In eight cases of arteriosclerosis in which the primary complaint was intermittent claudication, padutin, administered both by mouth and by intramuscular injection over periods of 14-21 weeks, had no effect on the claudication index or the post-exercise blood flow through the calf.

Eight cases of arteriosclerosis with claudication examined before and at varying times after sympathetic neurectomy showed no evidence of improvement in the claudication index or the post-exercise blood flow through the calf.

I would like to thank Mr. E. J. Finnan, M.Sc., of the Department of Civil Engineering, Queen's University of Belfast, who designed and constructed the ergograph; also the patients, who willingly co-operated. I would also like to thank Messrs. Bayer Products, Ltd., for their co-operation and for the supplies of padutin.

REFERENCES

- Abramson, D. I., Zazeela, H., and Schkloven, N. (1941). *Amer. Heart J.*, **21**, 756.
 Acheson, G. H., and Moe, G. K. (1945). *J. Pharmacol.*, **84**, 189.
 — (1946). *Ibid.*, **87**, 220.
 Allen, E. V., Barker, N. W., and Hines, E. A., jun. (1946). *Peripheral Vascular Diseases*, p. 716. Saunders, Philadelphia.
 Barcroft, H., and Walker, A. J. (1949). *Lancet*, **1**, 1035.
 Boyd, J. D., and Monro, P. A. G. (1949). *Ibid.*, **2**, 892.
 Gibbon, J. H., jun., and Landis, E. M. (1932). *J. clin. Invest.*, **11**, 1019.
 Goetz, R. H. (1942). *Amer. Heart J.*, **23**, 782.
 Grant, R. T. (1938). *Clin. Sci.*, **3**, 157.
 Lynn, R. B., and Barcroft, H. (1950). *Lancet*, **1**, 1105.
 Shepherd, J. T. (1950). *Clin. Sci.*, **9**, 49.
 Werle, E., and Mulhaupt, G. (1937). *Munch. med. Wschr.*, **84**, 407.

INTRAMUSCULAR HEPARIN

BY

D. GORDON ABRAHAMS, M.A., M.D., M.R.C.P.

Senior Registrar, Institute of Cardiology, National Heart Hospital

It is generally considered that heparin is the most efficient and the safest anticoagulant in common clinical use. However, satisfactory therapy with this drug has hitherto necessitated frequent intravenous injections, which are irksome to both patient and doctor. Since heparin cannot be given by mouth, a method of administration which avoids the intravenous route and decreases the frequency of injections would have obvious advantages. Attempts to achieve this have been made in the past with various preparations of "depot" heparin, incorporated in Pitkin menstruum or other media. These have not proved completely successful.

A concentrated aqueous solution of heparin, 25,000 units per ml., for intramuscular injection has recently come on the market. This paper describes trials with this preparation carried out on 20 cases at the Institute of Cardiology.

Methods

All clotting times were determined by the method of Dale and Laidlaw (1911-12). Objections have been raised to this test, since it employs capillary blood. However, most authorities agree that all methods of estimating clotting time are unsatisfactory, and that techniques employing capillary blood are no more inaccurate than those in which venous blood is used. Moreover, the Dale and Laidlaw method is easy to carry out, gives an excellent end-point, and avoids the necessity for repeated venepuncture on the same patient. It was therefore admirably suited to the present type of study. The normal clotting time determined with this technique is two and a half to three minutes.

It was necessary to establish a criterion for adequate anticoagulation when using this method. This was done

by injecting a standard dose of heparin intravenously into normal subjects and measuring by Dale and Laidlaw's method the extra time before clotting occurred.

Fig. 1 shows the average delay of clotting at ten-minute intervals in 16 normal subjects following the intravenous

FIG. 1.—Average curve obtained in 16 normal subjects after an intravenous injection of 100 units of heparin per kg. body weight. Delay of clotting = actual clotting time minus control clotting time.

when given intravenously. After one hour the delay of clotting was two minutes. It was felt that a satisfactory blood level of heparin should exist for one hour after the intravenous injection of a therapeutic dose, and accordingly this was the criterion for adequate anticoagulation adopted in this work.

Results

The usual dose of heparin when given intravenously is about 30,000 units a day. It was reasonable to suppose that intramuscular injection would demand higher dosage, and trial and error showed that a single dose of 35,000 to 40,000 units given intramuscularly would delay clotting satisfactorily for twelve hours. The results obtained were extremely uniform, with only minor variations from patient to patient.

Fig. 2 shows the curves from two patients. After a single intramuscular injection of 37,500 units of heparin (1.5 ml. of solution) the delay of clotting has been plotted for twelve hours. Both these curves differ markedly from that

FIG. 2.—Clotting delay in two patients, followed for twelve hours after an intramuscular injection of 37,500 units of heparin.

obtained following intravenous injection (Fig. 1). With intramuscular injection, clotting is never considerably prolonged even in the initial stages, and the anticoagulant effect is very well maintained. This would seem to show that the drug is absorbed from muscle at a constant

rate. Even after twelve hours the delay of clotting is still adequate when judged by the criterion previously stated.

