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PREVENTION OF THROMBOEMBOLISM*

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FIRM evidence is now available that sudden fatal pulmonary thromboembolism occurring in patients who have undergone major surgical operations is safely preventable. It is unnecessary to restate the frequency and gravity of this major complication of surgery. Coon and Willis in 1959[1] estimated that 57,000 deaths from this cause occur in this country alone annually; this is in my opinion a rather conservative estimate. Others have reported an incidence of 2 to 6%.

Before presenting the evidence I should like to describe the most significant observations and studies which led to the present routine of heparin prophylaxis for the prevention of fatal thromboembolism. I did not deliberately seek a solution to this problem but was led to it step by step while attempting to explain a histological observation.

In 1956 I first observed a cellular phenomenon, until then unknown to me, in a case of rapidly fatal thrombotic thrombocytopenic pur-

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pura.[2] I instituted a number of studies, which convinced me that I had been observing the pulmonary megakaryocyte.[3, 4] I soon found out that the cell was first observed by the famous German pathologist Aschoff in 1893;[5] he had expressed the opinion that these normal bone-marrow cells occasionally escaped intact into the venous circulation and, because of their large size, were trapped in the pulmonary capillaries. Aschoff described this as an end-stage or "effete" phenomenon of no significance. The escape concept was questioned for some time, but through our studies and those of other investigators it has gained acceptance.[6] Our subsequent investigations[7] soon disclosed that these cells could be observed normally in the pulmonary capillary bed of man —even in unborn fetuses, newborn children, and at all later stages.

The pathologists of the Bronx Zoo kindly allowed me to study the pulmonary histology of their mammals and birds; a similar phenomenon was found in all the mammals. It was evident that the cells, because of their large size, are found routinely in all stages of fragmentation in the pulmonary capillary anastomoses, being squeezed into them by the pulsations of the right heart. The cells often emerge as casts of the capillaries[8] and as fresh platelets, which enter the general circulation. In most individuals a search of several high-power microscope fields is necessary in order for one such cell to be discovered.

In 1959 I reported[9] that patients who had died of thrombotic disease frequently revealed a marked increase in such entrapped megakaryocytes in the lungs; as many as 10 or 12 of these cells were found in every high-power light microscopic field. How this increase came about was not clear at that time. It was surmised that the sudden accelerated heart action which occurs in stressful situations might force a more rapid disintegration of the cells and might thereby cause a fresh thrombocytosis, releasing a platelet factor as yet unknown and producing the hypercoagulable state and thrombosis. It became desirable to test this hypothesis and to determine whether the blood in the left ventricle contained more platelets than the right ventricle, the platelets having been derived from the pulmonary megakaryocytes. A careful study of 20 rabbits was undertaken.[10] The first 10 rabbits, studied during the spring and summer, revealed no significant difference in the platelet counts of blood taken from the right and left ventricles. The second 10 rabbits, examined during the winter, revealed a most marked difference; blood drawn from the left ventricle at times contained twice

as many platelets as did blood taken from the right ventricle. This seemed strange. It could be concluded only that the pulumonary capillaries of the animals studied in winter had many more trapped megakaryocytes and that these gave off platelets. No explanation was then at hand. Later it became clear that during winter the animals were housed in unheated quarters and were in a state of immobility; they were hibernating in the cold. After the accumulation of megakaryocytes was confirmed by microscopic examination, it was concluded that the inactivity of hibernation had slowed the heart and thereby had slowed the breakup of the entrapped megakaryocytes. This was considered the priming mechanism for the period of stress which followed in examining the animals, thus causing the thrombocytosis.

It now became desirable to determine whether similar thrombocytosis and altered coagulation could be observed in man. The patient undergoing the stress of a major operation was deemed to be a good experimental subject. With the cooperation of our surgeons a study was made of 41 patients undergoing major surgical operations; platelet counts and Lee-White coagulation tests were performed before, during, and immediately after operation and daily thereafter until discharge or death. There were three deaths and two autopsies. In all three fatal cases the most significant increase in platelets and an acceleration of whole-blood coagulation to abnormal levels occurred during the height of the operation. The remaining 38 patients disclosed a less-marked thrombocytosis and a shortening of coagulation times to the lower limits of normal. Of the two autopsied patients one had massive pulmonary thromboembolism; the other had coronary-artery thrombosis and acute myocardial infarction. The third fatality occurred in a 58-year-old male. The course was typical of pulmonary thromboembolism: sudden death on first leaving bed after a gastrectomy.[11]

