Mortality and Other Studies Questioning the Evidence for and Value of Routine Anticoagulant Therapy in Acute Myocardial Infarction

By Sidney Schnur, M.D.

This study of 1350 patients with acute myocardial infarction admitted to several hospitals during a 10-year period attempts to answer several questions currently in dispute: the correlation of the patient's condition on admission with the mortality rate, the relation of the patient's age to prognosis, and the value of routine anticoagulant therapy. It presents the major statistical objections to the study by the Committee for the Evaluation of Anticoagulants of the American Heart Association, questions the evidence upon which the Committee made its recommendations and concludes that incontrovertible proof of the advantages of routine anticoagulant therapy in patients mildly ill on admission to the hospital has not been presented thus far.

The specific value of a drug or a procedure in the treatment of acute myocardial infarction is difficult to ascertain because of the tremendous number of variable factors which affect recovery. The statistical approach, the only adequate method of study, is fraught with many dangers which may lead to incorrect interpretation. Thus, in spite of a plethora of papers in the literature, the value of and indications for routine anticoagulant therapy* are still in doubt.1,2 Even among those† who participated in the anticoagulant study sponsored by the American Heart Association in 1948,4 there is no present unanimity of opinion. All investigators are aware that the patient's condition prior to therapy has a definite influence upon the mortality rate, but the exact role of this factor has been difficult to assess because of inability to express it quantitatively. This has led to uncertainty as to whether control and treated groups are equally ill and, therefore, whether any difference in mortality found at the conclusion of a study was due to unequal selection of cases or to the specific therapy employed. Until a few years ago the patient's age had been accepted as an important factor in mortality due to acute coronary thrombosis.5,6 The Committee for the Evaluation of Anticoagulants of the American Heart Association‡ observed that routine anticoagulant therapy was effective in lowering the mortality rate in the older age group, but did not alter the rate in those under 60 years of age. Russek2,7 recently has raised serious doubts concerning the validity of the age factor in prognosis and routine anticoagulant therapy in general. Thus it is obvious that certain basic facts regarding mortality statistics in acute coronary thrombosis with myocardial infarction require elucidation; that the status of anticoagulant therapy is still unsettled; and that new technics for more adequate study might be required to resolve the points at issue.

This investigation, designed to answer several

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* "Routine anticoagulant therapy" in this paper signifies compliance with the recommendations of the Committee on Anticoagulants of the American Heart Association: "Anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless a definite contraindication exists."4

† In answer to a questionnaire regarding their present policy in treatment of acute myocardial infarction, three of the responsible investigators stated they do not use anticoagulants routinely in their own practice, nine follow the recommendations of the Committee, one does not practice clinical medicine.3

‡ The studies, publications and recommendations of the Committee for the Evaluation of Anticoagulants of the American Heart Association will be designated in this report by the term, Committee.
of the preceding questions and to examine some questionable statistical practices exhibited in various published reports, consists of the following four studies, each directly related to the general problem of routine anticoagulant therapy in acute myocardial infarction: (1) correlation of patient’s condition on admission with mortality rate, utilizing a quantitative method for determining degrees of illness; (2) ascertaining of the relationship of age to the mortality rate; (3) comparison of certain items in this group with similar items in the Committee’s study, using its technic and methods; (4) noting the effect of anticoagulant therapy upon the mortality rate in several hospitals during one year and comparing it with mortality rates in the preanticoagulant era.

**METHODS AND MATERIALS**

The clinical records of 1350 patients with coronary thrombosis and myocardial infarction, hospitalized in several hospitals in Houston from 1941 to 1950, form the basis of this report. Only those records have been included in which the diagnosis could be reasonably substantiated from the electrocardiograms, physical examination, history, clinical course and occasionally the postmortem examination. Patients who suffered an infarction while hospitalized for other causes were not included. From those clinical records reviewed, the specific information noted in table 1 was extracted, classified and analyzed in the following manner:

1. **Correlation of the Patient’s Condition on Admission with the Mortality Rate.** This was done by assigning a numerical value to certain specific admission clinical findings and historical data by a predetermined formula. The factors considered significant were based upon previous studies of factors known to influence the mortality rate, and the actual number assigned to each factor was determined by the author’s clinical estimate of relative importance of each in the prognosis, using former studies as a guide. Although this is admittedly somewhat inexact (and others may wish to add other factors or weight them somewhat differently), only those factors which could be determined immediately at the bedside examination were con-

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**Table 1.—Information Obtained from Clinical Records, Ratings for Various Clinical Findings, and Method of Determining Pathologic Index Rating**

