythema, the urticaria almost invariably presents itself first, a sequence which was pointed out by Rolleston. The longest interval I have met with has been 12 days. Usually it is less than a week. There may be pyrexia with both or only one of the rashes.

Another curious fact is that a solitary injection of serum may give rise to two and even three rashes, distinct as to their nature and date of appearance. I have elsewhere suggested that this phenomenon might be due to the practice which obtains of mixing the sera of different horses, partly to provide for use a serum of fairly constant antitoxic value, and partly to dilute a serum which might prove to be unwontedly irritating. It is known that the serum of one horse is prone to produce urticaria, while that of another will give rise to some form of erythema. As a rule urticaria comes out earlier than any other form of rash; so that if a mixed serum gives rise to two rashes the urticaria will appear first.† On the other hand, the second of the two rashes may, though rarely, be urticaria; and urticaria may appear as the first and only rash at a later period than it usually does.

The rashes, but especially the urticaria, of serum sickness may be accompanied by such other symptoms as are found with like rashes due to other causes. Thus itching is very common; and, if the rash is profuse, there may be considerable, though transient, œdema of the skin. Von Pirquet and Schick met with œdema apparently much more frequently than I have done. According to them it can, when not very obvious, be demonstrated by the increase in the weight of the patient while the œdema is present. During this period the excretion of urine is diminished. In my experience obvious œdema is rare, and is to be seen only in cases in which the rash is very profuse.

A rash occurs in rather more than one-third of the cases injected; but inasmuch as a considerable number of cases of diphtheria are fatal before a rash has time to make its appearance the incidence is more accurately determined by calculating it upon the cases which recover. Of 8726 recoveries amongst 10,000 consecutive cases of diphtheria I found that in 3502, or 40.1 per cent., a rash occurred. But if the deaths are included the percentage incidence is 35.02.

Other Symptoms.

The rash is often accompanied by pyrexia. Its degree bears no constant relation to the character or extent of the rash; but a rash seldom persists for more than two or three days without some elevation of the temperature. In a severe case the fever may go on for ten days, a fortnight, or longer. The temperature chart is usually of the intermittent type, and seldom shows a very high degree of pyrexia. Occasionally one meets with cases in which there is reason for believing that an attack of serum sickness shows itself by fever without a rash; but such cases are neither common nor, except in healthy persons who have received the serum as a prophylactic, easy to diagnose, and I have excluded them from my statistics.

In some of the more severe cases there is moderate enlargement of the glands, especially those of the neck; but this enlargement is seldom seen in mild cases. There may also be tonsillitis. Von Pirquet and Schick have demonstrated that during the illness there is marked leucopenia due to a

† This explanation, however, is not the true one. It has been shown by H. H. Dale and P. Hartley (*Biochem. Jour.*, 1916, x., 408) that each of two different proteins in the serum can produce a separate reaction and that the latent periods of these reactions differ in length of time. This fact appears to afford a clue to the interpretation of the phenomena described above.

diminution in the number of the polynuclear cells. According to Rolleston²⁷ the blood pressure is, as a rule, unaffected when the rash appears early, but when the rash is late it may rise. His observations were made while the rash was out in patients who were convalescent from diphtheria. This latter fact would vitiate the conclusions so far as serum sickness is concerned.

Perspiration is usually a prominent symptom in all but the mildest cases. Not infrequently, too, there is albuminuria, and vomiting is not uncommon.

Complications.

These, then, are the usual symptoms of an ordinary attack of serum sickness; to them are sometimes added others which, by analogy with other diseases, may be termed complications. The most frequent of these is one which usually goes by the name of "joint pains," but which is, I have no doubt, an arthritis. It occurred in 376 of the 8726 above-mentioned cases of diphtheria—4.3 per cent. It is nearly always accompanied by a rash, and usually also by pyrexia. Rash and arthritis may coincide, or the former may precede the latter by an interval of a few days, in which case the rash is usually urticaria.

The joints affected are commonly the wrists, elbows, ankles, and knees; but not seldom those of the hands, shoulders, and hips are involved. In one case and another there is hardly a joint which I have not seen affected, including such as the sterno-clavicular and the temporo-maxillary. In some cases there is swelling, which is rarely extreme. In the majority of the cases, however, as the name I have mentioned above implies, there is only pain in some of the joints, with stiffness but without swelling. Occasionally the pain appears to be seated in the periartritic structures rather than in the joints themselves, and it may also appear to be located in the fasciæ. In the case of a young woman, aged 20, who was under my care and who said that she was subject to pains in the loins, there was severe lumbago, with rash and pyrexia.

