Is vasospasm related to proliferative arteriopathy?

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Although proliferative arteriopathy has been postulated to play a role in the etiology of vasospasm after subarachnoid hemorrhage (SAH), histological and morphological studies examining cerebral vasospasm have produced conflicting results. To help settle this controversy, the authors used an in vivo label of cell division, bromodeoxyuridine, to assess cell proliferation in a primate model of SAH. Fifteen cynomolgus monkeys received a clot of either whole blood (11 animals) or red blood cells (four animals) placed around the right middle cerebral artery (MCA). On the day of surgery continuous intravenous infusion of bromodeoxyuridine was begun and continued until the animal was sacrificed immediately after arteriography on Day 7, 12, or 27 following surgery. Sections from the right and left MCA's were stained with a monoclonal antibody against bromodeoxyuridine, and labeled cells were counted.

Arteriographic evidence of vasospasm occurred in nine monkeys on Day 7. On Day 12 and Day 27 no monkeys had persistent vasospasm. Placement of subarachnoid clot around the right MCA increased proliferative activity across all layers of the arterial wall. Most of the labeled cells were in the adventitia and the endothelium. Although there were more dividing cells in all layers of the right MCA than the left MCA (p < 0.01), the number of stained cells per section was limited (range 0.1 to 21.2, mean 8) and the occurrence of vasospasm was not associated with the number of dividing cells in the right MCA on Day 7, 12, 27, or for all days combined (p > 0.6).

Cerebral vasospasm after SAH was not associated with the extent of proliferation of cells in the vessel wall, nor could the intensity of the limited proliferative changes have been responsible for narrowing of the vessel diameter.

Key Words • subarachnoid hemorrhage • cerebral vasospasm • bromodeoxyuridine • cynomolgus monkey

The basic mechanisms involved in delayed spasm of cerebral arteries after subarachnoid hemorrhage (SAH) remain poorly understood. A tenuous consensus now exists that the etiology of vasospasm is multifactorial. Because of the delayed occurrence of vasospasm, its persistence, and the unresponsiveness to dilatory drugs, and the structural changes in the artery after SAH, several investigators attribute the diminished luminal diameter of involved vessels to thickening of the vessel wall. Some have concluded that proliferative arteriopathy, rather than active vasoconstriction, produces delayed vasospasm. However, the conclusions of these prior studies were based only on assessment of morphological changes in the vessel after SAH.

Until recently, autoradiography, using tritiated thymidine, was the only well-established method for in vivo labeling of dividing cells. In 1982, Gratzner described a new method for detecting dividing cells in vivo using bromodeoxyuridine, an analog of thymidine which is incorporated into deoxyribonucleic acid during the S phase of mitosis. Bromodeoxyuridine uptake is demonstrated histologically by immunohistochemistry with a specific monoclonal antibody. Bromodeoxyuridine is a more soluble analog of bromodeoxyuridine now used in in vivo labeling studies.

To test the hypothesis that vasospasm is caused by proliferative arteriopathy, we used continuous intravenous infusion of bromodeoxyuridine to detect and quantify proliferation of the cells of the vessel wall.

Materials and Methods

Study Protocol

The protocol for this study was reviewed by the National Institute of Neurological Disorders and Stroke "Animal Care and Use Committee" and met National Institutes of Health guidelines for animal care.

We employed a primate model of SAH in which
Proliferative arteriopathy in vasospasm

Precollotted blood was placed around the exposed right middle cerebral artery (MCA).10 For this study we used 15 cynomolgus monkeys (10 males and five females), each weighing 2.3 to 5.8 kg (mean ± standard error of the mean, 4.1 ± 1.3 kg). Each animal underwent placement of either whole blood (11 animals) or red blood cells (RBC, four animals) suspended in an artificial collagen clot around the proximal portion of the right MCA. A subcutaneous micro-osmotic pump* was implanted simultaneously for continuous intravenous infusion of bromodeoxycytidine. We initially examined the utility of this method for labeling proliferating smooth-muscle cells in a pilot study, which demonstrated staining of endothelial, smooth-muscle, and adventitial cells in the rat common carotid artery after traumatic damage.