<table>
<thead>
<tr>
<th>Date of admission</th>
<th>Congestive heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Serious arrhythmia</td>
</tr>
<tr>
<td>Sex</td>
<td>Associated serious diseases: pulmonary, renal, other</td>
</tr>
<tr>
<td>Results: lived or died</td>
<td>History of serious vascular or other disease</td>
</tr>
<tr>
<td>Died: within 24 hrs. or later</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Shock</th>
<th>Associated serious diseases</th>
<th>10-25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Failure</td>
<td>Diabetes</td>
<td>10-25</td>
</tr>
<tr>
<td>Serious Arrhythmias</td>
<td>Uremia</td>
<td>10-25</td>
</tr>
<tr>
<td>Ocas. vent. contract</td>
<td>Urinary tract infection</td>
<td>10</td>
</tr>
<tr>
<td>Freq. vent. contract</td>
<td>Emphysema</td>
<td>10</td>
</tr>
<tr>
<td>Auricular tachycardia</td>
<td>Cerebral thrombosis</td>
<td>10-25</td>
</tr>
<tr>
<td>Auricular flutter</td>
<td>History of heart or vascular disease</td>
<td>10-30</td>
</tr>
<tr>
<td>Vent. tachycardia</td>
<td>Hypertension</td>
<td>10</td>
</tr>
<tr>
<td>Gallop Rhythm</td>
<td>Cardiac enlargement</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Angina</td>
<td>10-30</td>
</tr>
<tr>
<td></td>
<td>Congestive failure</td>
<td>20-30</td>
</tr>
<tr>
<td></td>
<td>Prev. coronary occlus.</td>
<td>20-30</td>
</tr>
</tbody>
</table>

**Examples:**

- Patient entered in shock (40) with history of previous hypertension (10) and mild diabetes (10) P. I. R. = 60.
- Patient entered in shock (40), congestive failure (20) and ventricular tachycardia (40) with history of hypertension (10) and previous severe coronary occlusion (30) P. I. R. = 140.
- Patient entered with negative findings (no shock, congestive failure, arrhythmia or associated serious disease) with history of hypertension (10) P. I. R. = 10.
advantage of this quantitative determination is that all patients evidencing the same clinical findings receive the same rating, no matter whether they are in another group, hospital or city, and those findings which are of greater prognostic significance are given greater weight in the final summation. The impracticability of determining the mathematically precise role of each factor is discussed elsewhere. Shock was considered to be the most serious state and given a maximum value of 40. This number had no special significance; any number could have been chosen. With this as a basis the clinical findings and historical data listed in table 1 were then assigned values according to what was considered to be their relative importance in causing death. The sum of these in each patient was designated the pathologic index rating. This rating was, therefore, a quasi-quantitative measure of the severity of the disease and the clinical status on admission, prior to institution of therapy. In this study the pathologic index rating ranged from 0 to 140. For ease of statistical analysis patients were placed in one of five pathologic index rating groups: 0 to 19; 20 to 39; 40 to 59; 60 to 79; and 80 and above. These groups reflected gradations in severity and would correspond roughly with the following clinical classifications: mild, moderate, moderately severe, severe, and critically ill. These groups were then studied for mortality, age, and other factors to be discussed.

2. Determination of the Relationship of Age to the Mortality Rate. Early in the study it was observed that crude mortality-age statistics would confirm previous publications indicating increased mortality with increased age. The pathologic index rating technic was then utilized to provide groups of patients who were equally ill on admission. Each group was subdivided according to age into four classifications (30 to 45; 46 to 60; 61 to 75; and 76 and above), and the number of patients and mortality rate of each age category was determined.

3. Comparison of Certain Items in This Group with Items in the Study Sponsored by the American Heart Association, Using Technic and Methods Applied in That Study. Patients were placed in two groups, according to whether or not they were admitted on odd or even days. These groups were compared for total cases, average age, average age of males, average age of females, sex ratio, and mortality rate. This study was undertaken to determine whether there would be any significant difference in any of the items compared between the odd and even day series, if a completely unselected group were chosen consisting of approximately the same number of patients as in the Committee's study.

4. Study of the Effect of Anticoagulant Therapy upon the Mortality Rate in Several Hospitals during One Year. The mortality rate in each of three hospitals using anticoagulant therapy during the year 1950 was studied and compared with the average mortality rate in each hospital the previous 10 years. In one hospital there was a large enough group of patients who received no anticoagulants so that comparison could be made with the anticoagulant group. In this study the mortality rate and percentage of patients in each pathologic index rating group was determined. The average pathologic index rating for each hospital was calculated, and the theoretical or expected mortality rate corresponding to this rating was determined by using the preanticoagulant era Jefferson Davis Hospital mortality study as a basis. The actual rate in 1950 was then compared with the expected mortality rate.

Table 2.—Yearly Mortality Rate* in "Preanticoagulant" Decade (1940-1950) from Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Year</th>
<th>Jefferson Davis Hospital</th>
<th>St. Joseph's Infirmary</th>
<th>Methodist Hospital</th>
<th>South Pacific Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>1941</td>
<td>57</td>
<td>39</td>
<td>40</td>
<td>17</td>
</tr>
<tr>
<td>1942</td>
<td>50</td>
<td>48</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>1943</td>
<td>65</td>
<td>47</td>
<td>41</td>
<td>17</td>
</tr>
<tr>
<td>1944</td>
<td>53</td>
<td>32</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>1945</td>
<td>71</td>
<td>31</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>1946</td>
<td>40</td>
<td>35</td>
<td>46</td>
<td>21</td>
</tr>
<tr>
<td>1947</td>
<td>43</td>
<td>28</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>1948</td>
<td>45</td>
<td>40</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>1949</td>
<td>61</td>
<td>41</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>1950</td>
<td>57</td>
<td>43</td>
<td>30</td>
<td>16</td>
</tr>
</tbody>
</table>

Average ......... 52 38 32 10

* Includes deaths within 24 hrs.

