FURTHER EXPERIENCES WITH INTRAVENOUS ANTITOXIN TREATMENT OF SCARLET FEVER.

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A preliminary paper of mine (1929) on 404 cases of scarlet fever treated during the epidemic period May to December, 1928, in Leicester, by *intravenous* administration of scarlatinal antitoxin suggested that (1) the acute stage of the disease could be shortened, (2) complications could thereby be largely prevented, and (3) the period of residence required in hospital could be very materially reduced. The present paper supplements the former one, dealing, in addition, with 800 cases treated without fatality, during the post-epidemic years 1929–32, a period of low prevalence of the disease. The case for *intravenous* antitoxin treatment now presented is thus based on a personal experience of 1204 cases so treated during a time of epidemic and of non-epidemic prevalence covering a period of 4½ years.

It has not been possible to provide a strictly comparable series of controls. The writer has become so convinced of the outstanding value of this treatment that he has considered it unjustifiable to withhold its benefits from any considerable series of cases committed to his care, merely for the purpose of providing a pretty control experiment. The introduction in 1928 of general intravenous serum treatment of definite pyrexial cases of scarlet fever effected a sudden and complete transformation of the work of the scarlet fever wards. Complications, desquamation, duration of residence in hospital, cross-infections and relapses fell away to an incredibly low level and remained so, to the time of writing. In the following table a contrast is made between the cases treated in 1927, when no serum was used, and those of the present series:

Table I.

	Year 1927 (no serum) 285 cases	Years 1928–32 (intravenous serum) 1204 cases
Complications of scarlet fever:		
Otitis media	6·7 %	0·9 %
Mastoiditis	1·0 %	0·08 %
Nephritis	3·7 %	0·8 %
Arthritis	1·7 %	0·16 %
Total complications	33·0 %	5·2 %
Mortality	1·05 %	0·08 %
Average stay in hospital	46 days	16·6 days

https://doi.org/10.1017/S0022172400018581 Published online by Cambridge University Press

When an obvious improvement of this magnitude on the previous work of years is effected, and maintained for a period of 4½ years, the question of controls becomes of mere academic interest. If controls are wanted, they are to be found in the published statistics and in the practice of dozens of fever hospitals throughout the country. It is hoped that sufficient data are included in the tabular statement Table II, p. 284, to enable a fair comparison with other series of cases to be made. It is not proposed to deal in detail with the literature on the subject, which has recently been adequately summarised by Thompson and Thompson (1930). It appears that other published series of intravenously treated cases are very few and deal with small numbers. Thus Anderson and Leonard (1926) reported 4·6 per cent. of complications and no deaths in a series of 130 cases in 1926; and Toomey and Dolch (1928), using various makes of concentrated and unconcentrated serum, reported excellent results in 14 out of 54 cases, but 3 deaths among the remaining 40 cases.

In the present investigation, the results obtained in each year are set out in Table I.

Points of interest which emerged were as follows.

I. RAPID ARREST OF ACUTE STAGE.

This comprised, in the average case, (*a*) fall of temperature by crisis in 6–12 hours, (*b*) disappearance of toxaemic symptoms with general feeling of well-being in 6–12 hours, (*c*) *subsidence of faucial oedema in about* 12 *hours*, (*d*) fading of rash in 12–24 hours.

When these effects are obtained in any given case, certain substantial advantages follow. The rapid arrest of the fever restores comfort and brings about almost immediate return of appetite and normal sleep. Ordinary diet is tolerated after 24 hours; there is little, if any, loss of normal nutrition, and convalescence is correspondingly rapid. The patient may then be safely allowed up after 4 or 5 days.

The rapidity with which faucial oedema subsides is even more important. It appears, indeed, to be the *key* effect, and to be particularly associated with antitoxin administered *intravenously*. As oedema subsides, the pain associated with swallowing is relieved, Eustachian drainage is quickly re-established, allowing middle ear inflammation to resolve, and the flow of septic material to the cervical glands is checked. The rapid resolution of the inflammatory infective stage in the majority of new entrants to a hospital ward prevents the accumulation of mass infection in the ward, and such secondary effects as recurrent tonsilitis, adenitis, arthritis and relapse become exceedingly rare.

