A New Tolerance Test as a Guide to Clinical Heparin Therapy

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with the statistical assistance of Con O. T. Ball

It is a common clinical observation that the response to a specific dose of heparin in a retarding menstruum is unpredictable. The fallacy of using weight as a guide to dosage is well shown by the results here reported. To simplify the approach to a therapeutic regimen, it seemed advisable to assess all of the variables in an individual patient by the administration of a test dose of intravenous heparin. A dosage schedule is outlined, based on the response to the tolerance test, which proved accurate in 105 patients and requires the performance of only one coagulation time every 24 to 36 hours.

THE VALUE of heparin in the treatment of phlebothrombosis and pulmonary embolism has been established,1-3 and by many it is believed to be the treatment of choice. It is also useful as adjunctive therapy in the treatment of thrombophlebitis, arterial embolism and thrombosis, and coronary heart disease.4,7 Its therapeutic application, however, has been retarded by (1) the individual variation in the response when the dosage was based on weight, (2) the necessity of frequent determinations of coagulation time to disclose the duration of therapeutic effect, and (3) the cost of the medication itself.

Factors leading to individual variation in the response to heparin that have been suggested are weight,1,8 age,8 adequacy of renal function, the severity of the thrombotic disease,1 and various blood dyscrasias. It has been recommended that all patients weighing 150 pounds and over be given an initial injection of 400 mg. of heparin in a retarding menstruum and that all patients below that weight be given 300 mg.1 A recommendation of 2 mg. per Kg. of body weight has also been suggested.8

In order to simplify the practical approach to a therapeutic regimen, it seemed advisable to assess all of the variables in an individual patient by the administration of a test dose of intravenous heparin. All might then be classified according to their response to a standard amount of the drug. It seems reasonable to believe that the response to heparin in this form might be valid as a basis for the prediction of response to heparin in any form in that same individual.

Heparin tolerance tests have been used in the past to classify patients as to their normal or abnormal reactions to heparin4 and to detect the tendency to intravascular clotting.9 10 De Takats has suggested the use of 10 mg. of sodium heparin intravenously, followed in 10 minutes by a capillary tube coagulation time determination. The capillary tube method of determining coagulation time, we believe, reflects inadequately the actual response of a patient to heparin.11 In another problem, we had used an injection of 50 mg. of heparin intravenously and determined the coagulation response by the modified three tube Lee-White method.12 These results established a tentative basis for classification, and the dosage of heparin in a retarding menstruum was varied from 200 to 500 mg., depending upon the individual's response.

It was hoped that this method of fitting the dosage to the individual patient would result

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in (1) avoiding expensive excess administration of the drug, (2) decreasing the occurrence of excessively prolonged blood coagulation with the attendant danger of hemorrhage, and (3) preventing the administration of subtherapeutic dosages to hyporeactors.

**Method**

One hundred and five cases on the Surgical Service from October 1948 to the present were candidates for heparin therapy. These were consecutive cases and no selection was made. If the history revealed no evidence of blood dyscrasia and if the coagulation time was normal and no active bleeding was occurring, then a 50 mg. intravenous injection of sodium heparin was given and subsequent dosages of heparin in a retarding menstruum were based on the response to that tolerance test. Twenty minutes later, a coagulation time was obtained. For the purpose of the study the following empiric schedule was followed: if the 20 minute coagulation time was below 60 minutes, 500 mg. of heparin in a retarding menstruum were given; if the tolerance coagulation time was between 60 and 119 minutes, 400 mg. were given; 120 to 179 minutes, 300 mg.; and 180 minutes and over, 200 mg. (table 1). Thirty patients were given more or less than the scheduled dosage in an attempt to ascertain the precise limitations of dosage categories. Seventy-five cases did receive therapy as indicated by the 20 minute tolerance time and these cases form the principal basis of the final results of the study.

A. **Coagulation Time Method**

We have used a modification of Loew's method and the end point is read by the appearance of a clot in the red cell layer. In performing the test the tubes are disturbed as little as possible.

It cannot be emphasized too strongly that the accurate performance of this test is a basic requirement for safe heparin therapy.

1. **Using a dry syringe, do a venipuncture and withdraw 5 cc. of blood.** If the venipuncture is traumatic, use another syringe and needle and draw the blood from another vein.

