A Controlled Study of the Effect of Intermittent Heparin Therapy on the Course of Human Coronary Atherosclerosis

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Heparin, 200 mg. subcutaneously, was administered twice weekly to a group of 105 patients with known previous myocardial infarction. A comparable control group of 117 individuals received saline placebos. Over a two-year period, there were 21 deaths due to cardiovascular disease in the placebo group, 4 cardiovascular deaths in the heparin group. The observed differences in deaths between the two groups is statistically significant, \( p < .01 \). The results indicate that heparin, in the dosage and manner administered, retards the progress of atherosclerotic disease in patients with coronary atherosclerosis.

The state of the circulating lipids has been the subject of intensive study in the past few years. These lipids do not exist in plasma as pure cholesterol, phospholipid or neutral fat but are bound to protein in the form of complex lipoprotein molecules. Lipoproteins form a spectrum of compounds of varying size and density, and contain different proportions of cholesterol, phospholipid, triglycerides and protein. They can be grossly separated into alpha and beta lipoproteins by electrophoretic or chemical technics, and more quantitatively defined by ultracentrifugal analysis into high and low density lipoproteins of varying \( S_t \) classes. Precise delineation of plasma lipoproteins is not only valuable in furthering our understanding of fat metabolism, but is clinically important since the circulating lipids are probably the major source of the increased fats found in atherosclerotic vessel walls. Entrapment of infiltrating lipid particles occurs in the arterial wall, which acts as a filter of molecules circulating in the blood. In this process particle size, shape and charge are undoubtedly of importance, and it may well be that changes in the vascular ground substance also play a major role. Thus the straining properties of the vascular wall rather than the varying chemical composition of the lipoprotein complexes affords a rational explanation for the differential etiologic significance in atherosclerosis of the various lipoproteins.\(^1,2\)

In general, the ultracentrifugally defined low density lipoproteins, and the electrophoretically or chemically separated \( \beta \)-lipoproteins, demonstrate a close correlation with clinical coronary atherosclerotic disease, whereas the smaller high density (alpha*) lipoproteins do not. Since all lipoproteins contain cholesterol in varying concentrations, it is apparent that cholesterol levels on the one hand and low density or beta lipoprotein levels on the other are not necessarily parallel.

A body of evidence has been accumulating which suggests that heparin plays a physiologic role in the serum transport phase of fat metabolism. Chargaff and coworkers in 1941\(^3\) noted that heparin possessed the property of altering the characteristics of naturally occurring lipoproteins. In 1943 Hahn\(^4\) found that heparin abolished alimentary lipemia, an observation extended to other species by Weld.\(^5\) Anderson and Fawcett\(^6\) demonstrated that postheparin plasma could clear lipemia in vitro. The lipid alterations involved in the "clearing" or reduction in turbidity of lipemic plasma were clarified by the observation from Gofman's group,\(^7\) with subsequent confirmation\(^8\) that there is a rapid and profound alteration in the blood lipoprotein spectrum, following the administration of heparin. When it is injected into humans or experimental

\(^*\) The precise relationship between high density lipoproteins (ultracentrifugal analysis) and \( \alpha \)-lipoproteins (electrophoretic or chemical analysis) has not been defined.
animals whose plasmas contain elevated levels of chylomicrons or of abnormal low density or beta lipoproteins, these components rapidly disappear from the plasma. Subsequent investigation disclosed that a true lipolysis of neutral fat occurs with a splitting off of free fatty acids and glycerol and that this process is associated with a removal of fat from the blood stream.

The demonstrations that biologically active heparin is normally present in the blood, that plasma may have clearing activity without the prior injection of heparin, and that lipemia increases following the injection of antiheparin agents lend support to the concept that heparin plays a normal role in the interconversion of serum lipoproteins.

