AN EXPERIMENTAL STUDY OF THE NEOINTIMA OF SYNTHETIC VASCULAR PROSTHESIS

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I. INTRODUCTION

Although various vascular homografts and synthetic prostheses have widely come into use in the past decade, with the passage of time it is becoming increasingly clear that synthetic prostheses are indeed superior to homografts, principally because after fairly long periods of observation synthetic prostheses show no evidence of the medial degenerative changes that weaken the wall with resulting occasional rupture or aneurysmal dilatation.[6, 38, 40, 41]

In contrast to the excellent results obtained with resection and prosthetic replacements of segments of the aorta and the large arteries,[12, 34] replacements in the smaller peripheral vessels are often impracticable because of a disturbingly high incidence of thrombosis[3]. The early completion of neointima of prostheses after implantation appears to be a critical factor in replacing small vessels; incompleteness of this layer may expose a raw fabric surface and may cause mural thrombi to occur.[17] The problem as far as intimal formation are concerned, has not yet been adequately solved. For this reason and in order to improve the results in replacement of small vessels it is desirable to complete as early as possible the neointima.

While it has been observed experimentally and clinically that growth of surrounding fibrous connective tissue through interstices of the prostheses can affix the graft to the host tissues and at the same time speed up organization of the fibrin which has deposited along the internal surface of prostheses immediately after establishing blood flow through it,[2, 4, 37] we have as yet little information as to which of the fibrous tissue and the fibrin plays a leading role in the development of the neointima. It is the purpose of the present paper to achieve this objective and to seek for the method improving a development of the neointima.

II. MATERIALS AND METHODS

Synthetic vascular prostheses used in this study were the crimped knitted tetoron tubes; "TETROLL", and the crimped woven teflon tubes (Fig. 1). The former was supplied by "ZINKO NAIZO KENKYUKAI" in Japan, the latter was manufactured

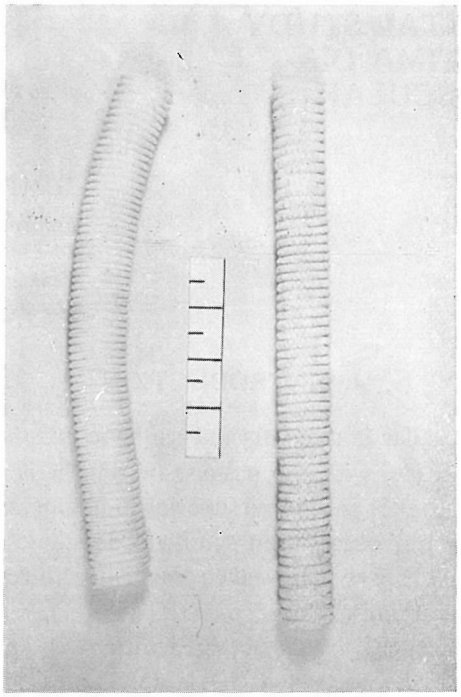


Fig. 1. Photograph showing the synthetic prostheses used in this study; right tube is the knitted tetoron tube, left one is the woven teflon tube.

by U.S. Catheter & Instrument Corporation.

Prior to the use, these prostheses were autoclaved for about 20 minutes. Healthy mongrel dogs weighing 7 to 17 kg., were anesthetized by intravenous injection of pentobarbital sodium (30 mg./kg.). All operative procedures were performed with sterile technique.

To clarify a participation of the fibrous tissue and the fibrin in the development of the neointima, the animals were divided into three groups as follows;

Group 1. *Insertion of the prostheses in the subcutaneous tissue.*—

To assess influence of the penetrated fibrous tissue on the internal surface of prostheses, each of the knitted tetoron and the woven teflon tubes varying in length from 3 to 5 cm. were embedded in the subcutaneous tissue of the anterior abdominal wall (Fig. 2). These tubes were 5 to 8 mm. in diameter, and each of the ends was closed by suturing so that no fibrous tissue could be penetrated through it, except the porosity of fabric. The abdomens were shaved and disinfected after Grossich's method. All the tubes were subcutaneously placed well away from the 4 skin incised lines and meticulous tissue handling and hemostasis were employed throughout.