2. **Into three dry Wassermann tubes, numbered 1, 2, and 3, inject 1.5 cc. of blood into tube 3, 1.5 cc. into tube 2, 1.5 cc. into tube 1.** The remaining 0.5 cc. is discarded. The blood should be allowed to flow down the side of the tubes with as little mixture with air as possible. The first blood withdrawn from the vein contains most of the tissue thromboplastin and is therefore placed in tube 1.

3. **The tubes are placed in an upright position.** Blood which is well heparinized will separate into a layer of red cells and a layer of plasma (fig. 1A). In a heparin tolerance test, the tubes are not examined for 45 minutes. When doing a 20 hour coagulation time, the tubes are not examined for 20 minutes.

4. **Tube 1 is picked up and gently inclined until the red cell mass flows (fig. 1B).** The tube is replaced in the rack and the same procedure is repeated at five minute intervals until the red cell mass does not flow. The plasma will not flow as long as the red cell mass because it coagulates at the interface between air and plasma (fig. 1C). At first the red cell mass is very liquid and flows readily, but as coagulation approaches, the red cell mass becomes more viscid and flows sluggishly. Just before the end point is reached, the red cell mass will flow in the center but not around the periphery (fig. 1D). The point is reached when the red cell mass does not flow. Beyond this, a narrow, tongue-like projection of red cells may continue to flow, even though the main mass of red cells has clotted (fig. 1E). The same procedure is then carried out with tube 2 and then tube 3. Clotting in the third tube is recorded as the coagulation time. The tubes should be agitated as little as possible to avoid artificially decreasing the coagulation time.

5. **In doing coagulation times on unbeparinized blood, which does not separate into layers, the end point is reached when the blood ceases to flow when the tube is inclined.** There is a tendency for the blood at the interface between air and blood to form a surface film before the remainder of the blood coagulates. It is permissible to "flick" the tube gently to break up this film. The blood will then flow freely, but coagulation usually will occur three to four minutes after the tube has been "flicked.”
We believe this method represents more nearly the status of the heparin effect in vivo than methods involving more frequent examination and agitation. A practical advantage exists in that this allows other work to be done during the performance of the clotting test.

B. The Use of Vasoconstrictor Drugs

All but 12 of the 75 cases received the total dosage, as recommended by the tolerance schedule, with approximately one-third of the total made up of drugs containing vasoconstrictors. It has been shown\(^1,8\) that the addition of epinephrine and ephedrine to the retarding menstruum results in a prolongation of the duration of effect and lowers the height of the maximum effect. It is inadvisable to use the medication containing vasoconstrictors in patients with coronary heart disease, arterial thrombosing diseases or thrombophlebitis.

C. Definition of Adequate Therapy

A prolongation of the coagulation time to 25 minutes, by the above described method of reading the end point, was considered to be sufficient to obtain protective therapeutic effect. This is approximately two times the average baseline coagulation time. In the great majority of all instances of therapy, the coagulation time was allowed to fall to a level between 25 and 30 minutes before another injection was given. It is our opinion that this is a safe level, since we encountered no therapeutic failures using this point as a guide.

D. Site of Injection

The preferred site of injection is in the lateral aspect of the thigh. The medication is placed in the deep subcutaneous tissue and not intramuscularly. In our experience, intramuscular implantation is too often accompanied by pain and hematoma. The advantage of placing the deposits immediately superficial to the fascia lata lies chiefly in the relative absence of blood vessels and nerves in this area. The rate of absorption thus is apt to be reproducible in the same patient and to be slowed maximally. In our experience, Depo-Heparin\(^*\) has been much less painful than heparin in Pitkin's menstruum. It is of interest to note that the occasional patient who has severe pain from Depo-Heparin seems to tolerate the injection very much better when it is placed in the subcutaneous tissue of the upper arm, posterior and superior to the insertion of the deltoid tendon. In those cases in whom a four to six week course of therapy is planned, rotation of the site of injection between the thighs and arms should be performed in a definite manner. The duration of effect has been essentially the same regardless of which of the above mentioned sites was used.

E. Statistics

In the statistical interpretation of the data in this study, differences of 2.6 standard deviation (a probability of .01 or less) are considered "significant." Differences of twice the standard deviation are considered "probably significant."