Other lines of investigation suggest that a deficiency of endogenous heparin may be one of the primary causes of excessively elevated serum lipids (more specifically of chylomicra, low density lipoproteins, or β-lipoproteins). It has been found in studies of mast cells (the source of heparin in the animal body) in rats and rabbits that rats, which are highly resistant to experimental atherosclerosis resulting from fat feedings, have many more mast cells than rabbits, which are highly susceptible to atherosclerosis. More recently, it was shown that there are significantly less mast cells in humans with extensive atherosclerosis at autopsy than in nonatherosclerotics in the same age groups. Using protamine and toluidine blue titration technics, which are not specific for heparin, slightly decreased amounts of substances which combine with these chemicals were found in the blood of atherosclerotic patients as compared with the blood of normal individuals. Measurements of circulating heparin indicate that there is an inverse relationship between the low density S1, 0-400 lipoproteins and endogenous plasma heparin levels. If these latter results are confirmed by further investigation, it will suggest an analogy between insulin deficiency, abnormal carbohydrate metabolism and diabetes mellitus on the one hand, and heparin deficiency, abnormal serum lipid metabolism and atherosclerosis on the other.

Several investigators have found that the daily injection of adequate amounts of heparin in cholesterol-fat fed experimental animals minimizes the degree of hypercholesterolemia and reduces the extent of subsequent atherosclerosis. Unfortunately in humans, conflicting reports as to the efficacy of heparin in the treatment of angina pectoris have diverted attention from the more fundamental biochemical and pathologic studies. Angina is difficult to evaluate at best and therapeutic results can be submerged when the patient group is diluted with placebo reactors. Furthermore, we believe there is a carryover effect for several weeks to months after heparin is stopped which has led to misinterpretation of the results in blind studies, using placebos. However, results in angina are of secondary importance since it is, after all, a symptom of pre-existing disease which may or may not be amenable to therapy. In view of the alteration of circulating lipoproteins in the direction of increased normality after the injection of heparin, it was important to determine the effect of heparin upon the objective manifestations of the progress of atherosclerotic disease in humans.

Various studies have proven that atherosclerosis is the underlying disease process in 85 to 90 per cent of patients who have sustained a myocardial infarction, or who have typical angina pectoris with abnormal electrocardiograms. Such a group, therefore, lends itself well to the evaluation of the effect of long-term therapeutic measures upon the course of atherosclerotic disease.

**Material and Methods**

Accordingly over 200 patients in the Cardiac Clinic of the Cedars of Lebanon Hospital who had previously had a myocardial infarction, were alternately placed into two groups. A small number of patients with angina of effort and abnormal electrocardiograms were also included in each group. Doubtful cases were rigidly excluded from the study. All patients were thoroughly examined, preliminary electrocardiograms and ballistocardiograms were taken, and blood samples were drawn for cholesterol and ultracentrifugal lipoprotein determinations. No patients were included who

* The ultracentrifugal analyses were performed at the Donner Laboratory, University of California at Berkeley, through the cooperation of Dr. John Gofman.
had sustained an acute myocardial infarction within three months prior to the onset of therapy.

The patients were all told they would receive injections of a new medication which seemed promising in the therapy of atherosclerosis. One group was given 200 mg. of concentrated aqueous heparin† (100 mg. or 200 mg. per cc.) subcutaneously twice weekly, and the other received isotonic saline placebo injections in a similar manner. In all other respects, therapy was identical in the two groups. Vasodilating drugs were prescribed when needed for angina or claudication and hypertension was treated by the usual methods. Diabetic therapy was supervised in the diabetic clinic. Low fat diets were not prescribed except when caloric restriction was indicated for obesity, attempts at weight reduction in these clinic patients were usually unsuccessful. Oral anticoagulant drugs were not used.

A fair percentage of the patients in both groups, or their close relatives, were taught to give the injections at home, usually at bedtime.‡ Where this was not feasible, the patients in both groups came to the clinic for the medication. It was injected slowly in the relatively painless subcutaneous tissue just above or below the posterior iliac crest, using a 25 gage hypodermic needle. One technician gave all the injections in the clinic and was the only person, apart from the authors, who knew whether the patient was receiving heparin or the placebo. This project was not conducted as a blind study, since symptomatic results were not being evaluated and it seemed safer, in view of the anticoagulant action of heparin, for us to know what each patient received.