Finally, the rapid fading of the rash prevents desquamation. Desquamation was entirely absent as a rule if the serum was given not later than the third day of the disease, and modified to a fine powdering, with or without small

Table II. *Intravenous Antitoxin Treatment of Scarlet Fever in Leicester*, 1928–32.

	Year					
	May–Dec. 1928 Epidemic	1929	1930	1931	1932	Totals
Intravenous cases	404	179	148	222	251	1204
Percentage of all verified cases	41	57	67	90	76	56
Average stay in hospital:						
All verified cases (days)	24	21	22·7	18	19	20
Intravenous cases (days)	17·7	15·7	18·4	15	16·7	16·6*
Serum reaction (thermal) with rigor (%)	60	42	7	16	15	33
Severe types:						
Septic	3	4	5	1	4	17
Semi-septic	8	2	4	7	6	27
Complications occurring after admission:						
Otitis media	—	1	3	3	4	11
Mastoiditis	—	—	—	1	—	1
Nephritis and albuminuria	—	2	3	1	4	10
Arthritis and rheumatism	—	1	1	—	—	2
Adenitis	2	1	4	8	2	17
Tonsilitis	2	—	4	2	1	9
Others	2	—	1	2	1	6
Noted *after* discharge from hospital	2	—	2	—	3	7
Infective foci (skin abrasions, etc.) in hospital	2	2	3	11	5	23
Infective foci (skin abrasions, etc.) after discharge	5	2	4	3	2	16
Total complications (excluding "infective foci")	8	5	18	17	15	63
Total complicated cases	8	4	11	13	14	50
Complication rate (%)	2	2·8	12	7·6	6	5·2
Complicated case rate (%)	2	2·2	7·4	5·8	5·6	4·2
Complication rate (including "infective foci") %	3·9	5	12	10·8	7·6	8·5
Complications present on admission:						
Old otitis or otorrhoea	3	3	5	6	3	20
Nephritis and albuminuria	3	—	1	1	—	5
Rhinitis	1	—	2	4	5	12
Others	1	2	5	9	2	19
Secondary pyrexia (%)	8	4·6	6·8	3·6	5·7	6·1
Relapse	—	—	—	1	—	1
Re-admission with scarlet-fever	—	—	—	—	2	2
Age grouping (years):						
0–5	40	16	19	41	72	15 %
6–10	145	73	63	105	90	40 %
11–15	123	34	27	33	54	22 %
16–20	51	19	22	12	11	10 %
Over 20	45	37	17	31	24	13 %
"Return" case rate of all discharges (%)	1·5	1·2	0·9	1·9	2·7	3·4
Cross-infection of scarlet fever wards:						
Mumps	2	—	—	—	—	2
Chickenpox	—	1	—	—	—	1
Measles	—	1	—	—	3	4
Other fevers	—	—	—	—	—	—

* Exclusive of 26 cases retained in hospital for reasons unassociated with scarlet fever.

https://doi.org/10.1017/S0022172400018581 Published online by Cambridge University Press

flakes on the hands and feet, if administration of the serum was delayed to the fourth or fifth day.

II. REDUCTION OF COMPLICATIONS.

Complications were reduced to a remarkable extent even when due allowance is made for the milder type of scarlet fever prevalent in recent years. The few complications which did occur were of short duration and so mild as to leave no ascertainable permanent damage.

Acute suppurative otitis media occurred in only 0·9 per cent. of the cases; the ear discharge was in most cases of short duration, and in all cases (generally after treatment by zinc ionisation) the perforation in the membrane was healed and all discharge had ceased for at least 7 days before the patient was discharged from hospital. As far as could be ascertained, the cure was permanent, no recurrence of ear discharge in any of these cases having been discovered at the School Ear Clinic or elsewhere in the district.

Mastoiditis occurred in one case only, a case of old-standing recurrent otitis media.

Nephritis and albuminuria was a complication in only 0·8 per cent., and not a single case exhibited oedema, puffiness or any classical sign of nephritis, with the exception of mild transient pyrexia in a few cases. The average duration of the albuminuria was 12 days, and of the haematuria (which was present in about half of the cases), 7 days.

Arthritis or rheumatism, nominally 0·16 per cent., was negligible: one of the two cases was apparently an acute exacerbation of old rheumatism, and the other had pain in the wrist with pyrexia of 4 days' duration. In addition, a few cases complained of joint pains for a day or two in association with the serum rash but without actual swelling of the joints.

