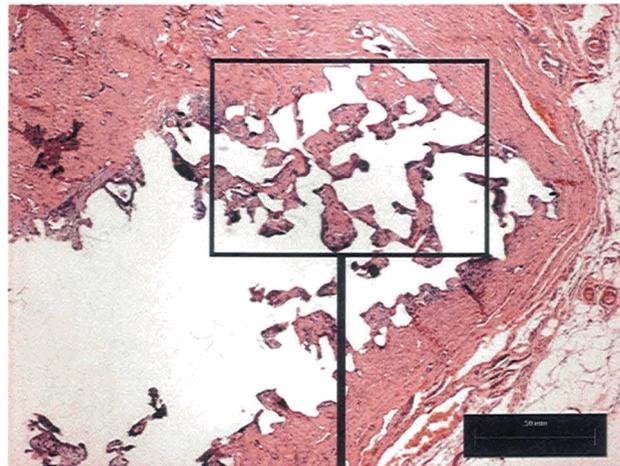


Table 4.44: Histological Results

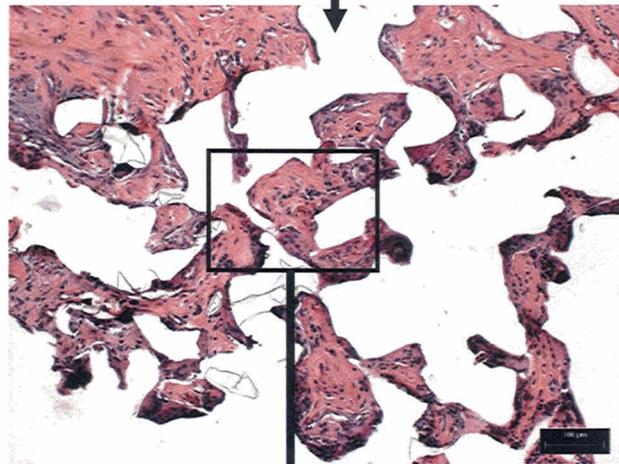


The blood vessel counts (CVS or Closed Vascular Spaces) were high and showed improvement from 6 to 12 months. Blood vessel counts for Steam sterilization were higher than [REDACTED] both time points. The percentage of remaining epithelium at 6 months appeared higher than that seen in the 12 month group, but did not appear to negatively influence occlusion. Inflammatory cell counts were low with the exception of [REDACTED] at 12 months where the lymphocyte counts increased. This was not seen in the steam sterilized matrices at either time point. Giant cells were generally acceptable, especially in the steam sterilized Matrices. The score of 2 is regarded as a low number of giant cells. Fibrotic capsule formation was not observed in either treatment as scores less than two are a virtual absence of capsule formation. The necrotic index was also very good for both treatments and time points as scores less than 2 indicate only trace amounts of necrosis. This is believed to be a reflection of the good vascular supply.

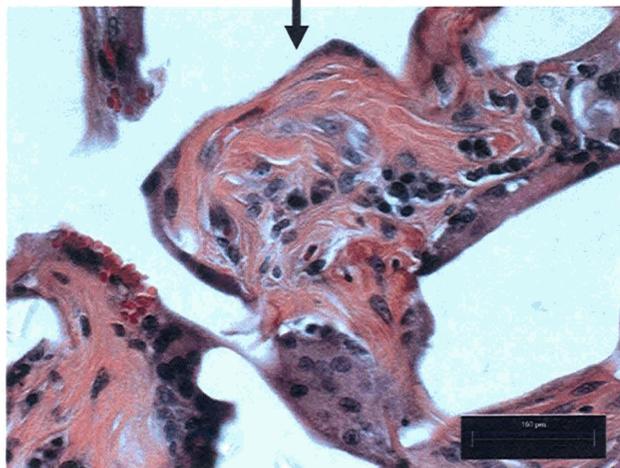
In summary, histological results for the two groups showed the Steam Sterilization resulted in superior in-growth at both 6 and 12 months.



