Effects of Skilled Forelimb Training on Hippocampal Neurogenesis and Spatial Learning After Focal Cortical Infarcts in the Adult Rat Brain

Fanny Wurm, MD; Silke Keiner, MSc; Albrecht Kunze, MD; Otto W. Witte, MD; Christoph Redecker, MD

Background and Purpose—Environmental stimulation consistently increases dentate neurogenesis in the adult brain and improves spatial learning. We tested the hypothesis whether specific rehabilitative training of an impaired forelimb influences these processes after focal cortical infarcts.

Methods—Focal cortical infarcts were induced in the forelimb sensorimotor cortex using the photothrombosis model. One group of infarcted animals and sham-operated controls housed in standard cages received one daily session of skilled reaching training of the impaired or dominant forelimb, respectively. A second group was transferred to an enriched environment, whereas a third group remained in the standard cages without further treatment. Bromodeoxyuridine was administered from day 2 until day 6 postinfarct. Proliferation and differentiation of newborn cells was analyzed at day 10 and 42 using immunocytochemistry with neuronal and glial markers and confocal laser scanning microscopy. Spatial learning was tested in the Morris water maze between days 35 and 41.

Results—After cortical infarcts in the forelimb sensorimotor cortex, environmental enrichment as well as daily reaching training of the impaired paw both increase dentate neurogenesis and improve functional performance in the Morris water maze. Nevertheless, the reaching training-induced neurogenic response was significantly greater in nonlesioned controls associated with the best spatial learning performance in the water maze.

Conclusions—Skilled forelimb training effectively stimulates dentate neurogenesis and spatial learning in the infarcted and healthy brain. However, this reaching training-induced increase in neurogenesis was reduced after cortical infarcts. (Stroke. 2007;38:2833-2840.)

Key Words: dentate gyrus • plasticity • progenitor cells • rehabilitation • stroke

The adult brain responds to physical exercise and environmental stimulation with an increased generation of new neurons in the dentate gyrus (DG).1–4 These new cells mature locally into granule neurons, form axonal projections and dendritic arbors, and functionally integrate into the existing hippocampal network.5–7 Several studies demonstrated that increased levels of dentate neurogenesis were paralleled by an improvement in hippocampal learning tasks,8,9 although the causality of this correlation has not been unambiguously demonstrated yet. However, the modulation of dentate neurogenesis by different physiological stimuli suggests a new form of cellular plasticity by which the adult brain’s performance can be optimized for new environmental conditions. Dentate neurogenesis is also stimulated by focal ischemic infarcts even when the site of the injury is located in remote cortical brain areas.10,11 New neurons in the dentate gyrus might modify the corticohippocampal network and thereby support the recovery process, but until now, there has been no direct proof of this assumption. Nevertheless, it is also conceivable that cortical lesions may disturb the physiological neurogenic response to environmental stimuli in the DG.

To shed more light on these interactions, we analyzed whether specific rehabilitative training or unspecific stimulation in an enriched environment influences dentate neurogenesis in animals with small cortical infarcts. We photochemically induced circumscribed ischemic lesions in the forelimb sensorimotor cortex and trained one group of infarcted as well as sham-operated animals to reach pellets with the impaired or dominant forelimb. A second group was directly transferred to an enriched environment, whereas a third group remained in the standard cage as before the surgery. Using this approach, we demonstrate that daily sessions of skilled reaching training effectively stimulate dentate neurogenesis and improve functional performance in hippocampal learning tasks. However, sham-operated controls showed a significantly greater increase in reaching training-induced neurogenesis indic-
ing that the cortical infarct impairs the physiological neurogenic response to specific motor training.

Materials and Methods

**Photothrombotic Infarcts**

The experiments were performed on a total number of 102 male Wistar rats (250 to 270 g, 10 to 12 weeks). Focal photothrombotic infarcts were induced in the forelimb sensorimotor cortex in 47 animals as described previously in detail. In brief, the animals were anesthetized with 2.5% to 3.5% enflurane in a mixture of O₂/N₂O. An optic fiber bundle mounted on a cold light source (Schott KL 1500, Jena, Germany) was positioned on the skull 0.5 mm anterior to bregma and 3.7 mm lateral to the midline above the forelimb sensorimotor cortex. Immediately after onset of illumination (duration, 20 minutes), Rose Bengal (1.3 mg/100 mg body weight in 0.9% NaCl) was injected through a femoral vein catheter. Sham-operated animals (n = 55) received the same treatment without illumination of the brain.

