Some Effects of Heparin on Autogenous Vein Replacement with Special Reference to the Endothelial Healing Process at Anastomotic Site*

HISAWO ISHIGURO

This experiment was carried out to evaluate heparin effect on the replacement of the autogenous femoral vein in dogs. Heparin was administered intramuscularly at a daily dosage of 6 to 9 mg per kg of body weight for 7 postoperative days. Clotting times were maintained 20 to 25 min. by Lee-White method.

The administration of heparin seemed to improve the patency rate and to prevent the mural thrombi forming at the injured anastomotic intima. Furthermore, the administration did not inhibit the endothelial regeneration at anastomotic injured portion, but rather enhanced up to the 4th day.

In vascular surgery, especially in cases of small calibrated venous vessels, thrombus formation has been well encountered. Heparin has been considered as an useful antithrombotic drug clinically and experimentally. Kiesbetter, Carey, Williams, and Hunt have experimentally found heparin effective in prevention of thrombus propagation. Bradham has also assessed experimentally that heparinization prevented the early reformation of thrombus after thrombectomy. In view of these, it is surprising that in clinical studies heparinization has not proved more effective therapeutic results than in experimental studies. This may reflect inadequacy of dosage or too long interval between doses, or this may indicate that clinical condition is more hypercoagulable. In 1964 Kamiya stressed that postoperative anticoagulant therapy favorably resulted in securing vascular patency, and it was not necessary to keep absolute noncoagulable state but a certain degree of hypocoagulability was required. Heparin seems to interfere with the thrombin-fibrinogen reaction and probably also inhibits the conversion of prothrombin to thrombin. Apart from its anticoagulant activity heparin has numerous other actions. It increases blood fibrinolytic activity and stimulates cell locomotion and pseudopod formation, etc. Moreover, with reference to heparin effect on subcutaneous wound healing, various informations have been reported. In 1960 Ohlwiler and his assistants found heparin to impair granulation tissue formation in guinea pigs. Recently Zahir has reported the contradictory observation that heparin had no significant effect on the healing process of an incised abdominal wall.

So it is desirable to ascertain whether systemic heparinization inhibits the endothelial wound healing at anastomotic portion or not. End to end anastomoses of femoral veins were performed by manual method. Repeated phlebo graphical and histological studies at anastomotic portions were performed. The purpose of this paper is to prove:

(1) systemic heparinization improves patency rate of autogenous small venous replacement,

(2) systemic heparinization prevents the mural

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thrombi forming at the injured intima, and (3) systemic heparinization does not disturb the endothelial healing process at anastomotic site.

**Materials and Methods**

This study was carried out in two experiments. (Experiment 1.) Thirty-six mongrel dogs were used weighing 12 to 16 kg. A 4 cm length of the right superficial femoral vein was excised and replaced with a 6 cm segment of the contralateral femoral vein (Figure 1.). Each segment bore one or two valves and the diameter ranged from 3.0 to 4.3 mm. After regional heparinization, end to end anastomoses were carried out with the interrupted evert sutures of No. 5.0 tetron. The adventitia was carefully stripped away, and a great deal of care was taken not to injure the intima and to maintain normal tension in the reconstructed vein segment. Each dog received a 500 mg dosage of tetracyclin intramuscularly for 3 days postoperatively. The operative wound was closed with the interrupted sutures in the deep fascia and skin. Experimental dogs were divided in the heparinized group and the control, without respect to sex and weight. Seventeen dogs served as the control. In nineteen dogs heparin was administered intramuscularly at daily dosage of about 6 to 9 mg per kg of body weight for 7 postoperative days. During heparin treatment clotting time was maintained 20 to 25 min. by Lee-White method. It was also demonstrated by thrombelastography where it was confirmed that initial fibrin formation was delayed. (Experiment 2.)