RESULTS

1. Correlation of Patient’s Condition on Admission (Pathologic Index Rating) with Mortality Rate

The mortality rate for each year for each hospital is noted in table 2. A study for the year of the highest (1945) and lowest (1946) mortality rate at Jefferson Davis Hospital indicates a majority of cases in the highest pathologic index rating groups in the year of high mortality, and a preponderance of cases in the lowest pathologic index rating group in the year of low mortality (table 3). In the years of equal mortality (1947 and 1948) a close similarity in distribution of cases between the various pathologic index rating groups is noted (table 4). A definite relationship between the mortality rate in each hospital in 1950 and

considered. Laboratory and other aids, some of which are of prognostic significance were not included.
the distribution of patients in the various pathologic index rating groups is evident in table 5. The mortality rate and percentage of cases in each pathologic index rating group in Jefferson Davis Hospital for the entire 10 year period is presented in figures 1 and 2. Excluding patients dying within 24 hours after admission to the hospital, the rate ranged from 8 per cent in the 0 to 19 (mild) group to 95 per cent in the 80+ (critically ill) group.

<table>
<thead>
<tr>
<th>P.I.R. Groups</th>
<th>1945</th>
<th>1946</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Deaths</td>
</tr>
<tr>
<td>0-19</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>20-39</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>40-59</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>60-79</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>80+</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentage of Patients in Various P.I.R. Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>0-19</td>
</tr>
<tr>
<td>33%</td>
</tr>
<tr>
<td>63%</td>
</tr>
<tr>
<td>60+</td>
</tr>
<tr>
<td>58%</td>
</tr>
<tr>
<td>26%</td>
</tr>
</tbody>
</table>

* Standard error of the difference is 11.

The hospital mortality rate for this disease is determined by the proportion of seriously ill patients to the total number of patients admitted with acute myocardial infarction. Thus a charity hospital (Jefferson Davis Hospital) with an active emergency service which admits only seriously ill patients because of shortage of beds, is expected to have a high mortality rate (52 per cent) and also a high proportion of deaths (30 per cent) within 24 hours. A private hospital (Methodist Hospital), with no emergency service, which admits patients with no regard to severity (in recent years patients with mild illness have been admitted to the hospital for the sole purpose of obtaining anti-

<table>
<thead>
<tr>
<th>Table 3.—Comparison of P.I.R., Average Age and Sex Ratio in Years of Highest (1945) and Lowest (1946) Mortality Rates at Jefferson Davis Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.I.R. Groups</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>0-19</td>
</tr>
<tr>
<td>20-39</td>
</tr>
<tr>
<td>40-59</td>
</tr>
<tr>
<td>60-79</td>
</tr>
<tr>
<td>80+</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentage of Patients in Various P.I.R. Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>0-19</td>
</tr>
<tr>
<td>33%</td>
</tr>
<tr>
<td>63%</td>
</tr>
<tr>
<td>60+</td>
</tr>
<tr>
<td>58%</td>
</tr>
<tr>
<td>26%</td>
</tr>
</tbody>
</table>

* This does not imply that a patient's prognosis is not affected within certain limits by the quality of medical and nursing care and the proper use of various therapeutic measures—factors which require no dis-
coagulant therapy), should have a low mortality rate (32 per cent) and comparatively few deaths within 24 hours (11 per cent). A private hospital (St. Joseph's Infirmary) with a large emergency service should have a mortality rate between the two (38 per cent). A specialized private hospital such as a railroad hospital (Southern Pacific Hospital), which maintains average mortality rate which is largely dependent upon its criteria for admission and the type of patients treated. The yearly rate, however, in each hospital will vary widely and will depend upon the proportion of seriously ill admitted for that particular year—in addition to the chance variation of small samples. This would indicate that any study which draws

conclusions solely on the basis of a difference in mortality rate from a preceding year is likely to be in error because of the extreme "normal" variation of rates from year to year, due largely to the constantly fluctuating proportion of seriously ill patients admitted.

2. Relation of Age, Pathologic Index Rating and Mortality Rate

Figure 4 indicates the average age of males and females in each pathologic index rating group. It is noted that the average age increases for both males and females in the higher pathologic index rating groups and that in four of the five groups the average age of females is higher than males. The mortality rate in each pathologic index rating group, subdivided

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### Table 5.—Correlation of P.I.R. with Mortality Rate* in Patients Treated with Anticoagulants in 1950