Several considerations led to the selection of the 200 mg. dose of subcutaneous aqueous heparin twice weekly, although we appreciated the fact that this might not be sufficient for a marked sustained lipoprotein reduction particularly in patients with highly elevated levels. It had previously been found7 that 200 mg. of repository heparin produced a substantial though temporary drop in the low density lipoproteins. The subcutaneous route was more practical than the intravenous one; it avoided the extremely high peaks of anticoagulant activity and afforded a much more sustained reduction of lipoproteins. Furthermore, subcutaneously administered concentrated aqueous heparin, which has anticoagulant and lipoprotein effects similar to intramuscular repository heparin, is far less painful, less expensive and much easier to administer than the latter. Although injections of 200 mg. of heparin three times weekly would have afforded a greater average lowering of lipoproteins, we were limited by the amount of heparin available to us, and by the consideration that we wanted to minimize the duration of the anticoagulant effect. It had previously been found23,24 that therapeutic levels of anticoagulant activity are maintained for an average of 16 to 18 hours after a 200 mg. subcutaneous dose of concentrated aqueous heparin.

The following criteria were adopted at the onset of the study as affording objective evidence of progress of the underlying atherosclerotic process: (1) cardiovascular death; (2) recurrence of myocardial infarction; (3) gangrene of a limb necessitating amputation and (4) a cerebral vascular accident with objective findings of resultant cerebral damage. When patients were hospitalized, the diagnosis of the in-patient attending staff (who did not know whether heparin or the placebo had been given) was accepted as to whether an infarction had occurred or not. Since we could not logically anticipate any effect of heparin therapy on the atherosclerotic process in a few weeks, recurrences during the first month after the onset of treatment in either group were not included in the results.

Table 1 shows the composition of the two groups. The control series is slightly larger since our heparin supply was adequate for only slightly more than 100 patients. The groups were fairly well balanced, although the patients were alternately allocated with no attempt at matching, in order to eliminate bias in the selection. The heparin series was slightly older and heavier and had somewhat more elevated lipid values, whereas there were proportionately more hypertensives and diabetics in the placebo group and a slightly higher average number of previous infarctions per patient. Chi square analysis

| Table 1. Analysis of the Composition of the Heparin and Placebo Groups |

<table>
<thead>
<tr>
<th></th>
<th>Total No. of Patients</th>
<th>Male</th>
<th>Female</th>
<th>Average Age in Years</th>
<th>Average Weight</th>
<th>Average Cholesterol</th>
<th>Average* A.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heparin</strong></td>
<td></td>
<td>105</td>
<td>73</td>
<td>32</td>
<td>62.6 Range 57-79</td>
<td>150 250 ppm</td>
<td>99</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td>117</td>
<td>81</td>
<td>37</td>
<td>61.7 Range 36-80</td>
<td>148.3 324 ppm</td>
<td>96</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>No. of Previous Infarcts</th>
<th>Angina Cases</th>
<th>Average No. of Infarcts per Patient</th>
<th>Years from Last Infarct</th>
<th>Hypertensives</th>
<th>Diabetics</th>
<th>Congestive Failure at Onset of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heparin</strong></td>
<td></td>
<td>119</td>
<td>12 1.13</td>
<td>3.7</td>
<td>28</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td>145</td>
<td>11 1.24</td>
<td>3.5</td>
<td>35</td>
<td>30</td>
<td>5</td>
</tr>
</tbody>
</table>

† Generously supplied by Lederle Laboratories, Inc. and Darwin Laboratories.
‡ We are indebted to the Los Angeles Visiting Nurses Service for their cooperation in teaching the patients.

The slight discrepancy of the various factors in the two groups are statistically insignificant.
* A.I.—Atherogenic Index
TABLE 2. Analysis of Results

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Months of Therapy</th>
<th>Average Months of Therapy per Patient</th>
<th>Cardiac Deaths</th>
<th>Corrected Ratio of Deaths</th>
<th>Non-fatal Recurrences</th>
<th>Total of Deaths and Recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>105</td>
<td>2067</td>
<td>19.7</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Placebo</td>
<td>117</td>
<td>Range 21-27</td>
<td>18.7</td>
<td>21</td>
<td>19.9</td>
<td>18</td>
</tr>
</tbody>
</table>

The observed difference in the proportion of deaths in the two series is statistically significant, p < .01.

