

THROMBOPHLEBITIS FOLLOWING INTRAVENOUS INFUSIONS

A Review of its Aetiology and Prevention

By PETER F. JONES, M.A., M.Chir., F.R.C.S.

Senior Surgical Registrar to the Middlesex and Central Middlesex Hospitals

The development of abdominal surgery has been to a considerable extent dependent on improved methods of continuous intravenous infusion and a greater understanding of fluid and electrolyte balance. This extended use of intravenous fluids has produced a large number of cases of thrombophlebitis of the vein into which the fluid has been introduced. This is, however, not a new condition and Warthen (1930) gives a clear description of it: 'About the third or fourth day the vein wall becomes oedematous and painful from the constant flow of dextrose, which is mildly irritating. The lumen of the vessel is decreased by this oedema and the flow gradually diminishes.'

This complication, though not dangerous, can be sufficiently painful to trouble the patient more than the abdominal operation which made the drip necessary: it is not uncommon to see a band of cellulitis extending from the wrist to the elbow for a week or more after an infusion is taken down. So common is this event that it has come to be expected as a sequel to most intravenous infusions running for more than a few hours. It is the purpose of this article to show that this need not be the case and, by reviewing the known causes, to demonstrate methods of prevention.

Incidence

In four recent reports of nearly 300 infusions given through National Blood Transfusion Service sets and lasting more than 12 hours, 60 per cent. of patients suffered from thrombophlebitis. A majority of these patients would have suffered a material degree of discomfort or pain. These figures were obtained from all over the British Isles, so the problem is widespread and of some magnitude (Table 1).

The Possible Causes of Thrombophlebitis *Infection*

The thrombophlebitis which appears after prolonged intravenous infusions is always associated with some degree of perivenous cellulitis. This may be widespread and severe and is at first indistinguishable from a spreading cellulitis of

TABLE 1.—INCIDENCE OF THROMBOPHLEBITIS FOLLOWING INFUSIONS THROUGH RED RUBBER SETS, LASTING MORE THAN 12 HOURS

Paper	No. of cases	No reaction	Thrombophlebitis	
			No. of cases	% of total
Handfield-Jones and Lewis, 1952	54	17	37	68
Page <i>et al.</i> , 1952 ..	29	10	19	65
Jones, 1954..	26	7	19	73
M.R.C. Report 1957 ..	189	84	105	56

bacterial origin. This has led some observers to believe that this type of thrombophlebitis is due to organisms introduced at the time of venepuncture or through bacterial contamination of the infusion fluid. There is some important evidence against this assumption:

1. Although the most severe degrees of cellulitis can be seen around the affected vein, suppuration practically never ensues. Handfield-Jones and Lewis (1952) did not see an example in 81 cases of thrombophlebitis and the author has inspected over 200 limbs into which prolonged infusions have been given—many with severe thrombophlebitis—and no case of suppuration has been seen. Slow but steady subsidence of the inflammation has followed the stopping of the infusion and a severe thrombophlebitis can be prevented by stopping an infusion as soon as the vein becomes palpable.

2. If intravenous fluids are given through a plastic cannula passed some inches up the vein, thrombophlebitis (when it occurs) commences at the tip of the cannula. The site of venepuncture stays uninfamed. This does not favour bacterial contamination from the skin or cannula as the cause and suggests that an irritant arrives in the vein in the infusion fluid.

3. Michaels and Ruebner (1953) cultured the fluid passing through the rubber tubing of 32 intravenous infusions and all specimens were

sterile. Thirteen of these infusions had been running more than 48 hours.

4. Bolton Carter (1951) showed that thrombophlebitis can be prevented by not permitting any intravenous infusion to run more than eight hours. A recent M.R.C. survey (Report, 1957) contained 52 infusions lasting exactly 12 hours given through plastic and rubber sets; no case of thrombophlebitis occurred. If bacterial infection is a major cause, it would be expected that a few cases would occur in short infusions. Further, the time factor suggests that the vein has to be exposed to an irritant for a length of time before an appreciable effect is produced.

Trauma

It has been suggested (James, 1954) that thrombophlebitis is much more common when housemen lacking experience set up drips. There may be a few cases in which this factor is associated with undue trauma to the vein, but it probably rarely causes thrombophlebitis. In a personal series of 22 infusions all were set up by one experienced operator. Particular care was taken to reduce trauma. A West Middlesex needle (which leaves only a blunt cannula lying in the vein) was always used. The limb was carefully splinted to reduce movement of the cannula against the intima. All drips ran for more than 24 hours and were given through red rubber sets. Fifteen cases of thrombophlebitis occurred. This is an incidence of 68 per cent., which may be compared with the general incidence of 60 per cent. in Table 1: in that series no special precautions against trauma were taken and most infusions were set up by newly qualified housemen.