**Experimental Design**

The rats were divided into 3 different groups, each including infarcted (infarct) and corresponding sham-operated animals (control) (Figure 1). One group of animals was kept under standard housing conditions (standard-infarct: n = 13; standard-control: n = 15) in ordinary cages (4 animals/cage, 54 cm × 38 cm × 19 cm). A second group was transferred into an enriched environment (enriched-infarct: n = 16; enriched-control: n = 14) at day 1 after the infarct and housed in a larger cage (6 to 8 animals per cage, 85 cm × 75 cm × 40 cm) containing different stimulating objects such as, tunnels, ladders, chains, a seesaw, and places of escape, but no running wheel. The configuration of these objects was changed daily. A third group of animals was kept in a standard cage and received one daily session of skilled reaching training of the impaired or dominant forelimb in a Plexiglas reaching box (reaching-infarct: n = 18; reaching-control: n = 19) beginning at day 1 after the surgery. The rats had to grasp 50 pellets per session (Dustless Precision Pellets 45 MG; BioServ) in the first week and subsequently 100 pellets (Figure 2A; see also the supplemental movie, available online at http://stroke.ahajournals.org). Before surgery, forelimb preference was assessed to locate the photothrombotic lesion on the dominant hemisphere. All animals received a slightly reduced, controlled feeding keeping the gain in body weight constant between the different experimental groups (+30% during the experiment). All rats obtained daily intraperitoneal injections of bromodeoxyuridine (BrdU, 50 mg/kg; Sigma-Aldrich, Taufkirchen, Germany) from day 2 until day 6 postsurgery. On day 10 or 42 after infarct induction, the rats were anesthetized with diethyl ether and perfused transcardially with 4% phosphate-buffered paraformaldehyde. Brains were postfixed for 24 hours and equilibrated in 30% sucrose. Sequential 40-μm sections were taken and stored at −20°C.

**Water Maze**

Rats were trained in the Morris water maze on days 35 to 41 postsurgery (4 trials per day). The tank had a diameter of 180 cm, an altitude of 50 cm, and was filled to a height of 30 cm with 20°C to 22°C warm water. The platform was placed 2 cm beneath the surface of the water. Starting points were changed everyday. Each trial lasted either until the rat found the platform or for 90 seconds. After each trial, animals were allowed to rest for 20 seconds on the platform. Latency, swim path length, and swim-
ming speed were recorded using Etho Vision software (Noldus Information Technology, Wageningen, The Netherlands) and evaluated by calculating the area under the curve (AUC), respectively.

**Infarct Volumetry**

For further histological and immunocytochemical processing, 40-μm thick coronal brain sections were cut using a freezing microtome and infarct volumetry. Using a CCD camera and National Institutes of Health Image software, the area of the cortical infarct and that of both hemispheres were measured. Volumes were then determined by integrating the appropriate region with the section interval thickness (320 μm). The infracted brain volume was given as a percentage of the infracted area compared with the total volume of the measured brain segment.12

**Immunocytochemistry**

Immunocytochemistry for BrdU and immunofluorescent triple labeling for BrdU, doublecortin (DCX), neuronal nuclei (NeuN), and S100β were performed as described previously in detail.11 We used the following primary antibodies: monoclonal rat anti-BrdU IgG (1:500; Harlan Sera-Laboratory, Loughborough, UK), goat anti-doublecortin (1:200; Santa Cruz, Calif), mouse anti-neuronal nuclei antigen (1:500; Chemicon, Temecula, Calif), and rabbit anticalcium-binding protein beta (1:2500; S100β; Swant, Bellinzona, Switzerland). Immunofluorescent triple labeling was performed using the following secondary antibodies: Rhodamine anti-rat (1:250; Dianova, Hamburg, Germany), Cy5 anti-mouse (1:250; Dianova), Alexa Fluor 488 anti-rabbit (1:250; Molecular Probes, Leiden, The Netherlands), and Alexa Fluor 488 anti-goat (1:250; Molecular Probes).