TABLE 3.—Complications Encountered in Patients who Received Heparin

<table>
<thead>
<tr>
<th>Complications</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major hemorrhage</td>
<td>3</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>6</td>
</tr>
<tr>
<td>Large local hematomata</td>
<td>3</td>
</tr>
<tr>
<td>Minor remote ecchymoses</td>
<td>6</td>
</tr>
<tr>
<td>Minor traumatic hemorrhage</td>
<td>2</td>
</tr>
<tr>
<td>Thrombophlebitis of leg veins</td>
<td>2</td>
</tr>
<tr>
<td>Urticaria</td>
<td>3</td>
</tr>
<tr>
<td>Lumbar pain</td>
<td>3</td>
</tr>
<tr>
<td>Severe asthma</td>
<td>1</td>
</tr>
<tr>
<td>Moderate alopecia</td>
<td>4</td>
</tr>
</tbody>
</table>

TABLE 4.—Examples of Acute Ultracentrifugal Lipoprotein Changes in Two Patients After Subcutaneous Aqueous Heparin

<table>
<thead>
<tr>
<th>Time after Therapy</th>
<th>S1-12 mg %</th>
<th>S1-20 mg %</th>
<th>S2-10 mg %</th>
<th>S3-6 mg %</th>
<th>S3-100-400 mg %</th>
<th>A.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Pt. O. M.</td>
<td>553</td>
<td>76</td>
<td>101</td>
<td>34</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>12 hrs. after 200 mg heparin</td>
<td>547</td>
<td>56</td>
<td>31</td>
<td>0</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Control Pt. R. D.</td>
<td>526</td>
<td>103</td>
<td>137</td>
<td>38</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>23 hrs. after 200 mg heparin</td>
<td>506</td>
<td>72</td>
<td>85</td>
<td>16</td>
<td>81</td>
<td></td>
</tr>
</tbody>
</table>

These changes are typical of the effect of heparin.

TABLE 5.—Low Density Serum Lipoprotein Determinations Prior to Therapy and One Year Later

<table>
<thead>
<tr>
<th>Time after Therapy</th>
<th>S1-12 mg %</th>
<th>S1-20 mg %</th>
<th>S2-10 mg %</th>
<th>S3-6 mg %</th>
<th>S3-100-400 mg %</th>
<th>A.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/24/53 Control prior to therapy</td>
<td>412</td>
<td>36</td>
<td>194</td>
<td>234</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>8/27/54 72 hrs. after last dose of heparin</td>
<td>426</td>
<td>52</td>
<td>109</td>
<td>13</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

Patient received 200 mg heparin twice weekly subcutaneously. This maintained reduction of lipoproteins is not the usual response.

of each of these possibly important factors, however, reveals that these variations were statistically insignificant. It is evident that these were older individuals with elevated serum lipoproteins, a factor perhaps related to the fairly high proportion of diabetics in the study. Although it would have been desirable to classify the severity of the previous infarction, we were unable to do so as adequate information was not available in many of the patients. However, we believe the extent and severity of the prior episodes of myocardial infarction were comparable in both series.

RESULTS

Table 2 summarizes the results of the two-year study. In the placebo group there were 18 nonfatal recurrences (14 myocardial infarctions, 3 cerebral episodes, and 1 leg amputation for gangrene) and 21 cardiovascular deaths (2 following known cerebral accidents, 2 in congestive failure and 17 after an acute infarction or just sudden death). Thus the death rate in the control patients was approximately 10 per cent per year, which is in keeping with the anticipated yearly mortality in any large group of elderly patients with coronary heart disease. In this group, the recurrences and deaths occurred fairly regularly throughout the period of the study.

In the heparin group, there were 5 nonfatal recurrences (three acute myocardial infarctions and two minor cerebral episodes) and four cardiovascular deaths. The recurrences occurred after 7, 10, 13, 18 and 19 months of therapy and the fatalities after 2, 4, 19 and 21 months. Postmortem examination in 3 of these 4 patients revealed old and recent myocardial infarction in two, and an old but no recent infarct in the third case. No autopsy was obtained in the fourth patient who collapsed and died while at work. There were no known cerebral deaths, and no fatalities due to severe congestive failure without recent acute infarction in the patients who received heparin. The death rate in this group was 2 to 2.5 per cent per year.

