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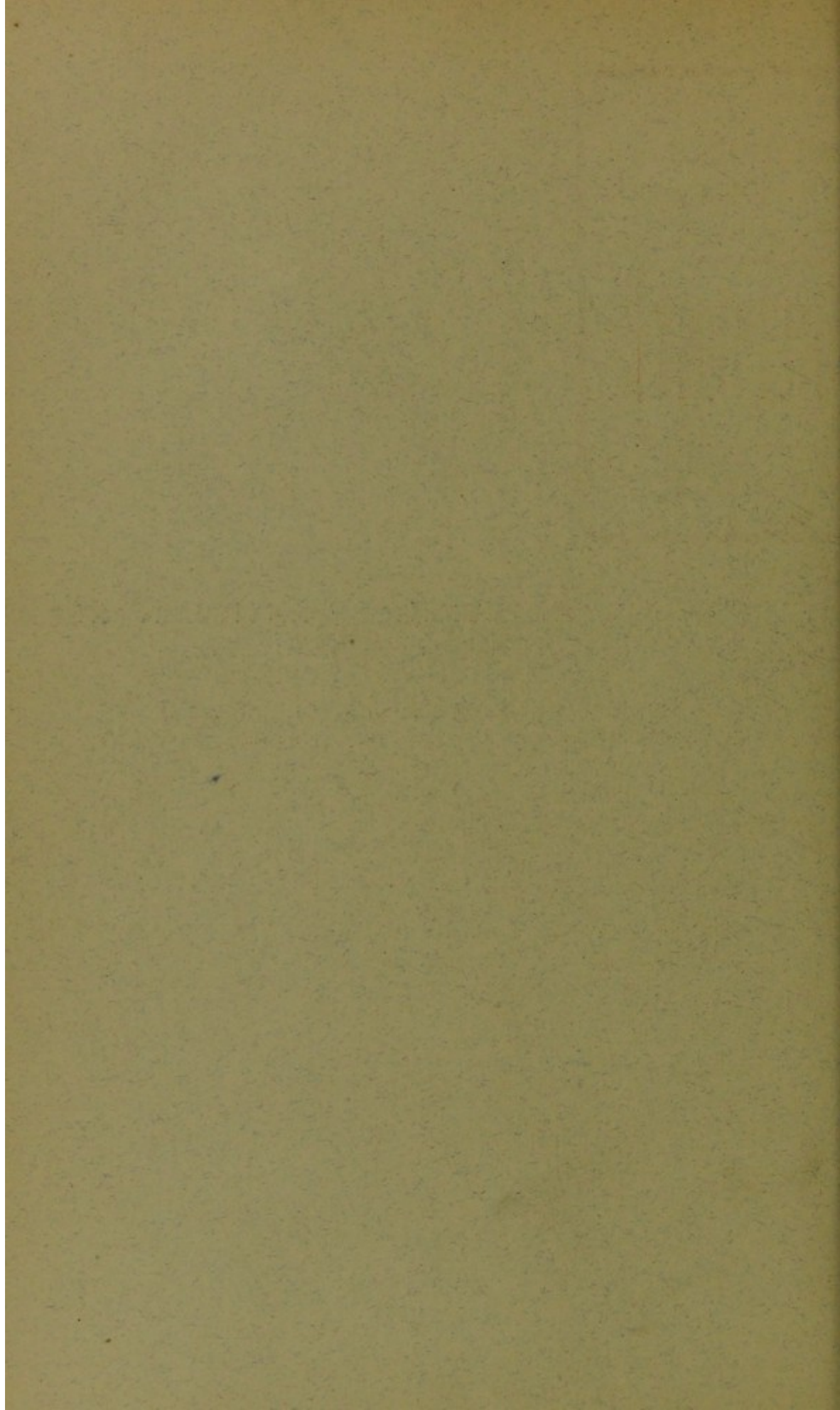
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INTRAMUSCULAR INJECTIONS OF ANTITOXIN IN
THE TREATMENT OF DIPHTHERIA.

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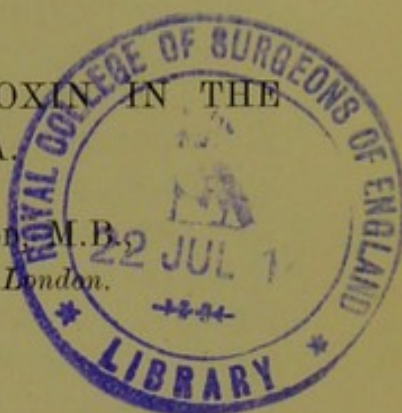
HISTORICAL NOTE.