The conclusion must be that efforts to reduce trauma to the vein will not significantly reduce the incidence of thrombophlebitis, desirable as these efforts are in themselves.

Irritant Substances

The evidence already presented in this paper strongly suggests that the most important cause of thrombophlebitis is the action of an irritant on the vein. Bacterial toxins and trauma seem to be of minor importance and the irritant is probably a chemical which arrives in the vein dissolved in the infusion fluid. If this hypothesis be true, then the irritant may be contained in the infusion fluid itself, or it may be dissolved or leached out of the tubing of the giving set during the slow passage of the aqueous solution through it.

Irritants in the Infusion Fluid. The fluids most often associated with cases of thrombophlebitis are those containing dextrose; these are usually 5 per cent. dextrose or 4.3 per cent. dextrose with 0.18 per cent. saline. This is partly because these

are the solutions most often used for maintenance of fluid balance, but it may also be associated with the fact that their reaction is acid after sterilization in the autoclave. Hudson and Tarlowski (1947) showed that, whereas 5 per cent. dextrose with 0.9 per cent. saline has a pH of 6.5 after sterilization by filtration, after sterilization in the autoclave the pH is 4.7. These figures are confirmed by a number of workers. This change in reaction appears to be due to the production of gluconic acid by oxidation during the heating of the solution.

Most infusions are given into small veins through needles which more or less obstruct the flow of blood in the vein. An acid solution will not, therefore, be immediately diluted by the blood stream, and might reasonably be expected to have an irritating action on the vein. This theory has been tested by neutralizing solutions containing dextrose by the addition of a buffer. Bolton Carter *et al.* (1952) could not demonstrate any favourable effect from this manoeuvre, but their greatest correction was to pH 6.05 and only a few drips ran for more than eight hours. Page *et al.* (1952), in a controlled trial, produced a considerable diminution in the incidence of thrombophlebitis by giving dextrose solutions corrected to a pH of about 7.0. However, the giving sets were made of unselected rubber and their figures may not be reliable. Horvitz *et al.* (1943) gave clear evidence that amino-acid solutions caused less damage to the intima of veins of experimental animals when the pH was corrected from 4.6 to 7.4. They only reported experiments in four animals, but in three the damage produced by the acid solution was very significantly greater than in the case of the neutralized solution.

It is not yet possible to be certain whether the undoubted acidity of dextrose solutions is the cause of some cases of thrombophlebitis, but there is enough evidence to make it worth while pursuing this matter.

Irritants Leached Out of Flexible Tubing. There is increasing evidence that the principal factor determining the incidence of thrombophlebitis following intravenous infusions is the chemical composition of the flexible tubing in the giving set.

Handfield-Jones and Lewis (1952) were the first to make this clear. They showed that, among patients receiving intravenous infusions through red rubber sets which lasted over 12 hours, more than 60 per cent. suffered from thrombophlebitis. This figure could be appreciably lowered by changing the composition of the rubber used for the tubing; a special type of tubing, made in co-operation with the manufacturers, caused thrombophlebitis in only two out of 14 patients (14 per cent.). When giving sets were made with

TABLE 2.—RESULTS OF A COMPARATIVE TRIAL OF LATEX RUBBER AND RED RUBBER GIVING SETS, ALL INFUSIONS RUNNING FOR MORE THAN 12 HOURS

	Latex	Red rubber
No reaction	19	5
Thrombosis	2	2
Mild thrombophlebitis ..	4	4
Severe thrombophlebitis	0	15
Total	25	26

latex rubber tubing thrombophlebitis was rarely seen. Jones (1954) fully confirmed this work and showed that severe cases of thrombophlebitis were more or less eliminated in a ward using latex rubber sets, while the incidence of thrombophlebitis remained at 60 per cent. in other wards using red rubber sets (Table 2).

The conclusion to be drawn from this work is that red rubber tubing contains chemicals, used in its manufacture, which can pass into solution in the fluids being infused through the tubing. The trials quoted were carefully controlled and it seems clear that latex rubber tubing—a purer product not subject to such complex processes as red rubber—does not contain these harmful chemicals. It is not surprising that red rubber should contain irritants when the large number of chemicals used in its manufacture as vulcanizers, accelerators, activators and antioxidants are considered (leading article, 1952). Mallette and von Haam (1952), for instance, tested three commonly used activators and found all of them to be severe skin irritants. It should be remembered, in this connection, that there is evidence to suggest that urethral catheters made of red rubber may have irritant properties when left indwelling for several days (Page, 1952).