In our opinion the number of cardiovascular deaths is the most reliable index for evaluation since the diagnosis is beyond question. Statistically, using the figures for deaths and total patient months of therapy, the observed differences in proportions of deaths between the two series is 3.3 times the standard error of
the difference in proportions or $p < .01$. If the $\chi^2$ square test is applied, using total deaths and number of patients (and disregarding the fact that the patients receiving heparin had slightly more months of therapy per patient), $p$ is between 0.01 and 0.001. Thus, using either calculation, the difference in deaths is statistically significant.

Since to our knowledge, this is the first instance in which fairly large doses of heparin have been given intermittently for several years in a sizeable number of patients, the symptomatic response was carefully recorded. Although for reasons of safety, blind study technics were not employed, the patients' observations were of interest to us.

As is usually noted, 25 to 35 per cent of the control group reported decreased symptoms on placebo therapy, but the favorable response gradually decreased in some patients. Symptomatic improvement occurred in 50 to 75 per cent of the patients who received heparin and was usually fairly well maintained. We also noted that most often, in contrast to the placebo patients, there was slowly progressive improvement for several months in the heparin group. The patients reported improvement in headaches, vertigo, tinnitus, angina, dyspnea, hip and thigh pain, claudication, weak spells and fatigue, all of which may be symptoms of widespread atherosclerosis. A generally improved sense of well being with an increased effort tolerance was the usual response after several months of heparin therapy.

Table 3 shows the complications that were encountered in the heparin group, other than minor ecchymoses at the site of injection which occurred occasionally in most of the patients and were insignificant. There were three instances of major hemorrhage; two were intestinal and one was renal. X-ray study revealed adenocarcinoma of the stomach in one patient and a kidney stone in another. Thus, there was only one instance of major hemorrhage that was apparently due to the heparin itself and in this patient the drug was not continued. There were no hemorrhagic fatalities. There were six minor episodes of bleeding: one nasal, four rectal and one pulmonary. All the rectal cases had had previous hemorrhoidal bleeding and the patient with bloody sputum had known bronchiectasis. Heparin was successfully continued in all, except in the patient with bronchiectasis where further therapy was not given as bleeding occurred after each injection. There were two instances of post-traumatic minor hemorrhage: one followed a tongue bite incurred while chewing, and the other occurred when a small rectal abscess was mistakenly incised one hour after an injection of heparin. During the entire study intravenous protamine sulfate* was used three times for bleeding and was very efficacious. There were only three instances of large, painful hematoma at the site of injection. The use of small needles and a slow speed of injection were important factors in minimizing the occurrence of local ecchymoses. Six patients complained of an increase in discrete ecchymotic spots remote from the injection site. All were given oral P factor therapy† for several months which was helpful. Thrombophlebitis of the leg veins occurred in two patients while on heparin therapy, perhaps related to a rebound effect. One of these patients had a nonfatal pulmonary infarct and refused to continue the heparin. He was then dropped from the study and was subsequently uneventfully maintained on oral anticoagulants. In the other patient heparin was subsequently successfully continued in 150 mg. doses three times weekly in order to decrease the interval between injections and so possibly decrease any rebound effect. Three patients had lumbar pain and three had urticaria following each dose of heparin. All six had relief from these complaints, when colorless heparin was used instead of light brown material, indicating that these symptoms were not due to heparin itself. One patient had a severe asthmatic reaction after every heparin injection regardless of the color of the material and was forced to discontinue therapy despite the concomitant use of antihistamine drugs. In four patients a mild-moderate alopecia occurred.

In all, heparin therapy was stopped in four cases because of complications. It has been our

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* Kindly supplied by Dr. K. Kohlstadt of Eli Lilly and Co.
† Kindly supplied as Cepevit by Wynlit Pharmaceuticals, and as C. V. P. capsules by U. S. Vitamin Corporation.
experience that hemorrhagic complications are infrequent, usually minor, and rarely demand cessation of therapy. If major hemorrhage occurs, a diligent search should be made for some other factor initiating the bleeding which is then intensified by the anticoagulant action of heparin.