Surgical Procedure

Generally, the procedure was the same as that described previously.10 Before surgery the monkeys received atropine sulfate (0.05 mg/kg), sodium thiopental (25 mg/kg), dexamethasone (0.7 mg/kg), cefazolin (500 mg), and ketamine (10 mg/kg). They were intubated and ventilated with N₂O/O₂ (1:1), and 0.5% to 1% isoflurane was used as the anesthetic agent. The expired Pco₂ level was maintained at approximately 40 mm Hg by ventilatory control and confirmed by arterial blood gases. A micro-osmotic pump was buried subcutaneously in the back of the animal. A right fronto-temporal craniotomy was then performed under aseptic conditions and the arachnoid over the proximal portion of the MCA and bifurcation of the internal carotid artery (ICA) was sharply opened. Then, 5 ml of either whole blood or RBC in a collagen clot was placed around the right MCA (JK Morgan, et al., unpublished data). After the craniotomy was complete, the cathether from the pump was inserted into the external jugular vein. The pump contained 340 mg of bromodeoxycytidine dissolved in 2 ml of normal saline for continuous intravenous infusion of 48 mg/day (about 12 mg/kg/day) for 1 week. The delivered dose per kilogram was 10 times higher than the dose sufficient for staining dividing cells in traumatized peripheral arteries in the pilot study in rats. To provide continuous exposure to bromodeoxycytidine until sacrifice, the infusion pumps were replaced on Days 7, 14, and 21 after SAH.

Arteriographic Studies

To assess vasospasm, cerebral arteriography was performed 2 to 4 days before surgery and on Days 7 and 12 postoperatively. For arteriography, monkeys were anesthetized intramuscularly with ketamine (10 mg/kg) and xylazine (1 mg/kg). A femoral artery cutdown was performed under aseptic conditions and a No. 3 French (animals weighing < 5 kg) or No. 4 French (animals weighing > 5 kg) polyethylene catheter was advanced, under fluoroscopic control, to the right ICA. Contrast medium (0.5 to 0.75 ml Conray 60%) was injected by hand. The filming sequence was 2 films/sec for 3 seconds then 1 film/sec for 6 seconds. All filming was done with a magnification factor of × 2. Subtraction films of the anteroposterior (AP) projections were made. The presence of vasospasm was detected by comparing the results of cerebral arteriography of the right MCA before surgery to those of arteriography on Days 7, 12, and 27 after surgery. A computerized image-analysis system† for the Macintosh II computer was used to measure the area of the proximal 14 mm of the right MCA using the AP projection (A Zauner, et al., unpublished data). The animals were assigned to either of two groups, those with vasospasm and those without vasospasm, according to whether the pre- and postoperative arteriography measurements of the right MCA indicated narrowing of the vessel lumen (defined as a > 25% reduction of measured area).

Histological Assessment

To identify proliferative changes, monkeys were sacrificed with an intravenous overdose of 125 mg pentobarbital anesthesia immediately after arteriography on Days 7, 12, and 27 following clot placement. The brain was quickly removed and the right and left MCA's, peripheral arteries, and duodenum were harvested. All tissue samples were immediately frozen and stored at −20°C for 1 or 2 days. Nine monkeys developed vasospasm that was evident on Day 7. Vasospasm subsided in all monkeys by Day 12. On Day 7, three monkeys with vasospasm and two without vasospasm were sacrificed. On Day 12, four monkeys with previous vasospasm and two without previous vasospasm were sacrificed. Four monkeys, of which two had vasospasm on Day 7 and two did not have vasospasm, were sacrificed on Day 27.

Control Tissues

To assess pump performance and to document the validity of the labeling technique, peripheral arteries and the duodenum were examined in addition to the right and left MCA's. The puncture site of the left brachial artery, which was catheterized for blood pressure monitoring during surgery (Day 0), was used to establish function of the first pump. The puncture site of the right femoral artery, which was used for arteriography on Day 7, was employed to establish function of the second pump; the puncture site of the left femoral artery, which was used for arteriography on Day 12, was utilized to establish function of the third pump. In addition, the duodenum was stained in order to monitor pump function and bromodeoxycytidine delivery during the day before sacrifice. The right brachial artery was harvested as a negative control for peripheral arteriography.