INTRAMUSCULAR injections of drugs were first employed about forty years ago, when it was found that deep injections of mercurial salts into the gluteal regions were less painful and less likely to give rise to abscesses than the subcutaneous method which had been recently introduced by Scarenzio in the treatment of syphilis. Other drugs, such as digitalis, camphor and quinine, were subsequently given intramuscularly for the same reasons. It was not, however, until intramuscular injections had been in use for nearly thirty years that Meltzer and Auer (17), of the Rockefeller Institute, New York, by experiments on rabbits and guinea-pigs with curare, fluorescein, morphine and adrenalin, showed that intramuscular injections were more rapidly absorbed than subcutaneous. Hitherto it had been supposed that absorption from muscles was slower than from subcutaneous tissue, owing to the comparative scarcity of lymphatics in the muscles. Subsequently physiologists proved that absorption of fluid occurred primarily through the wall of the blood-capillaries, and only exceptionally through the lymphatics.

Meltzer and Auer suggested that the more rapid absorption from muscles was due to the unit of space in muscles containing more blood and more blood-vessels, and, therefore, taking up more liquid injected into it in a unit of time.

Further experiments by the same writers (18), published six years later, disproved the objection that the more rapid absorption was due to the needle having entered into the lumen of a vein.

The credit for the first experimental work on the comparative absorption of diphtheria antitoxin by intravenous, intramuscular and subcutaneous routes is to be given to Prof. Morgenroth, of Berlin (21). In conjunction with R. Levy (22), he showed that absorption of a colloid solution, such as diphtheria antitoxin, was



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subject to just the same conditions in the subcutaneous tissue and muscles as Meltzer and Auer had shown to apply to crystalloid solutions, viz. delayed absorption after subcutaneous injection, and rapid absorption after intramuscular injection.

The highest antitoxin value in the blood was naturally found after intravenous injection, but even after eight hours this concentration was found to have diminished, whereas in intramuscular injections, after eight hours, the antitoxin content of the blood came very close to that after intravenous injection. In four to five hours the antitoxin content with intramuscular injection was five to twenty times, and in seven to eight hours at least three to ten times, that after subcutaneous injection.

Confirmatory experiments were performed by Levin (14), who found that absorption of diphtheria antitoxin in goats occurred much more quickly with intramuscular than with subcutaneous injections.

This difference was particularly marked during the first few days, as the antitoxin concentration reached in the blood after ten hours was fourteen times greater after intramuscular than after subcutaneous injections.

Morgenroth's investigations induced clinicians to give intramuscular injections of antitoxin in the treatment of diphtheria, and this method was first used in E. Neisser's clinic at Stettin, as will be seen from Gabriel's paper published in 1909 (11).

Since then, intramuscular injections have largely superseded subcutaneous in German hospitals, as reference to the writings of Baginsky (1), Bauer (3), Blühdorn (6), Eckert (8), Hoesch (13), Lorey (16), and Schreiber (26) will show. Ganghofner (12), of Prague, and Feer (9), of Zürich, have also recently adopted the method. So far, however, to judge from the literature,* the practice of intramuscular injections of diphtheria antitoxin has been confined to German-speaking countries. As regards the site of injection, Gabriel, Eckert, Berlin, and Hoesch use the gluteal region, while Baginsky, Feer, and Ganghofner, following the advice of Morgenroth Levy, prefer the outside of the thigh.

* We are indebted to Dr. Germain Blechmann for informing us that intramuscular injections of antitoxin are not employed in any of the children's hospitals in Paris. Dr. C. B. Ker, however, in a letter dated February the 13th, 1914, informs us that he has been using the method exclusively at the City Hospital, Edinburgh, for the last six months, owing to the recommendation of the practice in the new edition of Baginsky's book. Lastly, Dr. Brückner, Medical Superintendent of the Dresden Children's Hospital, writing on May the 3rd, 1914, tells us that for the last year he has given diphtheria antitoxin intramuscularly and occasionally intravenously as well.

A recent visit by one of us (J. D. R.) to Prof. Schlossmann's clinic at Düsseldorf, where we were assured by Dr. J. Bauer of its harmlessness and simplicity, induced us to make a trial of the method. The present paper is based on our experience of the last six months, during which period, thanks to the collaboration of our colleagues, intramuscular have entirely supplanted subcutaneous injections at the Grove Hospital.

In all, 412 injections have been given to 339 patients, whose ages ranged from two weeks to thirty-seven years, but only 35 were above the age of fifteen years. After subtracting 33 cases still under treatment, as well as 45 patients who, after injection, were found not to have diphtheria, 261 completed cases of diphtheria, to whom 324 injections were given, are left. Fifteen died, a mortality of 5·7 per cent., which is reduced to 4·6 per cent. on excluding 3 cases who died within twenty-four hours of admission.