6 Month, Steam, AR 922, 40X (marker = 0.5 mm).

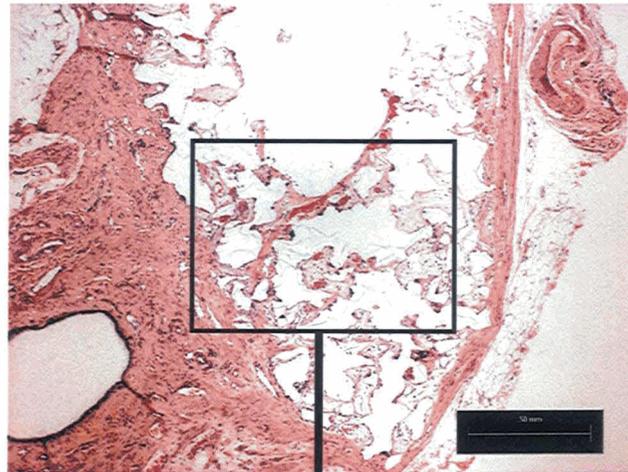


6 Month, Steam, AR 922, 100X (marker = 100 u).

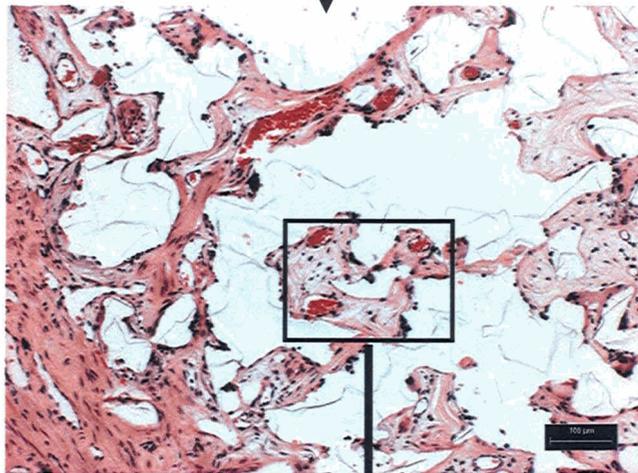


6 Month, Steam, AR 922, 400X (marker = 100 u).

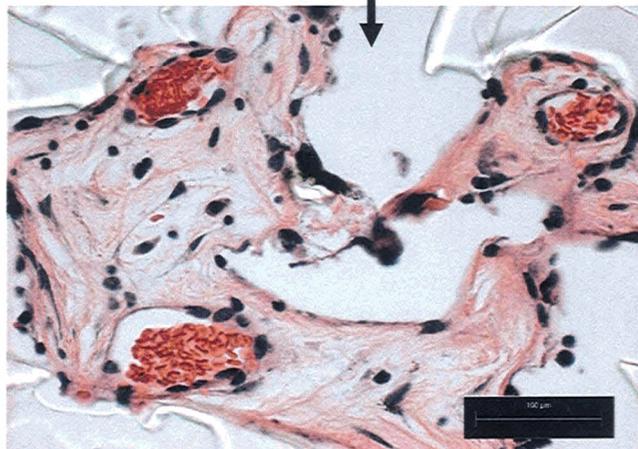
Figure 4.7: In-growth into six month steam sterilized Matrices from P0035. Note that it is not always possible to see the silicone Matrix material in histological sections due to loss during processing. In addition, slight tissue shrinkage allows the tissue to separate from the Matrix material slightly. There is excellent growth into the Matrix pores throughout the Matrix. Cells appear to fully conform to the internal Matrix architecture.



12Month, Steam, AR 1080 40X (marker = 0.5 mm)



12 Month, Steam, AR 1080, 100X (marker = 100 u).



12 Month, Steam, AR 1080, 400X (marker = 100 u).

Figure4.8: In-growth into twelve month steam sterilized Matrices from [REDACTED]
This sample shows remnant Matrix material. The bottom photomicrograph shows blood vessels (Closed Vascular Spaces- CVS) typically seen in these studies.

4.3.5.2.3. Conclusions [REDACTED]

The primary goals of the study were accomplished as no rabbits became pregnant during the study, and the in-growth characteristics of porous silicone Matrices implanted in rabbit fallopian tubes for 6 and 12 months were evaluated.

No pregnancies occurred and all tubes retaining a Matrix resulted in tubal occlusion as assessed by dye passage and histological evaluation. All but one of the Matrices were retained for the duration of the experiment, and the Matrix that was not retained was likely due to misplacement at time of implant.

Based on the Adiana scoring system, the in-growth characteristics of the steam sterilized Matrices were judged to be of a higher quality than the [REDACTED], especially at 12 months. However, both sterilization processes produced results that were effective at occluding fallopian tubes and at preventing pregnancy. Based on this study, it was determined that the [REDACTED] sterilization process [REDACTED] was undesirable for the Adiana product. It was determined that Moist Heat sterilization would be used for this product.

Tissue in-growth, particularly in the steam sterilized group, was excellent and showed a high degree of benign host integration. Section 4.3.5.4. provides a detailed discussion of conclusions drawn from all long term animal fertility implant studies.

4.3.5.3. Long-Term Implant; Matrix Length Evaluation (Adiana Protocol [REDACTED])

4.3.5.3.1. Study Design and Number of Animals

The study consisted of six different treatment groups. Three different Matrix length groups [REDACTED] were either implanted for 6 or 12 months (Table 4.5). All were steam sterilized. A total of 15 animals were treated.