* Alzet micro-osmotic pump, Model 2ML1, manufactured by Alza Corp., Palo Alto, California.
† Image 1,25 image-analysis software developed by Wayne Rasbrand, National Institutes of Health, Bethesda, Maryland.
ies. The left MCA was harvested as the control for the right MCA.

**Staining Procedure**

Frozen tissue samples were sliced in sections 10 µm thick for immunohistochemistry. Sections were taken for staining every 100 µm throughout the length of the harvested MCA's (mean number of assessed sections per MCA in each animal, 38 from the right MCA and 42 from the left MCA). After sectioning, all of the specimens were immediately processed or covered with plastic wrap and frozen to −70°C for storage for 2 weeks. After thawing, the slides were air-dried and fixed in acetone for 15 minutes. After rehydration in phosphate-buffered saline for 5 minutes, the slides were quenched with 1% hydrogen peroxide solution in methanol for 20 minutes. They were then washed in phosphate-buffered saline three times for 10 minutes, exposed to the monoclonal anti-bromodeoxyuridine antibody (clone BU-1)† for 60 minutes, and washed in phosphate-buffered saline three times for 5 minutes each. Detection of bound antibody was achieved using an anti-mouse immunoglobulin G, peroxidase-linked species-specific whole antibody.‡ Slides were washed in phosphate-buffered saline three times for 10 minutes. The immunoreaction was evoked by incubation of slides with polymerizing diaminobenzidine for 1 to 2 minutes. The slides were counterstained with hematoxylin and eosin.

Positively labeled endothelial, subintimal, smooth-muscle, and adventitial cells were counted in each specimen. The number of dividing cells per section, calculated for each animal as the number of labeled cells per section, in the specimens from the right MCA was compared with the number of labeled cells in the specimens from the left MCA. Also, the results from the right MCA of animals with vasospasm were compared to the results from the specimens of the right MCA of animals without vasospasm and the results from the right MCA of animals with vasospasm were compared with those from the left MCA for each interval (Days 7, 12, and 27). To evaluate changes over time, the number of labeled cells that crossed the vessel wall was traced. The number of positively labeled cells in the right MCA and left MCA were also compared in the groups with the different types of clot placed around the right MCA.

**Statistical Analysis**

The nonparametric Wilcoxon signed-rank test, Mann-Whitney U test, and Kruskal-Wallis analysis were used. Significance was accepted at p < 0.05.

**Results**

Substantial vasospasm (defined as a > 25% decrease in the area of the right MCA in the AP view) occurred in nine of the 15 monkeys (eight in the whole-blood group, one in the RBC group) on Day 7 after placement of the clot. Vasospasm resolved in all monkeys by Day 12 (the reduction in area of the right MCA compared to the control measurement was then < 25%).

Histological specimens of the vasospastic right MCA revealed the typical changes previously associated with vasospasm, with corrugations and thickening of the media but not of the subendothelial layer (Fig. 1). Immunohistochemical labeling of dividing cells could be seen clearly in all layers of the MCA (Fig. 2).

**Assessment of Proliferative Changes**

When the number of labeled cells was compiled for all monkeys (all survival intervals), there were more labeled cells in the right MCA than in the left MCA (Table 1, Fig. 3) Highly significant differences in the number of labeled cells between the right and the left MCA were observed in all layers of the arterial wall. In the right and left MCA's, most dividing cells were in the adventitia, followed in descending order by the endothelium, the media, and the subintimal layer. There was a positive correlation between the number of labeled cells in the right and the left MCA's (Fig. 4, correlation coefficient 0.75).

Red blood cell clots produced fewer labeled cells in the right MCA wall than did the whole-blood clots, especially in the adventitia and endothelium (Table 1, Fig. 5). Moreover, in the whole-blood group but not in the RBC group, significant differences existed between the number of labeled cells in the right and left MCA's.