In the five dogs the knitted tetoron tubes had been inserted and in remaining five

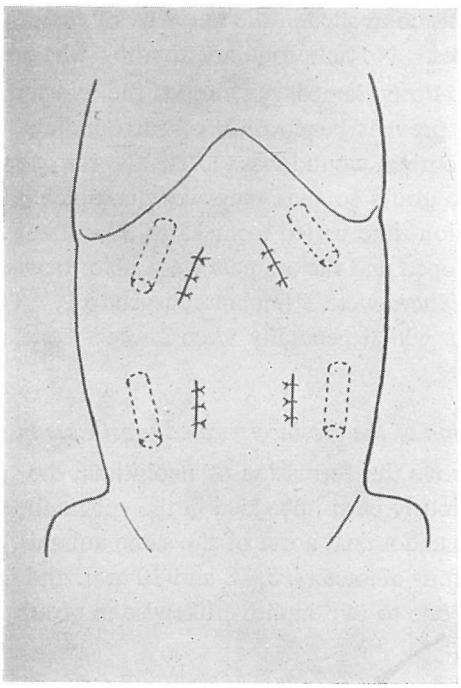


Fig. 2. A diagram to show the sites of subcutaneous insertion of the prostheses.

animals the woven teflon tubes had been introduced.

Comparisons of tissue reaction between the both tubes were performed at each of four intervals of time as follows: 2 weeks, one month, 2 months and 4 months.

Group 2. *Implantation of the prostheses wrapped by polyethylenefim in the abdominal aorta.*—

This experimental group was designed to study participation of the fibrin in the development of neointima. The abdominal aorta was exposed through a left pararectal incision, the intestine was packed into the upper abdomen, with excellent exposure of the aorta resulting, and suitable segment of the aorta from below the renal arteries to above the bifurcation was freed from the retroperitoneal tissues. After the aorta had been dissected out, it was clamped above and below with Potts aortic clamps and divided between the clamps, and then replaced with such isodimensional prostheses as was feasible. The prostheses ranged from 2 to 5cm. in length, with an average length 3.6 cm. Prior to insertion, the porosity of prostheses had preclotted by dipping it in a basin containing 20 cc. of the self blood and allowing blood to coat throughly the outside of it. Continuous over-and-over suture of 5-0 arterial silk was used to construct the anastomosis, the proximal clamp was temporarily released to allow push out of air in the tubes. Bleeding from the suture

line and the porosity was controlled in the majority of cases simply by external pressure for about 5 minutes. No anticoagulant therapy was used in this experiment.

After removal of the Potts clamps we wrapped the inserted prosthesis snugly with a polyethylene-film to prevent penetration of surrounding fibrous tissue into the fabric. Before the abdominal wound was closed, the retroperitoneum was carefully approximated over the grafts so that they were completely surrounded by viable tissues. Aortic occlusion time varied from 15 to 30 minutes. No evidence of hind quarter paralysis developed and the animals were able to walk usually on the 2 to 3 postoperative day. There were 5 implants in group 2. The animals were sacrificed at stated intervals which generally were 2 weeks, one month, 2 months and 4 months postoperatively.

Group 3. *Implantation of the pre-incorporated prostheses in the abdominal aorta.*—

On purpose to improve the formation of neointima, the pre-incorporated prostheses which had previously been imbedded in the subcutaneous tissue were used to replace segment of the abdominal aorta of the same animals. The prosthetic tubes had been prepared in four diameters, 5,6,8 and 10 mm. and inserted in the subcutaneous tissue for about one to two months, likewise in group 1, but without closure at each of the ends.

Thus, the pre-incorporated tubes were firmly affixed in the both external and internal fibrous covering, so that the fibrous tissue capsule could be not easily stripped away from it at the transplantation.

The grafting procedure employed was essentially the same as described in the group 2. In spite of loss of elasticity of the prostheses, the end-to-end anastomoses could be readily made. The pre-clotting procedure was unnecessary, because no significant bleeding from both the suture line and the porosity was permitted at the time of establishing of the blood flow through the prostheses. This group was, however, observed only in short-term up to 2 months after transplantation.

Postoperatively, all dogs in these three groups were received 300,000 units of penicillin and one gram of streptomycin intramuscularly for three days. They were followed carefully for changes in the femoral pulse distal to the prostheses.

At necropsy, each of the implants were examined grossly in its place, then excised with surrounding tissues and placed in 10% formalin. Blocks were embedded in paraffin or celloidin and sections stained with hematoxylin and eosin, with Weigerts elastic tissue stain and with Van Gieson's connective tissue stain for microscopic study.

III. RESULTS

Group 1. *Insertion of the prostheses in the subcutaneous tissue.*—

The two types of synthetic prostheses, namely the knitted tetoron tubes and the woven teflon tubes were compared as regards the fibrous tissue ingrowing through interstices of the fabrics.

