Standardization of Anticoagulant Treatment: the Manchester Regional Thromboplastin Scheme

L. POLLER,* M.D.

Brit. med. J., 1964, **2**, 566–567

The scheme is an entirely new venture and has just completed its first year of operation. It was devised to standardize oral anticoagulant treatment in the hospitals in the Manchester Regional Board area. To our knowledge it is the first time such a scheme has been operated other than on a local hospital basis, and certainly the first time on such a scale.

The scheme was introduced entirely on a voluntary basis with the collaboration and help of consultant pathologist colleagues.

The Manchester Regional Hospital Board is the second largest, covering a population approaching 4½ million. It extends geographically over an area comprising the larger part of North-west England from the Lake District in the north to the South Cheshire border (Fig. 1).

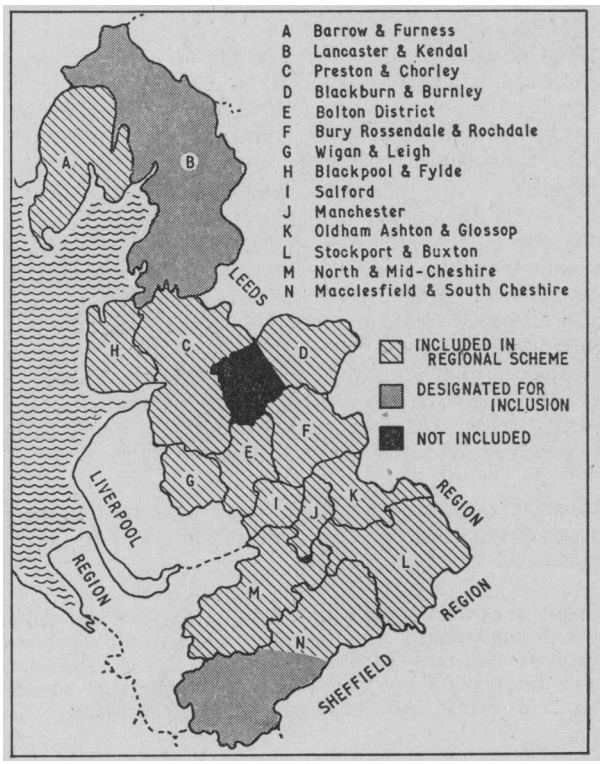

FIG. 1.—Area covered by the scheme.

Previous Arrangements

All the hospitals in the region prior to the introduction of the scheme used some modification of the one-stage prothrombin technique. In this, calcium is added to decalcified plasma in the presence of tissue extract (thromboplastin). (Decalcified plasma + calcium + tissue extract (thromboplastin)→prothrombin time.)

Some hospitals manufactured their own tissue thromboplastin from human brain, but the majority preferred to purchase commercially available tissue extracts made from animal brain or lung. Although there were confusing differences in the interpretation of results given either as prothrombin time, ratio, or index, the main variable was the type of tissue extract employed. A preliminary study reported elsewhere showed that different results were obtained with the same blood specimens with the various extracts in use in the region. Under carefully controlled conditions, mean results of patients on anticoagulant treatment varied between 14 and 40% with these reagents (Poller, 1964).

Individual blood specimens showed much greater discrepancies. Little account was taken of these differences in the therapeutic ranges, and 10–30% prothrombin activity was generally in use irrespective of the type of thromboplastin or the way in which the results were interpreted. With a number of the commercial animal extracts the therapeutic range advocated was either not stated or else was given without clinical data in its support. Using the term "prothrombin ratio" instead of "activity" did not simplify the position, as the mean ratios—that is, $\frac{\text{prothrombin time of patient}}{\text{prothrombin time of control}}$ varied between 1.3 and 2.4 with the thromboplastin extracts used in the region before the inception of the scheme.

There is no reason to believe that the situation here was very different from that which obtains in other regions. In the United States, Hougie (1963) showed that variations of prothrombin activity with different thromboplastins were of a similar order to those we have observed.

Choice of Human Brain Thromboplastin

Human-brain tissue extract was preferred because of its known factor VII sensitivity (important in the early days of oral anticoagulant treatment) and because of the absence of species sensitivity found when human blood is tested with some animal brain thromboplastins. The particular preparation of human brain was selected because the therapeutic range was known from clinical experience. Therapeutic ranges with thromboplastin reagents must be established either by comparison with a known established thromboplastin or on the basis of prolonged clinical trial. We were fortunate in having used a human-brain extract in almost unchanged form for over 10 years. The lower limit of the therapeutic range has been established by the experience of the level at which spontaneous bleeding may occur. This has been found to be 10% prothrombin activity (four to five times control time). The other limit is rather more difficult to define, but must be regarded as the upper level of prothrombin activity which is effective in prophylaxis or treatment. This appears to be in the region of 40% activity (one and a half times the control). A safety margin is necessary on either side, and the therapeutic range advocated is therefore 15–30% prothrombin activity, which corresponds approximately to two to three times the control reading. A saline extract of human brain was preferred because it gave better reproducibility in bulk.

* Consultant haematologist, Withington Hospital, Manchester.

Procedure

Human brain is obtained within 48 hours of death and a saline extract prepared (Poller, 1962). A number of brain extracts are collected and pooled. They are stored for at least two weeks to stabilize their activity. Graded dilutions of a sample from the bulk extracts are prepared. Plasma from at least six normal adults is used to calibrate a dilution curve ranging from 10 to 100% with normal saline (see Table).