**Proliferative Changes and Vasospasm**

Arteriographic vasospasm occurred on Day 7 in nine of the 15 animals. The number of labeled cells had
Proliferative arteriopathy in vasospasm

FIG. 2. Photomicrographs stained with monoclonal antibody against bromodeoxyuridine and H & E. A: Labeled cells (some are indicated by arrows) in the endothelial, subendothelial, smooth-muscle, and adventitial layers in the spastic right middle cerebral artery (MCA) of Monkey D454, which was sacrificed on Day 7 after a whole-blood clot was placed around the right MCA. Labeled cells can be distinguished by the brown deposits of polymerizing diaminobenzidine. × 70. B: The left MCA of the same animal, × 60. C and D: For comparison, the right MCA (C, × 70) and left MCA (D, × 90) of Monkey D467, which was sacrificed on Day 7 after placement of a whole-blood clot around the right MCA. This animal did not develop arteriographic evidence of vasospasm.

FIG. 3. Graph showing the mean number of bromodeoxyuridine-labeled cells in the right and left middle cerebral arteries (MCA's) of 15 monkeys sacrificed on Day 7, 12, or 27 after a whole-blood clot was placed around the right MCA. The differences between the number of labeled cells in the right and the left MCA's are significant in all layers of the vessel wall (p < 0.01, Wilcoxon signed-rank test). SEM = standard error of the mean.

FIG. 4. Graph showing the relationship between the number of labeled cells in the right and the left middle cerebral arteries (MCA's) in all animals after a whole-blood clot was placed around the right MCA. Animals with a greater number of labeled cells in the right MCA had more labeled cells in the left MCA (correlation coefficient 0.75; r² 0.564).
TABLE 1

Number of dividing cells in the right and left MCA’s after placement of subarachnoid clot around the right MCA in 15 monkeys*

<table>
<thead>
<tr>
<th>Group &amp; No. of Monkeys</th>
<th>Sex (F, M)</th>
<th>Side of MCA</th>
<th>No. of Labeled Cells Per Section†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Endothelium</td>
</tr>
<tr>
<td>all animals (15)</td>
<td>5, 10</td>
<td>rt</td>
<td>0.87 ± 0.27‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lt</td>
<td>0.30 ± 0.10</td>
</tr>
<tr>
<td>no vasospasm (6)</td>
<td>2, 4</td>
<td>rt</td>
<td>0.88 ± 0.42‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lt</td>
<td>0.38 ± 0.15</td>
</tr>
<tr>
<td>with vasospasm (9)</td>
<td>3, 6</td>
<td>rt</td>
<td>0.86 ± 0.37‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lt</td>
<td>0.24 ± 0.13</td>
</tr>
<tr>
<td>type of clot</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WB (11)</td>
<td>3, 8</td>
<td>rt</td>
<td>1.11 ± 0.34‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lt</td>
<td>0.35 ± 0.13</td>
</tr>
<tr>
<td>RBC (4)</td>
<td>2, 2</td>
<td>rt</td>
<td>0.20 ± 0.07§</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lt</td>
<td>0.15 ± 0.04</td>
</tr>
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</table>

* Abbreviations: MCA = middle cerebral artery; WB = clot of whole blood around the right MCA; RBC = red blood cells suspended in collagen clot around the right MCA.
† Sections are 10 μm thick. Values are expressed as means ± standard error of the means.
‡ Significant differences between the right and left MCA: p < 0.05, Wilcoxon signed-rank test.
§ Significant differences between the right MCA’s: p < 0.05, Kruskal-Wallis analysis of variance.

TABLE 2

Number of dividing cells in the right and left MCA’s in five animals sacrificed 7 days after placement of subarachnoid clot around the right MCA*

<table>
<thead>
<tr>
<th>Group &amp; No. of Monkeys</th>
<th>Side of MCA</th>
<th>No. of Labeled Cells Per Section</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Endothelium</td>
</tr>
<tr>
<td>all animals (5)</td>
<td>rt</td>
<td>1.62 ± 0.70</td>
</tr>
<tr>
<td></td>
<td>lt</td>
<td>0.70 ± 0.18</td>
</tr>
<tr>
<td>no vasospasm (2)</td>
<td>rt</td>
<td>1.96 ± 0.87</td>
</tr>
<tr>
<td></td>
<td>lt</td>
<td>0.83 ± 0.21</td>
</tr>
<tr>
<td>with vasospasm (3)</td>
<td>rt</td>
<td>1.40 ± 1.15</td>
</tr>
<tr>
<td></td>
<td>lt</td>
<td>0.61 ± 0.31</td>
</tr>
</tbody>
</table>

* MCA = middle cerebral artery. Sections are 10 μm thick. Values are expressed as means ± standard error of the means.