The arthritis seldom persists for longer than two or three days, and very rarely recurs. In only one of the 376 cases was there a relapse; it was that of a boy, aged 8 years, who suffered from multiple arthritis of four days' duration. A fortnight later there was well-marked inflammation of the right knee. Suppuration of a joint is very rare; I have met with it only twice. One of the cases was one of the series of 376. In both instances there was a pyæmic focus present before the arthritis set in. One patient was the subject not only of diphtheria but also of severe scarlet fever with a sloughing throat; in the other the cervical lymphatic glands were suppurating. In each instance I think it almost certain that the inflamed joint was infected, through the circulation, from the pyæmic focus.

I have never met with a case of the arthritis of serum sickness in which the heart was involved, as happens in rheumatic fever; and I know only of one recorded case, namely, that reported by Rosenhaupt³⁰ in 1905, in which there was pericardial effusion.

One or two rare complications remain to be mentioned. In a very few cases I have seen œdema of the scrotum, and occasionally also of the penis, lasting from one to eight days. The œdema occurred independently of a rash on the part affected and of œdema elsewhere. In three or four of the cases I suspected orchitis, but could not be certain of it because of the scrotal swelling. All the patients were children.

In a very few cases, three or four altogether, I have observed transient hæmaturia. But I have never met with a nephritis due to serum, unless one, of five days' duration, may be accounted as such, which occurred in a girl of 10 years, who had just recovered from an attack of post-scarlatinal nephritis. The urine had been free from albumin for 18 days before the antitoxin was given. But the post-serum nephritis may have been a recrudescence of the renal lesion due to scarlet fever, an event which occasionally takes place. Otherwise I have no clinical evidence to show that serum injures the kidneys. On the other hand, I have observed at least 18 cases in which serum was given to patients who were at the time the subject of acute or chronic nephritis, and no effect, good or bad, was produced on the kidneys, so far as clinical observation could determine.

Incidence.—Latent Period.

So far, I have been dealing with the ordinary form of serum sickness. Before I pass on to consider the unusual varieties there are one or two general points to which I wish to draw your attention.

It might be supposed *a priori* that if a number of persons of both sexes and of various ages were to be injected with serum the cases of serum sickness which occurred would be equally distributed amongst them. But it is not so, at any rate so far as my figures go. An analysis of the cases shows that the disease is more frequent in the female than in the male sex, and the difference in the incidence is most marked in patients over ten years of age. As regards those cases of sickness of which the chief sign is a rash, children are more frequently affected than adults, especially in the male sex; for in the female the difference is not striking. (See Table II.) In respect of arthritis, however, the reverse is the case, and children are less liable to be attacked than adults. (See Tables I. and II.)

Another point is that the frequency of the disease varies directly with the volume of serum injected. I am unable to prove this from *my* cases, because the serum has been given

TABLE I.—Age-incidence of Serum Sickness (Rash and Joint-pains) occurring amongst 10,000 Consecutive Cases of Diphtheria Treated with Antitoxic Serum. Males.

Ages.	No. of cases.	Rashes.		Joint-pains.	
		Cases.	%	Cases.	%
0-	2266	788	34.7	35	1.5
5-	1580	499	31.5	48	3.0
10-	489	153	31.2	24	4.9
15-	148	46	31.0	10	6.7
20-	115	27	23.4	9	7.8
30-	44	5	11.3	1	2.2
40-	12	1	6.6	0	0.0
50-	2	0			
60-	1	0			
Total ...	4657	1519	32.6	127	2.7
<i>Females.</i>					
0-	2234	819	36.6	32	1.4
5-	1921	689	35.8	78	4.0
10-	642	254	39.5	60	9.3
15-	269	84	40.1	24	11.4
20-	227	90	39.6	32	14.0
30-	81	33	40.7	17	21.0
40-	21	9	48.2	4	20.6
50-	6	3			
60-	2	2			
Total ...	5343	1983	37.1	249	4.6
<i>Total: Males and Females.</i>					
All ages..	10000	3502	35.0	376	3.7

TABLE II.—Age-incidence of Serum Sickness (Rash and Joint-pains) occurring amongst the Non-fatal Cases of Table I. Males.

