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Histological Change in Permanently Clipped or Ligated Cerebral Arterial Wall

Part II: Autopsy Cases of Aneurysmal Neck Clipping

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With 12 Figures

Summary

An investigation was carried out on clinical autopsy cases into histological changes in the vessel wall and into the surrounding tissue reaction after permanent clipping.

1. There were 17 autopsy cases of cerebral aneurysm, which included seven cases treated with the Yaşargil clip, five with the Heifetz clip, and five control cases.

2. Clipping period ranged from 6 days to 11 months. Both the Yaşargil and the Heifetz clips, even with long duration of clipping, caused no changes, and inflammatory reaction was slight.

3. As for the necrosis of the vessel wall beneath the blade, the Yaşargil clip produced marked necrosis at the blade edge in 4 of 7 cases (57%), while the Heifetz clip caused necrosis under the midconvexity of the blades in all 5 cases (100%).

4. The granulation tissue reaction round the clip began to occur after one month, and was enough to embed the blade of the clip after three months. We considered it very unlikely for a slip-out accident to occur after this stage.

5. Formation of mural red thrombus and deposition of fibrin with irregular intimal thickening were noted in the aneurysmal lumen in cases clipped for less than 13 days. After one month the intimal thickening was diffuse, and organized thrombus was noted. After three months or more, the aneurysmal lumen was found to have been filled almost completely by intimal thickening.

Based on the above finding, the optimum condition for temporary and permanent clips was also considered.

Keywords: Aneurysmal clip; permanent clipping; pressure necrosis; reactive granulation.

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Introduction

Some reports of studies of the mechanical properties of the clips used for cerebral aneurysmal neck clipping have already been published. Some studies of the changes which occur in the vessel wall as a result of temporary clipping have also been reported in recent years. But it seems that few investigations have been made so far into the changes that occur in the vessel wall of the aneurysmal neck after permanent clipping or ligation. In this connection we made the experiment which was described in our earlier report, part I, using mongrel adult dogs, on the changes which occur in the vessel wall after application of spring type clips, non-spring type clips, and ligation; and we reached the conclusion that there is a high incidence of necrosis of the vessel wall at the site of clipping or ligation, but at the same time reactive granulation tissue forms round it, and intimal thickening of the adjacent vessels develops to prevent the vessel involved, or the aneurysmal neck, from rupturing.

We undertook a similar investigation involving clinical cases, and took as our subjects clinical autopsy cases that had undergone radical operations on cerebral aneurysms.

Subjects and Methods

The subjects consisted of 17 cases of cerebral aneurysm on which we were able to do autopsies. Seven of them were treated with Yaşargil clips, and the other 5 were treated with Heifetz clips, while the another 5 aneurysmal cases who died without surgery were studied as a control group (Table 1).

Beside these, there was another case in which a Heifetz clip had been applied, but had slipped out later, and this clip was taken out eight years after operation. This case was also taken into consideration in this study.

As for the preoperative condition of the 12 cases that underwent operation and on which autopsy was carried out, it was in many cases relatively serious. Indeed 11 of the 12 cases were grade III or worse in the Hunt and Kosnik classification.

No particular mention is made in this report of the age and sex of the cases examined.

As for the location of the cerebral aneurysm, in seven cases it was on the anterior communicating artery, in six on the internal carotid artery, and in four on the middle cerebral artery.

The cause of death in patients who died after operation was gastrointestinal bleeding in five cases, cerebral angiospasm in two, intracerebral haematoma in two, renal failure in two, sepsis in one, pneumonia in one, and serious subarachnoid haemorrhage due to the rupture of an aneurysm in one; while in the cases which were not operated on, the cause of death was serious subarachnoid haemorrhage in four cases and cerebral angiospasm in one case. The case in which a clip slipped off had internal carotid-posterior communicating junctional aneurysm. This was clipped with a Heifetz clip, and despite confirmation of perfect neck clipping not only by intraoperative inspection but by postoperative angiographic studies, the patient rebled eight years later. Re-examination by

Table 1. *Autopsy Cases of Cerebral Aneurysm*

No.	Age	Sex	Site of aneurysm	Operation	Clip	Cause of death	Time interval after clipping (days)	Preoperative grade (Hunt and Kosnik)
1	44	F	anterior comm. artery	+	Yaşargil	ICH	6	III
2	45	M	anterior comm. artery	+	Yaşargil	angiospasm	6	III
3	44	M	right middle cerebral artery	+	Yaşargil	GI bleeding	9	V
4	50	F	left internal carotid artery	+	Yaşargil	GI bleeding	10	IV
5	56	M	anterior comm. artery	+	Yaşargil	GI bleeding	14	III
6	64	F	anterior comm. artery	+	Yaşargil	pneumonia	68	III
7	59	F	left internal carotid artery	+	Yaşargil	renal failure GI bleeding	343	IV
8	46	M	anterior comm. artery	+	Heifetz	severe SAH	7	IV
9	63	F	left internal carotid artery	+	Heifetz	renal failure GI bleeding	11	III
10	54	F	left internal carotid artery	+	Heifetz	angiospasm	13	III
11	39	M	anterior comm. artery	+	Heifetz	ICH	30	II
12	53	M	right middle cerebral artery	+	Heifetz	sepsis	31	III
13 *	73	F	right internal carotid artery	—		severe SAH		
14 *	55	M	left middle cerebral artery	—		severe SAH		
15 *	42	M	anterior comm. artery	—		severe SAH		
16 *	71	F	left internal carotid artery	—		angiospasm		
17 *	56	F	right middle cerebral artery	—		severe SAH		

ICH: intracerebral haematoma.
GI bleeding: gastro-intestinal bleeding.
SAH: subarachnoid haemorrhage.
*: control cases.

carotid angiography revealed that the clip had slipped off the aneurysmal neck, and the aneurysm was seen (Fig. 1). According to the operative findings, the Heifetz clip was located *outside* and below the cerebral aneurysm and was completely embedded in granulation tissue (Figs. 2 A and B).