Discussion

The irreversibility of delayed vasospasm after SAH1,3,6 or by death,7 and the absence of a response to numerous vasodilator drugs2,6–8 provide the basis of the concept that narrowing of the cerebral arteries is caused by proliferation of the smooth-muscle cells and/or of the endothelium,9,10,17,19,24,27,36,37,43 rather than by active contraction of the smooth muscle.1,3,9,37,43,57 In human cerebral arteries endothelial desquamation,2,12,24,25,39,43 endothelial-subendothelial proliferation,9,23,36,37,43,55,56,59 internal elastic lamina disruption,1,3,36,37,57 and myonecrosis,1,3,7,9,12,23,36,37,43,55,56 had been used to support arguments of proliferative arteriopathy as a cause of vessel narrowing after SAH. To a lesser extent, similar changes have been observed in various experimental models of SAH.2,8,12,13,18,27,30–32 However, other investigators deny the existence of cell proliferation in the vessel wall with vasospasm,9,29,56 since evidence of proliferative arteriopathy occurs without vasospasm51,56 and smooth-muscle cell proliferation is not associated with intimal thickening.4,58 Thus, both the existence of proliferation of cells in the arterial wall51 and its relationship to cerebral vasospasm remain unclear.

We examined the vessel wall for the presence of proliferative arteriopathy using a continuous intravenous infusion of bromodeoxyuridine to label dividing cells in vivo in a primate model of vasospasm after SAH that is known to reproduce the characteristic histopathological arterial changes occurring in humans.1,3,13,42 In this model, the histological changes in
Proliferative arteriopathy in vasospasm

The right MCA can be related only to the presence of vasospasm and/or to the type of clot placed around the artery because this model of SAH avoids the early cerebral ischemia produced by aneurysm rupture and the delayed ischemia (none of the monkeys in this study developed delayed neurological deficits) that can produce proliferative changes in the vessel wall. Moreover, this model allows comparisons between the vasoplastic right MCA and the unaffected left MCA in the same animal.

Proliferative Activity vs. Proliferative Arteriopathy

Placement of the clot around the right MCA induced proliferative activity across the entire arterial wall. Most cell division occurred in the adventitia and the endothelium. Proliferative activity was also measured in the left MCA, but it was limited to the endothelium and subendothelial layers. The number of dividing cells in the right MCA was quite limited (Table 1). Thus, the term "proliferative arteriopathy" cannot be justified for the changes observed after SAH in this model.

Pattern of Cellular Proliferation in Vessel Wall

Since endothelial injury by any means — mechanical, viral, toxic, immunological, or chemical via lipid peroxidation in homocysteinemia or by hypercholesterolemia — elicits smooth-muscle cell proliferation and migration into the intima, it is not surprising that proliferative changes in the intima arise after SAH. It is not surprising that proliferative changes in the intima arise after SAH. However, these changes are limited to production of arteriosclerotic plaque-like formation in the subintimal layer. Although proliferation occurred in the endothelial-subendothelial layer, it was not associated with the cross-section diameter of the vessel.

Most labeled cells were in the adventitia (Tables 1 and 2, Fig. 3). We did not establish if the labeled cells were adventitial or inflammatory cells. Other investigators have observed monocytes, macrophages, and leukocytes in the adventitia after SAH, which suggests that the dividing cells in the adventitia observed in the current experiment may be migrating inflammatory cells. Where did the cells in the adventitia originate? They may have migrated from the luminal side as a result of the increased endothelial permeability produced by SAH or they could have originated from proliferation and migration from the constituents of the clot (the whole-blood clot was associated with more labeled cells in the adventitia than was the RBC clot) and/or from the cerebrospinal fluid (CSF).