<table>
<thead>
<tr>
<th>P. I. R. Group</th>
<th>Jeff Davis Hospital</th>
<th>Methodist Hospital</th>
<th>So. Pacific Hospital</th>
<th>Total All Hospitals</th>
<th>Jeff Davis Hosp. No Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>20</td>
<td>0</td>
<td>0%</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>20-39</td>
<td>20</td>
<td>0</td>
<td>0%</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>40-49</td>
<td>20</td>
<td>0</td>
<td>0%</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>60-79</td>
<td>20</td>
<td>3</td>
<td>100%</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>80+</td>
<td>20</td>
<td>3</td>
<td>100%</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>7</td>
<td>37%</td>
<td>46</td>
<td>10</td>
</tr>
</tbody>
</table>

| Average P.I.R. | 47    | 30     | 24%  | 15    | 24%   | 13%  | 31    | 24%   | 29%  |
| Expected Mort. Rate† | 32% | 22%   | 10%  | 25%   |
| Average Mort. Rate | 32% | 22%   | 10%  | 25%   |

| 1941-1950*       | 32% | 22%   | 10%  | 25%   | 32%  |

### Percentage of Patients in Various P.I.R. Groups

<table>
<thead>
<tr>
<th>P. I. R. Group</th>
<th>0-19</th>
<th>0-39</th>
<th>60+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>11%</td>
<td>50%</td>
<td>33%</td>
</tr>
<tr>
<td>0-39</td>
<td>50%</td>
<td>76%</td>
<td>15%</td>
</tr>
<tr>
<td>60+</td>
<td>33%</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

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* Excludes deaths occurring within 24 hours of admission.
† Calculated from the Mortality Rate—P.I.R. Graph (fig. 3) by determining the rate (ordinate) corresponding with the average P.I.R. (abscissa).
ANTICOAGULANTS IN MYOCARDIAL INFARCTION

according to age groups, is indicated in table 6. Apparently, in patients whose clinical condition on admission is similar, there appears to be little difference in the mortality rate between the various age groups from 30 to 75. The slight deviations may be explained by the nonspecific increase in mortality rate associated with increasing age, and the chance variation of small samples.* However, over the age of 75 there is a significant increase in mortality rate in each pathologic index rating group. This finding is somewhat similar to actuarial tables of mortality, and may also be indicative of the nonspecific effect of advanced age rather than an unusual increase in the death rate due to the disease itself. This presumption appears to be supported by a preliminary study of an unselected group of patients admitted to the medical service for all diseases in which the mortality rate of those above 75 years of age seems to be significantly higher than those in

* These conclusions are tentative pending a study of a larger series.13
the younger age groups.† A greater proportion of younger persons is in the lower pathologic index rating groups, while older persons are more likely to have higher pathologic index ratings. Young persons with high pathologic index ratings have higher mortality rates than older persons with low index ratings.

Comment. Crude mortality statistics indicate that with increasing age there is increased mortality from acute myocardial infarction. In the past this has seemed to indicate that the patient's age is an important factor in causing death from this disease. This study indicates that increased age usually reflects a higher pathologic index rating, that is, that these patients are more seriously ill on admission and that the increased mortality is due to this fact, rather than to age, per se. However, in patients who are equally ill on admission age appears to have no more striking effect upon the mortality rate in this disease than it has in any other serious disease requiring hospitalization, except possibly in those above the age of 75, when the rate is doubled. To determine whether the patient's age significantly affects recovery from any disease, the nonspecific increasing death rate associated with advancing age must first be discounted. The reason a higher proportion of older persons are in the higher pathologic index rating groups is probably due to the fact that they have had more years to develop the ills and infirmities that increase the pathologic index rating and lower life expectancy. Thus it would appear that a man 60 years of age would have approximately the same chance of recovery as one 45 years of age (discounting the nonspecific decrease in life expectancy), if the clinical conditions of both on admission were the same (that is, the pathologic index ratings of both were similar), but the prognosis for recovery of either would be twice as good as the man of 76 who entered the hospital in a comparable clinical state.

There is apparently an erroneous belief that two groups may be considered to be equal in severity of illness if the average age and the sex ratio is similar. Averages may mask significant differences which can be revealed by distribution curves. Thus it is possible that two groups of patients may have the same average age but dissimilar mortality rates because of a preponderance of patients over 75

† Of 386 consecutive cases admitted to the medical service and classified into age groups, the mortality rate for each group was as follows: 14 to 30 years, 6 per cent; 31 to 45 years, 12 per cent; 46 to 60 years, 22 per cent; 61 to 75 years, 35 per cent; above 75 years, 45 per cent.

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>30-45</td>
<td>11</td>
<td>2</td>
<td>18%</td>
<td>15</td>
<td>3</td>
<td>20%</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>46-60</td>
<td>28</td>
<td>1</td>
<td>4%</td>
<td>24</td>
<td>5</td>
<td>20%</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>61-75</td>
<td>32</td>
<td>3</td>
<td>10%</td>
<td>25</td>
<td>6</td>
<td>24%</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>76+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3</td>
<td>2</td>
<td>60%</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Total... 71 | 6 | 8% | 67 | 16 | 24% | 46 | 15 | 33% | 25 | 20 | 80% | 21 | 20 | 95% | 230 | 77 | 33% | 38 | 29% |

Percentage of Patients in Different Age Groups Correlated with P.I.R.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>0-39 P.I.R. Group</th>
<th>60+ P.I.R. Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-45</td>
<td>70%</td>
<td>13%</td>
</tr>
<tr>
<td>46-60</td>
<td>66%</td>
<td>14%</td>
</tr>
<tr>
<td>61-75</td>
<td>61%</td>
<td>21%</td>
</tr>
<tr>
<td>76+</td>
<td>16%</td>
<td>47%</td>
</tr>
</tbody>
</table>