Clearly it was impossible to determine in advance which operative patient might harbor an increased number of entrapped pulmonary megakaryocytes that could lead to thrombocytosis during the stress of surgical operation. Although thrombocytosis could not be prevented, perhaps the hypercoagulability could be anticipated and the blood maintained at normal levels of coagulation in order to prevent thrombosis. Since coagulation levels in the 38 persons who did not have thrombosis had remained normal and were not far from the abnormal levels observed in the three fatal cases, it was believed possible that

small quantities of anticoagulant would suffice to maintain normal coagulation.

Aqueous sodium heparin was chosen as the anticoagulant which would best meet the need. Heparin, a natural substance, does not interfere with the healing of wounds. It has predictable limited action, is not affected by other medication, and is readily inactivated by protamine sulfate. A trial of heparin was begun in August 1960. The drug was given subcutaneously in small doses before and after operation to patients in the experimental group. There were two control groups: the first received postoperative heparin only, the other did not receive any. The results were striking.[12] The patients were of both sexes and averaged 60+ years. The operations were the usual surgical procedures performed in a community hospital: e.g., intestinal resection, cholecystectomy, hysterectomy, insertion of pins and prostheses into the hip, gastrectomy, and herniorrhaphy. Except for the nonheparinized group, all patients were considered to be at risk. Each member of the experimental group of 140 patients was given 10,000 units of aqueous sodium heparin subcutaneously at about midnight on the night before the operation and 2,500 to 5,000 units postoperatively every six hours until discharge from the hospital. The first control group of 92 individuals was usually given 2,500 units of heparin subcutaneously every six hours postoperatively only until death or discharge. The second control group, consisting of 1,396 individuals not considered at risk, was given no heparin. In the experimental group there were nine deaths, but without clinical or postmortem evidence of pulmonary thromboembolism. In the two control groups, however, fatal pulmonary thromboembolism was found in 62.5% and 68.1% respectively of the patients who came to autopsy. The difference between the treated group and the control group was overwhelming. The preoperative and postoperative use of heparin was introduced as a routine and has been continued up to the present time.

The administration of heparin was controlled by determinations of coagulation time. Initially the Lee-White method was used chiefly. But after a simultaneous trial[13] the Dale and Laidlaw coagulometer[14] was found to be simpler and more dependable. The results were reproducible and the procedure required only a small drop of fingertip blood, drawn at the bedside. Accordingly the Lee-White method was abandoned. The Dale and Laidlaw method has a normal range of 1½ to 2½

minutes. The purpose was to maintain coagulation in this range. Coagulation times are determined preoperatively, immediately after operation and daily before the next noon dose of heparin. The dose is adjusted if necessary according to the determination. With this control, and with the use of small doses, hemorrhage was seldom a problem.[15, 16]

Now, after 10 years, there has been a total of more than 1,450 successful heparinizations and only two failures as confirmed at autopsy. The failures were unusual, identical, and instructive. Both were cases of fractured hip, one in a man of 74, the other in a woman aged 96. Both patients were immobilized for eight days and were not given heparin until just before operation. As a result we have learned to give heparin to such patients upon admission and follow with the preoperative routine that has been described.

Others are now reporting similar success with the same or a slightly modified prophylactic program in which small doses of heparin are given subcutaneously. A Johannesburg surgeon writes[17] that he has had no fatal thromboembolism in 1,004 cases. All other successful studies[18-22] have been reported in the *Lancet* in the past two years. These are controlled studies in which the I^{125} fibrinogen uptake test is used to determine the presence of deep venous thrombosis in heparinized and nonheparinized surgical patients. In these trials success is determined not by the rate of fatal pulmonary thromboembolism but by the prevention of thrombosis in the veins of the lower extremities.

The problem of sudden unexpected death due to pulmonary thromboembolism has long defied our best efforts. Our program offers great promise of safely eliminating this obstacle.

One final comment is in order. It appears that the triad originally proposed by Rudolf Virchow to explain the development of thrombosis is still valid. The components are stasis of blood, vascular alteration, and intrinsic changes in the blood. I offer the opinion that the last element in this triad—hypercoagulation—is most critical.