Mechanisms of Proliferative Activity in the Endothelium and the Adventitia. The mechanism of cell proliferation in the endothelial and subendothelial layers produced by the presence of blood in the subarachnoid space is unknown. It is also unclear which component of blood in the subarachnoid space is responsible for the proliferative changes in the endothelium and subendothelium. Adventitial changes produced by migration of inflammatory cells and macrophages, from clot and CSF or from plasma showed the increasing number of cells in the right MCA that correlated with the number of cells in the left MCA (Fig. 3). Although proliferative activity was more distinct in the right MCA in the whole-blood group than in the RBC group, this activity was also observed in the left MCA. Furthermore, there was a correlation between the number of labeled cells in the walls of the right and left MCA's in individual animals (Fig. 4). This suggests that the proliferative response is not limited to a local phenomenon, such as a local inflammatory reaction, but that it is, at least partially, a function of the variability of a more generalized response of individual animals to SAH.

Histopathological findings in the endothelium similar to those that occur after SAH in humans have been

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experimentally induced by noradrenaline,\textsuperscript{2} hemorrhage,\textsuperscript{7,12,13,21,24,29,57,58} oxyhemoglobin,\textsuperscript{8,30,32} neuropeptide Y,\textsuperscript{13} and endothelin.\textsuperscript{40} Administration of these substances produces immediate vasospasm. Early vasospasm produces endothelial cell distortion,\textsuperscript{60} endothelial "desquamation",\textsuperscript{12,21,26,31,33,59,60} and derangement of the internal elastic lamina.\textsuperscript{71} These anatomical changes allow leakage of platelet-derived growth factor from platelet thrombi into the media\textsuperscript{15,16} through fenestrations in the internal elastic lamina. The cell migration-proliferation that occurs 1 to 2 days after SAH\textsuperscript{2} may be related to cell proliferation starting 12 to 16 hours after binding of platelet-derived growth factor to the smooth-muscle cell.\textsuperscript{20,44} This sequence of events is supported by the observations of Kapp, et al.,\textsuperscript{16} and Okada, et al.,\textsuperscript{41} that heparin reduces proliferative arteriopathy.\textsuperscript{6} However, early vasospasm, which may be associated with the events described above, may not occur in humans,\textsuperscript{25,50,63,64} and other mechanisms of proliferative activity in the vessel wall must be considered.

Ischemia damages the arterial wall\textsuperscript{23,39,60} and causes platelet aggregation and the release of platelet contents,\textsuperscript{14} which could trigger injury-dependent proliferative activity.\textsuperscript{23,28,45,55} In humans, proliferative changes in the arterial wall could be evoked by endothelial damage\textsuperscript{52} produced by a brief interval of ischemia during increased intracranial pressure immediately after aneurysm rupture\textsuperscript{34,40,61} or by delayed ischemia associated with delayed vasospasm. The influence of delayed vasospasm and/or ischemia on proliferative arteriopathy is supported by the presence of proliferative changes in the vessels of patients who die several weeks after SAH and vasospasm.\textsuperscript{23,56}

Proliferative Changes and Vasospasm

If it can be assumed that cells labeled during replication survive for several days, most cell proliferation in response to subarachnoid blood occurred during the first 7 days (Fig. 6), the same interval in which cerebral vasospasm developed. If the labeled cells represent inflammatory cells, a product of white blood cells could play a role in the development of vasospasm. However, neither the total number of labeled cells nor those in any specific layer of the right MCA correlated with the occurrence of cerebral vasospasm. Furthermore, although we observed proliferative changes in the endothelial and subendothelial layers (Table 1, Figs. 1 and 2), the number of cells per section was limited and the vessel lumen was never narrowed by an increased bulk of cells in the vessel wall. These results exclude proliferative arteriopathy as a cause of cerebral vasospasm after SAH.

Conclusions

Subarachnoid blood around the right MCA resulted in mitosis of cells in all layers of the arterial wall. The most distinct changes occurred in the adventitia. Whether they were produced by the proliferation of constituents of the vessel or were the results of infiltration of the vessel wall by monocytes and macrophages remains unknown. The number of dividing cells of the arterial wall was not related to the presence of delayed vasospasm.

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Proliferative arteriopathy in vasospasm


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