How can small quantities of heparin, in amounts that will not even budge the whole-blood clotting time, possibly provide effective anticoagulant protection? This is the most frequently asked and also the most intriguing question concerning prophylactic regimens employing low doses of heparin in surgical patients.

Such concerns are not new. Almost one quarter of a century ago De'Takats suggested that: "It takes much less heparin or Dicumarol to prevent clotting than to treat it." Bauer, in 1954, and Leggenhager, in 1957, recommended small doses of heparin after surgery to reduce the incidence of postoperative thrombosis. Subsequently, Sharnoff reported that patients receiving subcutaneous heparin prior, during, and subsequent to surgery had less pathologically demonstrable thromboembolism at necropsy than those receiving the anticoagulant only subsequent to surgery, and that the latter group did no better than untreated patients given no anticoagulant therapy in relation to their surgery. He believes that operative and postoperative thrombosis relates to the role of the pulmonary megakaryocytes in the development of "hypercoagulability." Sharnoff's prophylactic regimen consists of the administration of 10,000 units of heparin subcutaneously at midnight prior to surgery. In his view, this dose provides an anticoagulant effect lasting approximately 12 hours. If surgery extends beyond this protective period, the coagulation time is repeated, and, if "critically short," additional heparin (rarely more than 2500 units) is administered subcutaneously during the operation. At the completion of the operation, the coagulation time is again determined, and usually 2500 units of heparin are administered subcutaneously every 6 hours until the patient is fully active or discharged. Negus et al. have suggested that the transient reduction in platelet adhesiveness induced by small quantities of heparin may play a role in the prophylaxis of thromboembolism.

Our interest in minidose heparin stems from work, in our laboratory, identifying a potent, naturally occurring inhibitor to activated factor X (synonymous with the terms "antithrombin III" and "heparin cofactor") in rabbit and human plasma. Some of these findings have been confirmed by other investigators. The indications that minidose heparin might be of prophylactic value as an antithrombic agent are several. First, the anticoagulant effect of the inhibitor against activated factor X in vitro is profoundly augmented by trace amounts of heparin. Secondly, 1 µg of the inhibitor, by neutralizing 32 units of activated factor X, indirectly prevents the potential generation of 1600 NIH units of thrombin. To neutralize this amount of thrombin, 1000 µg of inhibitor are required. Third, more heparin is necessary to bring about the instantaneous, but readily reversible, blockade of
the thrombin-fibrinogen reaction by the inhibitor than is required to neutralize activated factor X irreversibly. Finally, activated factor X is a more potent thrombogenic agent than thrombin itself.\textsuperscript{14}

The theory proposed by us for the efficacy of minidose heparin prophylaxis among surgical patients is not “anticoagulation” in the classic sense, because no state of hypocoagulability is induced. Circumstantial evidence strongly suggests that during and after operation a state of “hypocoagulability,” not previously present, is initiated but remains “nonthrombotic” so long as the rate of activated factor X neutralization exceeds that of the generation of this activated species. Since this reaction rate is dependent on the inhibitor concentration, the latter becomes rate limiting. Thus, as the inhibitor becomes increasingly utilized, there will come a point in time at which some activated factor X will escape its inhibitor, combine with lipid, calcium ion, and factor V, and rapidly generate vast quantities of thrombin that, once formed, cannot be prevented by low doses of heparin from converting fibrinogen to fibrin. It is, in essence, the presence of small amounts of plasma heparin augmenting severalfold the rate of normal activated factor X neutralization prior to the development of hypocoagulability that can prevent venous thrombosis in patients undergoing operation.

At Kings College Hospital Medical School, Mr. V. V. Kakkar and his associates have studied surgical patients by means of lower limb venography and limb scanning with \textsuperscript{125}I-fibrinogen.\textsuperscript{15, 16} They agreed to try a regimen consisting of 5000 units of heparin subcutaneously beginning 2 hours prior to surgery. We selected this time interval for the initial heparin injection because we required the heparin effect on the inhibitor to be at its height prior to the operative incision and because we knew it took 30 min for heparin, at this dose, to become demonstrable in plasma by our heparin assay.\textsuperscript{17} Beginning 24 hours after the initial dose, the drug was to be administered every 12 hours for 5 days. This preliminary study was not randomized and did not employ the heparin regimen finally settled upon. Nevertheless, the effectiveness of this regimen in the prophylaxis of deep venous thrombosis was determined in 53 consecutive patients over the age of 50 years undergoing inguinal herniorrhaphy. Deep-vein thrombosis was detected by means of \textsuperscript{125}I-fibrinogen limb scans in seven (26\%) of 27 control patients, and in only one individual (4\%) among 26 similar patients who received heparin.