In twelve dogs the left superficial femoral vein was ligated high and bypassed via the opposite femoral vein which was transected low (Figure 1). Direct anastomosis of the caudal end of the right femoral vein to the cranial end of the left femoral vein was carried out and tunneled subcutaneously. In six dogs heparin was administered as above mentioned. Other six dogs served as the control.

Roentgenographical studies were carried out under the light pentobarbital anesthesia on the 3rd to 7th day postoperatively. Ten ml of contrast medium were injected into the right (Exp. 1) or the left (Exp. 2) saphenous vein over 2 to 3 seconds, and an exposure was made at the end of injection. At sacrifice, the venous graft was dissected free and examined for patency and tissue reaction. The vein was opened longitudinally to permit gross inspection of the intimal surface and valve cusps. Longitudinal histological sections including anastomotic sites were performed on the 3rd to 14th postoperative day. The specimens were preserved in 10 per cent formalin. Various stainings were performed as follows:

1. Haematoxylin and eosin stain,
2. Weigert's resorcin fuchsin and van Gieson's

<table>
<thead>
<tr>
<th>Table I</th>
<th>Patencies of End to End Autogenous Venous Replacement</th>
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<td></td>
<td>Dog's Number</td>
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<td>(Experiment 1)</td>
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<td>The First Group</td>
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<td>Control Animals</td>
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<td>Heparinized An.</td>
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<td>The Second Group</td>
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<td>Control Animals</td>
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<td>Heparinized An.</td>
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<td>(Experiment 2)</td>
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<td>Control Animals</td>
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<td>Heparinized An.</td>
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stain,
(3) Toluidin blue stain by Oono's modification (at Hp 7.0),
(4) Azan Mallory's stain.

RESULTS

(1) PHLEBOGRAPHICAL FINDINGS:
Repeated venographies after surgery should be accepted as a proof that venous grafts had remained continually open.
(Experiment 1)
Thirty-six dogs were divided into the first group and the second, unskilled technique and skilled. As Table I clearly showed, 16 cases of the first group were devised to develop a satisfactory technique. So the results reflected the learning processes. As Table I showed, far better results were obtained in 20 dogs of the second group, because the operator became more familiar with the technique of anastomosis and administration of heparin. So the comparative data between the control and the heparinized cases can be reliable. The control cases exhibited patent 8 of the 11, or 73 per cent, on the 3rd to 7th day postoperatively. On the other hand, the heparinized series showed no occlusion, indicating that early thrombosis was effectively protected by the administration of heparin. Figure 2 showed a patent phlebogram 7 days after surgery.
(Experiment 2)
Twelve dogs were used. Six dogs served as the control. Phlebogram revealed continually patent in 2 dogs of the control. Four dogs showed occlusion. One was patent when the original phlebogram was carried out 3 days postoperatively, but latter became occlusive. Figure 3 and 4 showed this case phlebographically. Figure 3 represented the mural thrombus that developed at the site of anastomosis. The mural thrombi forming was probably the

Fig. 2. Autogenous venous transplantation. (Experiment 1)
Phlebogram done 7 days postoperatively. The venous lumen is widely patent, but moderate spasm is still present in graft and recipient site stump. The heparinized dog.

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cause of the late occlusion, showed in Figure 4. In 6 heparinized dogs a patency rate of 67 per cent was obtained. Anticoagulant therapy improved results distinctly.

(2) Histological Findings at Anastomotic Site

In all cases no serious wound hematoma was observed. Forty-five specimens were chosen from thirty-two continually patent cases in Experiment 1 and 2. These microscopical findings, which were concerned with the fate of anastomotic sites, were summarized in Table II. This illustrated the correlation between heparinization and endothelial healing process.

The intima consists of a layer of endothelial cells at its inner margin and a subendothelial zone. The zone contains cells in addition to the intercellular elements. The cells observed within the zone have the morphological features of fibroblasts. The author calls them "intimal cell" in this paper. However, no further information about the origin of these cells is performed in this study.