**Table 1.—Heparin Tolerance Test and Treatment Schedule**

(1) Base line coagulation time (three tube, Lee-White).
(2) 50 mg sodium heparin I.V.
(3) 20 minutes later do coagulation time.
(4) If coagulation time is

| <1 hr. | 500 mg. |
| 1 hr.-2 hrs. | 400 mg. |
| 2 hrs-3 hrs. | 300 mg. |
| >3 hrs. | 200 mg. |

(5) 20 hours later do coagulation time:
If coagulation time is

| well over | Wait 16 hrs.—Repeat same dosage |
| well around | Wait 10 hrs.—Repeat same dosage |
| well below | Wait 4 hrs.—Repeat same dosage |

(6) Repeat regimen (5) as long as therapy is indicated.

(4) The 13% of our patients who have had therapeutic levels for 48 hours following an injection may be spotted by an appreciable rise in their 20 hour coagulation time, following their second or third injection.

**Results**

A. Depo-Heparin Dosage—Response Relationship, Based on Heparin Tolerance Test

Treatment was begun in all cases by the performance of the heparin test as outlined in table 1. The cost of the sodium heparin used in the tolerance test cannot be considered wasted, since the patients received immediate protection on injection and this continued while the clotting time was being determined. Indeed, some believe that adequate heparin therapy can be accomplished safely by the admin-

\* Each cc. Depo-Heparin contains:
- Heparin sodium (20,000 U.S.P. units) 200 mg.
- Gelatin 180 mg.
- Dextrose 80 mg.
istration of such a dose every four hours, without performing any coagulation time studies.

Depending upon the length of the 20 minute coagulation time, two to four hours after the injection of intravenous heparin, the dosage of Depo-Heparin indicated by the test was given. In the first 50 cases the response to the dose of heparin in a retarding menstruum was determined by coagulation time studies made 12, 24, 36, and occasionally 48 hours following each injection. Figure 2 depicts the results of therapy in these cases. Cases in the 300 mg. dosage category had a higher percentage of adequate therapy at the 24 and 36 hour interval than did the 200 and 400 mg. categories. However, only at 36 hours was the percentage of success significantly higher. At the 48 hour interval, the percentage of success was practically the same in all groups.

Ninety-two per cent of all cases receiving a dosage according to the 20 minute clotting time schedule, enjoyed adequate protection for 24 hours. Statistical analysis of the variation in this dosage-response relationship indicates that the incidence of satisfactory response to such a dosage schedule in a similar group of patients would range from 84 to 100 per cent, 99 times out of 100. It will be seen that two-thirds of all patients received adequate therapy for 36 hours, whereas only approximately 10 per cent had adequate therapy for 48 hours.

For the purpose of statistical analysis, table 1 (line 4) was changed tentatively to the following schedule: 400 mg. of Depo-Heparin for all patients with a tolerance time of 100 to 149 minutes, 300 mg. for a tolerance time of 150 to 199 minutes, and 200 mg. for a tolerance time of 200 minutes and over. Although this schedule would result in giving a larger dose of heparin to many of the patients in each of these dosage categories, the percentage of adequate therapy was not increased at the 24, 36 or 48 hour interval. This increase in dosage seems to result in a higher peak response without increased duration of effect (table 2). Even though the schedule in table 1 (line 4) had been more or less arbitrarily selected, the final analysis of the data indicated that it had the highest correlation with adequate dosage therapy.

![Graph showing dosage and clotting time](image)

**Fig. 2.** Per cent of 75 cases with adequate therapy. Dosage based on 20 minute clotting time after 50 mg. sodium heparin given intravenously.

In all of the first 50 cases, in addition to the specimen drawn 20 minutes following the intravenous heparin injection, a 90 minute sample was obtained. It was hoped that this sample might give a better prediction of the expected duration of adequate therapy than would the 20 minute sample. In only the 200 mg. dosage category was a slightly better prediction rate observed. This difference was minimal and was not statistically significant.