Ages.	No. of cases.	Rashes.		Joint-pains.	
		Cases.	%	Cases.	%
0-	1853	788	42.5	35	1.8
5-	1424	499	35.0	48	3.3
10-	471	153	32.3	24	5.0
15-	144	46	31.9	10	6.9
20-	111	27	24.3	9	8.1
30-	44	5	11.3	1	2.2
40-	11	1	7.6	0	0.0
50-	1	0			
60-	1	0			
Total...	4060	1519	37.8	127	3.1
<i>Females.</i>					
0-	1796	819	45.5	32	1.7
5-	1724	689	39.9	78	4.5
10-	609	254	41.7	60	9.8
15-	206	84	40.7	24	11.6
20-	224	90	40.1	32	14.2
30-	80	33	41.2	17	21.2
40-	20	9	48.2	4	22.2
50-	5	3			
60-	2	2			
Total...	4666	1983	42.4	249	5.3
<i>Totals: Males and Females.</i>					
All ages..	8726	3502	40.1	376	4.3

in unit and not in c.cm. doses. The volume containing the same number of units has varied from time to time, and the records state the doses in units and not in c.cm. Other observers have investigated this question and have, as a rule, found that the larger the volume for the average dose the higher the frequency of the rash. Weaver,³¹ for instance, gives figures which show this clearly, and Rolleston states that in his series of cases "the frequency of rashes and other serum phenomena are in direct relation to the size of the dose and in inverse relation to the character of the diphtherial attack." It must, however, at the same time be remembered that the serum of some horses is more provocative of serum sickness than is that of others—a factor which would have a disturbing influence on the conclusions

above. These second injections were given for relapses or second attacks of diphtheria, or in cases of scarlet fever or diphtheria which had received a prophylactic injection some time previously.

The first published cases of this unusual form of illness seem to have been two recorded by Hartnung¹⁷ and one by Denys and Leclef⁸ in 1836. I submitted an account of three cases to the Antitoxin Committee of the Clinical Society, and they were published in the Committee's report⁶ in 1898. But no particular significance was attached to the facts recorded, chiefly, I suppose, because they were few and far between. Opportunities for re-injection under the circumstances I have mentioned presented themselves only now and again, at any rate, in this country.

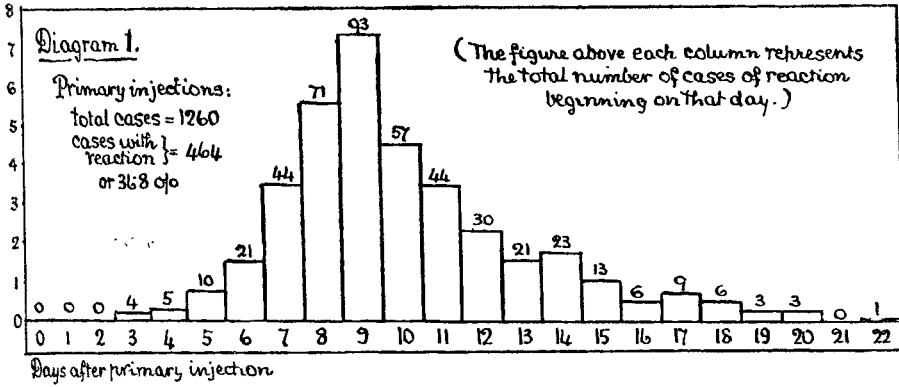
At first I was under the impression that the abnormal symptoms were due to some peculiarity of the particular brand of serum used. But as time went on more cases of a like nature came under observation, and it became clear that the abnormal reactions were to be met with almost solely in patients who had been re-injected for an actual or supposed relapse or second attack of diphtheria. I drew attention to these cases in an article on diphtheria published in 1900,¹³ and also in an address on serum therapy which I gave at the Oxford meeting of the British Medical Association in 1904.¹² But I was unable to give an explanation of them. The experimental work which bore on the subject had only recently been made known, and I was not aware of it. In 1905 von Pirquet and Schick brought out their book, "Die Serumkrankheit," and in it these curious phenomena were described in detail, and an attempt was made to explain them by reference to the experimental work of Richet,²⁵ Arthus,¹ and others.