Three Days following Surgery

It was observed at anastomotic site that the intima was damaged and internal concavity was formed in each specimen, as shown in Figure 5. The intimal damage seems to be produced by operative procedure, instrumentation, and nutritive disturbance of vessel wall caused by anastomosis. The existing intimal cells migrated toward the depth of the damaged intima and buried the internal concavity. These intimal proliferation reparatively began on the 3rd postoperative day. Administration of heparin seemed to enhance the intimal proliferation (Figure 6). Moreover, mural thrombus at ana-

Fig. 3. Subcutaneous tunneled replacement. (Experiment 2) Phlebogram done 3 days postoperatively, showing abnormality (mural thrombus?) at anastomotic site. The control dog. The graft is narrow in lumen with open collateral veins that suggest the reduced flow through the graft.

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stomotic site was observed in some instances. It was less pronounced by the administration of heparin. As Table II showed, it was estimated that mural thrombus at anastomotic site was presented in 66 per cent of the control and 29 per cent of the heparinized animals.

Four Days following Surgery

Proliferation of intimal cells at anastomotic site became more remarkable, and began to be
lined by a layer of flattened cells which were usually considered as pseudoendothelium. It is of interest that the newly formed pseudoendothelium, irregular in size and shape, was observed to grow inwards from the edges of the host and graft endothelium (Figure 7). As represented in Figure 7, 8, and 9, the endothelial regeneration was more pronounced in the heparinized animals than in the control. Fur-

Fig. 4. Phlebogram is the same extremity of Fig. 3, done 2 weeks after operation. Note the obstruction of graft with extensive collateralization.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Endothelial Repair at Suture Line of Autogenous Venous Graft</th>
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<td>3rd day</td>
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<td>1. Negative endothelial lining</td>
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<td>(a) without mural thrombus</td>
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<td>(b) with mural thrombus</td>
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<td>2. Partial endothelial lining</td>
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<td>(a) without mural thrombus</td>
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<td>(b) with mural thrombus</td>
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<td>3. Complete endothelial lining without thrombus</td>
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- • A specimen from the control dog
- ○ A specimen from the heparinized dog

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thermore, mural thrombus at anastomotic portion was often seen in the control animals and the endothelial reparative procedure was clearly disturbed by the existence of mural thrombus.

**Five Days following Surgery**

The regeneration of the endothelial and subendothelial tissue advanced more. Anastomotic injured portion was apparently filled with the

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**Fig. 5.** Microscopic appearance of the anastomosis of a graft 3 days old, showing the damaged endothelium and intimal cells. The control animal. Intimal concavity is observed at anastomotic portion, and reparative phenomena of intimal cells are as yet poor. The elastic membranes are present, though fragmented. (Weigert's resorcin fuchsin and van Gieson's stain ×100)

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**Fig. 6.** Microscopic appearance of the anastomosis of a graft 3 days old, showing the damaged intima. The heparinized animal. Proliferation of intimal cells is seen at the right of the anastomosis and the left of the field. (host site) (Weigert's resorcin fuchsin and van Gieson's stain. ×100)
intimal cells and evenly arranged. It was surprising to find that the newly formed pseudoendothelium covered the intimal reparative tissue at anastomotic portion and appeared to be continuous with the endothelial surface of the host and graft vessels. The endothelial cells appeared to be more elongated and regular (Figure 10 and 11). In comparing the hepari-
nized animal with the control, the endothelial healing process had no more significant difference. If the pseudoendothelium covers completely the injured area, a risk of thrombosis may decrease. Thrombus, which had been once formed for 5 days following insertion, was not yet covered with the pseudoendothelium, as shown in Figure 12. However, the minute

Fig. 9. A microphotograph of anastomotic site inserted 4 days before. The heparinized animal. Intimal repair is prominent at anastomotic site, and superficial endothelial lining covers almost completely at anastomotic portion. (Weigert's resorcin fuchsin and van Gieson's stain ×100)

Fig. 10. A microphotograph of anastomotic site inserted 5 days before, with suture materials visible at the left in the lower portion of the field. The control animal. Intimal proliferation is more remarkable. Endothelial coverage is almost complete at the superficial layer of anastomotic site. (Hematoxylin and eosin stain ×100)
mural thrombus was well covered with endothelial cells in some instances (see Figure 13). In general, the newly formed pseudoendothelium tended to develop more poorly over the clotted surface than the clot-free site.