The post-clipping period in the patients who died after operation ranged from 6 days at the shortest to 11 months at the longest. We made the study of the passage of time by dividing the cases into 4 groups; those who died within 7 days, those within 14 days, those within one month, and those within on year (Table 2).

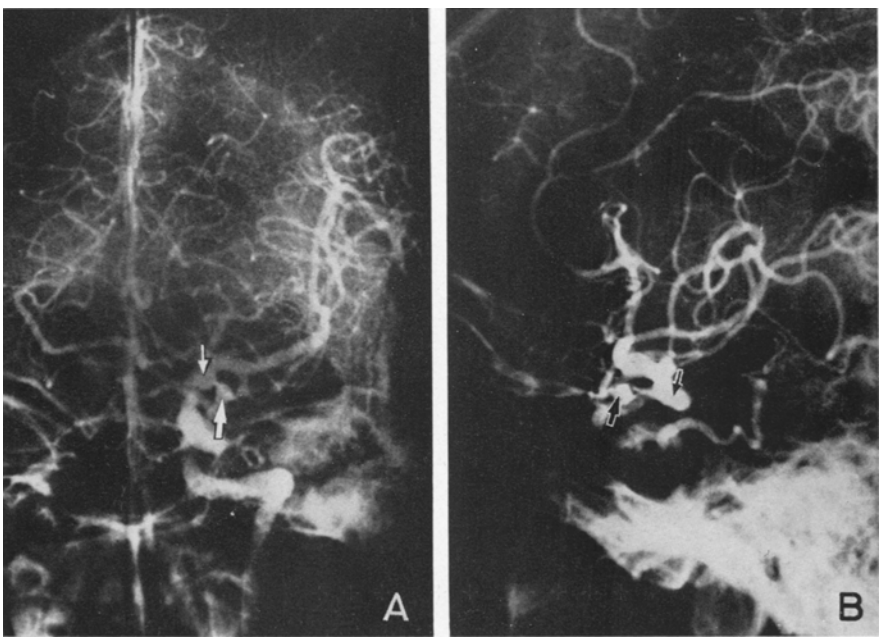

Fig. 1. Left carotid angiograms eight years after neck clipping of the aneurysm with the Heifetz clip, showing a persistent internal carotid-posterior communicating junctional aneurysm due to a slipping of the clip. *A* A-P view, *B* lateral view, small arrows: aneurysm, larger arrows: clip

Table 2. *Number of Autopsy Cases for Each Group*

Procedure	Time interval *				
	— 7 days	— 14 days	— 1 month	— 1 year	Total
Yaşargil clip	2	3	0	2	7
Heifetz clip	1	2	2	0	5
Control ** 5					5

* Time interval after aneurysm neck clipping.
** Non-operated ruptured aneurysm cases.

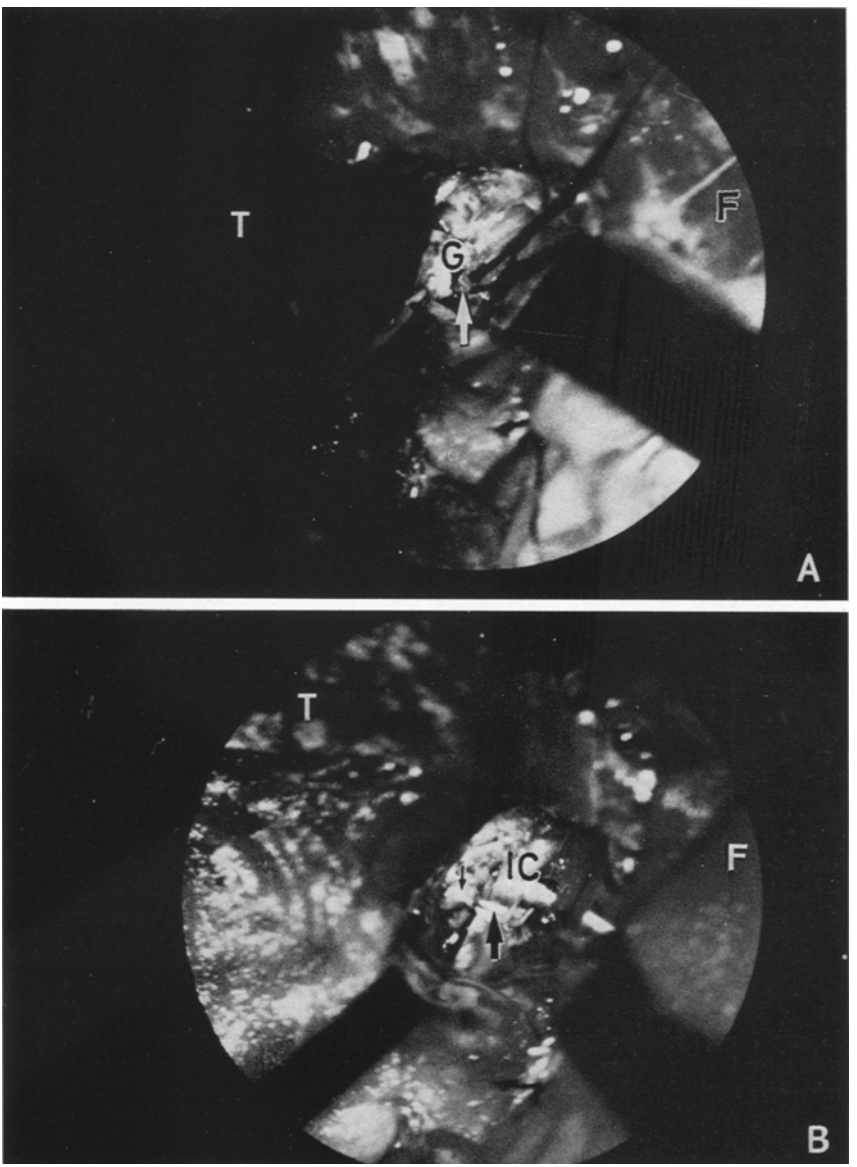

Fig. 2. A. The slipped clip was found buried in granulation tissue at the second operation. B. Aneurysm neck was clipped again with a Sugita clip at the second operation. Small arrow: aneurysm, *G* granulation, white arrow: Heifetz clip, black arrow: Sugita clip, *IC* internal carotid artery, *T* temporal lobe, *F* frontal lobe