The knitted tetoron tubes which had been embedded in the subcutaneous tissue for two weeks revealed granulation tissue covering on its external surface, but this granulation tissue capsule could be easily separated from the fabrics. The inner aspect of the tube showed still the bare fabric.

Microscopic sections were mostly difficult to obtain because of the loose attachment between the fabric and granulation tissue. In a prosthesis which fortunately was possible to examine, there was not yet microscopic evidence of growth of fibrocytes into the cloth.

During the period of observation from one to two months following insertion the surrounding fibrous tissue capsule was firmly adherent to the wall of the prostheses and could be separated only by sharp dissection.

In cutting longitudinally the prostheses the internal surface was entirely lined by smooth, thin, translucent and glistening layer of fibrous tissue (Fig.3).

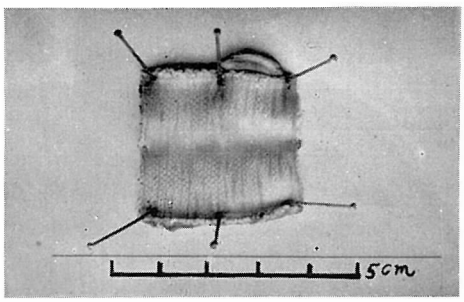


Fig. 3. The knitted tetoron prosthesis removed at 2 months after subcutaneous insertion. A thin, glistening layer of fibrous tissue covers the inner surface; this has been not easily peeled away from the fabric.

It was demonstrated that at the cross section the fabric was penetrated by fibrous tissue, connecting the outer fibrous tissue envelope with a much thinner internal lining (Fig. 4). Microscopically, the internal layer was of thin, hyalinized fibrous tissue and its surface was coated with flatten cells suggestive of fibrocytes (Fig. 5).

This inner layer resembled grossly or microscopically the neointima which was formed inside of the prostheses after replacement of the aorta (Fig. 6). In comparison with findings present in the fibrous tissue capsule at two weeks, by the second month this capsule had become a thin. hyalinized layer of fibrous tissue, in which mild response of inflammatory cells was present only around the strands of yarn. No significant changes were noted in this fibrous tissue covering throughout the ensuing four months. Two grafts showed slight tortion and stenosis for period ranged from two to four months. It is likely that the tubes are distorted on the

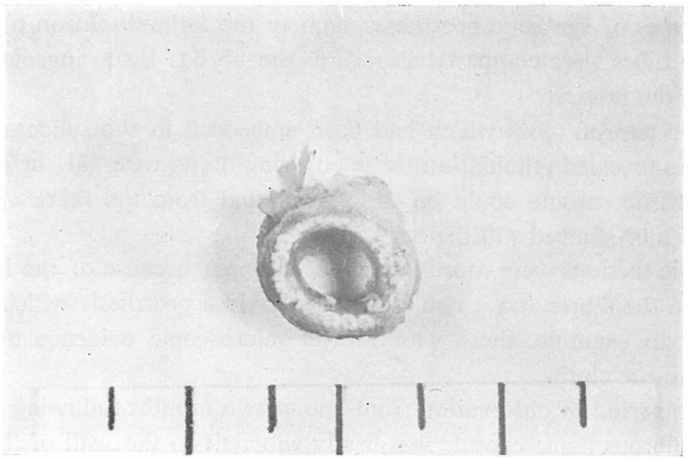


Fig. 4. Cross section of the knitted tetoron prosthesis recovered at 2 months after subcutaneons imbedding. The inner lining consists of fibrous tissue which communicates through the interistces of the prosthesis with a similar fibrous tissue layer on the outside.

activities of the dogs and the lumen becomes gradually narrower due to cicatrical shrinkage. To be sure, it is conceivable that the knitted tetoron prostheses were completely incorporated by the fibrous tissue ingrowing through interstices of the fabrics for about two months.

Although the tightly woven teflon prostheses were entirely covered with a thin coat of fibrous tissue at two weeks after insertion, there was no evidence of growth of fibrous tissue into the interstices of the fabrics, so the prostheses were peeled easily from the coats. These outer capsules were notably thinner compared with those in the knitted tetoron prostheses (Fig. 7). It seems to indicate that the biologic response to teflon fabric in terms of fibroblastic response was minimal. When opened longitudinally the prostheses were not found to be lined by inner layer.