The problem of long-term anticoagulant therapy with intramuscular heparin was also studied in the same way.

Fig. 3 shows the dosage of heparin and the delay in clotting times in one patient over a period of four days. An initial dose of 37,500 units of heparin was given intramuscularly, followed by injections of 25,000 units (1 ml. of solution) twelve-hourly. The delay of clotting was satisfactory

FIG. 3.—Long-term anticoagulant therapy with intramuscular heparin.

throughout and there was some indication that the dosage of heparin could be decreased after the initial stages. This was shown by the increase in the delay of clotting after the first two or three days. It therefore seems probable that either the dosage of heparin may be decreased after this time or the time interval between injections may be increased.

Discussion

There are some disadvantages to the intramuscular injection of heparin. It was at first found that the injection was attended in some patients by local pain. This, however, was satisfactorily overcome by the simultaneous injection of procaine: 1–1.5 ml. of a 1% solution of procaine should be given in the same syringe as the heparin. This has no effect on the action of the drug and considerably diminishes the pain.

The discomfort of the injection may also be ameliorated by injecting into the vastus lateralis muscle, and not into the buttock upon which the patient has to lie.

Very occasionally a haematoma may develop at the site of injection. This is not a common complication, and was encountered only twice during the course of this work. Bauer *et al.* (1950) reported five significant haematomata in a series of 41 patients treated with intramuscular heparin. These workers used large needles for the injection, presumably because of the consistence of their heparin solution. The heparin solution used in the present work was aqueous, and so this disadvantage was overcome. Indeed, a fine needle, 18–20 gauge, should be used, and not the ordinary intramuscular needle. In this way the possibility of trauma is reduced to a minimum, and haematomata can usually be avoided. Elaborate precautions are unnecessary when making the injection, but care should always be exercised.

Hitherto, treatment with anticoagulant drugs has almost invariably demanded admission of the patient to an institution. This has been rendered necessary by the numerous intravenous injections required for heparin therapy, and

by the frequent laboratory tests which must always be done to control dicoumarol dosage. Neither of these factors need be considered when heparin is given intramuscularly. The clotting time is never grossly prolonged, and the risk of haemorrhage is extremely slight. The results obtained in this investigation indicate that the treatment may be conveniently and safely carried out in the home. If this conclusion is confirmed by subsequent work, the use of an anticoagulant in domiciliary practice would constitute a significant advance for both patient and doctor.

Summary and Conclusions

The possibility of giving heparin by intramuscular injection has been studied in 20 patients. A concentrated aqueous solution of heparin of strength 25,000 units per ml. was used. Results indicate that this is a satisfactory method for short-term or long-term anticoagulant therapy.

An initial dose of 1.5 ml. of this solution followed by 1 ml. twice daily is recommended as a scheme of dosage.

Local pain and occasional haematomata which may result are discussed, and the way in which these disadvantages may be prevented or minimized is indicated.

I wish to thank Dr. Paul Wood, Director of the Institute of Cardiology, for his advice and encouragement, and the physicians of the National Heart Hospital for permission to carry out this work on patients in their care.

REFERENCES

- Bauer, G., Boström, H., Jorpes, E., and Kallner, S. (1950). *Acta med. scand.*, **136**, 188.
Dale, H. H., and Laidlaw, P. P. (1911–12). *J. Path. Bact.*, **16**, 351.

ANAESTHESIA IN THE NEWBORN*

BY

G. JACKSON REES, M.B., Ch.B., D.A.

Demonstrator in Anaesthetics, University of Liverpool

The newborn infant differs so greatly from the adult in his anatomy and physiology that the approach to anaesthesia in the two groups must be quite different. In the past there has been a tendency to adapt to infants those methods of anaesthesia which have proved to be of value in adults. The time has come to consider the problem of anaesthetizing the newborn in relation to their peculiar physiology.

During early life the ribs of an infant are disposed almost horizontally when the infant is in the erect position. Movements of the ribs can therefore produce only insignificant effects on the capacity of the thoracic cage, and costal respiration is practically impossible.

The Neonatal Lung

In addition to the relatively poor mechanism for its ventilation, the neonatal lung itself is a comparatively rudimentary structure. The area available for respiratory exchange is small in comparison with that of the adult lung: the amount per cubic centimetre of lung volume is half that of adult lung tissue, and the respiratory surface of the lungs per kilogram of body weight is about one-third that of the adult (Engel, 1947). To compensate for these deficiencies, as well as for the high oxygen consumption per kilogram of body weight, the infant has a rapid respiratory rate.

The infantile tracheo-bronchial tree is to some extent adapted to function in these circumstances, and the area of

*Read to the Section of Anaesthetics at the Annual Meeting of the British Medical Association, Liverpool, 1950.