The details of how the specimens and slices were prepared will be omitted to avoid duplication, as these are described in part I of this report. These slices were stained by haematoxylin-eosin method (referred to as HE stain hereafter), Masson-trichrome method (referred to as MT stain hereafter), Azan-Mallory method (referred to as AZ stain hereafter), and elastica-van Gieson method (referred to as EvG stain hereafter), and were observed under a light microscope. Moreover,

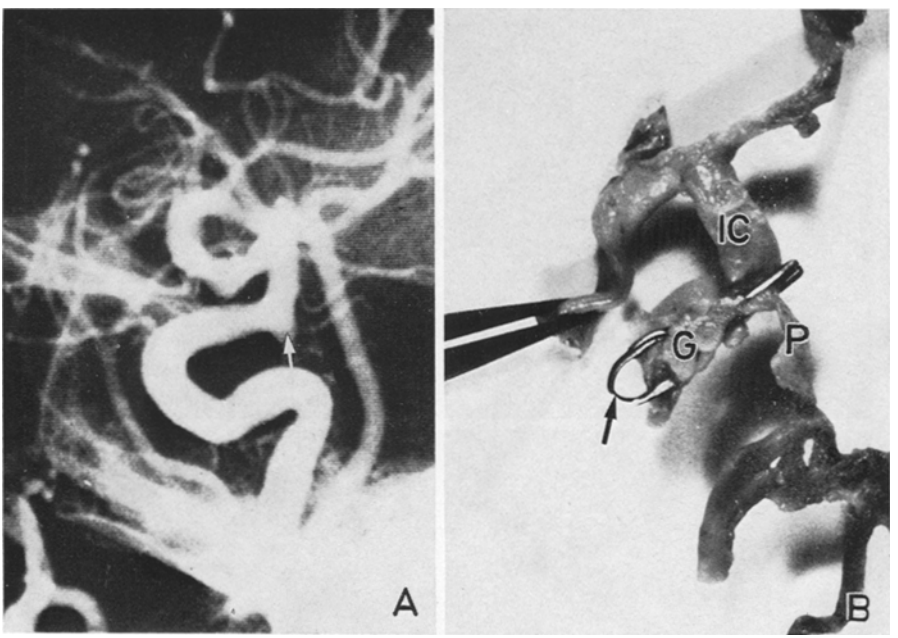

Fig. 3. A. Preoperative left carotid angiogram demonstrating a left internal carotid-posterior communicating junctional aneurysm (case 7). B. Autopsy findings 11 months after operation. Granulation tissue response round the Yaşargil clip was noticed without any change of the clip metal itself. White arrow: aneurysm, black arrow: Yaşargil clip, *G* granulation, *IC* internal carotid artery, *P* posterior communicating artery

in case 7 whose post-clipping period spanned 11 months, the observation of the aneurysmal neck surface at the clipping site was made under a scanning electronic microscope.

Results

1. Macroscopic Findings

As for the clip itself, the surface appearance was quite unchanged both in the case of the Yaşargil clip taken out at autopsy after 11 months and in the case of the Heifetz clip which was taken out after 8 years.

In all cases, the vessel walls just beneath the clip blade were thinned to the point of having become translucent, and the inside pattern of the blade was clearly imprinted on the vessel walls.

In cases which survived for one month or more, granulation formation was noted round the clip, and in case 7 that survived 11 months the clip was covered with granulation tissue to the extent that it was difficult to remove it (Figs. 3 A and B).

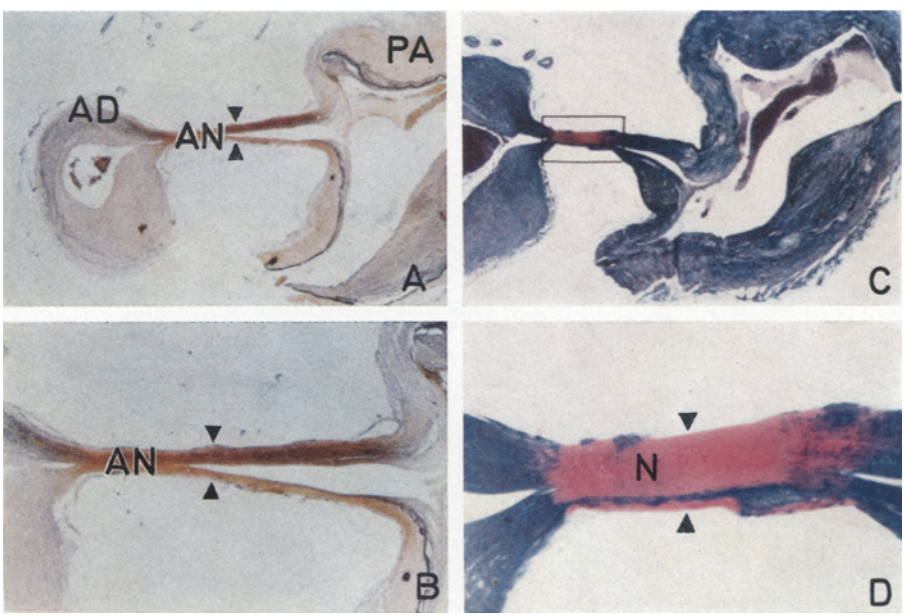

Fig. 4. Necrosis of the arterial wall was found most markedly at the edges of the blades of the aneurysm clip in the Yaşargil clip group (A: EvG ×20, B: EvG ×49, C: MT ×100). ▲: places of clip blades, □: magnifying part, *AD* aneurysm dome, *AN* aneurysm neck, *PA* parent artery, *N* necrosis