Now before I describe in what way serum sickness in re-injected persons differs from the ordinary form of the disease I must make it clear what is meant in this connexion by a re-injected person.

I have already stated that these abnormal reactions were noticed in persons who received a second injection of serum some time after the first. It is a very common practice in serum treatment to give several injections. As a rule, they are administered at short intervals, usually of a day or two, and the series of injections may extend over several days. But it must be particularly pointed out that, in persons treated in such a manner, abnormal reactions are not to be expected after any of the serial injections. Currie⁷ made a careful study of these cases and showed that doses repeated at short intervals were not followed by abnormal reactions.

But it is quite a different matter when between the primary injection, whether a single one or the first of a series given at short

Percentage of cases with reaction



when the number of cases analysed was scanty. Still, the evidence available goes to show that the incidence of the disease depends upon the volume of serum injected. As children receive a relatively larger volume of serum than do adults, they may perhaps be expected more readily to fall ill of serum sickness.

But the most important point is that in the vast majority of cases there is a distinct period, free from any symptoms attributable to the serum, between the injection of the serum and the onset of the sickness. Of 464 consecutive cases which I have analysed the rash appeared in 3 to 22 days after the first injection. In 404 of these cases the duration of the latent period was 6 to 14 days. In only 19 cases was it shorter than 6 days. (See Diagram 1.) The most common length of the period was 9 days (93 cases). These results agree almost exactly with those which have been arrived at by other observers. But though it so happened that in this particular series of 464 no case showed symptoms earlier than the third day, yet in a very few cases outside the series I have observed a rash to come out the day after or two days after an injection; and in one instance there were vomiting and urticaria three and a half hours after. In none of these cases were there any other reasons for supposing that the patient had been injected with serum on a previous occasion.

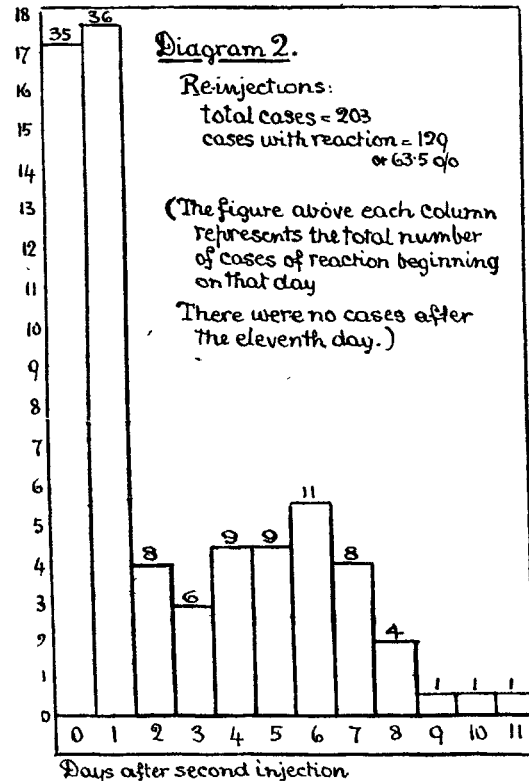
So much for serum sickness as it occurs in most cases after a primary injection or series of injections. After a latent period of several days, commonly 6 to 15, there is an attack of fever with a rash, occasionally accompanied or followed by arthritis. It will be convenient when I am considering the other varieties of the disease to designate the usual form as the "normal reaction" to serum.