Table 4.5: Treatment Groups

Duration of Implant	Length of Matrix	N (tubes)
6 months	[REDACTED]	4
6 months	3.5 mm	4
6 months	[REDACTED]	4
12 months	[REDACTED]	5
12 months	3.5 mm	4
12 months	[REDACTED]	7

It should be noted that this study included Matrix configurations that were not utilized in the IDE trial and are NOT being proposed in this PMA. [REDACTED] are not currently being used. Only the 3.5mm matrix is the current Adiana Matrix.

One rabbit was found to have a congenital condition where it had only one tube so no procedure was possible on the missing side. One tube did not receive complete treatment due to technical difficulties. For these two reasons, Matrices were placed in only 28 tubes in these 15 rabbits.

4.3.5.3.2. Results

Pregnancy prevention and Dye Test Results

There were no pregnancies at either time point in any of the animals, with a total of 28 tubes treated in 15 animals.

The dye pressure test was conducted on all treated fallopian tubes. All 12 tubes implanted for 6 months were occluded (as measured by the dye pressure test at 50 and 100 mmHg) as were all 16 tubes implanted for 12 months.

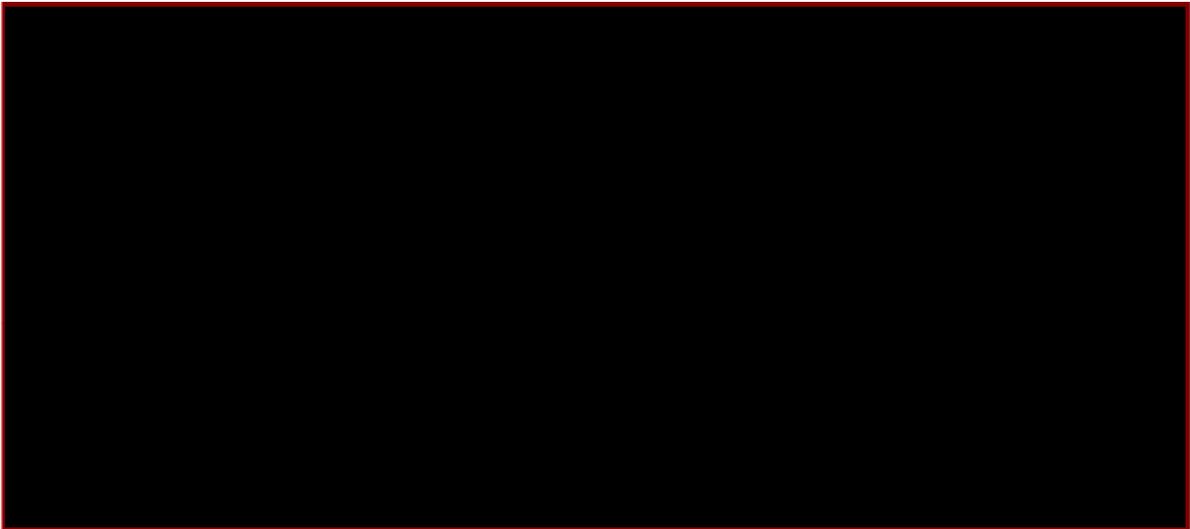
Table 4.46: P0040 Breeding and Dye Test Results

Duration of Implant	Length of Matrix	N	Pregnancy?	Pressure Test
6 months	[REDACTED]	4	None	Blocked
6 months	3.5 mm	4	None	Blocked
6 months	[REDACTED]	4	None	Blocked
12 months	[REDACTED]	5	None	Blocked
12 months	3.5 mm	4	None	Blocked
12 months	[REDACTED]	7	None	Blocked

Histological Results - Tissue In-growth

All treated tubes (n=28) were examined. One tube couldn't be scored due to tissue damage during histological processing. In one tube from the 6 month, 3.5 mm group the Matrix was found to be placed in the UTJ, therefore data from this tube were excluded.