2. Microscopic Findings

The histological findings concerning the part of the vessel wall just beneath the blade, at the clipping site, revealed no difference between the Yaşargil and the Heifetz clips. In both cases necrosis, the disappearance of nuclei, homogenization, and loss of structure were most commonly noted, and the vessel wall was shown as pink in HE stain, pale yellow in EvG stain, and bright red with clear demarcation in MT stain. However, some difference between the effects of the two clips was noted at the site of necrosis and also in the correlation between the necrosis and the duration of clipping.

Because the edge of the blade of the Yaşargil clip is right angled, it damages the vessel wall considerably. Marked necrosis at the site of the edge was seen in 4 out of 7 cases (57%) (Fig. 4). The degree of necrosis, granulation, and cell infiltration was evaluated on a similar grading to that described in part I of this report, the correlation between the necrosis and the duration of clipping was noted, and it was shown that it increased with the passage of time ($P < 0.05$, $R = 0.842777$) (Fig. 5).

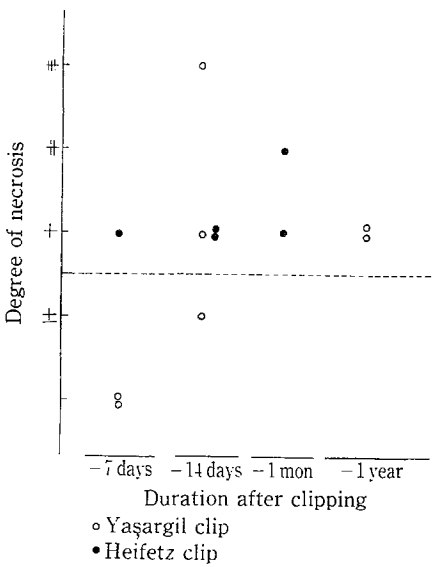

Fig. 5. The relation between the degree of arterial necrosis and the time interval after the clipping. All cases with the Heifetz clip showed necrotic change. In the Yaşargil clip group, necrosis was found after 10 days

However, in the case of the Heifetz clip, almost no damage to the aneurysmal neck was seen to have been caused by its edge, because the cross section of the blade is oval and mildly convex at the vessel side, but in all of the five cases localized necrosis was noted in the part beneath the central convex part of the blade (Fig. 6).

No correlation was noted in the case of the Heifetz clip between the degree of necrosis and the passage of time. Even in the case of a short clipping period of only six days, necrosis was already marked. The conclusion was that the Heifetz clip can cause necrosis more readily than the Yaşargil clip.

At the aneurysmal neck in the control group there were no findings of necrosis at all, but thinning and fragmentation of the

internal elastic lamina were noted. Smooth muscle cell were either remarkably decreased or quite absent, presenting the structure of "true cerebral aneurysm".

The granulation tissue reaction round the clip was observed in the cases which had been clipped for one month or more, in accordance with the results of the animal experiment described in part I

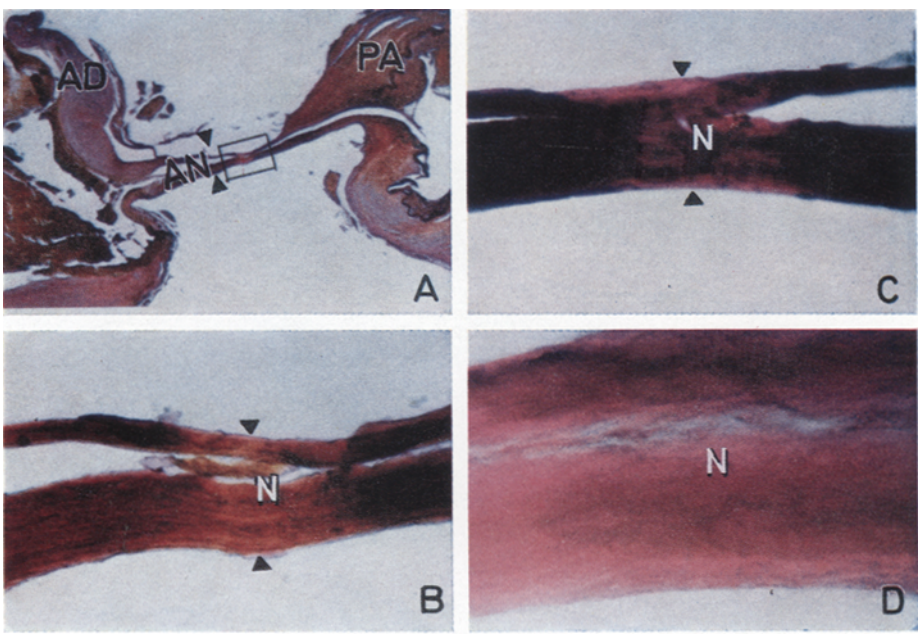

Fig. 6. Necrosis of the arterial wall was found most markedly at the centre of the inside convexity of the blade in the Heifetz clip group (A: EvG ×20, B: EvG ×100, C: MT ×100, D: HE ×200). ▲: places of clip blades, □: magnifying part, *AD* aneurysm dome, *AN* aneurysm neck, *PA* parent artery, *N* necrosis

of the report (Fig. 7). The granulation tissue was constructed of fibroblast and collagen fibres which originated from the adventita round the clip. The degree of granulation formation was also divided into five grades for evaluation, and reviewed in relation with the passage of time. Correlation between them existed ($P < 0.01$, $R = 0.906692$) (Fig. 8).