Adenitis (simple) occurred in 1·4 per cent.; was always mild, and some cases were doubtless acute manifestations of chronic adenitis.

Suppurative adenitis occurred in one case only (Case II, see p. 289).

Tonsilitis cases (0·7 per cent.) were all very mild, and some were probably due to infection passing between patients and staff in times of epidemic catarrhs.

Secondary pyrexia: a bout of 3-day pyrexia commencing about the third day after the intravenous injection, occurred in about 4–8 per cent. of the cases. It was unaccompanied by symptoms or signs, except headache in some cases. It has not been classed as a "complication."

Deaths: one case (reported in my 1928 series). *Case Mortality* 0·08 per cent.

Total complication rate was 5·2 per cent. (including those noted after discharge from hospital) and the *complicated case rate* 4·2 per cent., more than one complication being present in a few cases. This figure for complications is, however, *exclusive* of serum rashes, complications present on admission (4·6 per cent.) and of "infective foci" (3·3 per cent.), *i.e.* minor septic skin abrasions, rhagades at angle of mouth and nares, etc., which were too trivial to be classed

as complications. If, however, for the sake of comparison, it is desired to include all infective foci, inclusive of those noted after discharge from hospital (in connection with the "follow-up" scheme) the complication rate would then become 8·5 per cent., and if, in addition, complications present on admission are included, the figure so swollen would not exceed 13·1 per cent. The pure complication rate of 5·2 per cent. is considered, however, to give a fairer representation of the facts.

III. Reduction of period of residence in hospital.

The typical case, showing a normal response to intravenous serum treatment, shows no evident loss of nutrition, no desquamation nor complication, and may be discharged from hospital after 8–10 days, or a few days longer, if it is considered desirable that the patient should remain in hospital over the period of the serum rash. Patients discharged after such a short stay were requested to report at an out-patient clinic for examination 1–2 weeks after their discharge, bringing with them a specimen of urine. Patients whose general condition was poor or who had any complication or associated disease were, of course, retained until well. *Hence, in actual practice, the average stay in hospital for the series worked out at* 16·6 *days.* This figure is exclusive of 26 cases which were retained in hospital for long periods on account of conditions quite unrelated to scarlet fever, *e.g.* pertussis, fractures, burns, old otitis, old rheumatism, etc. At the out-patient clinic it was very rare to find any complication. Two cases turned up with mild acute adenitis and two with albuminuria (faint trace). Three of these four cases were re-admitted to hospital, but their complaints were found to be trivial and they were discharged again after a few days. There were also a small number of patients who turned up with skin abrasions and minor sepsis. Defaulters at the out-patient clinic were few, and when followed up to their homes were able to give reasonable explanations of their absence.

IV. Relapses, cross-infections, "return" cases and re-admissions.

Only one relapse, or re-infection with scarlet fever, occurred in the hospital during the whole of the period of this investigation ($4\frac{1}{2}$ years). In this case, the child was retained in the ward, on account of skin abrasions, for more than 3 weeks, that is, beyond the period of the passive immunity conferred by the serum. It appears probable that the two chief factors preventing the occurrence of relapse in a ward of serum-treated cases are: (*a*) "early" discharge from hospital, while passive immunity is still present, *i.e.* after 2–3 weeks' residence, and (*b*) elimination of mass infection by intravenous treatment of the majority of new entrants. The absence of these two conditions may possibly account for the number of relapses noted in other published series of serum-treated cases.

Cross-infections were remarkably few, viz. two cases of mumps in 1928, one each of chickenpox and measles in 1929, and three cases of measles towards the close of 1932. Up to the time of the latter incident a period of over 3 years elapsed without the occurrence of a single case of cross-infection with the common fevers in the scarlet fever wards, although diphtheria, chickenpox, mumps and whooping cough were known to have been inadvertently introduced at various times. It is suggested that "early discharge," in addition to prompt isolation of suspects, is a factor of some importance in preventing hospital cross-infections.

"*Return*" *cases* for each year of the investigation varied from a minimum of 0·9 per cent. to a maximum of 3·4 per cent. of all discharges. This is certainly not excessive. There was no evidence that infectivity was increased by "early" discharge. "Return" cases appeared rather to be associated with crowded homes.