**Quantification and Statistical Analysis**

Peroxidase-stained BrdU-positive cells were counted on every sixth sections of the complete ipsi- and contralateral DG. The phenotypes of 50 BrdU-positive cells were determined by colocalization of NeuN (or DCX) and S100β using confocal laser scanning microscopy (LSM 510; Zeiss). Colocalization was confirmed by z-series through the cell soma allowing the definite assessment of overlap between the antigens. The absolute number of a certain phenotype was calculated per animal by multiplying the absolute number of BrdU-positive cells (peroxidase method) with the percentage of the phenotype of interest. Statistical analysis of cell counts was performed using one-way analysis of variance followed by an unpaired 2-tailed t test. Differences in the behavioral performance in the water maze between the experimental groups were assessed with the 2-way analysis of variance. A Pearson correlation analysis was performed to correlate cell counts in the DG with the performance in the water maze.

**Figure 2.** Functional performance of animals with cortical infarcts and sham-operated controls during skilled reaching training. A, Photographs illustrating the skilled reaching movement (see Supplemental Movie). B, Ratio of successful reaching movements in animals with cortical infarcts and controls during the first 29 days postsurgery. Asterisks indicate significant differences (P<0.05). C, Diagram of the time needed to grasp 50 food pellets in lesioned and control animals. Infarcted animals took significantly longer compared with controls during the whole experiment (P<0.001 for each time point). Error bars represent SEM.
Results

Morphology of Photothrombotic Infarcts
All photothrombotically lesioned animals (n=47) had typical cortical infarcts located in the forelimb sensorimotor cortex with some extensions to the primary motor cortex and only little involvement of the somatosensory cortex according to Paxinos and Watson13 (Figure 1). The infarcts impaired all cortical layers while leaving the subcortical white matter intact. At day 10 postsurgery, the infarct volume was measured between 4% and 5% of the total brain volume in all 3 subgroups with no statistically significant differences (standard-infarct: 4.0±0.5%; enriched-infarct: 4.9±0.6%; reaching-infarct: 4.9±0.8%). Because of scar formation processes as well as a shift of surrounding tissue toward the lesion center, the size of the infarcts decreased until day 42 to approximately 2% of the total brain volume in all 3 subgroups (standard-infarct: 1.8±0.4%; enriched-infarct: 1.7±0.6%; reaching-infarct: 1.9±0.4%). Again, no statistical differences have been observed. Sham-operated animals did not show any structural damage (n=55).

Enriched Environment and Reaching Training
Infarcted as well as sham-operated animals, which were transferred to the enriched environment, both promptly used their new environment. They explored the seesaw and tunnels, climbed the ladders, and played with the chains. During daily reaching training, sham-operated controls showed a good performance with 76% to 82% successful reaches during the whole experiment (Figure 2B). At the first day of reaching training, it took 5 minutes±1 minute 24 seconds to grasp 50 pellets. The controls then quickly became faster during the first 5 days and took 2 minutes 12 seconds±21 seconds for the same amount of pellets at day 41 after the surgery (Figure 2C). Animals with cortical infarcts demonstrated a significantly impaired reaching performance during the first 2 weeks of daily training with only 29% successful reaching movements at day 2 (P=4.5−); 59% at day 9 (P=0.002), and 68% at day 14 (P=0.033) (Figure 2B). However, after day 19, no differences in reaching success were observed between infarcted animals (74%) and sham-operated controls (80%) (see Supplemental Movie, Figure 2B). In contrast to sham-operated controls, animals with cortical infarcts took 16 minutes 45 seconds±9 minutes 30 seconds to grasp 50 pellets at the beginning of the daily training period (Figure 2C). Although they also quickly became faster during the first 2 weeks after the infarct, they took significantly more time per 50 pellets in the course of the whole experiment (at day 41: 2 minutes 54 seconds±18 seconds in infarcted animals compared with 2 minutes 12 seconds±21 seconds in sham-operated controls, P=0.0003) (Figure 2C).