* Excludes deaths occurring within 24 hours of admission.
years of age in one series. Sex apparently affects the mortality rate through the age factor, females being approximately five years older than males with equivalent illness. The sex ratio of itself is of no prognostic value. The evidence for these statements is given in Table 3 and the following example. If two groups of patients are selected, one (series A) consisting of 15 males and 5 females with an average age of 55 for the males and 60 for the females, and another group (series B) of 30 males and 10 females whose average age is 50 and 76 respectively, even though the average age of each group is the same (56) and the sex ratio is similar (3:1), the mortality rate in series B will be "significantly" greater than in series A because of the preponderance of elderly females with high mortality in that group. The difference in the rate would therefore be due to an unusual "selection" of cases which would not be disclosed by computing the average age or sex ratio.

The disagreement between the conclusions of the Committee of the American Heart Association and Russek concerning the subject of age and prognosis is apparently an illusion, since each has viewed the problem from a different aspect. The findings in this study confirm several of their observations and may be summarized as follows: (1) The average age of seriously ill patients admitted to the hospital is higher than the age of those less seriously ill and this is reflected generally in a higher mortality rate in the older age group. (2) A greater proportion of the younger age group is found to be mildly ill on admission, in contrast to the older age group, the majority of whom are likely to be more seriously ill. (3) The average age of female patients is higher than male patients generally, and probably in the five groups which reflect increasing severity of illness. (4) In patients who are equally ill on admission, no unusual difference in the mortality rate from this disease is found between any of the age groups except in those above 75 years of age when the rate appears to be doubled. (5) Seriously ill young persons have a higher mortality rate than less seriously ill older patients. (6) The condition of the patient on admission to the hospital is a vastly more important determinant of prognosis than the patient's age.

This study suggests an additional interpretation of the Committee's observation that anticoagulants were effective in lowering the mortality rate in those above 60 years of age, whereas there was no significant decrease in mortality in the younger age group. Since it has been shown that age reflects severity of illness on admission to the hospital, it would appear that routine anticoagulant therapy had no effect upon the mortality rate in the mildly ill, but may have been effective in lowering the rate in the seriously ill. Actually, this analysis of their findings parallels the judgment of many experienced clinicians who do not favor routine anticoagulant therapy for mildly ill patients, but believe it may be prescribed for those seriously ill without regard to age. This policy, which is compatible with the Committee's findings, would appear to be preferred to any indications for therapy based primarily or solely upon the age of the patient.

3. Results of Anticoagulant Therapy

Table 5 indicates the result of anticoagulant therapy in three hospitals during the year 1950.* In one hospital (Jefferson Davis) there were a number of patients who did not receive anticoagulants. The results in this group are also presented. A comparison of the mortality rate in each hospital reveals little difference from the average mortality rate of the past 10 years in that particular hospital. However, this may be a fortuitous circumstance. If the average pathologic index rating is obtained for each hospital and the theoretical or expected mortality rate corresponding to this rating is determined by using the 10 year Jefferson Davis Hospital graph as a basis, the actual and expected mortality rates are found to be surprisingly similar. This might indicate that the graph could be used as a basis to determine significant shifts in prognosis due to new therapies or procedures. During 1950, however,

* Dicumarol was the anticoagulant used in over 90 per cent of the cases. Whether similar findings would occur with the newer anticoagulants is a matter for further investigation.
anticoagulant therapy did not appear to alter significantly the prognosis of patients with myocardial infarction. A similar study for 1951 and 1952 is presently underway and will be the subject of a future communication.*

The mortality rate in each hospital, as noted previously, appears to be closely related to the distribution of cases in the groups with high and low pathologic index ratings. Thus the low mortality rate for the Southern Pacific Hospital is due to the high proportion of cases in the 0 to 39 pathologic index group, whereas the high mortality for Jefferson Davis Hospital can be attributed to the preponderance of cases in the groups with high pathologic index ratings. The anticoagulant and no anticoagulant groups at Jefferson Davis Hospital appear to have the same proportion of cases in the high and low pathologic index rating groups and fairly similar average pathologic index ratings. They would, therefore, be strictly comparable, and one would be able to draw a definite conclusion if the series were larger. In this small series, however, there appears to be no significant difference in mortality between the treated and nontreated groups.

Comment. The negative results obtained in this study suggest one of two conclusions: (1) Anticoagulants have no appreciable effect upon mortality. (2) Anticoagulants are used ineffectively.