There was no unusual operative or postoperative bleeding; nor were there any pulmonary emboli.\textsuperscript{18}

At about the same time, Williams, at St. Georges Hospital, London, employing the Sharnoff regimen, studied 56 patients over the age of 50 years subjected to major abdominal surgery. Using \textsuperscript{125}I-fibrinogen, Williams found a 41\% incidence of positive limb scans in his control group compared to a 15\% incidence in the treated group.\textsuperscript{19} He, too, encountered no bleeding; but he did find that all four positive limb scans in his heparin-treated group occurred among seven patients subjected to prostatectomy.

Gordon-Smith et al. at the Middlesex and Central Middlesex Hospitals, London, utilizing isotopic limb scanning and heparin prophylaxis in a manner similar to that of Kakkar, divided 161 surgical patients, all over the age of 40 years, into three groups in a prospective randomized trial.\textsuperscript{20} Group 1 received no heparin and had a 41\% incidence of positive limb scans. Group 2 received only three 12-hourly doses of 5000 units of heparin subcutaneously, before and after surgery, and had a 13.5\% incidence of positive isotopic scans. Group 3, given 5000 units of heparin every 12 hours before and after operation for 5 days, had an 8.3\% incidence of positive limb scans. Groups 2 and 3 alone and together had a significantly lower incidence of positive scans than the control group, but the difference between the two heparin-treated groups, perhaps because of the limited number of patients, was not statistically significant. This investigation, in contrast to Williams’, demonstrated success in treating patients subjected to prostatectomy. One disturbing feature, however, was the appearance of nonlethal pulmonary emboli in two patients in group 3—not apparently evaluated by lung scan or pulmonary angiography.

In a second study by Kakkar and his associates,\textsuperscript{21} low-dose heparin was evaluated in 261 patients divided into three groups. A prospective, double-blind, randomized trial was completed among 78 patients over the age of 40 years who were subjected to major, elective, abdominal, pelvic, thoracic, and orthopedic surgery. The anticoagulant regimen was changed from the original schedule in two respects. First, heparin was resumed 12 instead of 24 hours after the 2-hour preoperative dose; and, second, the dose of 5000 units of heparin subcutaneously twice daily was extended from 5 to 7 days. The frequency of 42\% deep-venous thrombosis, determined by the \textsuperscript{125}I-fibrinogen technic, in the 39 control patients, was reduced to 8\% in the 39
heparin-treated patients without interfering with normal hemostasis. None of the 78 patients developed pulmonary emboli.

The same heparin regimen was also administered to a second group of 133 consecutive patients over the age of 40 years, not part of the above-mentioned control trial, who had major elective surgery. The overall incidence of positive limb scans among this group was 9.7%; but in one operation, total hip replacement, the results were not satisfactory. Four (27%) of 15 patients undergoing total hip replacement developed positive isotopic scans. In the third group, minidose heparin was entirely ineffective in preventing positive limb scans among 50 patients subjected to emergency surgery for fractured hips, 40% developing isotopic thrombi. In the entire series of 261 patients, however, only one individual, not in the controlled trial, had a clinically recognized pulmonary embolus which also contributed to his death. This was a patient, treated with heparin, who had had a total hip reconstruction. Four patients with fractured hips, three of whom had positive limb scans, died of nonthrombotic disease while on heparin prophylaxis. At necropsy, no venous thrombi other than those identified by limb scan were found; and in none was a pulmonary embolus uncovered on careful dissection of the lung. This is an important observation in view of the reported high incidence of pulmonary embolism among adults coming to autopsy in a general hospital.

Nicolaides and his colleagues at St. Mary's Hospital Medical School, London, tested the efficacy of minidose heparin according to the regimen of Kakkar in 251 patients over the age of 40 years undergoing major abdominal and thoracic surgery. This investigation assessed the benefit of subcutaneous heparin, not only in reducing the incidence of early thrombi, but also in affecting the propagation of thrombi into the popliteal and femoral veins. These investigators found that the heparin regimen did not interfere with normal hemostasis and yielded a reduction in positive scans from 24% in the control group to 0.8% among the treated patients. In addition, they confirmed by venography that there was a dramatic elimination of dangerous thrombi propagating to the popliteal, femoral, and iliac veins--of the type that are responsible for pulmonary emboli--from an incidence of 7.4% in the control group to 0% among the treated patients. No patient in either category developed a pulmonary embolus, but all control patients in whom thrombi reached the thigh were treated with full conventional doses of heparin followed by coumarin therapy. No orthopedic cases were studied.