**A. Prediction of Duration by the Twenty Hour Coagulation Time**

Only 8 per cent of all patients studied had less than 24 hours of adequate therapy when
given the dosage of Depo-Heparin indicated by the tolerance test. All of these cases did have adequate therapy for 20 hours, however. A final and simplified plan of therapy then must be so arranged as to protect these patients. A study was made of the coagulation graphs of the first 50 patients, and by interpretation of the curve, their actual or probable 20 hour coagulation time was determined. These figures, when correlated with the known duration of therapy in each individual patient, led to the selection of the figures shown in table 1 (line 5).

There was no absolute certainty that 20 hour times of even 90 minutes or over would be accompanied by a total duration of 48 hours. In the practical application of the schedule, a coagulation time of 55 minutes was considered “well over” the 45 minute point and 35 minutes, “well below.” Similarly, 70 minutes was “well above” the 60 minute division line and 45 minutes, “well below.”

Approximately one-tenth of the patients did obtain 48 hours of therapy from a single injection. In the majority of these patients, the second 20 hour coagulation time will rise 15 or more minutes above the first. When this occurs the coagulation time should be checked at 36 hours, before a third injection is given.

The therapy of the last 25 of the 75 cases was guided entirely by this schedule. The initial dose of Depo-Heparin was determined by the heparin tolerance test and 20 hours following the injection, a coagulation time was determined. A second coagulation time was repeated on each individual patient at the time interval indicated by his 20 hour response. These 25 patients received 136 doses of Depo-Heparin during the course of their treatment. In 134 of these instances, the coagulation time was 25 minutes and above at the predicted hour. Statistical analysis indicates that in a similar group of patients correct predictions would range from 96 to 100 per cent, 99 times out of 100.

C. Effect of Increasing or Decreasing Dosage from Level Indicated by Tolerance Test

In 30 of the 105 cases the dosage was 100 or 200 mg. more or less than the indicated dosage. Table 2 depicts the results of giving 100 mg. more or less than the suggested dosage, and it includes all such patients in our series. It will be noticed that 100 mg. more than the tolerance schedule dosage results in an increased height of effect at the 12 hour determination without any appreciable increase in duration of adequate therapy. Contrariwise, 100 mg. less than the proper dosage resulted in inadequate therapy in 7 of 8 such cases. These variations from accurate dosage lend further credence to the plan of fitting the individual dose to each patient's tolerance. In one instance the patient will be protected inadequately, and, in the opposite direction, an excess of the drug will be given with coagulation time elevated above the level necessary for adequate therapy. In a real sense, the cost of such excesses is an unjustifiable expense to the patient.

D. Accuracy of Tolerance Schedule Versus Weight Schedule

At the present time the weight of the patient is used as the major, if not the sole, guide to the dosage of heparin in a retarding menstruum. In table 3 is shown the response of patients of similar tolerance given identical dosages of Depo-Heparin even though they have a wide range of body weight. The similarity in response is noticeable in the group of 7 patients, with a similar tolerance, given 300 mg. of heparin in a retarding menstruum. It can be seen that their weight ranged from 106 to 180 pounds. Similarly, in the 200 mg. dosage category, 10 patients varying from 130 to 280 pounds show a striking similarity in response to Depo-Heparin. It is of interest to note that the patients in the 200 mg. category not only respond closely to each other, but also to members of the 300 mg. group, whose tolerance tests indicated them to be less sensitive to heparin. Most striking is a comparison of the first and last patients in the table. Although one patient weighs 106 pounds and the other 280, their coagulation response is remarkably similar. Thus, a patient weighing almost three times as much as the other had a similar therapeutic response to 100 mg. less of the drug. A small group of patients had tolerance times of 300 to 400 minutes. Although they were given
the same 200 mg. dosage as patients with a tolerance time of 180 minutes, their coagulograms were most apt to be similar, both as to height of response and duration of effect.