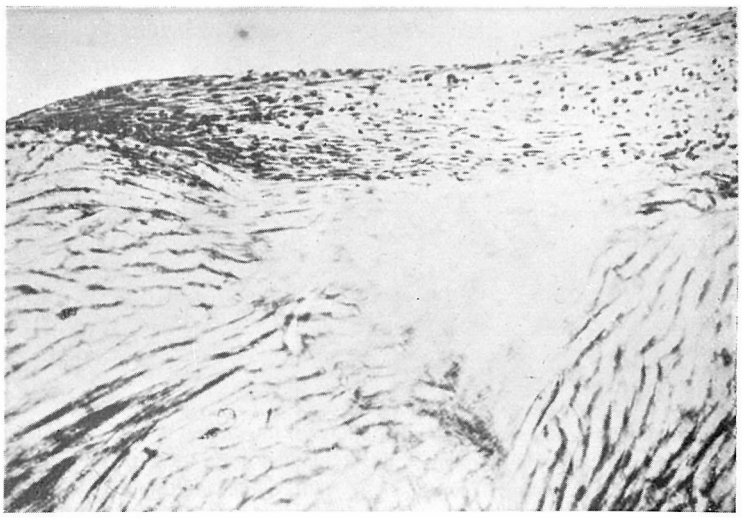
By the end of one month, thin, translucent layer of fibrous tissue had completely covered the outer surface of the cloth, but the inner surface incompletely. Four months after insertion, the inner lining of hyalinized fibrous tissue grew over the luminal surface, but it could be detached from the teflon fabric with ease.

Thus, as indicated from these observation, the tightly woven teflon prostheses were much more slowly and slightly incorporated in surrounding fibrous tissue than the knitted tetoron tubes. The differences of results observed between two types of the prostheses seemed to be concerned with the porosity that provided a scaffold for a host fibrous tissue tube.

Group 2. *Implantation of the prostheses wrapped by polyethylenefilm in the abdominal aorta.*—

Of the five animals involved in this group, there animals remained well until the

(A)



(B)

Fig. 5. Photomicrograph showing the internal layer of the knitted tetoron graft after subcutaneous insertion for one month (A), and for four months (B). Note the internal layer for one month composed of fibrous tissue with mild response of inflammatory cells and the layer for four months showed hyalinization of fibrous tissue.

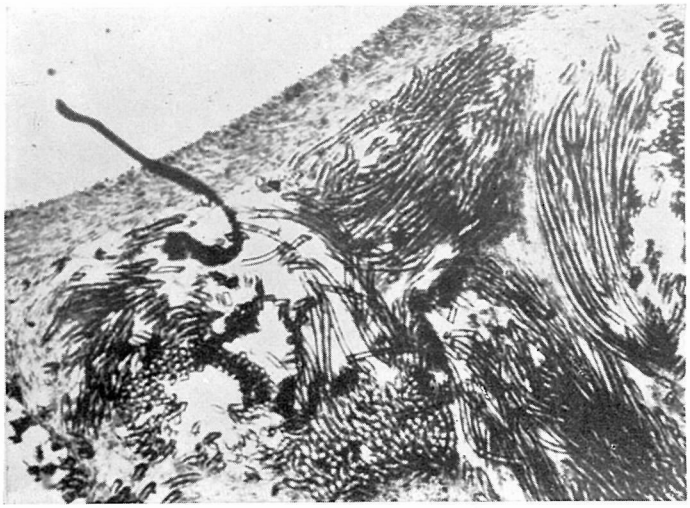


Fig. 6. Photomicrograph showing the neointima of the knitted tetoron prosthesis which was replaced for segment of the abdominal aorta for 2 months. Note a intimal layer consisting of fibrous tissue with cellular infiltration.

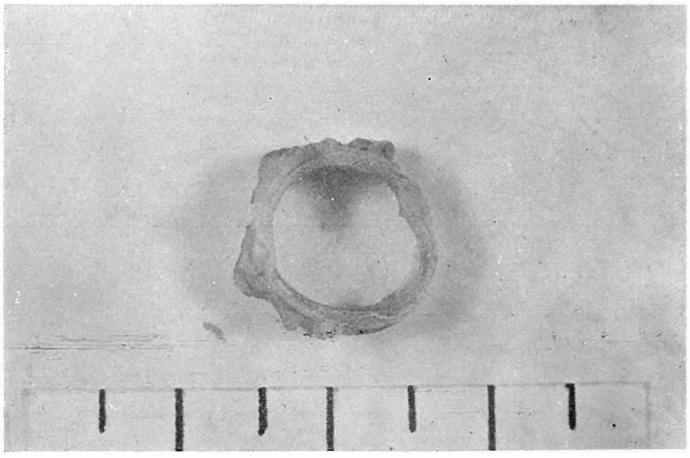


Fig. 7. Cross section of the woven teflon prosthesis 2 weeks post graft. Note the extremely thin layer of fibrous tissue around the prosthesis. The inner aspect exposes mostly a bare fabric.