Re-admissions with scarlet fever were only two in number, one 5½ weeks and the other 2½ years after discharge. The former probably represented a relapse or re-infection contracted from a case of scarlet fever in the same house. On theoretical grounds a fair proportion of re-admissions might be expected, where the natural process of immunity in each case is presumably interrupted by the shortening of the acute stage. Little support, however, was obtained for this view. A much longer period of observation would be required to elucidate the point.

V. THE "SEPTIC TYPE."

It is generally held that the serum, being antitoxic and not anti-bacterial, has no effect on the septic complications of the disease. This statement requires qualification in at least two respects:

(*a*) Although it is probably true that serum has no appreciable effect on established suppuration in middle ear, sinuses, glands, joints or skin, it would appear that septic complications, and, indeed, the septic type itself, *scarlatina anginosa*, may be almost entirely *prevented* by timely administration of antitoxin *intravenously*. Almost the only septic complication which occurred in this series was acute suppurative otitis media, and this in an incidence of only 0·9 per cent.; and as, in the majority of these, the ear discharge appeared within a few days of admission, suppuration had probably commenced or was commencing before the serum was given. Scarlatina anginosa did not once develop in this series *after* injection of the serum—a great improvement on the pre-serum days when it was common to see this dangerous and often fatal condition developing before one's eyes.

(*b*) Some evidence was obtained that the late septic case, admitted, say, from the fifth to eighth day of disease, or even later, could be favourably influenced by intravenous administration of antitoxin provided that oedema of the fauces was still present. With the rapid reduction of this oedema healing of the ulcers took place within a few days. In the series there were 17 cases

classed as the "septic type" on admission, *i.e.* with deep and extensive sloughing faucial ulcers, and much oedema, purulent nasal discharge, greatly enlarged glands, and grave general condition; and 27 cases as semi-septic or moderately septic, *i.e.* with extensive faucial ulceration, exudate and oedema, cervical adenitis and acute general discomfort. These were distinguishable from the ordinary sharp attacks of scarlatina simplex, so frequent in adults.

Septic (S.) and semi-septic (SS.) types.

Table III. *Age grouping.*

	0–5	6–10	11–15	16–20	Over 20	Total
S.	9	3	1	2	2	17
SS.	6	2	6	9	4	27

Table IV. *Complications.*

	Otitis	Adenitis suppurative	Skin sepsis	Secondary tonsilitis	Total
S.	3	1	2	—	6 = 35 %
SS.	1	—	—	1	2 = 7·4 %

Table V. *Day of disease on admission or when treatment commenced.*

	2nd	3rd	4th	5th	6th	7th	9th	22nd
S.	1	7	4	1	2	1	1	1
SS.	2	10	11	3	6	—	—	—

Average stay in hospital.

S. 30 days
SS. 17·7 days
Deaths. Nil

S. = septic type (scarlatina anginosa).
SS. = semi- or moderately septic type.

Illustrative cases of septic and semi-septic types.

Case I. *Septic type fifth day.*

W. R., male, age 3½ years; admitted 28. x. 30; notified as "Diphtheria." The child was drowsy and extremely ill: temp. 102·2° F.: pulse 116: resp. 28: slight albuminuria. Inspection of the throat showed intense oedema of fauces and soft palate with extensive sloughing ulceration of tonsils, pillars and uvula, and copious muco-purulent naso-pharyngeal discharge. The cervical glands were greatly enlarged, particularly on the right side, and there was some periglandular oedema. The tongue was of the "red strawberry" type. A scarlet fever rash was present, faintly marked on the trunk but more definite on the limbs, where it was of the "blotchy" character so often associated with sepsis. The case appeared to be a typical scarlatina anginosa. *Treatment on admission*: 7 c.c. scarlatinal antitoxin intravenously, and 12,000 units diphtheria antitoxin intramuscularly, together with routine irrigation of fauces. Next morning the throat swab proved to be negative for diphtheria

bacilli; faucial oedema was greatly reduced, but as the child was still very ill an additional 17 c.c. of scarlatinal antitoxin was given intravenously. The same evening the general condition showed marked improvement, faucial oedema had almost disappeared, although there was deep and extensive ulceration; temp. 97·4° F., pulse 108. Next morning (30. x. 30) faucial oedema was nil (36 hours) and nasal discharge had cleared up. Temperature remained normal from 24 hours after the first dose of serum, except for a rise to 100° F. on the fourth day after admission. Urine was albumin-free 48 hours after admission. The faucial ulceration was practically healed in 6 days. A serum rash was present from the sixth to the eleventh day after admission. The child was allowed up on the fifteenth day and was discharged well after 25 days in hospital.