The practical significance of these differences in tolerance to heparin would be slight if the vast majority of patients were so-called normal reactors of the 300 mg. dosage category. Table 4 shows the distribution of our cases, with 36 per cent of the cases in the 200 mg. group, and

Table 3.—Similar Tolerance with a Wide Weight Range

<table>
<thead>
<tr>
<th>20 min. time</th>
<th>Weight in pounds</th>
<th>Clotting time in min. at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>12 hours</td>
</tr>
<tr>
<td>300 mg. dose (7 patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 min.</td>
<td>106</td>
<td>70</td>
</tr>
<tr>
<td>150</td>
<td>135</td>
<td>80</td>
</tr>
<tr>
<td>145</td>
<td>140</td>
<td>70</td>
</tr>
<tr>
<td>145</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>150</td>
<td>150</td>
<td>75</td>
</tr>
<tr>
<td>150</td>
<td>164</td>
<td>90</td>
</tr>
<tr>
<td>155</td>
<td>180</td>
<td>65</td>
</tr>
<tr>
<td>200 mg. dose (10 patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>130</td>
<td>70</td>
</tr>
<tr>
<td>180</td>
<td>130</td>
<td>65</td>
</tr>
<tr>
<td>180</td>
<td>140</td>
<td>60</td>
</tr>
<tr>
<td>185</td>
<td>150</td>
<td>70</td>
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<td>190</td>
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<td>110</td>
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<td>185</td>
<td>167</td>
<td>75</td>
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<tr>
<td>185</td>
<td>170</td>
<td>85</td>
</tr>
<tr>
<td>190</td>
<td>186</td>
<td>100</td>
</tr>
<tr>
<td>240</td>
<td>220</td>
<td>95</td>
</tr>
<tr>
<td>220</td>
<td>280</td>
<td>75</td>
</tr>
</tbody>
</table>

24 per cent of the cases in the 400 mg. category. A study of the weight of these same individuals disclosed that 53 per cent of them would have been given 400 mg. of heparin in a retarding menstruum based upon their weight. There is no guarantee that the 24 per cent of our cases given 400 mg. would be contained in the 53 per cent given the same dosage based on weight. Not only does this lead to inaccurate therapy but it will result in a great waste of the drug.

In order to define the extent of the weight-dosage error, our data was approached in another fashion, as shown in table 5. Each case was studied individually and classified. It will be seen that in 55 per cent of our cases the dosage recommended by the patient’s weight would have been in excess of that needed. In many instances patients whose weights indicated 400 or even 500 mg. did have a satisfactory therapeutic response with only 200 mg. of Depo-Heparin. In 7 per cent of the patients the weight dose would have been less and the coagulation time at 24 hours indicated that the decreased dosage would have resulted in an

Table 4.—Actual Distribution by Tolerance Test Compared with Theoretical Distribution by Weight Schedule

<table>
<thead>
<tr>
<th>Dosage</th>
<th>No of cases</th>
<th>Tolerance test</th>
<th>Theoretically by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg.</td>
<td>27</td>
<td>36%</td>
<td>0%</td>
</tr>
<tr>
<td>300 mg.</td>
<td>30</td>
<td>40%</td>
<td>47%</td>
</tr>
<tr>
<td>400 mg.</td>
<td>18</td>
<td>24%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Table 5.—Actual Therapy by Twenty Minute Dosage Schedule in Comparison with Recommended Weight Dosage

<table>
<thead>
<tr>
<th></th>
<th>No of Cases</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total successful therapy</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Weight dose would have been excess</td>
<td>38</td>
<td>55</td>
</tr>
<tr>
<td>Weight dose would have been less and not adequate</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Total weight-dose error</td>
<td>43</td>
<td>62</td>
</tr>
<tr>
<td>Weight dose would have been less but probably adequate</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Weight dose would have been inadequate</td>
<td>24</td>
<td>35</td>
</tr>
</tbody>
</table>

inadequate therapeutic regimen. This gives rise to a total weight-dose error of 62 per cent. In only 35 per cent of the cases was the weight dose the same as that indicated by the tolerance test.

E. Adequacy and Duration of Therapeutic Regimen

Phlebothrombosis. When a diagnosis of uncomplicated phlebothrombosis is made, the patient is put to bed with the foot of the bed slightly elevated above heart level. Heparin therapy is begun as outlined and continued for two to three days following subsidence of all
signs and symptoms. This period is reached usually on the fifth day of therapy. The patient is then permitted to walk, with the leg wrapped in elastic bandages, and heparin therapy is continued as before. If at the end of two days there has been no return of the signs and symptoms, heparin therapy is discontinued. The patient is observed for two more days, while he ambulates, before he is discharged.