time of sacrifice. Two dogs could manifest no femoral pulse 30 days after transplantation and showed gradually atrophy of the hind limbs and finally died by the two and three months, respectively. At necropsy, the two grafts were found to be obstructed with mural thrombi and to be filled with partly organized hematoma in the space between the prosthesis and the polyethylene-film. It seemed that the delayed hematoma around the prosthesis caused defective intimal formation which

provided a surface for potential mural thrombus development.

By two weeks, a thick fibrous tissue had coated over the polyethylene-film covering. The polyethylene-film elicited a much greater fibrous tissue response than did the tetoron or teflon prostheses (Fig. 8).

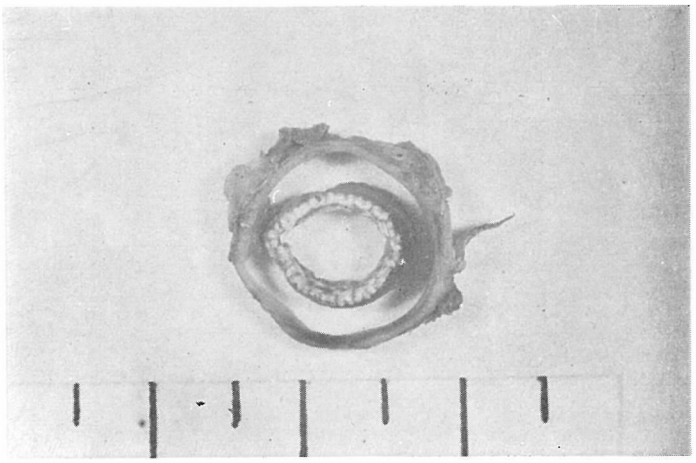


Fig. 8. Cross section of the prosthesis 2 weeks after transplantation. The outer ring is dense fibrous tissue layer and the inner ring is the knitted tetoron tube. The polyethylene-sheet is removed away.

It could be interpreted as representing marked host tissue reaction. In the space between the polyethylene-film and the knitted tetoron prosthesis there was sweating of blood varying in severity from exanguination to hematoma, whereas hematoma around the tightly woven teflon fabric was mostly minimal. Although corrugation on the luminal surface from the crimps were buried with fibrin deposition and generally were smoothed out, remaining area exposed a bare fabric. This fibrinous inner layer elicited neither gross nor microscopic evidence of growth of neointima occurring after implantation of the aorta.

By the one month, the dense fibrous tissue capsule which enclosed the polyethyene-film could be easily stripped away from it.

On microscopic examination, it was not possible to demonstrate penetration of the fibrous tissue through the polyethylene-film into the interstices of prostheses. The internal aspect was lined by a thin layer of fibrin with trapped red cells and leukocytes, which could be easily peeled off.

The remaining dog was sacrificed at the fourth month. Although the activities of the dog was not disturbed and the femoral pulse could be moderately palpable, the graft showed severe stenosis from the mural thrombi (Fig. 9). The mural thrombi affixed to the wall and markedly decreased the inside diameter. The hematoma around the prosthesis became partly organized at this period (Fig. 10).

Fig. 9. Photomicrograph showing the mural thrombus. Note a loss of neointimal lining.