Finally, Gallus et al., at St. Joseph's Hospital and McMaster University, Hamilton, Canada, modified the prophylactic regimen of Kakkar by giving 5000 units 2 hours before surgery and then repeating this dose three rather than two times daily beginning 8–10 hours after the preoperative dose. In 226 patients undergoing major elective surgery, they reduced the incidence of deep-venous thrombosis, as measured by limb scans, from 16 to 2%. Among 46 patients with hip fractures heparin treatment also reduced a 48% incidence of deep-venous thrombosis to 13%. The patients with hip fracture had heparin initiated, again in contrast to Kakkar's approach, within 12 hours of hospitalization and continued throughout the surgical period.

This study is of interest for several reasons. First, it helps define the upper limits of minidose heparin in elective surgical patients, when a single across-the-board dose is used for all patients and not tailored to the heparin tolerance of each individual patient. With a regimen of 5000 units of heparin three times daily, although clinically significant bleeding was not increased in the heparin-treated patients, the blood requirement for transfused patients was nevertheless moderately increased, and treated patients had a lower hematocrit. Second, despite the more vigorous approach to heparinization, the incidence of positive limb scans was not significantly different from that achieved by Nicolaides using the Kakkar regimen, including or excluding the elective orthopedic cases. Third, if a greater daily dose of heparin did not improve results for general elective surgery, what can be said about the data obtained from the fractured-hip population? Here, Gallus et al. achieved a significant reduction in positive scans, whereas the Kakkar regimen provided no such benefit to this selected population. Yet, we do not know whether it was increased daily dosage, per se, or the fact that heparin therapy was initiated as soon as possible after the patient entered the hospital system that was the key ingredient in the success of the Gallus regimen, or, in fact, whether both steps were necessary to obtain the result achieved. Fourth, the data on popliteal-femoral vein thrombosis, excluding elective orthopedic and fractured-hip cases, showed that four untreated surgical patients had popliteal-femoral vein thrombi; but, like Nicolaides, there was none in the heparin-treated group. That orthopedic cases still present a problem is suggested.
by the fact that, among the untreated cases, two emergency fractured-hip patients sustained a popliteal-femoral thrombosis; whereas comparable thrombi developed in the heparin-treated group among one elective hip and two emergency hip patients. Whether this problem is related to direct trauma to the femoral vein, to the release of marrow fat into the systemic circulation, or, in patients with fractured hips, to the development of hypercoagulability before heparinization is not known.

There were only two episodes of pulmonary embolism in this study, and these were in patients who had not received heparin. However, all patients in whom thrombi reached the thigh were treated with full conventional doses of anticoagulants. Although the authors are not entirely clear in providing the reader with their understanding of the mechanism of action of minidose heparin, they appear to agree with the views of Sharnoff.

Six clinical trials, five of them randomized, despite variabilities in design, have each demonstrated that minidose heparin begun prior to surgery and continued through the first 5-7 or more postoperative days significantly reduced the incidence (and in some instances the progression cephalad) of isotopically positive lower limb scans. Correlations between limb scans and venography are sufficiently precise and positive to justify the interpretation that the positive scan reflects deep-venous thrombosis. Can these data be used as evidence that minidose heparin will prevent postoperative pulmonary emboli, and, if in, death? An unequivocal response to this question is not possible at this time.

There were 1054 patients (treated and controls) involved in the six trials of minidose heparin, including 209 heparin-treated patients who were not randomized. All patients were over 40 years of age, and most were subjected to major surgery. Yet, in this heterogeneous group, which included many patients at presumed high risk of pulmonary embolism, only five were so diagnosed. Three, moreover, were in the heparin-treated groups including the single death attributed to pulmonary embolism. If these figures are representative of patients over the age of 40 years subjected to major surgery, they indicate that the event rate (the number of fatalities attributable to pulmonary embolism among patients over 40 years undergoing operations) is low. Accordingly, a patient population in excess of 50,000 would be required for a prospective, multicenter, randomized trial to establish the value of minidose heparin in the prevention of postoperative pulmonary embolism. These large numbers would be necessary, even if a 90% gain were anticipated from minidose heparin therapy. Trials of such size, by the mere logistics of handling large numbers, run the danger of swamping out the results through unrecognized errors. Moreover, if trials include the use of limb scans, it would be unethical to withhold full-dose heparin and coumarin therapy from patients, either control or heparin-treated, whose limb scans showed progression of thrombi above the popliteal area. Similarly, when a pulmonary embolus was diagnosed clinically or by lung scan, it would also be unethical to withhold full doses of anticoagulants, for the efficacy of such therapy has been well attested to over a decade ago in the now classic paper by Barritt and Jordan. Moreover, the issue of determining in a high-risk group whether the pathologically demonstrable pulmonary emboli were causal, contributory, or incidental to death is at best arbitrary. What, in fact, is being suggested is that direct proof of the efficacy of minidose heparin in preventing pulmonary emboli among general surgical patients may not be attainable by a trial using death as an end point. This dilemma could be circumvented, perhaps in part, by scoring as failures of minidose heparin any recent pulmonary emboli found at autopsy, any clinically recognized pulmonary emboli confirmed by scan or angiogram, or any femoral-iliac thrombi demonstrated by venography.