Case II. *Septic type sixth day.*

H. G., male, age 5 years; admitted 15. iii. 29; gravely ill; restless; delirious; semi-comatose. Faucial oedema was extreme, the fauces meeting in the middle line; copious purulent faucial and naso-pharyngeal exudate; profuse purulent nasal discharge; cervical glands enlarged to form a "bull neck"; tongue dry and cracked and with enlarged papillae; rash faded; dry rough skin; temp. 101° F., pulse uncountable; cyanosis marked at times with imperceptible pulse. *Treatment*: 20 c.c. scarlatinal antitoxin intravenously; stimulants (camphor and ether) oxygen, and salines subcutaneously. Next day, the child was still gravely ill and not fully conscious; rash petechial in character; crepitations at bases of lungs; oedema of throat slightly reduced, allowing breathing to be easier; profuse purulent discharge from nose and throat; large piece of necrosed tissue douched out from throat; bowel washed out with good result. On March 17, 36 hours after admission, temperature was normal, pulse 106; condition was greatly improved; child could answer questions; glandular swelling greatly diminished; throat cleaner and oedema greatly reduced; colour and pulse quite good. 24 hours later he was quite comfortable, playing with his toys; faucial and periglandular oedema had disappeared, although ulceration was still extensive; a large discrete gland could be felt on left side of neck and a few smaller glands on right side. Temperature rose again on third evening after admission and remained elevated while a gland abscess slowly formed on left side; this was incised on March 22nd and a similar gland abscess on right side was incised on March 25th. The child was discharged well after 41 days in hospital. N.B. In these two severely septic cases, otitis media did *not* develop.

Case III. *Septic type seventh day.*

C. B., male, age 4 years; admitted 21. viii. 30; child ill with marked pallor and restlessness; intense oedema of tonsils, palate and uvula with pultaceous exudate covering both tonsils, profuse purulent nasal discharge, and marked adenitis; "red strawberry" tongue; faded remnants of rash; temp. 100·2° F.,

pulse 136. *Treatment on admission*: 20 c.c. scarlatinal antitoxin intravenously, irrigation of fauces, etc. Next morning general condition excellent; playing with toys; faucial oedema practically disappeared; deep and extensive ulcerated area involving whole of tonsils, pillars, and uvula and covered with pus; adenitis reduced; throat swab negative for diphtheria bacilli. Temperature remained normal throughout this day, then rose again, and gradually fell to normal during next 6 days, while the ulcerated surfaces healed; the general condition remained good throughout this period. This case desquamated typically and was discharged well after 33 days in hospital.

N.B. This was less severe than Cases I and II but nevertheless was a true late scarlatina anginosa showing a very rapid and satisfactory response to intravenous antitoxin.

Case IV. *Septic type twenty-second day.*

C. L., male, age 2 years; admitted 2. ii. 32, about the seventeenth day of scarlet fever, which had followed burns of the forearm and abdomen on 13. i. 32. On admission, there was intense injection and oedema of fauces, palate and pharynx, the tonsils meeting, and the whole area being ulcerated and covered with pus; profuse purulent nasal discharge and marked cervical adenitis; respirations rapid and noisy; dyspnoea and dysphagia from obstruction in throat; the child was desquamating typically, with flakes of skin on the hands. Temp. 101° F., pulse 140. Serum was not given on admission owing to the late stage of the disease. On 7. ii. 32, the child was obviously going downhill; dyspnoea was continuous, and feeding was almost impossible; oedema, ulceration and discharge was, if anything, worse. The prognosis was grave, and it was decided to try the effect of intravenous antitoxin, 20 c.c. of which was given on this day. Six hours later, improvement was observed; the child sat up and talked for the first time. In 36 hours after the injection of serum, the faucial oedema had almost all disappeared; there was no dyspnoea and swallowing was easier; the throat was much cleaner and the extensively ulcerated area could be easily seen for the first time; the child was continually sitting up asking for food. Temperature remained normal for the next 24 hours, then rose again owing to otitis media. Left ear discharged on February 13th. Serum rash was troublesome on February 16th, and right ear discharged on February 27th. The faucial ulceration was healed on February 14th, 7 days after administration of serum. Both ears were treated by zinc ionisation several times, and were quite dry by March 10th. The child was discharged well on March 23rd, after 50 days in hospital.