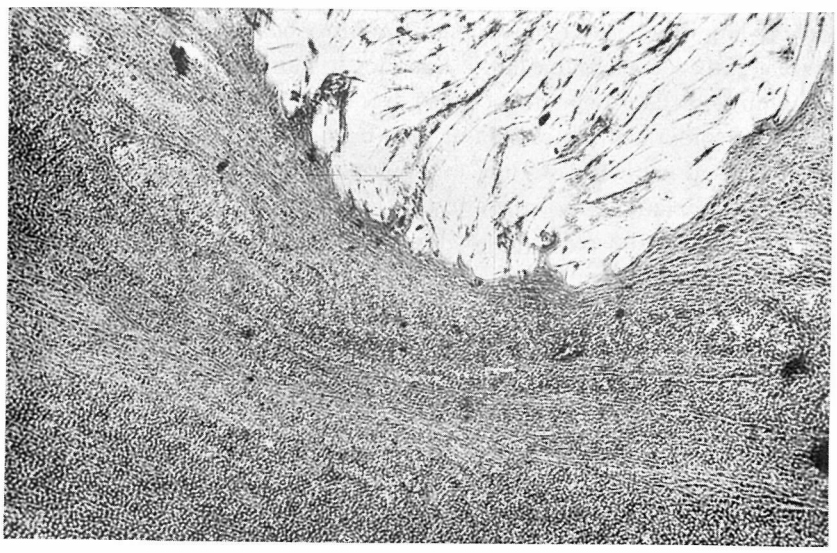


Fig. 10. Photomicrograph showing partly organized hematoma around the knitted tetoron prosthesis. Invasion of fibrous tissue is not revealed.

In these implants avoiding the penetration of fibrous tissue, the fibrin lining could not completely attach to the wall and toward the center of the graft the luminal surface displayed a raw fabric. The prostheses in this group showed no evidence of repair beyond the inner fibrinous coat phase. It was likely that stasis of blood in such defective fibrinous lining might result in thrombus formation.

In conclusion, these observation would indicate that the inpermeable prostheses wrapped by polyethylene-film led to occur delayed hematoma and mural thrombus. Thrombus with complete occlusion of the lumen of the graft had occurred in two animals by the period varied from two to three months.

There were minimal growth of fibrocytes within the mural thrombi adjacent to the suture line, but these fibroblastic proliferation were limited to the immediate vicinity of the suture line.

Group 3. *Implantation of the pre-incorporated prostheses in the abdominal aorta.*—

The most suitable sized prosthesis of the four knitted tetoron tubes which had been imbedded for one to two months were implanted into the abdominal aorta of the same dog. At the time of implantation these prostheses were lined by pseudointima which had the characteristics of hyalinized fibrous tissue. Immediately after implantation, virtually a new vascular conduit has been formed.

By the two weeks, a glistening layer of fibrous tissue had completely covered the inner aspect. Flat, elongated nuclei suggestive of fibrocytes were noted on the surface of the inner fibrous tissue layer and neither hematoma nor mural thrombus was present. Both anastomoses were not stenotic. At the anastomoses, union between the aorta and the prosthesis had taken place by means of dense fibrous connective tissue hyalinized in places. The inner lining contained across the suture line and on to the adjacent endothelial surface of the aorta.

The pre-incorporated prosthesis in one dog functioned as efficient arterial conduits for periods up to two months. The surrounding fibrous connective tissue was firmly adherent to the graft and was stripped with difficulty (Fig. 11).

A mild inflammatory reaction was present in the adjacent fibrous tissue. But the reaction was evident in the area where arterial silk suture material had been used to anastomosis (Fig. 12).

The histologic finding in the pre-incorporated prosthesis as to structural detail was in complete agreement with the finding in the synthetic prostheses formerly reported by numerous authors. It seems that the outer layer of fibrous tissue is the site of tissue reaction which represents the response of the host to the implanted graft.

No degenerative changes of the pre-incorporated graft itself occurred by this period (Fig. 13). It seems to indicate that the nutrition of these pre-incorporated grafts was predominantly dependent on the blood passing through the lumen.

The remaining three animals died within the 48 hours of transplantation. Two

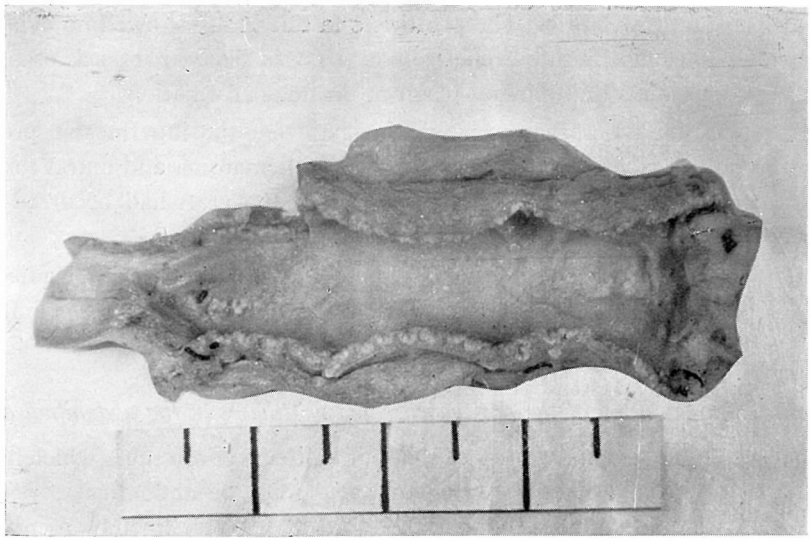


Fig. 11. Photograph showing the pre-incorporated prosthesis at the end of 2 months after transplantation. The inner aspect is coated with a opaque, smooth fibrous lining.