From this work it was concluded that a chemically inert tubing is needed for the making of giving sets, and when plastic (polyvinylchloride) sets became available in this country an M.R.C. sub-committee was set up to test them. A controlled trial was arranged in which the incidence of thrombophlebitis following long infusions through plastic sets was directly compared with the incidence for red rubber sets. The final analysis showed that in 189 infusions lasting more than 12 hours given through red rubber sets the incidence of major thrombophlebitis was 34 per cent. In a comparable series of 180 infusions given through plastic sets major thrombophlebitis occurred in only 18 per cent. (Report, 1957). These observations were collected from seven hospitals and were shown to be highly significant.

Silicone tubing has recently been introduced and may prove to be of value for intravenous infusions, as there is evidence that it is biologically inert (Wilkinson *et al.*, 1956). The only published trial of infusions lasting more than eight hours

(Fletcher, 1956) is too small for any conclusions to be drawn about the incidence of thrombophlebitis.

Other Factors

The work reported here shows that thrombophlebitis can be reduced to fairly small proportions, but that it does continue to occur even when a relatively inert tubing is being used. One factor which is most difficult to control in all trials is the injection of drugs into the vein by way of the drip tubing. A large number of surgical patients receive a variety of drugs in this manner and some of these may cause intimal damage which makes later thrombophlebitis more likely.

The other factor about which little is known is the reaction of the individual patient to intravenous infusions. Some patients who receive multiple infusions tend always to show a thrombophlebitis, whilst others seem to be unusually resistant. It may be that there are some individuals who will always react to the intravenous infusions of aqueous solutions over long periods, irrespective of the other precautions taken.

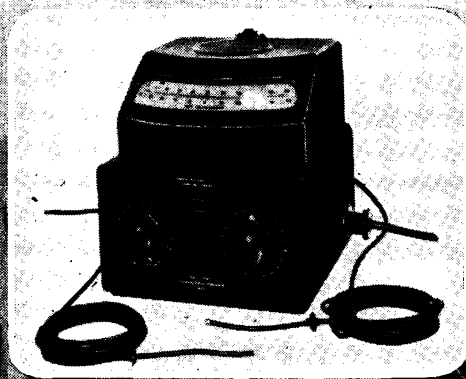
Prevention

There are various methods which can be used to keep the incidence of thrombophlebitis down to a minimum and these can be grouped in four main categories:

1. The most effective method of all is to make a rule that no intravenous infusion shall run for appreciably more than 10 hours, 12 hours being the outside limit. This ruling calls for a high standard of work from the resident and enough time in which to do a daily round of venepunctures. There is no doubt that this system allows the daily fluid needs of the patient to be supplied in one 12-hour period and that this leaves the patient free to move about, or sleep undisturbed, in the other half of the day. This regime does not lead to fluid overloading during the period of rapid infusion. This method cannot, however, be applied to all patients. Some need a large volume of fluid supplied throughout the 24 hours and others have so few veins that repeated venepuncture is not possible. Other patients very much dislike a daily venepuncture, though this is closely related to the skill of the houseman. This is a method of infusion which has many advantages and is a sure way of avoiding major thrombophlebitis. It is not, however, the final answer to the problem and the general aim must be to eliminate the causes of thrombophlebitis so that intravenous infusions can run for several days, if need be, without harm to the patients.

2. The use of red rubber tubing in giving sets should be avoided. Latex tubing is known to be very satisfactory, but is only available on a limited

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scale. It seems likely that disposable plastic sets will soon be produced in this country. They have been shown to be associated with a low incidence of major thrombophlebitis and it is the author's definite impression that these reactions are not so painful as reactions of a similar extent due to rubber tubing. Sets made of silicone tubing are worthy of trial.

3. If a complicated abdominal case is being managed and it is expected that intravenous fluids will be needed for many days, there is much to be said for introducing a polythene cannula into a large vein. The size of the cannula will then be small relative to the lumen of the vein and blood will circulate around the cannula and immediately dilute any irritants in the infusion fluid. One of the best veins to use for this purpose is the cephalic, which is entered at the anterior axillary fold: a cannula is passed up to a point just short of the angle in the vein where it passes through the clavicular fascia. These infusions run regularly for periods of six to 10 days with the minimum of attention and reaction. It is especially important to insert a cannula into a large vein if hypertonic solutions or broad-spectrum antibiotics are to be given intravenously.

4. Polak (1956) has suggested that the addition of hydrocortisone alcohol to intravenous fluids

makes thrombophlebitis less likely to occur. He states that a dose of 10 mg. per litre, which is without systemic effect, has a useful local action on the vein adjacent to the needle, and even allows 20 per cent. dextrose infusions to be given without thrombosis.

The facts given in this review are those which seem to be of importance at the moment. Nevertheless, there are a number of features of this type of thrombophlebitis which remain unexplained and further work must be done before this unpleasant complication can be prevented in all patients.

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