II. SERUM SICKNESS IN RE-INJECTED CASES.

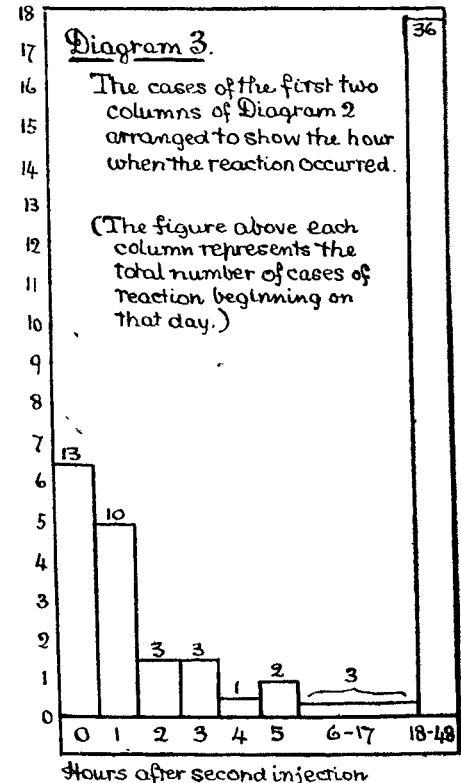
I will now turn to a study of the illness as it shows itself in persons who have been treated with serum previously.

After the serum treatment of diphtheria and certain other diseases had been in vogue for a few years it came to be noticed that when a person was injected with serum a second time some weeks or months after the first injection an attack of serum sickness might occur which differed in one way or another from the usual form which I have described

Percentage of cases with reaction



Percentage of cases with reaction



intervals, and the secondary injection there is an interval of at least ten days—that is to say, when the interval is longer than the ordinary latent period of the normal reaction. This important fact was elicited and emphasised by von Pirquet and Schick.

When, therefore, I speak of a re-injected person I mean one who has received serum treatment a second time after the lapse of a period from the first injection which is at least equal in length to the latent period of the normal reaction.

During the 16 years ending Dec. 31st, 1912, I had under my observation 203 patients who received serum treatment a second time for a relapse or second attack of diphtheria, actual or supposed, and it is of these patients I am now about to write. In 129 of them there was an attack of serum sickness after the re-injection.

Reaction in Re-injected Persons.

In a re-injected person the reaction may be a normal one, both as regards the latent period and the symptoms. But that is not common; usually the reaction departs from the normal, and its abnormality may be shown in one of three ways or a combination of them. In one the latent period is shortened, in another the attack of serum sickness is unusually severe, while in the third unwonted symptoms are present.

(1) The most common abnormality is *shortening of the latent period*. This is well shown in Diagrams 1 and 2. It is clear from these diagrams that in the bulk of the primarily injected cases the latent period is longer than a week, while in the bulk of the re-injected it is shorter than a week. In the latter group there are only 3 cases with a latent period of longer than eight days—2.3 per cent. of all the cases; while in the first group there are 309, or 66.5 per cent., with a latent period of over eight days. This is a very striking difference. But a still more striking difference is to be found in the fact that in 71 of the re-injected cases in which a rash occurred, or 55 per cent., the latent period was under two days. I have already stated that in ordinary serum sickness instances of latent periods of less than three days are rare.

Von Pirquet and Schick divided the cases with curtailed latent periods into two classes—those in which it was less than 24 hours and those in which it was longer than 24 hours but shorter than 7 days. To the former they applied the term "immediate reaction," to the latter "accelerated reaction." But there is a sharp distinction between these two classes which does not appear in Diagram 2. For of the 35 cases in which the latent period was less than 24 hours, in 32 it was less than six, and in 23 of the 32 less than two. In 3 cases, indeed, the latent period was absolutely abolished and the symptoms came on immediately, while in 10 they arose after an interval varying from 10 to 60 minutes. It is probable that in a few of the 36 cases in which the reaction was stated to have set in the day after the injection the latent period was somewhat under 24 hours. Probably, too, after six hours the cases were spread fairly evenly over the period 6 to 48 hours. There appears, therefore, to be a pronounced difference between the numbers of cases occurring during the first six hours, and especially the first two, and those occurring subsequently, so that I should be inclined to limit the term "immediate reaction" to all instances in which the latent period was less than six hours. (See Diagram 3.)

It should be mentioned that the same patient may undergo more than one reaction. Thus, 25 had both an immediate and an accelerated reaction, and 1 had not only both these but also a normal reaction. (See Table III.) From this

TABLE III.

Immediate reaction only	8	Accelerated and normal re-	
Accelerated	74	actions	5
Normal	15	All three reactions	1
Immediate and accelerated re-	25		
actions			129
Immediate and normal re-	1		
actions			

table it appears that the accelerated reaction is the most frequent. In 105 cases the patient underwent an accelerated, in 35 an immediate, and in 22 a normal reaction, alone or combined.