Cell Counts
Quantification of BrdU-positive cells in the DG at day 10 after the infarct revealed a total number of 2500 to 3600 in all experimental subgroups (Table) with no significant differences between the ipsi- and contralateral side. Only animals from the reaching-infarct group showed significantly more BrdU-positive cells in both DG compared with reaching-control (ipsilateral: P=0.02, contralateral: P=0.01) (Table), whereas no differences were observed in the standard and enriched group. At day 42 postsurgery, the number of BrdU-positive cells declined in all groups, but the survival of these cells strongly depended on the training (Table). In reaching-control rats, the number of surviving cells was doubled in both DG compared with standard-control (ipsilateral: +129%, P=0.001, contralateral: +92%, P=0.004), whereas in enriched-control rats, BrdU-positive cells were not significantly influenced (Table) (ipsilateral: +12%, P=0.5, not significant, contralateral: +3%, P=0.8, not significant). After cortical infarcts in the forelimb sensorimotor cortex, reaching training and enriched environment both enhanced the number of surviving BrdU-positive cells in the ipsi- and contralateral DG compared with standard housed animals (reaching-infarct: ipsilateral: +49%, P=0.005, contralateral: +42%, P=0.004; enriched-infarct: ipsilateral: +26%, P=0.032, contralateral: +33%, P=0.036). However, the enhancement of cell survival in sham-operated animals receiving daily reaching training was significantly stronger indicating that the cortical infarct reduces skilled training-induced cell survival in the DG.

Phenotype Analysis
BrdU-positive cells were analyzed for coexpression of the neuronal markers DCX and NeuN as well as the glial marker S100β (Figure 3). At day 10, the percentage of BrdU/DCX-positive cells (approximately 96%) did not differ between the experimental subgroups (Table). At day 42, reaching-control animals showed a significantly increased colocalization of BrdU and NeuN (95%, P=0.001) compared with the other experimental groups (approximately 90%). No differences in glial differentiation were observed (Table). Because of the increased survival of BrdU-positive cells in the reaching-control group, neurogenesis was more than doubled compared with standard and enriched animals (reaching-control to standard-control: +121%, P=0.001, reaching-control to enriched-control: +102%, P=0.003) (Figure 3). Infarcted animals from the reaching training and enriched environment group also showed a significant increase in neurogenesis compared with the standard condition (enriched-infarct to standard-infarct: +29%, P=0.028; reaching-infarct to standard-infarct: +43%, P=0.004), but this increase was significantly less pronounced compared with reaching-control animals (reaching-infarct to reaching-control: +54%, P=0.037) (Figure 3). Thus, cortical infarcts not only impair the reaching training-induced increase in survival of newborn cells in the DG, but also the facilitation of neuronal differentiation.

To clarify whether the increase in neurogenesis in the reaching-control group was mediated by the skilled forelimb training and not influenced by unspecific stimuli (transfer to the reaching box, nutrition with pellets), an additional group of sham-operated animals (n=7) received the same amount of food pellets on the bottom of the reaching box without skilled reaching training. Because the number of BrdU-positive cells in this group (2150±560) did not differ from the standard-control animals (1886±609, P=0.46), we conclude that the
strong increase in neurogenesis in the reaching-control group was induced by the reaching training.

Water Maze
To correlate the number of newborn neurons in the DG with hippocampal function, rats were tested in the water maze between days 35 and 41 (Figure 1). The water maze performance demonstrated significant differences in latency and path length between the experimental groups but no difference in swimming speed (Figure 4). Hence, motor abilities did not grossly differ between the groups. Animals from the reaching-control group showed the significantly shortest latency in swimming speed (Figure 4). Hence, motor abilities and that these newborn neurons were functionally integrated into the hippocampal circuitry. In previous studies, the strong reaching training-induced enhancement of neurogenesis was significantly reduced after the cortical infarct. Behavioral assessment demonstrated that increased numbers of newborn neurons in the different experimental groups correlated with a better spatial learning performance.

To our knowledge, this is the first study providing evidence that skilled training of a single forelimb affects neurogenesis in the adult dentate gyrus. Several recent studies in mice and rats clearly demonstrated that dentate neurogenesis was strongly stimulated by voluntary exercise in a running wheel and that these newborn neurons were functionally integrated into the hippocampal circuitry. In previous studies, the animals had free access to the running wheel and ran an average distance of approximately 4 to 5 km per day. This training increased the physical fitness of the animals.