Seven Days following Surgery
Anastomotic portion was occupied with the thickened intima, on which no discontinuity of

Fig. 11. A microphotograph of anastomotic site inserted 5 days before. The heparinized animal. It is important that the injured superficial layer at anastomotic site is completely recovered with the newly formed pseudoendothelium. Suture materials can be seen at the right of the field. (Hematoxylin and eosin stain ×100)

Fig. 12. A microphotograph of anastomotic site inserted 5 days before. The control animal. Endothelial recovery is not seen at the mural thrombus. (Hematoxylin and eosin stain ×100)

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the endothelial lining could be seen. Scattered tiny capillary lumina were observed beneath the newly formed pseudoendothelium. These capillary lumina were also lined with the flattened cells. Representative histological sections are shown in Figure 14 and 15. The heparinized animal showed no difference with the control.

Fourteen Days following Surgery

Fig. 13. A microphotograph of anastomotic site inserted 5 days before. The control animal. Small mural thrombus is well covered with the flattened cells which may originate from the host and graft endothelium. (Weigert's resorcin fuchsin and van Gieson's stain. ×100)

Fig. 14. A photomicrograph of anastomotic site inserted 7 days before. The heparinized animal. The anastomotic damaged site is well occupied with the intimal cells. Superficial layer is lined with the pseudoendothelium, under which scattered tiny cystic spaces are present. (Weigert's resorcin fuchsin and van Gieson's stain. ×100)
Figure 16 showed the appearance of anastomotic portion. Subendothelial tissue consisted chiefly of fibrous reinforcement. No difference on the endothelial healing procedure was seen between the heparinized animal and the control.

**DISCUSSION**

Heparin has been shown to cause interference with clotting at two points:
(a) it interferes with the interaction of thrombin with fibrinogen.

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**Fig. 15.** The same graft as shown in Figure 14. Tiny cystic spaces are particularly photographed. Note the presence of endothelial flattened cells around the lumen. (Weigert's resorcin fuchsin and van Gieson's stain ×400)

**Fig. 16.** A photomicrograph of anastomosis inserted 14 days before. The control animal. Anastomatic site is covered with more fibrous intimal thickness. (Hematoxylin and eosin stain. ×100)

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(b) it prevents the conversion of prothrombin to thrombin by the blood thromboplastin system.

Due to these properties heparin is a powerful anticoagulant. It, therefore, stops a thrombotic process expeditiously and prevents the provocation of a intravenous clot. Virchow’s trias has been well using as the basis of discussion on the aetiology of thrombosis. Quick39 offered a simple schematic explanation of thrombosis, and stressed an alteration in the vessel wall as the primary and initiating cause of thrombosis. It was well reported that the damaged endothelium had a loss of its normal property of being non-water wettable. According to the theory of Douglas41, endothelial antithrombotic property was speculated that since the damaged cells had similar “contact” effect to glass and provided the tissue component needed for extrinsic thromboplastin, the nonviable endothelium could initiate prothrombin conversion by this system.

Murray7 was first to use heparin to prevent thrombosis at suture line after operation on blood vessels. For some years heparin therapy was frequently used in vascular surgery. However, if the patients were maintained for a long time after operation under full heparin effect, this carried a very significant risk of serious wound hematoma. In 1964, Kamiya4 stressed that heparin was an useful and safe drug after vascular surgery. He administered heparin immediately after the time of surgery and maintained the patient on the anticoagulant level of 20 to 25 min in blood clotting times until the patient fully ambulated. According to this concept, an antithrombogenic effect of heparin on the autogenous vein replacement was researched in this study. Furthermore, as the role of blood coagulation in normal wound healing has been a subject of much dispute16,19,22, heparin effect on the endothelial healing process at anastomotic site was investigated.