Normal Plasma, Dilution Curve with M/40 Calcium

12·0	— 100%	22·0	— 30%	38·0	— 14%
13·0	— 80%	22·5	— 29%	40·0	— 13%
13·5	— 70%	23·0	— 28%	44·0	— 12%
14·0	— 65%	24·0	— 26%	47·0	— 11%
14·5	— 60%	25·0	— 25%	59·0	— 10%
15·0	— 56%	26·0	— 24%		
16·0	— 50%	27·0	— 23%		
17·0	— 45%	28·0	— 22%		
18·0	— 40%	29·0	— 21%		
18·5	— 38%	30·0	— 20%		
19·0	— 35%	31·0	— 19%		
19·5	— 34%	32·0	— 18%		
20·0	— 33%	33·0	— 17%		
20·5	— 32%	34·5	— 16%		
21·0	— 31%	36·0	— 15%		

THERAPEUTIC RANGE

The concentration of brain giving a dilution curve which corresponds with the previous standard curve was then determined. The bulk pooled brain is then diluted to the required volume and stored at −20° C. It keeps indefinitely in this state. Some hospital laboratories do not possess facilities for deep freezing, and specimens must be stable during time of transmission through the post. Consequently phenol 0.5% is added to the thromboplastin prior to distribution. In the phenolized state it is stable for several months at 4° C. and for several days at room temperature. When the thromboplastin is in constant use in the laboratory it eventually becomes infected even with the added phenol. The reagent is therefore dispensed in small volumes of 5–10 ml. and batches are issued weekly to each group or hospital as required (Fig. 2 illustrates the postal package.)

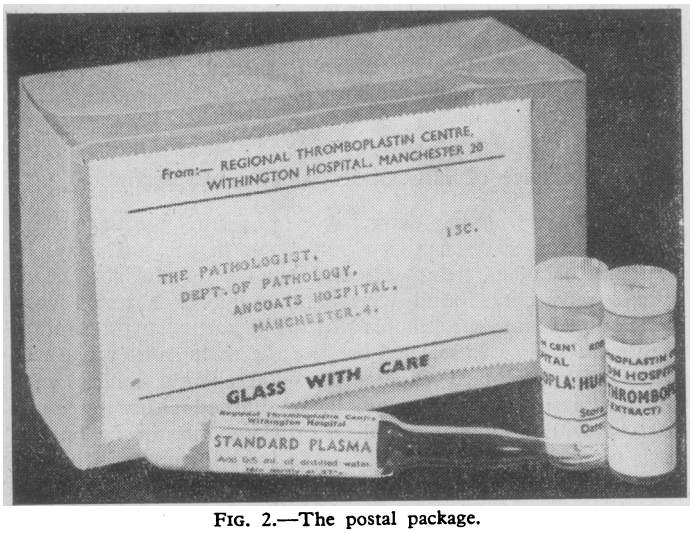

FIG. 2.—The postal package.

Standard Plasma

With each batch of reagent an ampoule of freeze-dried sheep plasma is issued as a control. This is prepared in the department and gives a prothrombin time of 10–11 seconds. This is to check the reliability of the technique in the different hospitals. Sheep plasma is valuable because of its availability in bulk and its stability on lyophilization because of its excess factor V (labile factor). A standard chart is provided with instructions on the technique to each hospital, so that there should be uniformity in method and expression of results.

Finance

The salary of a technician is provided by the Manchester Regional Board and the centre is housed in the haematology section of the pathology department. Containers and postal envelopes are those used by the Regional Serology Laboratory at Withington. The net expenditure on postage is less than £1 a week. Sufficient thromboplastin is provided through the centre for about 7,700 tests per week. The net cost of the whole scheme is less than we ourselves would spend on the commercial thrombotest reagent (Owren, 1959) at Withington Hospital alone. Although economy was not the aim of the scheme the estimated saving on the region is several thousand pounds.

Future Organization

The popularity of the scheme may be gauged from its widespread adoption in the space of 12 months. Participation has been entirely on a voluntary basis. One hospital group in the region did not participate because it had to depend on a capillary-blood method from lack of staff. Even in this instance a time has been made to standardize treatment by advocating the use of a therapeutic range with thrombotest which is known to correspond with the 20–30% prothrombin activity with the regional thromboplastin reagent.

Expansion of the scheme in its present form far beyond the limits of the Manchester Regional Hospital Board area would not be possible with the present staff. The obvious long-term aim would be the provision of a national standard for a thromboplastin extract. With a little extra staff a thromboplastin reference centre might be established whereby samples of thromboplastin could be issued as a standard to groups or individual hospitals in different parts of the country. An alternative might be the establishment of similar centres in different hospital board regions, although this might be much more expensive and difficult to arrange.

ADDENDUM.—Since this paper was written a number of adjacent hospitals in the Liverpool and Sheffield Regions have been incorporated in the scheme.

Thanks are due to those of my consultant pathologist colleagues who were kind enough to co-operate with us in the difficult early phase of the scheme. Particular thanks go to Dr. James Davson for provision of necropsy tissue, to Dr. P. Sequeira for advice, and to Mr. S. Hardman, A.I.M.L.T., for technical assistance.

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