Discussion
The present study clearly demonstrates that daily skilled training of a single forelimb strongly stimulated dentate neurogenesis in the healthy brain. Reaching training significantly increased the survival of newborn neurons, whereas environmental enrichment did not influence dentate neurogenesis in our study. We further found that after cortical infarcts in the forelimb sensorimotor cortex, rehabilitative training of the impaired forelimb and environmental stimulation both increased dentate neurogenesis. However, the strong reaching training-induced enhancement of neurogenesis was significantly reduced after the cortical infarct. Behavioral assessment demonstrated that increased numbers of newborn neurons in the different experimental groups correlated with a better spatial learning performance.

Table. Numbers of BrdU-Positive Cells and Colocalization

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Enriched</th>
<th>Reaching</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Ipsilateral</td>
<td>Contralateral</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>10 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct</td>
<td>(n=6)</td>
<td>(n=7)</td>
<td>(n=10)</td>
</tr>
<tr>
<td>BrdU+ total</td>
<td>3576±1014</td>
<td>2866±914</td>
<td>3566±852</td>
</tr>
<tr>
<td>DCK+ (%)</td>
<td>98.0±2.0</td>
<td>100.0±0</td>
<td>98.0±1.8</td>
</tr>
<tr>
<td>Neither (%)</td>
<td>1.0±2.1</td>
<td>0±0</td>
<td>2.0±1.8</td>
</tr>
<tr>
<td>S100β+ (%)</td>
<td>1.0±1.0</td>
<td>0±0</td>
<td>0±0</td>
</tr>
<tr>
<td>Control</td>
<td>(n=8)</td>
<td>(n=6)</td>
<td>(n=9)</td>
</tr>
<tr>
<td>BrdU+ total</td>
<td>2742±455</td>
<td>2722±559</td>
<td>3358±661</td>
</tr>
<tr>
<td>DCK+ (%)</td>
<td>99.0±3.1</td>
<td>99.0±2.8</td>
<td>94.0±5.3</td>
</tr>
<tr>
<td>Neither (%)</td>
<td>1.0±3.1</td>
<td>1.0±2.8</td>
<td>5.0±3.9</td>
</tr>
<tr>
<td>S100β+ (%)</td>
<td>0±0</td>
<td>0±0</td>
<td>0±0</td>
</tr>
<tr>
<td>42 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct</td>
<td>(n=7)</td>
<td>(n=9)</td>
<td>(n=8)</td>
</tr>
<tr>
<td>BrdU+ total</td>
<td>1128±241</td>
<td>1047±237</td>
<td>1422±246†</td>
</tr>
<tr>
<td>NeuN+ (%)</td>
<td>89.1±3.9</td>
<td>90.0±6.3</td>
<td>90.4±5.4</td>
</tr>
<tr>
<td>Neither (%)</td>
<td>9.2±4.6</td>
<td>8.6±4.9</td>
<td>8.0±5.0</td>
</tr>
<tr>
<td>S100β+ (%)</td>
<td>1.7±1.7</td>
<td>1.4±1.9</td>
<td>1.6±1.9</td>
</tr>
<tr>
<td>Control</td>
<td>(n=7)</td>
<td>(n=8)</td>
<td>(n=10)</td>
</tr>
<tr>
<td>BrdU+ total</td>
<td>969±198</td>
<td>1181±365</td>
<td>1085±388</td>
</tr>
<tr>
<td>NeuN+ (%)</td>
<td>89.2±3.8</td>
<td>91.4±2.4</td>
<td>89.8±6.3</td>
</tr>
<tr>
<td>Neither (%)</td>
<td>10.8±5.8</td>
<td>7.6±3.3</td>
<td>9.4±5.4</td>
</tr>
<tr>
<td>S100β+ (%)</td>
<td>0±0</td>
<td>1.0±1.7</td>
<td>0.8±1.1</td>
</tr>
</tbody>
</table>

*Significantly different from standard (P<0.05).
†Significantly different from control (P<0.05).
‡Significantly different from enriched (P<0.05).
stimulated the release of local hippocampal and circulating neurogenic growth factors, and also promoted angiogenesis in the hippocampal vasculature. In contrast to voluntary wheel running, daily reaching training only involved a single forepaw lasting only a few minutes in sham-operated animals after an initial training period. Surprisingly, these short daily sessions of skilled forelimb training elicited such a robust increase in dentate neurogenesis. In contrast to the effects of wheel running, we did not observe a significant increase in proliferative activity 10 days after the beginning of the reaching training. The increase in neurogenesis at day 42, therefore, was predominantly caused by an enhanced survival of newborn neurons.