(1) Patency Rate of Autogenous Vein Replacement

The problem of the patient with chronic venous obstruction of the lower extremity has received much attention23,24. The feasibility of venous reconstruction has become increasingly apparent over the last several years. Diseased and damaged veins have been frequently replaced with the grafts for the relief of the congestion, edema, and pain. Arterial homografts, plastic tubes, and venous homografts have been evaluated in major veins such as the superior vena cava and inferior vena cava25,26. However it is a general impression that the satisfactory patency rates and continual valve functions have been acceptable only with venous autografts27,28. Homologous and artificial grafts, while initially successful, have not remained patent50. Even autografts were not productive of excellent results in veins of small caliber. The reported patency rates with venous autografts in the femoral veins of the dogs varied widely, but were generally less poor than in the other areas such as renal veins or jugular veins.

Small calibered venous autografts have shown a success rate of 50 to 80 per cent by Dale29, De Weese30, Schabule31, and Wadell32. Cerino and his assistants33 showed the patency rate of 95 per cent of their experiments 3 to 5 months postoperatively. However, numerous veins which were reported as patent from 5 to 10 weeks after surgery were probably thrombosed earlier29,30. According to De Weese and Niguidula29, good valve functions were observed in 55 per cent of the grafts which remained patent 6 to 14 weeks after surgery. When recanalization occurred after occlusive thrombosis, the valve proved incompetent at sacrifice34. Wadell and his coworkers35 recently reported an 100 per cent patency rate with the use of their special staplers. Their phlebograms, however, had been accomplished 3 to 15 weeks after surgery, and only 57 per cent of these had the competent valves. As the restoration of the competent valve is essential to the venous surgery, it is required to protect the early and late thrombosis of the graft. Postphlebitic extremity having incompetent valves continues to be a devasting complication. Furthermore, occlusion of the portal and caval veins would result in immediate direct consequences, even if by the time later patency might be expected to occur.

Regional heparinization has been well used to expect the inhibition of early thrombus formation, but did not elevate the continual patency.
rate contrary to expectation. There is scant information that systemic heparinization affects the patency rate. Following representations Author have been encouraging and suggested further use of systemic heparinization.

In 1964, Baird and his associates represented that early thrombosis could be prevented by the administration of heparin. They transplanted valve containing venous autografts into the femoral veins of dogs. One third of inserted grafts were occluded within one day after surgery. A continuous flow of heparin across the anastomosis for four hours after surgery led to a 100 per cent patency one day after anastomosis, but the incidence of thrombosis during the first week and thereafter was much the same as in the control.

In 1965, McLachlin and his coworkers concluded that when systemic heparinization was continued 24 to 48 hours after insertion of the graft, there was a very suggestive but not conclusive lessening in the incidence of thrombosis (p = 0.075): the patency rates yielded 12 of the 18 in the control, and 12 of the 12 in the heparinized animals.

In this experiment, heparin was administered intramuscularly for 7 days postoperatively and maintained under thromboelastographic studies and surveys of clotting times. Clotting times and R intervals of thromboelastogram were controlled 20 to 25 minutes by a daily dosage of 6 to 9 mg heparin per kg of body weight. Of course clotting phenomenon was almost all variable in each animal. So it is very important to secure clotting times and thromboelastographic studies.

Mustard and his associates suggested that small doses of heparin were thrombogenic (50 mg of heparin twice a day), whereas 80 mg of heparin three a day produced a significant antithrombogenic tendency in clinical cases. Sasaki removed jugular venous vessels, opened longitudinally, and observed platelet adhesion and microthrombi forming on the intima. He pointed out that heparin in low dosage given in vitro and in vivo did not prevent platelet adhesion to the damaged endothelium, but in high dosage (0.04–0.1 mg per ml blood) it did considerably.