(2) The second abnormality is exhibited by *unusual severity of the attack*. This may occur irrespective of the length of the latent period. In these cases the rash, usually urticaria, often with gigantic wheals, is very profuse and comes out with extraordinary celerity. The mucous membranes of the mouth, nose, pharynx, larynx, and possibly also of the stomach, seem to be invaded. The tongue may be swollen and the respiration embarrassed, and there may be vomiting and epigastric pain. In a few cases the patient is seized with faintness and muscular weakness. The temperature may for a short time be high. Usually these most unpleasant, not to say threatening, symptoms pass off as quickly as they arose. Occasionally there is an exceptionally smart attack of arthritis. Fortunately this class of cases is by no means numerous. Those with a profuse urticarial rash, involvement of the mucous membranes, dyspnoea, and prostration, are prone to be associated with absence or extreme shortness of the latent period. But I have never seen arthritis occur earlier than the day after the injection.

(3) Lastly, there are some cases, happily also few in number, in which *unusual symptoms occur*. They are always part of an immediate reaction, and consist of rigors, sometimes severe and prolonged, muscular twitchings, and even convulsions, drowsiness, dyspnoea (not apparently due to urticaria of the larynx), collapse, vomiting, and a high temperature. There may also be abdominal pain and diarrhoea. The rash, always urticaria, may precede or follow these symptoms, which are not all present in every case. Nor are the most severe of them of long duration; but prostration may remain, and it is some time before the patient completely recovers. I have met with eight cases of this description, and all of them recovered.

The vast majority of cases of serum sickness, normal or abnormal, recover completely. I have never met with one which became chronic; but Blain⁴ records that of a young woman, aged 22, in whom urticaria, set up by a re-injection six months after the first, lasted for upwards of four months at the least.

The facts I have brought forward in respect of the re-injected cases, the shortening of the latent period, the occurrence of unwonted symptoms, and the greater frequency of severe attacks—that is, when compared with the number of severe cases amongst normal reactions—show that these persons are more susceptible to serum, not only than are others, but also than they themselves were at the time of the primary injection. This increased susceptibility is further shown by the higher frequency of reactions, normal and abnormal, amongst them. Of the 203 re-injected cases 129 underwent a reaction, 63.5 per cent., a figure which is in striking contrast with the 40 per cent. of the primarily injected cases.‡

There is some evidence to show—though I cannot say it is strong, for the cases are scanty—that those persons who suffer from an attack of serum sickness after the primary injection are more prone than those who do not to undergo an attack, and especially an unusual attack, after the second. In 188 of the re-injected cases the history of the primary injection is accurately known. Half of these suffered from serum sickness then, and half did not. In 70, or 74.4 per cent., of the former, and in 47, or 50 per cent., of the latter, a reaction occurred after the re-injection. Further, there is a larger proportion of the immediate reactions amongst the former, namely, 26 in 70, 1 in 2½, as against 7 in 47, 1 in 6½, amongst the latter.

Duration of Supersensitive State.—Arthus's Phenomenon.

It is a point of importance as well as of interest to know how long a person will remain in the supersensitive state which has been induced by the primary injection. I have already stated that a person gives no evidence of having been sensitised if he is re-injected during the latent period. The shortest period I have known between the primary and the secondary injection, when the occurrence of an abnormal reaction has demonstrated the supersensitive condition, has been 16 days, both for an immediate reaction and for an accelerated reaction. Both occurred in the same patient; the immediate reaction appeared 10 minutes, and the accelerated reaction two days, after the re-injection.

The answer to the question how long the supersensitivity lasts has not yet been furnished, at any rate so far as man is concerned. Possibly it may last for a person's lifetime. I have known it to be present upwards of seven years after the primary injection.

A boy, aged 10 years, suffering from diphtheria, was admitted to the Eastern Hospital on Oct. 15th, 1904, when he received 12,000 units of antitoxic serum. Eighteen days later there was a rash, followed in three days by arthritis and pyrexia. He was readmitted to the hospital for a second attack of diphtheria on Dec. 4th, 1911. At first the diagnosis of his case was doubtful, but on the 7th distinct membrane appeared, and he received 12,000 units. Half an hour later an urticarial rash came out. Next day there was pyrexia and on the 12th a rash. On the 14th arthritis set in. During the rash and arthritis there was fever.