Various other problems arose during the study which are worthy of discussion. Chronic duodenal ulcers were present in six of our heparin patients. Therapy was not withheld and no hemorrhage occurred in these cases. Antacid therapy was maintained in all. The presence of severe hypertension apparently added little danger to heparin therapy despite the hazard of vascular rupture. There were only two minor cerebral incidents during heparin therapy, and only one of these was in a hypertensive patient, whereas there were four cerebral accidents in hypertensive patients in the placebo series. When surgery was necessary, no heparin was given in the 48 hours prior to operation and no increased bleeding was noted at surgery. There were five major surgical procedures in the heparin group with no cardiovascular complications in the operative, postoperative or convalescent periods. There were six instances of major surgery in the control group with one episode of nonfatal acute myocardial infarction on the fourth postoperative day. Some of the patients with congestive heart failure reported a decrease in the need for mercurial diuretics, although no additional measures for decapsulation were used other than those previously prescribed.

This impression of improvement in congestive failure is borne out by the fact that in the heparin group none of the six patients with obvious heart failure at the onset of therapy died during the study, whereas in the control group, of the five patients with obvious failure at the onset of therapy, two subsequently died. In some of the elderly diabetics we again verified an earlier observation\(^5\) that insulin requirements may be decreased 10 to 20 units when heparin is given. One elderly diabetic woman on insulin, who had severe angina and a previous infarction, died suddenly one hour after her second injection of heparin. While the cause of death was not proven, it may be that a hypoglycemic reaction, which is known to be dangerous in the presence of coronary disease, precipitated a fatal cardiac incident in this patient. In view of this occurrence and other observations of decreased glycosuria and an increase in the frequency of mild hypoglycemic reactions when heparin is given to diabetics who are taking insulin, it is wise to reduce the dose of insulin by 15 to 20 units on the day heparin is started. The insulin dosage can be subsequently increased if necessary.

The prolonged administration of intermittent heparin injections has afforded the opportunity to observe the effects upon coagulation and lipoproteins. Three-tube Lee-White clotting times were determined after the first year of therapy in all the patients. Prolongation of the clotting time beyond an average of 16 to 18 hours (range 12 to 26 hours) was observed in only a few instances, perhaps 5 to 10 per cent of the patients. There is apparently very little tendency, in the dosage schedule we used, for a cumulative heparin effect sufficient to result in maintained therapeutic anticoagulation. Thus clotting time determinations are superfluous, when heparin is given subcutaneously in 200 mg. doses twice weekly to patients who do not have severe liver disease.

Table 4 shows two typical examples of the changes in the Sf 0–400 low density lipoproteins 12 and 23 hours after a 200 mg. subcutaneous injection of concentrated aqueous heparin. In some patients, these lipoproteins are back to control levels within 24 hours, in others the effect is more prolonged. Unfortunately, we only have lipoprotein determinations in a small percentage of the patients after 6 to 18 months of heparin therapy. In most of these the serum lipoprotein levels 48 hours after the previous dose of heparin were approximately the same as prior to the onset of therapy. In a few however, the low density lipoproteins, determined 48 to 72 hours after the last dose of heparin so as to avoid its acute effects, were considerably below control levels (table 5). It appears that in a minority of the patients, there is a marked sustained reduction in the average level of low density lipoproteins (on the dosage schedule administered), whereas the majority have only a temporary (24 to 36
hour) decrease following each injection of heparin. Cholesterol levels are variable in the 24 hours after 200 mg. of heparin is given subcutaneously and show relatively little change (perhaps a slight reduction in some instances), when determined after 6 to 18 months of therapy.

Discussion

In view of the multiplicity of actions of heparin and the numerous factors which may play a role in the progress of atherosclerotic disease, it is difficult to assess accurately the differential role of the various mechanisms through which heparin produced the beneficial effects noted in this study. As previously stated a therapeutic anticoagulant level persists for an average of 16 to 18 hours following a 200 mg. subcutaneous dose of concentrated aqueous heparin. Unless undetectable clinical levels of anticoagulant activity persist and are beneficial, a concept for which there is no evidence at all, it is unlikely that therapeutic anticoagulation for 12 to 24 hours twice a week is alone responsible for our results. It may have been an important factor. The prolonged use of anticoagulant drugs reduces the incidence of recurrences and death in patients with previous myocardial infarction, but the results reported 26, 27, 28 are not as good as those we obtained using intermittent heparin therapy which afforded therapeutic anticoagulation only 20 to 30 per cent of the time.