(Experiment 1)

As previously stated in this report, 16 dogs of the first group showed low patency rates. Systemic heparin therapy did not lead a poorly performed operation to a success. The technique of venous anastomosis, especially in small calibered of vein used in this study, must be carried out carefully. In 20 dogs of the second group, however, 85 per cent of venous grafts were continually patent, especially the heparinized dogs showed no occlusion. The fact that there was no early thrombosis with systemic heparinization, suggests that the prolonged administration of heparin may be a worthwhile.

(Experiment 2)

The attempt to cross over bypass saphenous graft for the relief of venous obstruction of an extremity was made by Palma and Esperon, and Dale. Experimental testing of the cross over femoral vein graft in the dog has been recently completed by Harris with results which promise the clinical use. They proved that the graft remained continually open in 28 per cent and recanalized in 32 per cent of the experiments. In this experiment, control animals showed patent in 50 per cent 3 days following surgery, and 33 per cent 14 days postoperatively. Heparinized animals which were administered for 7 postoperative days indicated that 6 dogs were all patent 3 days following surgery and patency rate decreased to 50 per cent 14 days postoperatively. This experience suggests that a longer time more than 7 days administration of heparin minimized the risk of thrombosis after operation, in the above mentioned dosage. Thus, although this experiment was performed in only 12 animals, the results obtained are interesting.

(2) Endothelial Regeneration at Anastomotic Portion

In analysing the results of this study, it is important to call attention to several facts. The extreme sensitivity of the venous endothelium to injury has been well shown by Robertson. The intima at anastomotic site was easily damaged by anastomatic procedures in all animals. Twenty-three animals were selected for the histological observation from thirty-two continually patent animals. Its selected point was that other sites than anastomotic site had not
been damaged, since wound healing is in the broadest sense one of the most specific of biologic reactions and it is related to both the nature and the extent of injury and to the capabilities of surviving tissues. Endothelial reparative procedures were well represented by Cotton, Florey, Mackenzie, and Ikek. They researched the endothelial repair after endarterectomies or implantation of plastic tubes.

In this report, an endothelial healing process at autogenous venous anastomotic site was observed by longitudinal sections. Longitudinal perpendicular sections to the inner surface were insufficient for determining the shape and size of endothelial cells. However, the sections were suitable to observe convincingly subendothelial and endothelial reparative processes.

Heparin and Mural Thrombus

The rate of mural thrombi forming at the intima may be regard as expressing the grade of thrombotic disposition of the intima. According to Sawyer and Pate (1953), the electrical potential of normal intima was negative to the adventitia and the electrical charge became reverse with injury, and then leucocytes and platelets were attracted to the positive pole. In 1961 Inokuchi and his coworkers demonstrated that radioactively labeled platelets strongly adhered to the damaged intima and its peak reached on about the 5th day after surgery.

The experimental results so far obtained in the present study seemed to indicate that the intimal surface of anastomotic site was exposed to a transitory risk of thrombosis for about five days postoperatively. It was also proved histologically that the period of thrombogenic disposition corresponded with the intimal reparative condition. Since the damaged intima had been covered by the pseudoendothelium after the 6th day postoperatively, intimal thrombogenicity seemed to decrease clearly. Furthermore, as showed in Table II, adequate heparin therapy could inhibit minute mural thrombi forming at anastomotic site.

In 1965 Salzman examined the influence of heparin on platelet adhesiveness by an in vitro technique. No significant change in platelet stickness was produced by the injection of even a large dose of heparin. This result correlated with the result of Borchgewink. In the venous system sluggish blood flow permits the local accumulation of intermediate reactants in coagulation. If their concentrations reach a sufficient level, they may lead to produce a fibrin gel. So the therapeutic value of heparin seems to inhibit the progress of coagulation in a vein.