Fig. 12. Photomicrograph showing inflammatory reaction in the area where arterial silk suture material have been used to anastomosis.

Fig. 13. Photomicrograph showing neointimal layer of the pre-incorporated tube after transplantation. Note hyalinized fibrous lining with no mural thrombi.

desths were attributed to excessive blood loss from the sites of anastomoses. The other one may be accounted by a long period of circulatory interruption.

Although not definitely ascertained because there was not yet obtained long-term follow-up, it appeared that in the pre-incorporated tubes the neointima functioned well as aortic replacements.

IV. DISCUSSION

One of the major problems in the field of vascular surgery is the selection of materials for use as a replacement graft. These materials include arterial autografts, homografts and heterografts, autogenous and homologous veins, inorganic materials and recently plastic materials. Although autogenous arterial or venous grafts will retain viability, preserved homografts and heterografts, or synthetic vascular prostheses are nonviable grafts. Viability of grafts is most desirable as a vascular replacements.[3] But the obstacles faced by surgeon is the difficulty in procurement of

suitable autografts. Attempts to solve this problem have been made by authors experimenting with the use of homo-[8,32]and heterografts[32] and concurrent with the development of artificial prostheses of plastics.[2,9]. Fresh homo-and heterografts are all found to be thrombogenic, suggesting an antigenic inflammation to foreign protein. The rationale in the use of lyophilization or alcohol-preservation is based on the presumption that chemical denaturization of the protein fraction and dissolution of lipoproteins with reduce antigenic potentialities.[7,32] Such preserved grafts become completely nonviable. When implanted into a recipient, the nonviable graft serve only as conduit for the flow of blood and as scaffold for ingrowth of the host's fibrous tissue and endothelium.[8,10,42] Such function of the grafts can be similarly obtained with synthetic prostheses. Thus, the preserved homografts and synthetic prostheses have been thought for several years to be the possible substitute for the resected segment of an artery.[7,8,10,15,16]

The major disadvantages of the homografts are degenerative changes in the media.[5,29,31] As the media, particularly of the muscular arteries, contains abundunt tissue protein which causes the host to produce an intense antigenic inflammation, it may be difficult to eliminate the antigenicity.[42]

These disadvantages of the homograft are corrected by the synthetic fabrics, especially teflon and dacron, which are strong enough to withstand the arterial pressure and sufficiently chemically inert to maintain this strength in the tissue fluids for a long period of time.[6,11,-14,20,22]

From a functional standpoint synthetic substitutes appear to be quite as satisfactory as homografts.[1,2,4,9,17,23,30,33,35,37,39,43,44,] The acceptance of these materials by recipient tissue is little different from that observed with homografts,[8,10] that is, both produce a moderate inflammatory reaction and eventually become incorporated into recipient tissue largely by growth of fibrous connective tissue. In general, it has been observed experimentally and clinically that immediately upon establishing blood flow through the prosthesis, a layer of fibrin is deposited along the inner surface of the tube. At the end of one week there is a layer of granulation tissue surrounding the prosthesis and continuous with the adventitia of the recipient vessel. Fibrous tissue organization of both the external and internal coverings of the prosthesis is evident by the end of one month. This process of fibrous tissue organization continues rapidly and by $2\frac{1}{2}$ to 3 months after implantation, connective tissue cells have invaded about three-fourths of the inner lining of the prosthesis. As time goes by, this fibrous connective tissue becomes hyalinized and on the inner surface the cells are flattened, resembling true endothelium. Thus, about 4 months are required to connect the internal and external fibrin deposits into fibrous connective tissue layers on the prosthesis.

In our experimental groups, the process of incorporation by host fibrous tissue is in all respects similar to that.

The results of synthetic prostheses replacing the small vessels or veins, however,

are far from ideal because of a disturbingly high incidence of failures.[3,17,19,27,45] Thus, this experiment was undertaken to study several factors which might influence the results obtained by synthetic prostheses.