CLASSIFICATION AND DOSAGE.

The cases have been classified according to the localisation of the membrane and the character of the attack, as follows:

TABLE I.—*Classification of Cases.*

1. <i>Faucial cases with or without nasal or laryngeal involvement:</i>	
Severe	67
Moderate	45
Mild	117
2. <i>Nasal cases only:</i>	
Mild	17
3. <i>Laryngeal cases only:</i>	
Severe	9
Moderate	2
Mild	2
4. <i>Conjunctival only:</i>	
Mild	1
5. <i>Aural only:</i>	
Mild	1
Total	261

The severe faucial cases received from 16,000 to 20,000 units on admission, usually the same, but sometimes a smaller dose, being repeated if necessary on one or two of the following days. The

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moderate faucial cases received from 8000 to 12,000 units on admission, the same dose being occasionally repeated on the following day. The mild faucial cases received from 4000 to 8000 units, and it was rarely found necessary to repeat the dose.

The cases of nasal, laryngeal, conjunctival or aural diphtheria in whom there was no faucial involvement, and consequently little, if any, toxæmia, received from 4000 to 12,000 units. Table II shows the total amount of antitoxin given in each case.

TABLE II.

Doses.	Cases.	Remarks.
4,000	40	
8,000	97	1 death on forty-fifth day from glottic spasm.
12,000	56	3 deaths, 2 from toxæmia within twenty-four hours of admission, and 1 from broncho-pneumonia.
16,000	18	
20,000	15	2 deaths, 1 from toxæmia, 1 from cardiac paralysis.
24,000	10	1 death from glottic spasm.
28,000	10	4 deaths from toxæmia, 1 within twenty-four hours.
32,000	7	2 deaths from toxæmia.
36,000	3	All recovered, and none had any rash.
40,000	4	2 deaths from toxæmia. One of the survivors had palatal palsy only, the other no complications. Neither had any rash.
44,000	1	Recovery with palatal palsy only. No rash.

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The average dose for each patient was 12,459 units—a dose slightly below the average used in the Board's hospitals, in which, since 1908, the average dose has ranged from 14,571 to 17,328 units (27).

Our dosage for intramuscular injections has indeed been decidedly smaller, especially in severe cases, than it had been for subcutaneous. In a paper published by one of us in the Board Reports for 1908 (23), it will be seen that out of 78 hæmorrhagic cases, 40, of whom 7 recovered, received doses varying from 42,000 to 72,000 units; while out of 22, who received less than 33,000 units, none recovered. With intramuscular, as with subcutaneous injection, the frequency of rashes and other serum phenomena, in spite of large doses, is less than usual, as is the rule in severe diphtheria.

The principal objection to large doses is their expense. Baginsky (2) calculates that an injection of 40,000 to 50,000 units costs from fifty to eighty marks. In the Board's hospitals, however, when the cost per 1000 units is but sixpence halfpenny, the expense would be less than half that amount. Although experimental evidence in favour of large doses of antitoxin has been brought forward by Dönitz (7) in 1899, and more recently by Fritz Meyer (19), most of the German authorities give relatively small doses. Thus Baginsky (1) gives 1500 units in mild cases and only 3000 to 4000 units in severe cases. The most that he has ever given has been 15,000 units. Similar doses are recommended by Bauer (3), Feer (9), Gabriel (11), Ganghofner (12), Hoesch (13), Lorey (16), and Schreiber (26). Eckert, assistant to Heubner at the Charité in Berlin, alone has employed such enormous doses as 36,000, 42,000, 53,000 or 64,000 units.

TECHNIQUE.

Without preliminary washing the outer side of the thigh in its middle third is painted with a 2 per cent. solution of iodine, the needle is driven deep into the body of the vastus externus, and the injection is given in the ordinary way. Twenty thousand units (= 50 c.c.) can be readily injected even in small children, but we have never exceeded this dose at one time. Our youngest patient, aged 2 weeks, received 4000 units for nasal diphtheria without any ill-effects. It is not necessary to follow Morgenroth and Levy's advice to aspirate before injecting in case a vein has been punctured. Directly the needle has been withdrawn after injection, the site of puncture is again painted with the iodine solution and a collodion scab is applied.

The choice of the thigh in place of the abdomen, the usual site for subcutaneous injection, facilitates examination of the liver, which, as one of us has previously shown (24), should form part of the routine examination of every severe case of diphtheria, but is often rendered difficult by the excessive tenderness due to the injection.

The thigh is to be preferred to the gluteal region not only because there is less probability of injuring important vessels or nerves, but also because the thigh muscles are much more compact and exercise greater pressure on the injected fluid, rendering absorption more rapid.