Fibrin’s Role in Wound Healing

In 1961 Inokuchi and his coworkers stated that adsorption of fibrin to the damaged endothelium at anastomotic site was essentially necessary in the initial stage of wound healing, and then the fibrin layer covered with new growing endothelial cells. If it is so, however, endothelial recovery may be inevitably impaired in the hypocoagulable state caused by administration of heparin. Although adsorption of fibrin also occurred frequently in this experiment, it played a harmful role on the endothelial repair. In case of minute mural thrombus as shown in Figure 13, the favorable reendothelialization was sometimes observed. It should be emphasized that the proliferation of intimal cells gave ground for a re-endothelialization at anastomotic site.

Pseudoendothelium

Pseudoendothelium can originate from four sources:

1. Host endothelium,
2. Original graft endothelium,
3. Proliferated intimal cells (fibroblasts),
4. Cellular elements derived from the circulating blood.

Since intimal cells had proliferated sufficiently at the damaged surface of anastomotic site, regenerating endothelium which arose from host and graft endothelium lined the anastomotic portion (see Figure 7).

As shown in Figure 11, 14, and 15, tiny cystic spaces or capillary lumina are well presented beneath the pseudoendothelium. The above finding suggests that pseudoendothelium may originate partially from the endothelial cells which lined the capillary inner margin. Intimal vascularisation is a phenomenon secondary to excess intimal growth, and is presumably formed by progressive sprouting of capillaries toward an area of relative ischemia. The existence of intimal blood channels may be neces-

sary to the nutrition of new born intimal cells and endothelial lining as well as the atherosclerosis. A somewhat likely explanation was suggested by the observation of Florey and his associates that endothelial proliferation from capillaries perforating the graft contributed to graft endothelialization. However, pseudoendothelium may be derived from young fibroblasts, namely functional adaptation, because complete endothelial lining was observed before the formation of capillary lumina in the intima.

The theory, in which pseudoendothelium originates from cellular elements derived from the circulating blood, was not verified in this study.

Endothelial Repair

Although systemic heparinization has been in use recently, this effect on the, cutaneous wound healing has been a subject of much dispute. In 1960 Ohlwiler and his associates reported that heparin impaired scar formation and bone healing. They stressed the necessity of fibrin in the first stage of wound healing. On the other hand, Riley (1962) show that heparin might stimulate fibroplastic proliferation or might be ingested and utilized in the production of mucopolysaccharides by fibroblasts. Furthermore, in 1965 Zahir concluded that heparin had no effect on the wound healing of an incised abdominal wound.

In this study, the effect of heparin on the endothelial healing process was investigated. Endothelial regeneration was seen to begin on the 4th postoperative day, and to accomplish on the 5th to 6th day postoperatively. Highlighted here is the question of heparin effect on the endothelial repair. Administration of heparin, given in the dosage employed in this study, invariably resulted in adequate enhancement of the endothelial healing up to the 4th postoperative day. However, the effect disappeared after the 5th day, and the endothelial repair finished so favourably as in the control. Poor cell growth and retarded reendothelialization were not observed by the administration of heparin.

SUMMARY

This experiment was carried out to evaluate heparin effect on the autogenous vein grafting.

Favourable results were obtained for the usage of heparin:

1. Continual patency rate was improved by the adequate administration of heparin, with which clotting time and R interval of thromboelastogram were maintained 20 to 25 min.

2. The administration of heparin did not inhibit the endothelial regeneration at anastomotic injured portion, but rather enhanced up to the 4th postoperative day.

3. The administration of heparin seemed to prevent clearly the mural thrombi forming at the injured intima.

4. As the endothelial recovery at anastomotic injured surface finished up to the 5th to 6th day postoperatively, and the mural thrombus formed at the damaged intima had a harmful role for the endothelial regeneration, heparin should be used at least for 5 days following surgery.

From these results it would be preferable to employ heparin for the reparative surgery of peripheral veins.

Acknowledgment

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