“Spontaneous Phlebothrombosis.” An occasional patient is seen who has had no obvious etiologic factor to cause a phlebothrombosis. He has been performing his usual daily tasks and cannot remember any illness or incident which may have served as a “trigger mechanism” for the onset of benign thrombosis. Early in the series of observation, these patients were treated by the above outlined regimen. Not infrequently the disease would recur in a few days to a week, when heparin had been given for only five days. For that reason the duration of heparin therapy was increased to 14 days. Under this therapeutic plan of attack, we have had no recurrence in these patients. It is true that some of them have returned, months later, with a new episode of the same type. Recently we have treated second episodes in these patients by anticoagulant therapy for a 90 day period.

Pulmonary Embolus. When an embolus has occurred in either of the two types mentioned above, the patient remains at bed rest for 12 days, with heparin therapy as previously outlined. He is then allowed out of bed with heparin being continued for two more days. Observation is continued at least 48 hours, without heparin. The extremities are wrapped as mentioned above.

DISCUSSION

It would appear from a survey of the data offered, that the final treatment schedule, as shown in table 1, offers a simple, safe and effective method to avoid the dangerous excesses and lapses in clinical heparin therapy. In a practical sense, it is possible to disregard all of the multiple variables that lead to therapeutic confusion, basing treatment solely on the individual’s response to a standard dose of intravenous heparin. Therapy can be controlled by the performance of a simple, accurate and reproducible coagulation time determination every 24 to 36 hours.

The duration of effect of heparin in a retarding menstruum, with vasoconstrictors, may well be greater than that of the same preparation without them. This does not seem to invalidate the accuracy of the 20 hour prediction, when the latter drug is used in the treatment of patients with coronary heart disease and arterial thrombosis and embolism. Whatever effect the vasoconstrictors may have had, it appears to have been dissipated by the 20 hour interval.

The fallacy of depending on weight as a guide to heparin dosage is well shown by a study of tables 3, 4 and 5. It was particularly obvious in one patient who, weighing almost three times as much as another, had the same therapeutic effect from 100 mg. less of the drug. Table 2 demonstrates that medication given in excess of that indicated by tolerance does not produce a comparable prolongation of therapeutic effect. The excessive decreases in blood coagulability produced by these overlarge doses are not necessary for the protective effect of heparin on the thrombosis. Even though over one-third of our patients had full protection by 200 mg., none of these patients would have been given that dose by a weight schedule. Most recently dosages of 500 and 600 mg. have been recommended. In none of 105 cases did we find this large dose necessary.

It is fundamental, and of primary importance, that the simple rules outlined for the performance of the coagulation test be followed. The coagulation times were all done at room temperature during the change of seasons over a period of one and one-half years. Unquestionably, extremes of temperature will influence the length of a coagulation time, but the variation encountered during this period did not seem appreciably to alter the results. Over 30 house officers and students have been involved in collecting the coagulation time data reported in this paper. That such reproducible responses were observed, indicates that the method can be learned by anyone who is sufficiently interested.

The final proof of any therapeutic regimen
must be measured against its effectiveness in treating the diseases for which it is designed. In none of the cases, was there a known failure of heparin therapy. There was no extension of the local signs in the cases of uncomplicated phlebothrombosis, nor did an embolus occur in any of these cases. In none of the 11 cases who were admitted with a pulmonary embolus, or whose first warning sign in the hospital was an embolus, did re-embolization occur. These results attest to the validity of the method of determining the coagulation time, to the safety of the 25 minute coagulation time as the lower limit for therapy, and to the fact that the suggested length of the therapeutic regimen has been sufficient.

**Summary**

1. A therapeutic regimen, based on a simple tolerance test, is outlined whereby heparin therapy can be fitted to the individual patient. It was evolved from a study of 105 patients.

2. Dependence upon weight as a guide to dosage has been shown to be grossly inaccurate.

3. A simple coagulation time method is suggested and its fundamental importance is stressed.

4. Results indicate that it is safe to allow the coagulation time to fall to a level of 25 minutes, before a new injection of heparin in a retarding menstruum is made.

5. The method proved accurate in the control of heparin therapy in various forms of venous and arterial thrombosis, and requires the performance of but one coagulation time every 24 to 36 hours.

**REFERENCES**


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