No difference in the degree of granulation tissue reaction was noted between the Heifetz and the Yaşargil clips. No granulation tissue reaction was found in the surrounding area of the untreated aneurysmal neck in the control group.

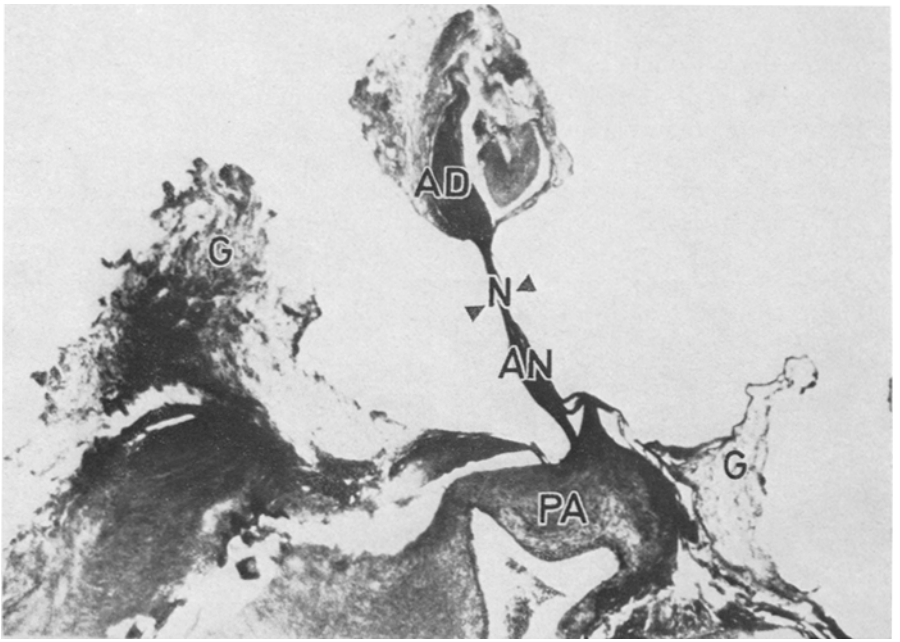

Fig. 7. Two month after the procedure (case 6), reactive granulation tissue was observed around the clip. It originated from fibroblasts of the adventitia near the clip. The aneurysm cavity was occluded almost completely by the intimal proliferation and thrombus (EvG ×20). ▲: places of clip blades: *AD* aneurysm dome, *AN* aneurysm neck, *G* granulation, *N* necrosis, *PA* parent artery

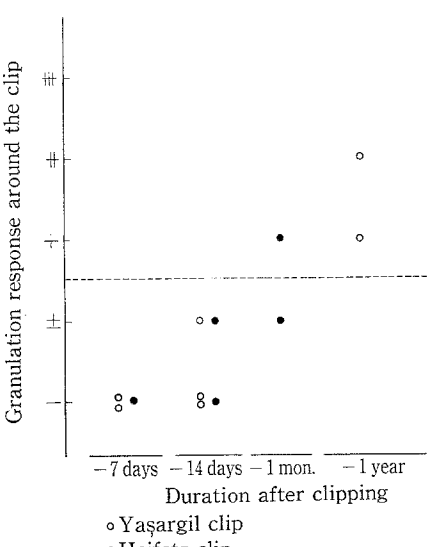

Fig. 8. The relation between granulation response round the clip and the time interval after the clipping. The degree of the granulation reaction was proportional to the time interval after the clipping

The cell infiltration round the clip, which was a foreign body, was slight with both the Heifetz and the Yaşargil clips, and almost no difference was noted in the degree of the cell infiltration between the two clips (Fig. 9). Also in the control group there was little cell infiltration round the aneurysmal neck.

In both the control and operation cases, there were marked arteriosclerotic changes in the vessel walls adjacent the clipping site such as intimal thickening, decrease of smooth muscle cells, atrophy,

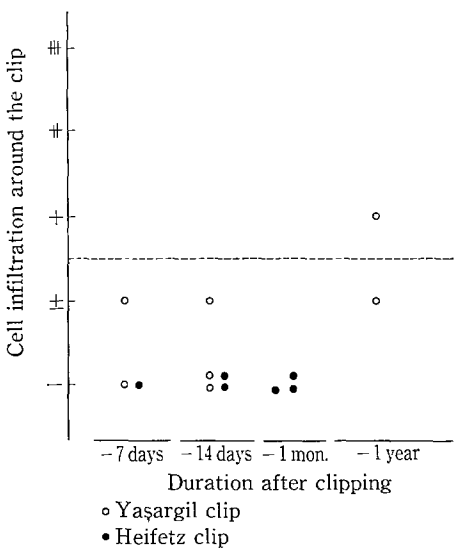

Fig. 9. The relation between cell infiltration round the clip and the time interval after the clipping. Almost no cell infiltration in either group

fibrosis, and fat deposit, making it impossible to evaluate the effect of clipping.

At the marginal part of the aneurysmal neck were generally seen thinning, fragmentation of the internal elastic lamina, decrease or absence of smooth muscle cells, and a saccular appearance.