Where does all this leave the practicing physician? Has he no alternative with minidose heparin but to await the outcome of randomized trials and, if no favorable result ensues, to abandon this therapeutic modality? Does, in fact, a failure to find significant differences in high-risk groups mean, a priori, that the treatment is of no value among low-risk populations? These are not rhetorical questions, for venous thromboembolism is a common, recurrent, age-related phenomenon that can be lethal without advance clinical warning. Pulmonary emboli, 95% of which originate as thrombi in the veins of the lower extremities or pelvis, cause an estimated 50,000-100,000 deaths annually in this country, and contribute as an ancillary factor to an untold number of additional deaths as well as to substantial disability in many more patients. Moreover, it can be calculated from special autopsy studies that 10% of all postoperative deaths are attributable to pulmonary emboli. Yet, even though
the data show that heparin and coumarin compounds are effective prophylactically against venous thromboembolism, there is no evidence that lethal pulmonary embolism is coming under control. On the contrary, some investigators have suggested that we are in the midst of an epidemic of deaths from pulmonary embolism.29

Part of this paradox derives from the fact that venous thrombosis is not often easily recognized clinically; and part also from the fact that, when the high frequency of venous thromboembolism surfaced as a result of the use of contrast materials, isotopes, and meticulous autopsy dissections, it became apparent that fatal pulmonary emboli were, by comparison, surprisingly infrequent, although still in actual number of deaths an important figure, comparable to the annual incidence of automobile fatalities in the United States.

Until now the use of antithrombotic therapy has required a balance in risk—the likelihood of thromboembolism against the hazard of drug-induced hemorrhage. The necessity of this choice has led inevitably to a consuming interest in defining risk groups,30 through which it might be determined that the likelihood of thromboembolism is sufficiently great to justify the possibility of inducing hemostatic failure. Whereas this approach has met with some success among selected surgical patients, it has eliminated from protection all patients at low risk, but who might nevertheless unpredictably develop pulmonary emboli. Even for high-risk patients undergoing surgery, anticoagulant treatment with heparin and coumarin compounds has been restricted to those institutions where the laboratory controls of anticoagulants provide adequate safeguards against drug-induced hemorrhage.

Minidose heparin essentially eliminates the drug risk of hemorrhage, except for human error in administering an overdose. Moreover, 35 years' experience with short-term heparin has not led to the recognition of any risks other than hemorrhage. Finally, heparin itself is a natural constituent of the human mast cell and, we believe, in low doses exerts its primary antithrombotic effect by increasing the anticoagulant activity of an alpha-2-globulin, normally present in human plasma and termed the inhibitor to activated factor X. The surgeon has, therefore, an antithrombotic approach tailor-made for primary care for patients subjected to operation, comparable in safety to penicillin prophylaxis for rheumatic fever or to a vaccine to prevent poliomyelitis, whereby thousands of individuals can be treated to prevent a single patient fatality. In the long run, it is only through such primary prevention of the adult population at large that the deadly impact of pulmonary embolism can be lessened.

From the surgeon's view the goal of prophylaxis is the total elimination of postoperative venous thromboembolism. Any compound recommended for primary prevention should satisfy four criteria in addition to efficacy: the drug should be well tolerated by the patient, it should be free of side effects, it should require no monitoring other than that the patient receive the drug appropriately, and, finally, it should produce no bleeding when the patient is subjected to major tissue trauma. In short, the therapeutic agent must prevent excessive intravascular coagulation without compromising normal hemostasis.

We believe the criteria outlined above, except for efficacy, have been adequately met by the recent trials of minidose heparin. If efficacy were, in time, to be established, then minidose heparin could be employed as primary prevention for all adults who are subjected to major abdominal, pelvic, or thoracic, but not, as yet, major orthopedic surgery.

A recommendation to administer minidose heparin to all hemostatically competent adults prior to, during, and following operation, although compelling, is presently based on the indirect and incomplete argument that any therapy diminishing or eliminating lower limb venous thrombosis prevents fatal pulmonary emboli. Many will understandably bridle at the inadequacy of such a position. On the other hand, each physician must decide whether withholding therapy incurs a greater hazard than the therapeutic initiation of minidose heparinization, at least until definitive answers on efficacy are forthcoming. This dilemma was effectively anticipated by an ancient Chinese curse: "May you live," it states, "in a time of transition."

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