although it may be continued in the out-patient department with one injection daily (according to F. Howitt) for several months, with advantage. Three examples will suffice to demonstrate the type of improvement in the body weight which may be expected in an average case during the initial period of treatment.

Weight Table

Case	Age	Weight on Admission			Date	Weight on Discharge			Date	Increase in Weight		No. of Days of Treatment
		st.	lb.	oz.		st.	lb.	oz.		lb.	oz.	
L. W.	28	6	12	4	20/5/31	7	2	5	24/6/31	4	1	35
B. L.	24	6	4	0	19/4/31	6	7	0	8/5/31	3	0	28
F. O'R.	54	6	13	1	4/8/31	7	4	3	28/8/31	5	2	24

COMBINED TREATMENT

The best method of dealing with a case of rheumatoid arthritis which fails to respond to ordinary measures appears, as the result of trial in a limited number of hospital cases, to be by a combination of the two preceding methods. No harm will result, and in most cases considerable benefit may be expected. The complete procedure will therefore be as follows.

SUMMARY OF COMBINED TREATMENT SUGGESTED

1. Search for toxic focus; appropriate treatment if found (not forgetting bowel as a "focus").
2. If this produces no improvement, estimate (a) the blood sedimentation rate, to see whether a hidden focus of infection is probable, (b) the sugar tolerance curve, in view of future treatment with insulin.

3. Place the patient in bed, and carry out the transfusion treatment as described above; two injections at an interval of eight days with intensive physical treatment after each. With nervous patients it is often best to refer to the procedure as a blood "injection," rather than as a "transfusion."

4. Get the patient up on the ninth day. It is important to do this (if she is fit enough) before the psychological effect of the procedure has worn off, particularly with a patient who is almost resigned to being bed-ridden, as is so often the case. The patient must be keen to help, and her co-operation and interest must be sought if the best results are to be obtained.

5. Put the patient on the insulin regime, as described above, and make her weigh herself every day and chart her weight as a curve to stimulate her interest in the method. Most patients will gain about 1 lb. in the first week, and after that about 1 to 2 lb. per week in favourable cases. If the patient has been losing weight prior to the institution of this method, a "latent period" of seven to ten days must be expected before any gain in weight is made. The patient must be cautioned against the expectation of any "miraculous" result, but should be told to expect and report gradual improvement in her general and local condition and weight, the effect on the general health and mental outlook generally being the initial signs of permanent improvement.

REFERENCES

- ¹ Ray, M. B.: *Rheumatic Diseases*, Kegan Paul, 1927.
- ² Wyatt, B. L.: *Chronic Arthritis and Rheumatoid Affections*, Livingstone, 1930.
- ³ Pemberton, R.: *Arthritis and Rheumatoid Conditions*, Lea and Febiger, New York, 1930.
- ⁴ Copeman, W. S. C.: *Proc. Roy. Soc. Med.*, September, 1931.
- ⁵ Hunt, T. C.: *Lancet*, 1930, ii, 1004.

THE RATIONAL DOSAGE OF DIPHTHERIA ANTITOXIN

BY

ERNEST GRUNDY, M.B., B.S., M.R.C.S., D.P.H.

Since the introduction of diphtheria antitoxin, many attempts have been made to standardize the dosage of serum, adequate and not excessive, for the different stages and varying degrees of severity of the disease. At one extreme Park¹ suggests that doses of 10,000 to 20,000 units are sufficient for the most severe cases, while Bie² maintains that the rational dosage for a severe malignant case should be at least 160,000 to 220,000 units, and, where possible, 20,000 of this should be administered by the intravenous route. In the treatment of cases in which the condition is local and not associated with appreciable toxæmia it is held³ that antitoxin is of no value, yet although this is probably true, a failure to inject any definite case of diphtheria, even though mild, would lead to difficulties should the infection progress to a more severe stage.

Another point in dispute is that of re-injection of the case after a preliminary injection on diagnosis. Park states: "The injection of a single dose only, of sufficient quantity, is required, and multiple doses, although not harmful, are useless." Friedemann⁴ holds that the repetition of large doses is an important factor in the cure of severe cases. It must be almost impossible to judge in advance the requisite dose in all cases, and re-injection must therefore be necessary in some cases at least. The route of administration has been the subject of a good deal of controversy in the past, but since Rolleston⁵ pointed out that intramuscular injection is not only more

efficacious, but also safer than subcutaneous injection, the latter method has become obsolete. Intravenous injection has recently been used, but this method is attended by many dangers in a severely ill and somewhat frightened child, and, unless used immediately, is not so satisfactory as an earlier intramuscular injection. An attempt will be made to show that intravenous injection is not called for.

The following table will indicate the diversity of opinion on the subject of necessary dosage.

	Mild	Moderately Severe	Malignant	Laryngeal
Park...	I.M. 3,000 to 4,000	I.M. or I.V. 5,000 to 10,000	I.V. 10,000 to 20,000	—
Thompson...	6,000	—	40,000	18,000
Banks and McCracken	I.M. 14,500	I.V. 19,000	I.V. 71,000	I.V. 22,000
Bie ...	I.M. 16,000 to 20,000	I.M. 19,000	I.M. 31,000	I.M. 29,000
		I.M. 64,000 to 80,000	I.V. 20,000	—
			I.M. 140,000 to 200,000	

I.M. = Intramuscular injection. I.V. = Intravenous injection.

Banks and McCracken, as well as Bie, re-inject after a short period, and, in malignant cases, repeat the injection once or twice according to the needs of the more severe cases. Parks injects all the antitoxin in the primary dose.