Intramuscular injection of antitoxin is thus quite as simple as subcutaneous, and infinitely less troublesome both to doctor and patient than the intravenous method, over which it offers this further advantage—that an antitoxin free from antiseptic is not required. A

still more important fact which has been ascertained by Morgenroth and Levy is that by the intramuscular method for the first few days after injection a fairly uniform and high concentration of antitoxin in the blood is effected, whereas after intravenous injection even at the end of twenty-four hours about two thirds of the antitoxin have already disappeared from the blood.

Not only is the actual injection much less painful, but the subsequent pain, which often causes a restless night and persists for two or three days after subcutaneous injection, is ill-marked and often entirely absent. On this point our observations have been confirmed by the unanimous testimony of nurses both in the receiving room and in the wards.

Fomentations, which used to be applied in a large proportion of all cases injected, are rarely required now.

Rashes and other serum phenomena occur at about the same time and present the same features after intramuscular as after subcutaneous injection. When the injection has been made in the vastus externus, urticaria first appears on the thigh, and subsequently either becomes general or remains localised.

Several cases gave a history of a previous attack of diphtheria within recent years, for which they had been injected subcutaneously; and three had a relapse while under treatment in hospital. None showed any symptoms of anaphylaxis as the result of reinjection, an accelerated reaction being merely observed in some, but not all the cases.

Table III shows that the frequency of serum phenomena after intramuscular injection is about the same as that set forth in the Board's Annual Reports since 1905, when a marked drop in their incidence took place.

TABLE III.—*Frequency of Serum Phenomena.*

	Cases.	Percentage.
Urticaria	90	34·4
Circinate erythema	25	9·5
Pyrexia	33	12·6
Joint pains	15	5·7
Adenitis	7	2·6

Abscesses at the injection site, the frequency of which in the Grove Hospital cases has varied during the last ten years from 0·2 to 1·4 per cent., did not occur in any of the 339 injected.

As regards the rapidity with which membrane disappeared from the fauces or laryngeal symptoms subsided, there was no appreciable

difference between the subcutaneous and intramuscular methods, but it is noteworthy that several observers (Berlin (4), Beyer (5), Fette (10), Mixsell (20), and Schreiber (26)) have said the same of intravenous as compared with subcutaneous injections. The incidence of albuminuria after intramuscular injection was also about the same as usual. Otitis occurred in 10 cases, and broncho-pneumonia in 3. Of chief interest, however, was the incidence of paralysis. Of the 261 cases, 33, or 12·6 per cent., showed some paralysis, but only two of these were severe. Eighteen were examples of palatal palsy, usually shown by a nasal voice only without regurgitation of fluids, 8 of ciliary palsy, 1 of squint only, 2 of palatal palsy and squint, 2 of palatal and ciliary palsy, 1 of cardiac palsy which died, and 1 of palatal pharyngeal and diaphragmatic palsy which recovered.

We are inclined to think that life might have been saved in the one case and the paralysis have been rendered less extensive in the other had larger doses of antitoxin been given during the acute stage. Though the total number of cases is too small to be absolutely conclusive, the comparatively low rate of paralysis, especially of a severe character, in the present series is worthy of note, and is in striking contrast to the higher incidence noted by one of us (25) in a study of 2300 cases treated by subcutaneous injection, of whom 477, or 20·7 per cent., had some form of paralysis with 181 severe and 85 fatal cases.

The mortality, especially considering the high percentage of severe cases, was remarkably low, but here again a larger number of cases is required before a definite conclusion can be drawn.

Of the 15 deaths, 13 took place before the throat became clean, 11 being due to toxæmia, 1 to broncho-pneumonia, and 1 to cardiac paralysis. The remaining 2 deaths occurred on the ninth and forty-fifth days respectively in tracheotomy cases and were apparently due to spasm of the glottis.

Our results appear to be sufficiently encouraging to justify the continuance of this method of antitoxin administration to the exclusion of any other, and it is with the hope that the method may receive more general recognition that this paper has been written.

SUMMARY.

Intramuscular injection, preferably in the vastus externus, deserves to supersede all other methods of administration of antitoxin in the treatment of diphtheria for the following reasons :

(1) It is quite as simple as the subcutaneous method, ensures much more rapid absorption, is less painful, and less liable to give rise to abscesses at the injection site.

(2) It is superior to the intravenous method, not only in the greater simplicity of its technique, but also in the less rapid excretion of antitoxin after injection.

(3) The more rapid absorption of antitoxin by the intramuscular route is shown, not by the effect on the faucial or laryngeal process, but by the lesser incidence of paralysis, especially of a severe kind.

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