To determine whether the latter was true, the record librarian in each of three hospitals was asked to select any 10 clinical records of patients with acute myocardial infarction who received anticoagulant therapy. Prothrombin determinations during the first 48 hours were not included. It was found that 66 per cent of 496 daily determinations were outside of what is generally considered to be the “effective” range which is 10 per cent to 24 per cent activity.* Actually, the precise range in which clotting would be inhibited in vivo is uncertain and still remains a matter of clinical conjecture. In none of the 30 cases was the prothrombin activity within the effective range during the entire course of therapy. The extreme variability of response of patients receiving an identical dose of Dicumarol and the inability to predict in advance the effect of a given dose upon the prothrombin time were confirmed in this study. These findings might also indicate that in this community because many physicians are not completely convinced of the value of this therapy or are concerned about its dangers,† it is prescribed half-heartedly and only because such treatment is “expected.” The following conclusions would appear to be valid: (1) It was most difficult to maintain the prothrombin activity within the prescribed range. (2) Patients were “protected” less than half the time while under therapy and were predisposed to hemorrhage approximately one day per week. (3) Since all patients had one or more determinations outside the effective range, the occurrence of a thromboembolic episode during therapy could always be explained by anticoagulant enthusiasts.

It may be concluded, therefore, that the absence of a significant difference in mortality between the group receiving anticoagulants and the control groups in this study may be due

* It should be noted that no attempt was made to study the incidence of nonfatal thromboembolism, an important consideration in anticoagulant therapy. Since the frequency of the diagnosis is related to the examiner’s index of suspicion, it was believed that any conclusions derived from a study of clinical records in which this factor is undetermined and uncontrolled could not be considered valid. This subject is discussed in greater detail elsewhere in this report. However, these objections do not apply to a study of death rates since the end point is definite, unequivocal and not subject to diagnostic errors.

† Recent reports of a rebound phenomenon causing hypercoagulability of blood following discontinuance of anticoagulants suggests an additional hazard in this therapy. Previously the occurrence of a thromboembolic episode immediately after cessation of anticoagulant therapy might have been interpreted as evidence of (1) the protective value of anticoagulants and (2) the need for long-term and possibly indefinite treatment. These reports suggest (1) thromboembolism might never have occurred if anticoagulants had not been prescribed; (2) a more conservative approach may be desirable in view of the many unexplored facets of this problem; (3) more searching studies are needed to determine which group of patients actually requires prophylactic therapy.
either to the ineffective use of anticoagulant drugs, or to the ineffectiveness of anticoagulants in general, or both. However, it should be noted that this particular aspect of the problem of routine anticoagulant therapy has received little or no attention in the medical literature. Reports of studies indicating the beneficial effect of this therapy which also present data concerning the efficiency of anticoagulant treatment as reflected in daily prothrombin determinations are meager indeed. If the unpublished experience of others parallels ours, it would be hard to conceive of anticoagulant therapy producing all the prophylactic effects attributed to it in patients whose “control” is from a single universe without selection; viz., the expected number of patients in the even group is 1.1 times the standard error of the theoretic number.

Comment. Recent objections have been raised to the Committee’s studies because of the probability that the cases in this study were not selected at random. Rytaud,\textsuperscript{14} in discussing the Committee’s follow-up report\textsuperscript{16} in which the odd day or treated group consisted of 589 cases, and the even day or control group consisted of 442 cases, noted that the excess of treated cases was 3.9 times the standard error of the theoretical number expected in a complete random selection of cases. Anything beyond 3 times the standard error is considered significant, cannot be attributed to chance, and indicates the likelihood of selection of cases, rather than random sampling. “Frequencies differing from the expected frequency by more than 3 times the standard error are almost certainly not due to fluctuations of sampling. They point to some departure of the sampling from simplicity, which may in turn point either to some flaw in the sampling technique or to causal effects in the universe itself.”\textsuperscript{17} Since a comparable study of a similar universe in Houston yielded a probable error well within the range expected of a random sampling, it may be concluded that the Committee’s figures are not due “to causal effects in the universe itself” but rather “to some flaw in the sampling technique.” This objection, if sustained, would invalidate, or at least cast suspicion upon the conclusions derived from the study made by the Anticoagulant Committee.

The difference in mortality rate in the American Heart Association study between the treated and untreated group is 7.4 per cent (23.4 per cent mortality in controls and 16 per cent in the treated group). It has been shown in our study that in a single hospital the mortality rate varied from 8 per cent to 95 per cent, a difference of 87 per cent, by selecting cases according to the degree of severity of illness on admission. In addition, the mortality rate from this disease reported in the literature has ranged from 8 per cent\textsuperscript{16} to 78 per cent,\textsuperscript{18} and in one year from 0 per cent at Southern Pacific Hospital in 1945 to 71 per cent in the same year at Jefferson Davis Hospital although these series are small, the findings are statisti-

### Table 7.—Comparison of Houston* and American Heart Association† Statistics

<table>
<thead>
<tr>
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<th>Houston</th>
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<th>Wright</th>
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<tbody>
<tr>
<td></td>
<td>Even</td>
<td>Odd</td>
<td>Even</td>
<td>Odd</td>
</tr>
<tr>
<td>Total Cases ..........</td>
<td>320</td>
<td>304</td>
<td>365</td>
<td>432</td>
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<tr>
<td>Average Age ..........</td>
<td>59</td>
<td>58</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Average Age Males</td>
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<td>57</td>
<td>58.9</td>
<td>57.2</td>
</tr>
<tr>
<td>Average Age Females</td>
<td>62</td>
<td>62</td>
<td>64.1</td>
<td>64.6</td>
</tr>
<tr>
<td>Ratio Males to Total</td>
<td>67</td>
<td>71</td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td>“Severe Cases”</td>
<td>—</td>
<td>—</td>
<td>28%</td>
<td>30%</td>
</tr>
<tr>
<td>Mortality Rate</td>
<td>24</td>
<td>26</td>
<td>24</td>
<td>15</td>
</tr>
</tbody>
</table>