Since elevated serum lipids and lipoproteins are an important factor in atherogenesis and since heparin lowers the low density lipoproteins and accelerates the removal of fat from the blood stream, we believe this action of heparin is probably primarily responsible for the differences in deaths we have observed. We have insufficient observations to determine accurately the average lowering of lipoproteins in our patients, a matter which would have necessitated many ultracentrifugal analyses per patient. However as table 4 illustrates, there was an average overall reduction in the low density lipoproteins, although the effect of each injection was temporary. This reduction itself is important in retarding the rate of progression of atherosclerotic disease although its quantitative contribution1 is difficult to assess exactly.

The decrease in low density or β-lipoproteins following heparin may be advantageous apart from the average lowering of the lipoprotein concentrations. In all studies of the infiltration of vascular walls by lipids, time is an important factor.29, 30 Thus, since the injection of heparin is followed by a marked though temporary reduction of the low density lipoproteins, a considerable interval may elapse after the concentration of the circulating lipoproteins has regained its preheparin levels before substantial amounts of lipid again penetrate into the arterial walls. Furthermore, macromolecules form films31, 32 upon the surfaces of the cells and the vascular intima. These films probably interfere to some extent with the normal molecular exchange between the plasma and interstitial fluid. Martin and Hueper33 found a decreased rate of oxygen uptake by erythrocytes in hypercholesterolemic rabbits, and we34 recently demonstrated increased arteriovenous oxygen differences (apparently the result of increased tissue oxygen consumption) after the injection of heparin in atherosclerotic patients. The largest lipoproteins, because of their decreased ability to escape through the capillary pores, would be most likely to form fat sludges on the endothelium. Since it is precisely these larger fat particles which almost disappear, following an adequate dose of heparin (table 4), the harmful effects of intimal films would be substantially ameliorated by heparin therapy. Reformulation of films almost certainly would take longer than the simple reaccumulation of circulating lipoproteins. Finally, the beta lipoproteins have been found to interfere with glucose uptake by the diaphragm.35 Thus, their lowered concentration following heparin may permit more normal carbohydrate metabolism, particularly in diabetics.

Heparin may also be of value in retarding cardiovasculard degeneration in atherosclerotic patients because of its affinity for the intercellular cement substance. In a recent study of venous endothelium,36 it was found that adherence of platelets to the endothelial surface was the initial occurrence following various types of injury and that heparin was effective
in preventing the deposition and agglutination of the platelets on the intercellular cement. Since this platelet agglutination on the cement substance may well be one of the initiating steps in thrombosis, heparin may be valuable at this site apart from its general anticoagulant action. Various workers \( ^{37,38} \) believe that minute mural thrombosis plays a part in the development of atherosclerosis entirely apart from its role in the formation of large clots.

There are other known actions of heparin which could be commented upon, such as its marked inhibitory effect in experimental pulmonary edema, \( ^{39} \) but the mechanisms already discussed appear to be those most apt to have been involved. Further speculation would add little. Perhaps of greater practical importance is the demonstration of how safely heparin can be used in this manner for years. This requires re-emphasis since there is a justified concern about the risks involved in the use of continuous oral anticoagulant therapy, particularly where excellent laboratory controls are not easily available. Intermittent heparin therapy does not produce a maintained anticoagulant effect and, therefore, no laboratory tests are required. It should not be given in the presence of active bleeding or of severe liver disease, but we have observed no particular danger when it is used in patients with chronic duodenal ulcers, hypertension, hemorrhoids or other possible minor sources of bleeding. If hemorrhage should occur, it can be easily and quickly controlled by the injection of protamine sulfate intravenously, or by blood transfusion. In two years we observed only one major hemorrhage, apparently due to the heparin itself, and no hemorrhagic fatalities, although over 17,000 injections of 200 mg. of heparin were administered. The markedly reduced incidence of recurrent coronary thrombosis as compared with the control group attests to the fact that the theoretic danger of intimal capillary hemorrhage initiating a thrombus has no practical significance.