In the lesioned brain, enriched environment and reaching training both significantly increased dentate neurogenesis. The effects of an enriched environment are in accordance with observations of Matsumori and colleagues. Using a model of permanent middle cerebral artery occlusion, they transferred the animals 7 days postinfarct into an enriched environment and observed a similar increase in survival of new neurons in the dentate gyrus 7 weeks later. Briones et al further demonstrated that enriched environment did not stimulate progenitor cell proliferation after transient global brain ischemia. Interestingly, Komitova et al only observed an increased dentate gliogenesis at day 35 after middle cerebral artery occlusion when the running wheel was excluded from the enriched environment. In contrast to these previous studies, we here used a model of small circumscribed cortical ischemic lesions with no direct or indirect damage to the hippocampus allowing the targeted induction of cortical infarcts in the forelimb sensorimotor cortex. It has been recently shown that these infarcts stimulate neurogenesis in the dentate gyrus, although this effect was only slight when the lesion was located in frontal brain regions.

The present study further indicated that the robust stimulating effect of skilled forelimb training on dentate neurogenesis in the healthy brain was significantly reduced by the infarcts. Interestingly, this lesion-induced reduction of the neurogenic response was only observed in reaching trained animals. Animals in the enriched environment did not show any significant effects because of the infarct. The ischemic lesions thus only diminish the physiological neurogenic response to skilled forelimb training, suggesting that the underlying mechanisms that mediate these activity-induced changes in dentate neurogenesis differ between environmental enrichment and forelimb training. Unfortunately, the mechanisms that decrease the training-induced dentate neurogenesis in the lesioned brain after 42 days are unknown. Inflammatory processes and microglial activation, which have been shown to involve widespread brain areas including the hippocampus after cortical infarcts, might disturb the microenvironment of the progenitor cells in the subgranular zone and thereby reduce neurogenesis as recently reported after cerebral radiation. This hypothesis is further supported by several studies that demonstrate an increased postischemic neurogenesis after antiinflammatory treatment. However, the animals with cortical infarcts in the forelimb sensorimotor cortex showed a reduced reaching success during the first 5 to 10 days after the lesion, which might stress the animals and thereby impair the neurogenic response. Further studies are needed to elucidate these issues.

The increase in number of newborn neurons observed in the different experimental groups significantly correlates with a better performance in spatial learning paradigms. Sham-operated animals, which underwent daily training of a single...
forelimb and showed the highest amount of dentate neurogenesis, were the best spatial learners. However, this is only a correlation but no proof of causality. We cannot exclude that additional activity-induced plastic changes on the level of synapses and dendrites contribute to this better functional performance.

Increasing evidence from different experimental studies supports the hypothesis that adult dentate neurogenesis is involved in hippocampal processes, which enable the brain to adapt to novel environmental conditions and to solve new problems in familiar environments. In addition to voluntary exercise, enriched environment, and some predominantly spatial learning paradigms, we demonstrate that dentate neurogenesis is also stimulated when rats learn a skilled reaching movement. It remains unclear whether these new neurons are specifically required for the improvement of forelimb function or just reflect a general adaptation of the hippocampal circuitry to novel learning stimuli. However,
after ischemic lesions in the adult brain, both are required: the compensation of the impaired function as well as the learning of new strategies to cope with the functional deficit. A better understanding of this training-induced neurogenic response in the adult dentate gyrus and the uncovering of the mechanisms that inhibit this process after focal ischemic infarcts may help to establish new rehabilitative strategies.

Note: The supplemental movie shows the skilled reaching training of the impaired forelimb. The same animal was videotaped at days 2 and 29 postinfarct in the left forelimb sensorimotor cortex. Note the clumsy and numerous unsuccessful grasping movements of the right forelimb at day 2 and the functional compensation at day 29.

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Disclosures

None.

References

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