REFERENCES

1. Coon, W. W. and Willis, P. W.: Deep venous thrombosis and pulmonary embolism, prediction, prevention and treatment. *Amer. J. Cardiol. 4*:611, 1959.
2. Sharnoff, J. G.: Thrombotic thrombocytopenic purpura. *Amer. J. Med. 23*:740, 1957.
3. Sharnoff, J. G. and Kim, E. S.: Evaluation of pulmonary megakaryocytes. *Arch. Path. 66*:176, 1958.
4. Sharnoff, J. G. and Kim, E. S.: Pulmonary megakaryocyte studies in rabbits. *Arch. Path. 66*:340. 1958.
5. Aschoff, L.: Ueber capillare embolie

riesenkernhaltigen zellen. *Arch. Path. Anat. 134*:11, 1893.

6. Scheinin, T. M. and Koivuniemi, A. P.: Megakaryocytes in the pulmonary circulation. *Blood 22*:83, 1963.
7. Sharnoff, J. G. and Scardino, V.: Pulmonary megakaryocytes in human fetuses and premature and full term infants *Arch. Path. 69*:139, 1960.
8. Sharnoff, J. G.: A possible explanation of the formation of long platelets from pulmonary megakaryocytes. *Nature 184*: 75, 1959.
9. Sharnoff, J. G.: Increased pulmonary megakaryocytes—probable role in postoperative thromboembolism. *J.A.M.A. 169*:688, 1959.
10. Sharnoff, J. G.: Platelet count differences in blood of the rabbit right and left heart ventricles. *Nature 187*:334, 1960.
11. Sharnoff, J. G., Bagg, J. F., Breen, S. R., Rogliano, A. G., Walsh, A. R., and Scardino, V.: The possible indication of postoperative thromboembolism by platelet counts and blood coagulation studies in the patient undergoing extensive surgery. *Surg. Gynec. Obstet. 111*:469, 1960.
12. Sharnoff, J. G., Kass, H. H., and Mistica, B. A.: A plan of heparinization of the surgical patient to prevent postoperative thromboembolism. *Surg. Gynec. Obstet. 115*:75, 1962.
13. Sharnoff, J. G.: An evaluation of the Dale and Laidlaw coagulometer in the heparin control of thromboembolism. *Proc. N.Y. State Ass. Public Health Labs. 43*:10, 1963.
14. Dale, H. H. and Laidlaw, P. P.: A simple coagulometer. *J. Path. Bact. 16*: 351, 1911.
15. Sharnoff, J. G. and DeBlasio, G.: Prevention of fatal postoperative thromboembolism by heparin prophylaxis. *Lancet 2*:1006, 1970.
16. Sharnoff, J. G.: Preventing fatal postoperative thromboembolism with heparin prophylaxis. *Contemp. Surg. 1*:51, 1972.
17. Lannon, J.: Personal communication.
18. Kakkar, V. V., Field E. S., Nicholaides, A. N., Flute, P. T., Wessler, S., and Yin, E. T.: Low doses of heparin in prevention of deep vein thrombosis. *Lancet 2*:669, 1971.
19. Williams, H. T.: Prevention of postoperative deep-vein thrombosis with perioperative subcutaneous heparin. *Lancet 2*:950, 1971.
20. Gordon-Smith, I. C., Grundy, D. J., LeQuesne, L. P., Newcomb, J. F., and Bramble, F. J.: Controlled trial of two regimens of subcutaneous heparin in prevention of postoperative deep-vein thrombosis. *Lancet 1*:1133, 1972.
21. Kakkar, V. V., Corrigan, T., Spindler, J., Fossard, D. P., Flute, P. T., Crellin, R. Q., Wessler, S., and Yin, E. T.: Efficacy of low doses of heparin in prevention of deep-vein thrombosis after major surgery. *Lancet 2*:101, 1972.
22. Nicolaides, A. N., Dupont, P. A., Desai, S., Lewis, J. D., Douglas, J. N., Dodsworth, H., Fourides, G., Luck, R. J., and Jamieson, C. W.: Small doses of subcutaneous sodium heparin in preventing deep venous thrombosis after major surgery. *Lancet 2*:890, 1972.