The patient, therefore, on this occasion underwent an immediate and an accelerated reaction. The reaction was more severe than that which he had exhibited seven years before.

It has been stated by more than one observer that there is an optimum period for the supersensitiveness in persons treated with serum.

Thus, Grysez and Bernard¹⁵ concluded from certain experiments made upon guinea-pigs with the blood and serum of persons who had been injected with horse serum that there is little development of the condition within 36 days of the injection, that the symptoms of abnormal serum sickness are most likely to be evoked from the 37th to the 188th day, and that between the 197th and the 342nd day the supersensitiveness disappears.

But these conclusions are not quite in agreement with what I have noticed in my cases.

‡ It should be added that of recent years not only the anaphylactic but also the normal serum phenomena have been less severe than formerly in cases under my observation, though they are still almost as frequent as they were. This is probably due to certain improvements in the making of the serum.—E. W. G., November, 1917.

1 In the 25 cases in which there was both an immediate and accelerated reaction there was a distinct interval, usually of at least 24 hours, between the two.

Of 45 patients re-injected within 36 days of the first injection, 17, or 37.7 per cent., were supersensitive, and 6 of them showed an immediate reaction, and of 26 injected later than the 183rd day 19 were supersensitive, and seven of them underwent an immediate reaction. Twenty-one of these cases were re-injected after the 342nd day, and of these 17 gave signs of supersensitiveness.

My cases therefore afford no evidence of the existence of an optimum period, or that the increased sensibility disappears after any particular length of time.

I have stated that the rash of both the normal and abnormal reaction may be limited to the seat of injection. I shall have occasion later to refer to certain experiments in which supersensitiveness is induced in animals. In rabbits this may be localised. The skin and subcutaneous tissues at sites of former injections become inflamed, and necrosis may follow. This is known as "Arthus's phenomenon." It is very rare in the human subject according to my experience. In fact, I have never met with precisely that phenomenon in man. The nearest approach has been induration at the site of the re-injection in two or three cases in re-injected persons as defined above. In one of these cases there was localised gangrene as a part of an accelerated reaction. I have never met with infiltration at previous injection-sites.

III. ABNORMAL SERUM SICKNESS WITHOUT PREVIOUS SERUM TREATMENT.

It now remains for me to speak of the third of the classes into which I have divided cases of serum sickness. They are to be met with in persons who have never previously been treated with serum. They possess to a marked degree the peculiarities of absence of the latent period and excessive severity of symptoms. It is, indeed, this group which has furnished nearly all the instances of death immediately after an injection of serum.

One of the earliest of these cases was the well-known one of the child of Professor Langerhans,¹⁹ who died suddenly after a prophylactic injection of antidiphtherial serum. This was in 1836. From time to time a case of a similar nature was reported. But no special attention seems to have been paid to them.

About the year 1905, however, the use of horse-serum as a remedy for asthma and hay fever began to be advocated in the United States. Apparently this use of serum was introduced as the result of a chance observation that an injection of serum, given as a prophylactic against diphtheria in a pe son who happened to be the subject of asthma, was followed by a decided relief of the symptoms of that disease. After a time, however, cases began to crop up in which the administration of serum in asthma and allied affections was almost immediately followed by symptoms which were always extremely serious and in some instances rapidly fatal.

The symptoms are: irritation (sensations of itching and burning), with very acute œdema of the skin and of the mucous membranes of the nose, mouth, and throat; urgent dyspnoea and cyanosis; and foaming at the mouth. In some cases there is a rash, usually urticaria; in others there is not. In fatal cases death has been due to inability to breathe, and there may be convulsions and coma. Respiration stops before the heart ceases to beat. It has been stated that in some cases there has been collapse. But in most of those of which details have been given the respiration and not the circulation has been the first to fail.

The occurrence of these untoward events in asthmatics to whom serum had been administered as treatment of their chronic disease drew attention to the fact that in not a few of the cases in which fatal or alarming results had followed the use of serum either as a remedy for or a prophylactic against diphtheria the patient was the subject of asthma in one of its many varieties, and those persons in whom an attack of asthma is excited by the emanations from the horse seem especially to be prone to fall victims to these evil effects of horse serum.