The walls of the aneurysmal bodies in the control group showed a combination of irregular thickening and thinning of the tunica interna, and the lumina were filled with blood. In the operation group, on the other hand, the intimal thickening was irregular, and mural thrombus with the presence of fibrin was seen in cases treated within the previous two weeks. In the cases of more than one month's duration, the aneurysmal lumina had diffuse intimal thickening and organized thrombus (Fig. 7), and in the cases of three months

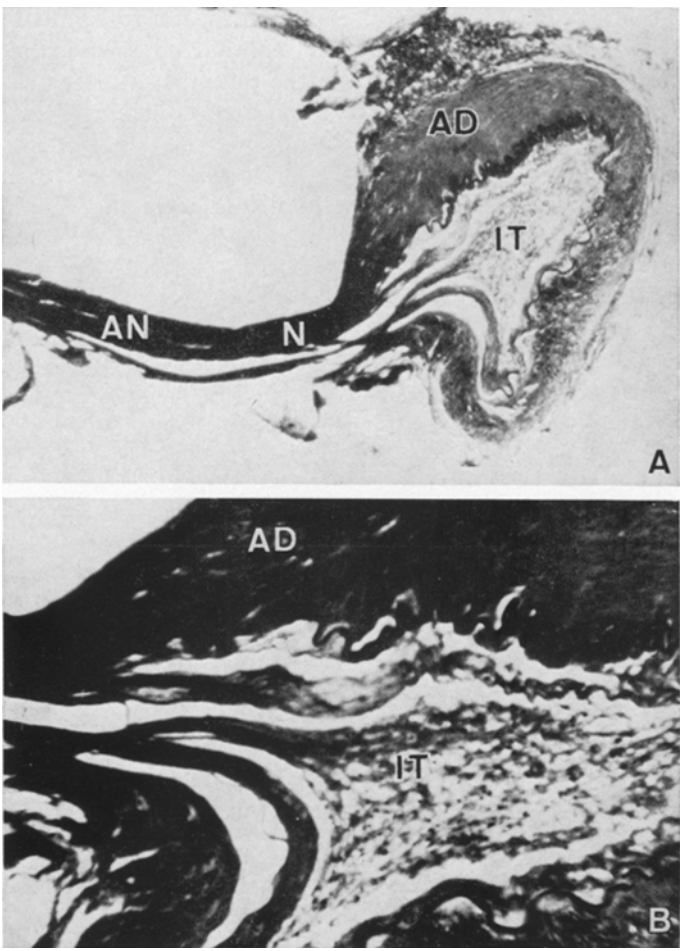

Fig. 10. Same case as Fig. 3. The aneurysm cavity was completely occluded by intimal thickening, and the clipped segment of the arterial wall showed necrotic change (A: MT ×20, B: MT ×40). *AD* aneurysm dome, *AN* aneurysm neck, *PA* parent artery, *N* necrosis, *IT* intimal thickening

or more, the lumina had been almost completely obstructed, with remarkable intimal thickening (Fig. 10).

Observation under a scanning electronic microscope of the clipping site of the aneurysmal neck in case 7 disclosed that the surface of the adventitia beneath the clip blade was undulated, corresponding to the serration pattern of the inside face of the blade (Figs. 11 A and B); the adventitia cells had been destroyed, and their surface structure had disappeared (Figs. 11 C and D). In the cross-section

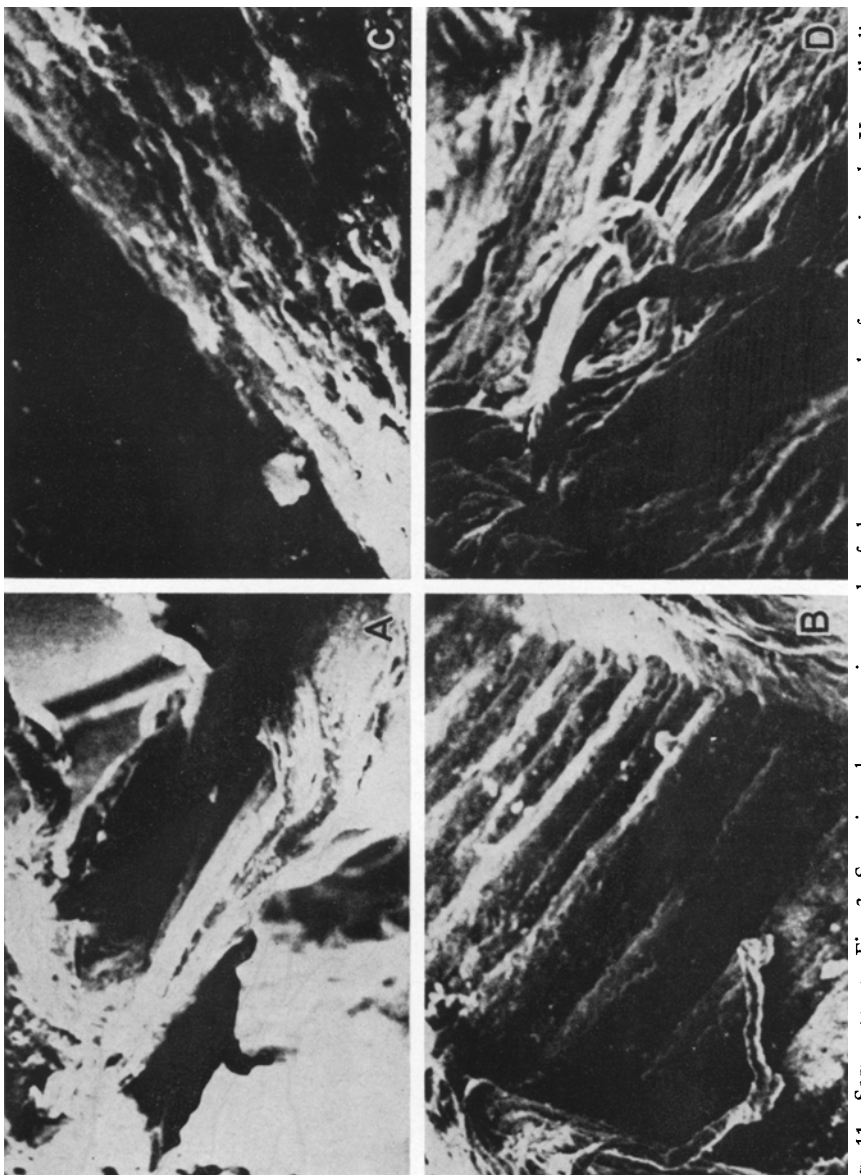

Fig. 11. Same case as Fig. 3. Scanning electron micrograph of the aneurysm neck after removing the Yaşargil clip. A step-wise compression of the arterial wall secondary to markings of the clip blade was evident (A, B). Flattening of the adventitial folds and disappearance of adventitial cellular structure were also shown (B, C, D). The adventitial layer changed into an amorphous structure (C) (A: cross-section view of clipped portion, ×50, B: surface view of clipped portion, ×60, C: surface structure under the clip, ×400, D: under the blade edge, ×100)