On the experimental basis that neointimal layer is consisted of hyalinized fibrous tissue, Dr. S. Ogino of our clinic had deviced a preincorporating procedure which aids to promote development of neointima at a more rapid rate.[36]

The experiment in group 1. set up as a group for purpose of testing the objective that neointimal layer can be formed or not by penetration of fibrous tissue. There is a limit in the tightness of knitted prostheses, because each interlocking stitch is made around a knitting needle and the pores can be made no smaller than the diameter of this small needle.[20,25] Woven fabrics, however, can produce minimum but adequate porosity. In this experiment the tightly woven teflon prostheses were used.

In knitted tetoron tubes with adequate pores there were completely incorporated by host fibrous tissue during early periods, while the tightly woven teflon tubes showed, to a lesser degree, incorporation by the same time. These observation suggest that the porosity of the prosthesis was concerned with formation or maintenance of the inner lining of the graft.

The difference between the both types of prostheses when incorporated, moreover, may be influenced by degree of biological inertness.[24,] Unquestionably, polyethylene-film caused a more dense and abundant fibrous tissue reaction about it. As pointed out by Harrison et al., teflon (tetrafluorethylene) is one of the most inert plastics yet discovered.[24] It has been shown that nylon prostheses from a lining which averages 2 mm. in thickness, while teflon tubes develop a lining 0.5 to 1.0mm. in thickness, dacron and orlon tubes form a lining 1.0 to 2.0 mm. thick. Use of teflon or dacron fabrics could avoid narrowing of lumen from thickend neointima.[26-28]

Therefore, porosity and tissue reactivity should be the cardinal factors in the choice of the ideal synthetic prosthesis.

The experiment in group 2. was designed for the purpose of clarifying participation of fibrin in the development of neointima. The pores of prosthesis was sealed with polyethylene-film to make them impermeable for ingrowing of fibrous tissue. Corrugations of the luminal surface were burried by thin layer of fibrin deposit, when blood flow is established through the graft, but thereafter, there were often detachments of the fibrinous lining and it was unlikely obtain complete neointimal formation. Postoperative thrombi frequently occurred on the area of defective intimal formation. As indicated from this observation, only the fibrin-lining itself may be not so essentially concerned with the maintenance of the neointima.

To our knowledge there has been no investigation that indicates the fate of the pre-incorporated prostheses. At the implantation the pre-incorporated prostheses have already had evidently the luminal covering of hyalinized fibrous tissue, resem-

bling neointimal layer. A superiority of the pre-incorporated prosthesis is suggested by the two successful cases with no failures, e.g. degenerative changes, intramural thrombi and external constriction.

The open framework may permit significant blood loss. This is a disadvantage of any porous type of arterial replacement regardless of construction.[2, 9, 20, 25] Such blood loss is usually combated by preclotting, intermittent reestablishment of blood flow, or treatment of prosthesis with plastic or organic film.[18] Our deviced pre-incorporating procedure could be controlled porosity with hosts own fibrous tissue.

Although most surgeons today have shunned application of the synthetic prostheses to small arteries or veins,[3, 21] these pre-incorporated prostheses seem to be selective substitute for replacing such vessels. The future use of the pre-incorporated prosthesis for longer periods will determine if it is actually superior.

V. SUMMARY AND CONCLUSION

Synthetic prosthesis as substitute for arteries is more desirable than homograft or heterograft, because it incites no degenerative changes that weaken the wall with occasional rupture or obstruct the lumen with resulting thrombosis. However, it has the disadvantage of defective intimal lining which promotes occurrence of mural thrombi by the early or late periods. In this paper the objective whether the fibrous tissue or the fibrin plays a leading role in the development of the neointima was discussed and our deviced pre-incorporated prosthesis was described.

While the synthetic prosthesis inserted in the subcutaneous tissue was incorporated by the host's fibrous tissue and elicited internal layer consisting of hyalinized fibrous tissue resembled the neointima developed after vascular replacement (Group 1), the prosthesis which has been wrapped with polyethylene-film to make it impermeable could not affix to the host's tissue and had defective fibrin lining which caused delayed hematoma and mural thrombus to occur (Group 2).

The assumption that synthetic prosthesis serves as a strut for ingrowth of the fibrous tissue and porosity is essential to allow the fibrous incorporation seems probably correct.

Although our deviced pre-incorporated prosthesis will have await further observation, it is likely that this prosthesis contributes to decrease occurrence of mural thrombi and delayed hematoma.

I am greatly indebted to Dr. Shunsuke Ogino of our clinic for his constant, kind guidance during the course of the present study.

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