* Jefferson Davis and Methodist Hospitals excluding deaths occurring within 24 hours of admission.
cally significant and indicate that patient selection is a most important determinant of the mortality rate. It would appear, therefore, that in any study of the effects of any new therapy upon mortality in this disease, the groups compared must be proved to be of equal severity. Even a slight difference between the two may be reflected in a difference in mortality which may be incorrectly attributed to therapy or other factors. Previous studies on mortality in acute coronary thrombosis, including several recent studies on the effect of anticoagulant therapy, apparently have paid too little attention to this important factor, perhaps hoping that the odd and even days, or alternating case technique might equalize the two groups. Although equivalent groups are more likely to be obtained by this method, the presence of a matched series cannot be assumed but must be proved in each case. A "statistically significant" difference merely means that the difference in mortality between two groups is greater than one would expect from two random samples from the same universe, but this could just as well be due to an unequal selection of cases as to a specific therapy. Since the Committee's study was a cooperative effort of many clinicians in 16 different hospitals, each of whom probably had his own criteria for degrees of severity, the figures indicating that the treated group generally was a more severely ill group than the control might be open to question.* According to Hill, such qualitative determinations by a large group of individuals who have no definite or uniform criteria for guidance may well lead to an erroneous conclusion.

The Committee's study of mortality by weeks of illness indicates that the control group had a higher mortality rate during the second week than the first, and a higher rate for the fourth week than the third, determined by the number of deaths per 100 survivors from the previous week. This finding is not in accord with clinical experience which indicates the longer one lives following acute coronary thrombosis the greater are the chances of recovery, and the established fact that the highest mortality rate occurs during the first week when determined by any statistical method. The treated group, however, showed the expected type of curve. One could well argue that since the mortality rate in the control group in the Committee's study does not coincide with the curve expected from past clinical experience, this may be additional evidence of the presence of a selected group, rather than a random sampling.

The difference in the mortality rate between the treated and control groups, according to the Committee, is due to deaths from thromboembolism. It is generally agreed that the clinical diagnosis of several thromboembolic phenomena is difficult, often inaccurate, subject to errors of omission and commission and directly related to the examiner's index of suspicion. Thus far, no postmortem studies have been presented to confirm those impressions relating to the increased incidence of fatal thromboembolism in the control group, nor has there been any mention of the accuracy of clinical diagnosis of nonfatal thromboembolism as verified by surgical and autopsy studies. It would appear, therefore, that since the crucial evidence has not been produced to date, any conclusions regarding this aspect of the Com-

* Superficial thrombophlebitis, cerebral and peripheral arterial emboli can generally be accurately diagnosed. However secondary myocardial infarctions due to extension, pulmonary infarction especially in the presence of myocardial failure and pulmonary congestion, and phlebothrombosis are subject to diagnostic errors. In the study by the Committee on Anticoagulants 18 per cent of thromboembolic episodes in the control group were of the easily diagnosed variety, whereas 82 per cent were of the difficult type. In the treated group the decrease in thromboembolism appears to be almost completely confined to the group in which the diagnosis is often questionable. A possible additional psychologic source of error is the unconscious bias of the medical examiner due to his increased suspicion of the presence of thromboembolism in patients not receiving anticoagulants, and the likelihood of an excessive number of potentially misdiagnosed psychosomatic complaints in "control" patients anxious about not receiving the "clot removing" drug. In a properly controlled study using the "blind" technique neither the examining physician nor the subject would be aware of the group to which the patient is assigned until the study had been concluded.18
mittee's report can only be accepted with reservations at this time.

**Discussion and Conclusions**

1. A method for quantitative determination of degrees of illness in acute myocardial infarction is presented and termed "pathologic index rating."

2. The Pathologic Index Rating, determined on admission to the hospital, is found to be closely related to the mortality rate. In one hospital the mortality rate ranged from 8 per cent in the mildest group to 95 per cent in the critically ill group.

3. The average yearly mortality rate for acute myocardial infarction over a period of years in a designated hospital is a reflection of its criteria for admission and the type of patient treated. The yearly mortality rate varies widely and depends upon the proportion of seriously ill admitted to the total number admitted for that particular year.

4. Age as a prognostic factor in acute myocardial infarction has little significance, except as it may indicate a more serious condition on admission to the hospital. In patients who are equally ill on admission, no important difference in the mortality rate is found between any of the age groups except in those above 75 years of age when the rate is doubled. Older persons have higher crude mortality rates because a greater proportion are seriously ill on admission.