of the clipping site, the three-layer structure of the vessel wall had disappeared, changing to a cord lumen in agreement with the light microscopic finding (Fig. 11 A).

Discussion

Neck clipping is the method which Dandy first successfully used in 1937 [3]. It has been believed to be an ideal radical operative procedure for cerebral aneurysm because it most effectively prevents recurrence of bleeding and it does not sacrifice the blood circulation of the parent artery. However, recently, many cases of recurrent bleeding or of enlargement of the aneurysm as the result of slipping or breaking of clips have been reported [5, 7, 9, 19, 21], and so the safety and sureness of the method is less than absolute. Therefore, we considered that a review of the optimum condition of the clip, taking into account changes that occur on the vessel wall, had become necessary.

The Yaşargil clip and the Heifetz clip are the clips generally used. The Yaşargil clip [26] is made of 316 stainless steel; its closing force at the centre of the blade measures 170–240 g, and it is one of the most powerful clips in current use [4]. The width of the blade is 1.25 mm, which is relatively narrow, the inside face is flat, and the edge is right-angled. The Heifetz clip [13], on the other hand, is made of 17-7 PH stainless steel, its closing force measures 110–130 g at the centre of the blade, and compared with other permanent clips its closing force is weak; its blade is wide, and measures 1.5 mm. The cross-section of the blade is slightly curved and convex at the centre of its inner surface, which has a serration pattern for the purpose of preventing slip.

In this study, with the Yaşargil clip necrosis of the vessel wall was seen to occur over the whole area in contact with the blade and especially at the edge; and in the case of the Heifetz clip marked necrosis, localized at the centre of the blade, tended to occur. Contrary to expectations, a higher degree and frequency of necrosis was observed in the case of the Heifetz clip even though its spring force is less than half as strong as that of the Yaşargil clip. This suggests that the broadness of the blade of the Heifetz clip, which readily causes trophic disturbance at the centre, and the morphological factor of the blade which concentrates the closing force at the centre of the inside convexity of the blade, are important; while the Yaşargil clip has a blade whose inside face is flat and therefore spreads the closing force evenly. In other words, we came to believe that not only the strength of the spring but also the closing force per unit area, determined by the shape of the blade, are the important factors.

We attempted to determine the minimum necessary closing force of a clip by the following calculation [6, 20]. Three hundred mm Hg, an exceptionally high figure, was taken as the highest reading for blood pressure of the intracranial internal carotid artery, and Laplace's principle or $P = BP \times W \times \frac{\pi D}{2}$ (where P = necessary closing force, BP = blood pressure, W = width, and D = diameter of vessel) was used, and it was reckoned that the minimum necessary closing force P will be 39 g for the Heifetz clip #659-105, whose blade is 0.15 cm wide, with the vessel diameter of the internal carotid artery being taken as 0.4 cm. In the case of the Yaşargil clip #FD 501 with W = 0.125 cm and vessel diameter, D = 0.4 cm, a figure for P of approximately 32 g will be obtained.

For the calculation of the closing force per unit area of the blade of the two clips, we actually measured the closing forces over the inside face of the blade, from the tip to base at 0.5 mm intervals. By approximately integrating the figures obtained above and dividing them by the areas of the blade in contact with the vessel wall, we found a figure for the closing force of 98 g/cm^2 in the case of the Heifetz clip (assuming that the inside face of the clip is flat, which it is not) and 171 g/cm^2 in the case of the Yaşargil clip. These figures are obvoiusly larger than the minimum necessary closing force previously found, and thus we can conclude that the clips have sufficient closing force. In actual fact, however, the inside face of the blade of the Heifetz clip is convex and, if the width over which necrosis was produced is taken as the effective contact width, it is 0.015 cm. From this figure the closing force per unit area was found to be as much as about 985 g/cm^2! This means that a very strong pressure is brought about to bear locally. We presumed that this is the reason why the Heifetz clip produces more necrosis than the Yaşargil clip. On the other hand, however, the small contact area means that the frictional resistance is also small; and it is one of the characteristics of the spring clip that the closing force gradually diminishes towards the tip of the blade. These, and several other unknown factors, are thought to be involved in the occurrence of slipping.

Drake [6] described a case in which the first bleeding was from a rupture of the aneurysmal fundus, but the recurrence of bleeding occurred at the clipping site. Our investigation also revealed that clipping could produce necrosis quite easily. It is quite possible that, if the slip of the clip happens after necrosis of the vessel wall and fragmentation of tunica media have occurred, and before the completion of granulation formation, a massive haemorrhage will result

in this fragile area. Servo *et al.* [21] reported a middle cerebral artery aneurysm that was supposed to have been clipped but enlarged because of breakage of the blade of the Heifetz clip on the proximal side. In the report, the broken clip was described as having been embedded in the granulation tissue so tightly that it could not be taken out. This seems to be the same tissue reaction as occurred in the case of slipping described in this paper.