N.B. In this very late and desperate case, intravenous serum was followed by a dramatic and quite unexpected improvement.

Case V. *Semi-septic type sixth day.*

K. C., female, age 19 years; admitted 6. x. 30, in sixth day of the disease; fauces oedematous and extensively ulcerated; profuse post-nasal purulent

discharge; marked adenitis; "red strawberry" tongue; remnants of faded scarlatinal eruption present. The girl was uncomfortable, had not slept for several nights, and had considerable pain on swallowing. Temp. 101·2° F., pulse 110. *Treatment*: 20 c.c. scarlatinal antitoxin intravenously. Next morning she felt "ever so much better"; faucial oedema was markedly reduced; there was no pain on swallowing, although the faucial ulceration was still extensive; adenitis much reduced. Temperature became normal on October 11th and on October 13th the fauces were quite healed and she was allowed up. She desquamated freely. She was discharged well on October 21st, after 15 days in hospital.

VI. THE SERUM.

(*a*) *Potency*. Since the standardisation of Streptococcus antitoxin has not yet attained the same pitch of perfection as that of other sera, *e.g.* diphtheria antitoxin, it is natural to expect some variation in potency between one batch and another. It would appear on clinical grounds that intravenous injection of a number of typical cases is a particularly searching practical test for potency. Experience gained in this investigation showed that although some batches were apparently more potent than others, the serum marketed by both the firms of Parke, Davis and Co. and Burroughs, Wellcome and Co. could generally be relied upon to give good results when injected intravenously in adequate dosage, *i.e.* a single dose of approximately 20 c.c. for an adult, 12–15 c.c. for a child over 10 years and 10 c.c. for a small child. The Parke-Davis serum was, on the whole, preferred, and was used in 1080 cases or 90 per cent. of the series, the Burroughs-Wellcome serum being employed in about 10 per cent. The Parke-Davis serum appeared to be particularly potent in 1928; some apparently weak batches were issued in 1930; and in 1931 and 1932 results were approximately constant with the various batches used.

(*b*) *Reactions*. From the point of view of serum reactions after intravenous injection, the Parke-Davis serum appeared to have a definite advantage over the other. *Immediate serum shock* was never seen when the Parke-Davis serum was employed, but it did occur with several batches of the Burroughs-Wellcome product. For example, one batch of the latter serum produced symptoms of shock, *i.e.* pallor, thready pulse and partial collapse, in each of three cases, before the injection was quite completed. In each case the foot of the bed was immediately raised, warmth applied, and ½ c.c. adrenalin injected intramuscularly, and a quick response to these measures was obtained. Such a batch of serum should be discarded as unsuitable for intravenous injection. The immediate *anaphylactic reaction* in protein-sensitive or serum-sensitive persons was not met with in this series. The *thermal reaction*, with or without rigor, which may occur about ¾ hour after intravenous injection, is in a different category. It is common and does not appear to be dangerous. It occurred with both makes of serum, the incidence varying from 7 to 100 per cent. according to the batch. It was always treated prophylactically and rarely

gave rise to anxiety. In one case, however (the only fatal case in the series), it was associated with convulsive twitchings, and death occurred 12 hours after the serum injection. This case occurred in November, 1928, and was reported in my preliminary paper (1929) on this subject. The nature of the reaction in this case still remains obscure. It appears to resemble at least one of the fatal cases reported by Toomey and Dolch (1928) and seems to be quite distinct from anaphylaxis, which is generally an immediate reaction. I have personally seen two similar cases where different makes of anti-diphtheria serum were mixed before intravenous injection. The possibility of faulty technique cannot be excluded in seeking an explanation of such very rare cases.

Serum rashes, rarely associated with joint pains, were very common from about the seventh to the fourteenth day after injection, but were never accompanied by any serious symptoms. These various reactions have been described by me (1932) at greater length elsewhere.