Other modalities have been successfully used in attempts to reduce the rate of recurrence and death in patients with known coronary disease. The results reported have not been as good as those we have obtained. Morrison\( ^{40} \) found a reduction in mortality over a three year period from 10 per cent per year in his control group to 4.7 per cent per year in his patients on a rigid (25 Gm.) low fat diet, a ratio of slightly better than 2:1. However, most patients will not strictly adhere to a low fat diet, and in our experience the diet alone does not effectively reduce serum lipids and lipoproteins in all instances. The prolonged use of oral anticoagulants has also been reported \( ^{26-28} \) to reduce the incidence of recurrences and death in approximately a 2:1 or 3:1 ratio. However, the incidence of major hemorrhage in these series was not small, even with good laboratory controls. Moreover, since the prothrombin depressing drugs do not have any effect upon serum lipoproteins, it is probable that although they reduce the occurrences of thrombotic incidents, they retard the basic atheromatous process very little if at all.\( ^{26} \) Estrogens have recently been advocated since they reduce the concentration of the \( \beta \)-lipoproteins. However, the large doses required produce such severe feminizing side effects that this form of therapy is most distressing, psychologically traumatic and impractical, \( ^{41,42} \) except in a very few instances. The other so-called lipotropic agents thus far available, such as various choline and inositol combinations, have little evidence to justify their use.

Objections to the administration of heparin in advanced human atherosclerotic disease are imposed by its cost, the fact that it must be taken by injection and that it apparently should be indefinitely continued. The analogy to the use of insulin in diabetes mellitus is apparent. Pursuing this analogy a step further, it may be that where diet, or perhaps thyroid in hypothyroid patients\( ^{43} \) markedly reduces the low density or \( \beta \)-lipoproteins, the use of heparin is unnecessary. Where the diet is intolerable or where the serum lipids are only moderately reduced thereby, our results indicate that heparin should be given. Although heparin alone was prescribed for our patients without restriction of fats or cholesterol, it appears logical that the combination of moderate fat restriction (which is not too difficult) plus heparin should give better results than the use of heparin by itself. We
do not know if different heparin schedules, such as small daily doses, would be more advisable than the one used in this study, or whether other routes would be preferable. Administration of heparin three times a week would seem to be indicated where there is evidence of complications due to a rebound effect, where the serum lipoproteins are excessively elevated or, for a short time, if anginal symptoms are increased for any reason.

The reduction in mortality in this elderly group of coronary patients, to 2 to 2.5 per cent per year during the first two years of heparin therapy, affords evidence once again that atherosclerosis is not an inevitable consequence of aging, but that it is a disease process at least partially amenable to prevention. Further advances in therapy will undoubtedly keep pace with increasing knowledge of its etiology and pathogenesis.

**Summary**

(1) The effect of prolonged, intermittent heparin therapy has been evaluated during the past two years in a large number of patients who had previously sustained a myocardial infarction.

(2) There were four deaths due to cardiovascular disease in a group of 105 patients (average age 62.6 years) who received 2067 months of heparin therapy (200 mg. concentrated aqueous heparin given subcutaneously twice weekly).

(3) In a comparable control group of 117 individuals (average age 61.7 years) who received 2183 months of placebo therapy there were 21 deaths due to cardiovascular disease.

(4) The observed difference in deaths between the two groups is statistically significant (p < .01).

(5) When heparin is given as described, therapeutic anticoagulant levels are not maintained. Clotting time tests are, therefore, unnecessary.

**Summario in Interlingua**

(1) In le curso del passate duo annos, le efecto de un prolongate intermittente terapia a heparina esseva evalulate in un grande numero de patientes qui habeva previemente suffrite un infarecimento myocardial.

(2) Occurreva 4 mortes debite a un morbo cardiovascular in un gruppo de 105 patientes (etate median: 62.6 annos), qui reciepeva un total de 2067 menses de terapia a heparina (200 mg de concentrahe heparina aquose administrate subcutaneemente duo vices per septimana).

(3) In un comparabile gruppo de controlo de 117 individuos (etate median: 61.7 annos), qui reciepeva un total de 2183 menses de terapia a medicacion fictive, il occurreva 21 mortes debite a un morbo cardiovascular.

(4) Le observate differencia del mortes in le duo gruppos es statisticamente significative (p < .01).

(5) Le supra-describite manera de admininistrar heparina non resulta in un mantenentia de therapeutic nivellos anticoagulante. Tests del tempore de coagulation es consequente-mente innecessari.

**References**

Heparin Therapy and Human Coronary Atherosclerosis

A Controlled Study of the Effect of Intermittent Heparin Therapy on the Course of Human Coronary Atherosclerosis
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