5. The mortality rate of patients treated with anticoagulants in three hospitals during 1950 was similar to the average mortality in each during the preceding 10 years. In one hospital a comparison of the treated and untreated groups with similar pathologic index ratings showed no significant differences in mortality. The mean pathologic index rating for each hospital was determined, and the mortality rate corresponding to it in the preanticoagulant days was found to be similar to the actual mortality rate in 1950 following the use of anticoagulant therapy.

6. In a random selection of patients in this community receiving anticoagulant therapy, 66 per cent of all daily prothrombin determinations were found to be outside the effective range, and during one day each week patients were predisposed to hemorrhage.

7. There would appear to be insufficient reason to use anticoagulant therapy in the low (8 per cent) mortality group. If one of every four deaths from acute coronary thrombosis is due to thromboembolism, then theoretically only two out of 100 patients in this group may be saved.* However, since anticoagulants in practice are neither 100 per cent efficient, nor effectively used, possibly at most only one death in 100 may be prevented, whereas two patients would be expected to have major hemorrhage. Routine anticoagulant therapy in this group, therefore, would subject 99 patients to the danger, inconvenience and expense of the treatment, in order to possibly prevent one fatality. In addition, the Committee's study appears to indicate that anticoagulants had no effect upon the mortality rate in the mildly ill.

8. The literature contains many papers indicating errors in statistical thinking, among which the following are a few examples: (a) Comparing crude mortality figures in one year with those in a previous year and attributing the difference to a new therapy. (b) Comparing the mortality rate in two groups of patients in the same hospital and attributing the difference in rate in the two groups to therapy without determining whether the two groups are of equal severity, had identical treatment by doctors, nurses, dieticians, and others. (c) Suggesting that two groups are of equal severity because the average age and sex ratio are similar. These easily measured factors can not be substituted for the actual determination of the patient's condition on admission. They are only indirectly related to the mortality rate and by themselves do not prove the existence of prognostically comparable groups. Moreover, it has been shown that averages can mask significant differences which may be revealed by distribution curves. (d) Misunderstanding of the term "statistically significant." This means that a difference in mortality found

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* This assumes the ratio to be the same for the mildly ill as for the unselected group, which is unlikely.
between two groups is probably not due to chance, but rather to some other factor which could be unequal selection of cases, special attention to one group, etc., as well as the use of particular drugs. When statistical significance has been shown, it then becomes imperative to determine whether any one of the many factors affecting mortality is responsible for the difference before it can be attributed to the drug or procedure under investigation.

9. Certain objections to the Committee's study were raised: (a) Cases in the treated and untreated groups do not appear to be random selections. (b) It was not shown conclusively that the control and treated cases were of equal severity. (c) Mortality statistics by weeks of illness in the control group were not in accord with past experience. (d) The clinical diagnosis of thromboembolism is difficult, often inaccurate, subject to errors of both commission and omission and directly related to the examiner's index of suspicion. Conclusions from statistics based upon questionable data, without pathologic confirmation, can only be accepted with reservations. (e) No postmortem studies have been published to support the statement that the difference in the mortality rate between the treated and untreated groups was due to an increased incidence of fatal thromboembolism in the untreated group.

Summary

1. No adequately controlled, statistically valid study has been published to date which indicates unequivocally that routine anticoagulant therapy in acute myocardial infarction decreases the mortality rate in all classes of patients from the mildly ill to the seriously ill.

2. The published reports of reduced incidence of thromboembolism in treated groups as compared with control groups have not conclusively demonstrated that the decrease is wholly attributable to anticoagulant therapy rather than to such other factors as erroneous diagnosis, unconscious bias of the medical examiner and deviations from the stringent requirements of truly controlled studies.

3. Unless additional evidence to the contrary is presented, there would appear to be little reason to prescribe anticoagulants routinely in persons who are mildly ill in view of the low mortality, as opposed to the expense, inconvenience, dangers and the universal difficulty of maintaining constantly "effective" prothrombin blood levels due to present inadequate drugs and/or other factors.

4. In the more seriously ill patients, the theoretical advantages of anticoagulant therapy justify this treatment even though there may be some question as to whether its value has been clearly demonstrated.

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Sumario Español

Este estudio de 1350 pacientes con infartos agudos del miocardio admitidos a diferentes hospitales durante un periodo de 10 años intenta a contestar algunos de los problemas actualmente en disputa; i.e., correlación del estado del paciente al ser admitido con la proporción de mortalidad, relación de la edad del paciente al pronóstico y el valor del tratamiento con anticoagulantes. Presenta las objeciones estadísticas mayores al estudio del Comité para la Evaluación de los Anticoagulantes de la Asociación del Corazón Americana, debate la evidencia mediante la cual el Comité hiciera sus recomendaciones y concluye que prueba incontrovertible de las ventajas del uso rutinario de anticoagulantes en pacientes moderadamente enfermos en el momento de admisión al hospital no se ha presentado aún.

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13 — : Mortality rates in acute myocardial infarction. III. The relation of patient's age to prognosis. (To be published)
14 — : Mortality rates in acute myocardial infarction. II. A proposed method for measuring quantitatively severity of illness on admission to the hospital. (To be published)
Mortality and Other Studies Questioning the Evidence for and Value of Routine Anticoagulant Therapy in Acute Myocardial Infarction

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