(*c*) *General.* It is of the utmost importance to obtain a serum of proved potency and known to be free from troublesome reactions. Each new batch of scarlatinal antitoxin used for intravenous injection in scarlet fever should be tested out in hospital in adequate dosage on a few cases in which complete tests for serum sensitiveness have been made. The knowledge that such tests had been satisfactory would inspire confidence in any particular batch and make of serum. Although no guarantee could be given, the information would be valuable. It goes without saying that it would still be as essential as ever to exercise in each individual case the greatest care and discrimination.

VII. Indications.

According to the experience gained in this series of cases, the indications for intravenous injection of antitoxin in scarlet fever would, except for the rare contra-indicated cases, appear to be, in order of importance: (1) Toxic scarlet fever. (2) Septic scarlet fever, even late in the disease, provided that faucial oedema is still present. (3) The severer forms of scarlatina simplex, *e.g.* that commonly occurring in adults. (4) Definite cases of scarlet fever with faucial inflammation, rash and pyrexia, especially those treated in a hospital ward along with other cases.

VIII. Contra-indications.

It would be generally agreed that the following categories should be excluded from intravenous injection of serum for scarlet fever:

(*a*) All cases with a history of asthma, eczema, hay fever, frequent urticaria or other manifestation of allergy.

(*b*) All cases which have had a previous injection of serum, especially within the previous two years, except when serum is urgently indicated, in which case desensitisation may be attempted.

(*c*) Cases where any test for serum-sensitiveness is positive.

(*d*) Very mild cases with little or no faucial inflammation and little or no rash.

Cases thus excluded form only a fraction of the total.

IX. TECHNIQUE.

The conjunctival, intradermal and scarification skin tests for sensitiveness to the batch of serum to be employed, may be done as a preliminary, one drop of undiluted serum being used for each test. These are simple tests which can be performed in a minute or two. They were employed during the latter part of this investigation but no serum-sensitive individual was encountered. The first few drops of intravenous serum should be given as slowly as possible, this technique constituting a fourth test for serum-sensitiveness, viz. the intravenous test. In any case of doubt as to serum-sensitiveness, the intravenous test in 1 in 10 dilution should be employed. A useful procedure in hospital cases is the subcutaneous injection of 1 c.c. horse serum by the nurse, one hour before the intravenous injection.

With all new batches of serum, adrenalin m. IV should be injected subcutaneously just before giving the serum. This prophylactic adrenalin may be given in all cases as a routine, but it is, as a rule, unnecessary when adequate experience of a particular batch of serum has been obtained. Alternatively the adrenalin may be given intravenously, mixed with the serum, but this method sometimes causes discomfort, from too great a concentration of adrenalin in the blood. After this procedure, which is really very simple and expeditious, the serum is injected undiluted into a vein by the syringe method. In this connection, certain technical points, mentioned in my preliminary paper (1929), are of importance, in particular the employment of a suitable needle for the injection, *e.g.* a short rigid needle with short bevel, sharp point, and about 8/10 mm. bore. After the injection, the foot of the bed is raised for an hour, the patient being wrapped in a warm blanket, and hot bottles put into the bed.

X. SUMMARY.

1. Experience of $4\frac{1}{2}$ years of intravenously administered scarlatinal antitoxin, in 1204 cases, confirms the tentative conclusions reached in 1928, viz. that the acute stage of the disease can generally be arrested in 12–24 hours, complications almost wholly prevented, and the period of morbidity reduced to a little over a fortnight.

2. These effects were obtained in hospital wards where over 50 per cent. of the cases, generally about 75 per cent. and including all the worst, were so treated, and it is possible that the reduction of mass infection obtained in the wards by this means is an essential condition for obtaining such results. Under such conditions relapses and cross-infections were very rare.

3. Some evidence was obtained that intravenous antitoxin administered in the acute stage of scarlet fever largely prevents the onset of septic complications, including the late septic type itself, scarlatina anginosa; and that it may be of striking benefit in the treatment of the septic type, even at a late stage.

4. The importance of proved clinical potency and freedom from dangerous reactions of each individual batch of serum to be employed, is stressed.

5. Indications and contra-indications are stated.

6. Certain precautions and details of technique are recommended.

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(*MS. received for publication* 12. 1. 33.—Ed.)