On the other hand, Quest *et al.* [19] reported a case in which the aneurysm vanished despite the breakage of a clip. Neck-clipping of an internal carotid artery-posterior communicating junction aneurysm was carried out, and angiography after four months confirmed the disappearance of the aneurysm and a normal condition of the clip. However, angiography after 10 months revealed that one of the blades of the clip had broken on the proximal side and was wide open, and yet the aneurysm had completely vanished. From the result of our study it is presumed that in this case, at the time when the clip broke, the filling of the aneurysmal lumen or the blocking of the aneurysmal neck had been completed by intimal thickening, and thus the aneurysm was not shown by the angiogram. That is to say, at this stage, even if the clip is broken, the possibility of renewed bleeding must be very slight.

It is presumed that many of the slipping accidents occur when a clip which is unsuitable for the particular shape of the aneurysmal neck is employed. Fink *et al.* [10] said that the size of the aneurysm should be taken into consideration in selecting a proper clip because a stronger closing force is required in order to make sure that the vessel remains closed, even if there is an increase in the diameter of the vessel and a rise in its internal pressure. Rosenbaum [20], who investigated nine kinds of aneurysmal clip including the Yaşargil clip, states specifically that the miniature Mayfield clip is suitable for a small aneurysm with a thin wall, the McFadden clip is suitable for a large aneurysm with a thick wall and broad neck, the Drake clip is suitable for a basilar aneurysm, etc. In addition he emphasized that because he had neither experienced nor seen any report of necrosis caused by the strength of a clip resulting in renewed bleeding at the clipping site, a clip with strong closing force should be used for the aneurysm with a broad neck and thick walls, in which slipping accidents occur relatively often.

Few existing clips have been distinguished as being specifically for permanent or temporary use. In many cases, the Heifetz clip, the Scoville clip, or the Mayfield clip, each of which has a relatively weak spring, is used for temporary use. According to Alexander *et al.* [1], however, the Mayfield clip used in one case for a temporary

purpose caused, by its edge, fragmentation of the tunica media of the vessel wall, and even formation of another aneurysm. Dujovny *et al.*[6] noted that only 45 minutes' application of the Mayfield, Heifetz, Khodadad, and other clips that were usually used for temporary purposes had produced marked intimal fragmentation and other histological changes along the edge of the clip, while in a case in which a long period of observation followed the release of the temporary clip he noted localized ballooning associated with fragmentation of the tunica media. These reports suggest that even in the temporary use of spring type clips there remain problems.

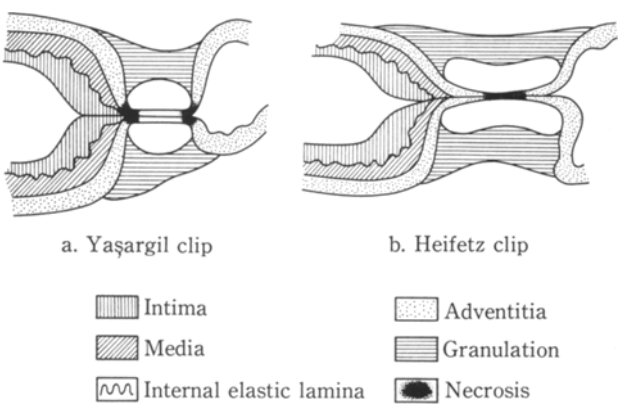

Fig. 12. Conclusive schematic illustration of the histopathological findings of this study (*a* Yaşargil clip group, *b* Heifetz clip group)

Taking into account both the present investigation of the direct histological changes of the vessel wall brought about by permanent clips conducted both experimentally and clinically and the reports by various authors on the damage to the vessel caused by temporary clips, the optimum conditions for the clip for temporary use can be listed as follows: minimum closing pressure compatible with resistance to blood pressure; blades that are wide and have a large contact area in order to reduce the pressure per unit area; an inside face to the blade which is flat and free from irregularities and unevenness so that the closing force can be applied uniformly; a blade whose edge should be round to eliminate shearing action and which is provided with some form of cushion on its inside so that the hard metal of the blade does not directly touch the vessel. Needless to say, other requirements for this sort of clip should include; ease in application and removal, light weight, and small size for the sake of good visual field for operation. Although there are some clips that have been

developed exclusively for temporary purposes [2, 18, 25], the undesirable effects they have on the vessel wall cannot be disregarded [6, 12, 14, 22, 24].

For the permanent clip, on the other hand, the surrounding granulation tissue and intimal thickening are useful, as earlier described, as reinforcing and reparative factors unless slipping occurs early, even if the clipping site becomes necrotic and broken (Fig. 12). Thus the clip for this purpose is required to have a sufficiently powerful closing force; relatively narrow blades to allow insertion in a narrow space; blades with round edges and with an opening angle wide enough to make possible clipping of a broad aneurysmal neck; material which does not break and which induces little biological reaction; a small clip head which does not obstruct the visual field at operation. The serration pattern of the inside of the blade is considered useful for the permanent clip, because it provides positive grip of the vessel wall and helps prevent slipping.

As for the silver clip, the histological study described in Part I of the report revealed it to be productive of very marked inflammatory reaction. The clip itself is highly corrosive and turns black. Thus we condemned silver as unsuitable for the material of a clip. Stainless steel remained quite unchanged in appearance, as earlier mentioned, even after eight years and more, and caused little inflammatory reaction. Various authors [8, 11, 16, 17] reported similar findings, and it seems that stainless steel and tantalum are the best for the clip material. In some reports titanium [15] was recommended, as it gave little artefact in the CT which had been widely used in recent years for postoperative examination. Other considerations for suitability for the clip include spring with superior spring characteristics, free from fatigue; ease and accuracy in application and removal; no shearing action near the end of the clip blade.

There was obvious difference between temporary and permanent clips in their requirements, and it appeared that sustained development of the types of clips which meet the various needs is necessary.

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