In a recent investigation, Bie came to the following conclusions:

1. Diphtheria antitoxin has no effect in reducing the temperature in cases of diphtheria.
2. The membranous condition in the throat frequently spreads after the first injection of antitoxin.
3. Antitoxin hastens the separation of the membrane, but this effect is not marked.

These clinical findings, then, afford no useful data for the determination of an adequate dosage, and, consequently, the percentage mortality of the disease has been chosen in this paper as an index of a satisfactory dosage.

An attempt to correlate the dosage of antitoxin with the percentage mortality from diphtheria in a number of London fever hospitals made it apparent that a relationship existed. The protection conferred by antitoxin is known to vary with the dosage and the day of disease on which the dose is given, but in the consideration of many hundreds of cases admitted to each of several hospitals, it is probable that the average day of disease on which the serum is administered is approximately the same. It would appear, therefore, that any difference in mortality is due to the differences in dosage at the several hospitals, the figures being taken during a non-epidemic period. In the annual report of the Metropolitan Asylums Board,⁶ in which are recorded, for each hospital, the total case mortality from diphtheria and also the average primary dose of antitoxin administered to each case on admission, the figures read as follows:

Hospital	Average Primary Dose	Mortality Percentage
A	9,000	7.81
B	13,700	3.84
C	15,000	5.43
D	16,000	4.40
E	17,200	2.87
F	22,000	2.66

The graph below, showing percentage mortality, brings out even more clearly the beneficial effects of the higher dosage (primary dose of antitoxin in 1,000 units).

It is evident, from a consideration of differences in dosage in the various hospitals, that a satisfactory standard of dosage has not been prescribed, or is certainly not widely applied in the infectious hospitals of this country.

An analysis of the exact methods of treatment was undertaken in the two hospitals marked A and F on the graph, and for the purpose of this analysis the cases were divided into three groups.

Group 1.—Malignant:

- Extensive membrane at least on fauces, tonsils, uvula, soft palate, and in the nasopharynx.
- Cervical adenitis and periadenitis producing bull neck, or this condition on one side.
- Severe toxæmia amounting at least to hebetude.

Group 2.—Moderately Severe:

- Membrane on both tonsils, and on one or both pillars of the fauces, and possibly extending to the soft palate.
- Cervical glands enlarged at least to the size of a walnut.
- Subdued demeanour, but mental alertness.

Group 3.—Mild:

- Membrane on tonsils and faucial pillars.
- Glands palpable.
- Patient somewhat subdued.

HOSPITAL A

During the period under consideration, the average dosage for the various groups of cases was as follows:

Group 1.—Primary injection (intramuscular), 15,400. Total, 27,400 units.

Group 2.—Primary injection (intramuscular), 10,000. Total, 18,000 units.

Group 3.—Primary and total injection (subcutaneous), 4,000 units.

This treatment is almost identical with the recommendation of Park. The high case mortality of 7.81 would appear to show that this dosage is inadequate.

HOSPITAL F

The average dosage used in this hospital was found to be:

Group 1.—Primary injection (intramuscular), 55,000. Total, 145,000 units.

Group 2.—Primary injection (intramuscular), 25,500. Total, 40,500 units.

Group 3.—Primary injection (intramuscular), 14,500. Total, the same.

REMARKS

In cases in the first group re-injection was practised after an interval of twelve to eighteen hours, and the serum again introduced by the intramuscular route, usually in doses of 32,000 units. After the second injection, subsequent treatment varied according to the progress of the case. The intramuscular dose of 32,000 units was repeated once or twice on successive days, or, if the faucial membrane showed definite signs of separation, a smaller and final dose was given.

Polyvalent anti-streptococcal serum in doses of 10 to 20 c.cm. was combined in cases showing a marked toxic oedema of the neck, or bull neck, if this condition was thought to be accentuated by invading streptococci. Cases in the milder groups were treated according to the severity of the local condition, but re-injection was never necessary in Group 3 cases, while Group 2 cases usually received only one re-injection of 16,000 to 18,000 units intramuscularly. The use of these larger doses reduced the case mortality to 2.66, including all fatal cases. Those cases where death prevented a full dose of antitoxin being administered are excluded only from the calculation of dosage, and not from the percentage of deaths.

The case mortality of 2.66 has previously been claimed by observers⁷ in this country using antitoxin by the intravenous route. If the same protection is conferred by an early intramuscular injection of slightly larger dose, then it would appear to be the more reasonable method of administration, having regard to the possible serious results of the use of the intravenous route.

CONCLUSIONS

- The case mortality in diphtheria varies almost inversely as the amount of antitoxin administered until an adequate dose is reached.
- The average dosage should be equal to that given in Hospital F.
- Intramuscular injection of antitoxin is a perfectly satisfactory method of administration.
- Re-injection of large doses after twelve to eighteen hours, with repetition in malignant cases, is indicated.

REFERENCES

- Park: *Journ. Amer. Med. Assoc.*, 1921, lxxvi, 109.
- Bie: *C. R. Soc. de Biologie*, 1921, lxxxv, 1189.
- Idem: *Acta Med. Scand.*, 1922, lvi, 573.
- Friedemann: *Der gegenwartige Stand der Serumtherapie, Klin. Woch.*, 1922, i, 1056.
- Rolleston: *Acute Infectious Diseases*, 1925.
- Annual Report Metropolitan Asylums Board, 1928-29, pp. 101-2 and 116.
- Banks and McCracken: *Lancet*, 1928, ii, 4.