I may remark in passing that while these tragedies have occurred, and the majority of the victims have been asthmatics, yet some individuals who are subject to that disease, far from suffering any of the alarming symptoms I have mentioned, receive most distinct relief from their asthmatic attacks. In some of them, indeed, even re-injections of serum repeated at long intervals have produced no symptoms of serum sickness. But the immunity from the fits of asthma has proved in most instances to have been only temporary, and Dr. Gillette,¹¹ who was the first to draw attention to the danger of giving serum to asthmatics, though he himself had received some benefit from its use, has informed me that, in consequence of the failure of the remedy to procure any lasting relief, and especially because of the undoubted risk the asthmatic runs from serum, its use as a remedy for asthma had been abandoned, at any rate in the United States.

SUMMARY.

It will be gathered from what I have said that so far as their susceptibility to horse serum administered by subcutaneous injection is concerned human beings are by nature ranged in three classes. The first consists of those who are unaffected by the serum, and contains the majority

of persons. The second consists of those who are so far sensitive that they give a normal reaction, and this class is fairly numerous. The third comprises those who are sensitive to such a degree that they respond with an extraordinary and severe reaction. Fortunately such individuals are comparatively rare, and many of them have exhibited the peculiarity of an asthmatic idiosyncrasy before they have been injected with serum. To these natural classes may be added a fourth, consisting of those who have been artificially rendered oversensitive. While individuals of this class respond abnormally, the reaction is seldom so unusual as is that of the third of the natural classes.

(To be concluded)

EYE-STRAIN : THE CONDITION OF "BLEPSOPATHIA."¹

By HAROLD A. DES VŒUX, M.D. BRUX.

WHETHER or not the conclusion to which I have been driven by the facts set out in the accompanying table will be generally accepted, it has been arrived at after years of observation and thought in studying some of the common symptoms which one frequently meets with in practice. These symptoms seem as usual in those who are of middle age or even young as in the elderly, and are variously described by the sufferers as being "liver," "heady," "stupid in the head," "good for nothing," "slack." One of the most constant symptoms is headache in a more or less severe degree.

Headache is so common a symptom of general diseases, of blood poisoning, of all acute and most chronic affections that it seems never to be considered as a disease entity in itself, or, in other words, that the pain in the head may have far-reaching results. It is usual when headache is a prominent symptom to attribute the pain to some distant organ, and even migraine until recent years has been regarded as a disease "of the liver" and not as a "nerve storm." When pain is situated in the region of any organ of the body—say the lung, the heart, or the kidney—it is considered as a sure sign of illness or affection of that organ, more especially if accompanied by tenderness. But when pain is concentrated in or about the eye, when the eye is tender on pressure, and when the patient is so sensitive to light that his only comfort is to lie in a darkened room, it is a heresy to consider the eye as a cause of the pain.

Early Observations.

My attention had been drawn for some years to the eye as the only possible cause of the train of symptoms about to be considered, but I obtained no satisfaction either from the patient or his oculist in deciding the question. The patient, very often a young man or woman, declared that the eyesight was perfect, and the oculist when referred to would say practically the same, but might add that there was $\frac{1}{2}$ D. or $\frac{1}{3}$ D. of hypermetropia, an amount that could be neglected. In fact, at the present day I have several patients, some who suffer pretty severely, who have on my advice consulted their oculist, and come back with the clinching reply, "I told you so, my eyesight is perfect."

It was not for some years after I had provisionally surmised that the eye was the cause of these illnesses that the late Mr. McHardy, by curing two of the worst (Nos. 9 and 74), absolutely convinced me of its truth.

Miss O., aged 26, seen in 1909, had for many years suffered from great depression, weakness, and general neurasthenic symptoms, and at times from frontal headache lasting for many days. She had undergone most of the usual treatments, including a rest-cure, without benefit. She was almost completely cured of all these symptoms by wearing glasses ordered by Mr. McHardy, though otherwise she is a delicate woman, having suffered, amongst other things, from mastoid suppuration (supposed to be tubercular) and sciatica. As illustrating a point which I shall refer to again later, I may mention that she has consulted four oculists since Mr. McHardy's death, one of whom told her that her eyes were normal and that she required no glasses; two ordered her glasses which did not relieve her, and the fourth only succeeded after several very long examinations.

¹ A paper read before the Medical Society of London on Feb. 4th.