The host cellular in-growth was characterized to include a combination of different types of cells: fibroblasts, macrophages and giant cells, inflammatory cells, extracellular Matrix, and epithelial cells. The six parameters comprising the total in-growth score and the score itself are shown in Table 4.47 below:



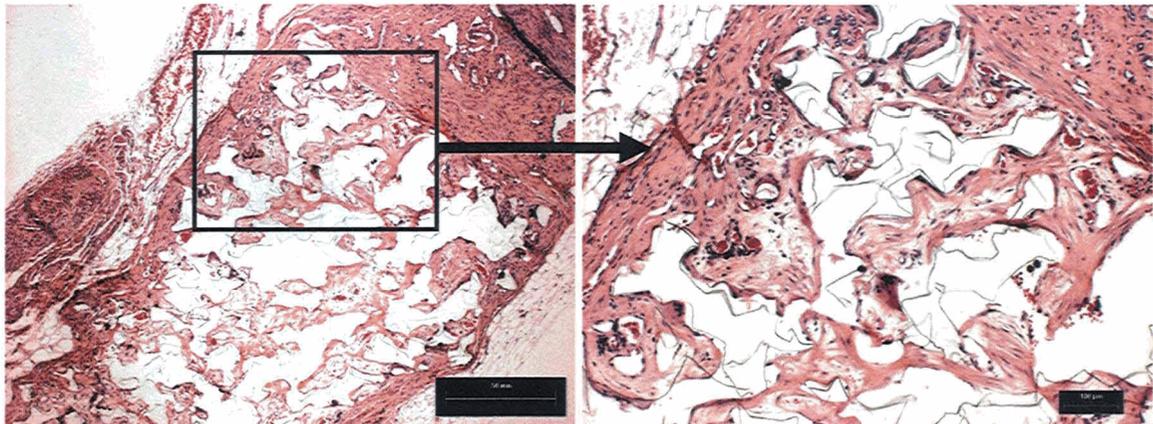
All groups showed space filling in-growth at both time points with tissue fully occupying the pores. In-growth penetrated to the Matrix core.

Blood vessel counts were generally very good, especially in the 3.5 mm matrix groups. The percentage of residual epithelium was generally acceptable with the exception of the [REDACTED] Matrix at 6 months. The number of inflammatory cells was slightly high at 6 months except for the 3.5 mm matrix group and all inflammatory cells decreased at the 12 month time point. Giant cells were somewhat elevated but not excessive. The fibrotic capsule and necrosis indexes indicated that these were virtually absent in all groups at both time points.

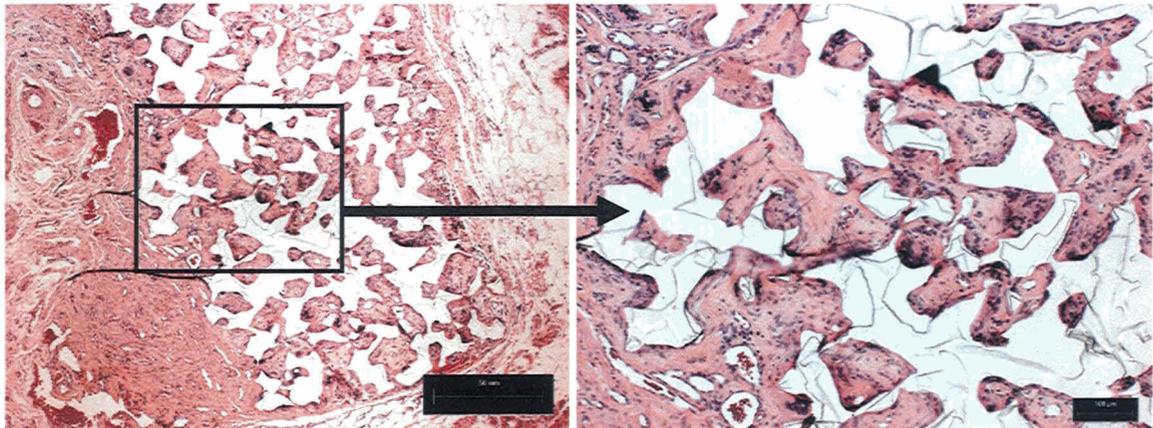
In-growth ranges are also presented in table 4.8. All groups appeared to have space filling in-growth. Representative images of the current Adiana Matrix (3.5mm) are included in figures 4.9 and 4.10.

Table 4.48: Summary Data

Duration of Implant	Length of Matrix	N	Ingrowth Score	Ingrowth Range
6 months				
6 months	3.5 mm	3	2.8	1.0-4.0
6 months				
12 months				
12 months	3.5 mm	4	2.1	1.6-2.7
12 months				



6 Month, 3.5 mm (AR 1090), 40 X(marker = 0.5 mm) 6 Month, 3.5 mm (AR 1090), 100X(marker = 100 u).



12 Month, 3.5 mm (AR1240), 40 X (marker= 0.5mm) 12 Month, 3.5 mm (AR1240), 100X (marker= 100 u).

Figure 4.9: In-growth at 6 months (top) and 12 months (bottom) into the Adiana 3.5mm Matrix (from [REDACTED]). Complete in-growth into the Matrix pores with little evidence of necrosis, inflammation or fibrotic capsule formation. No marked differences between 6 and 12 month in-growth, indicating stable in-growth.

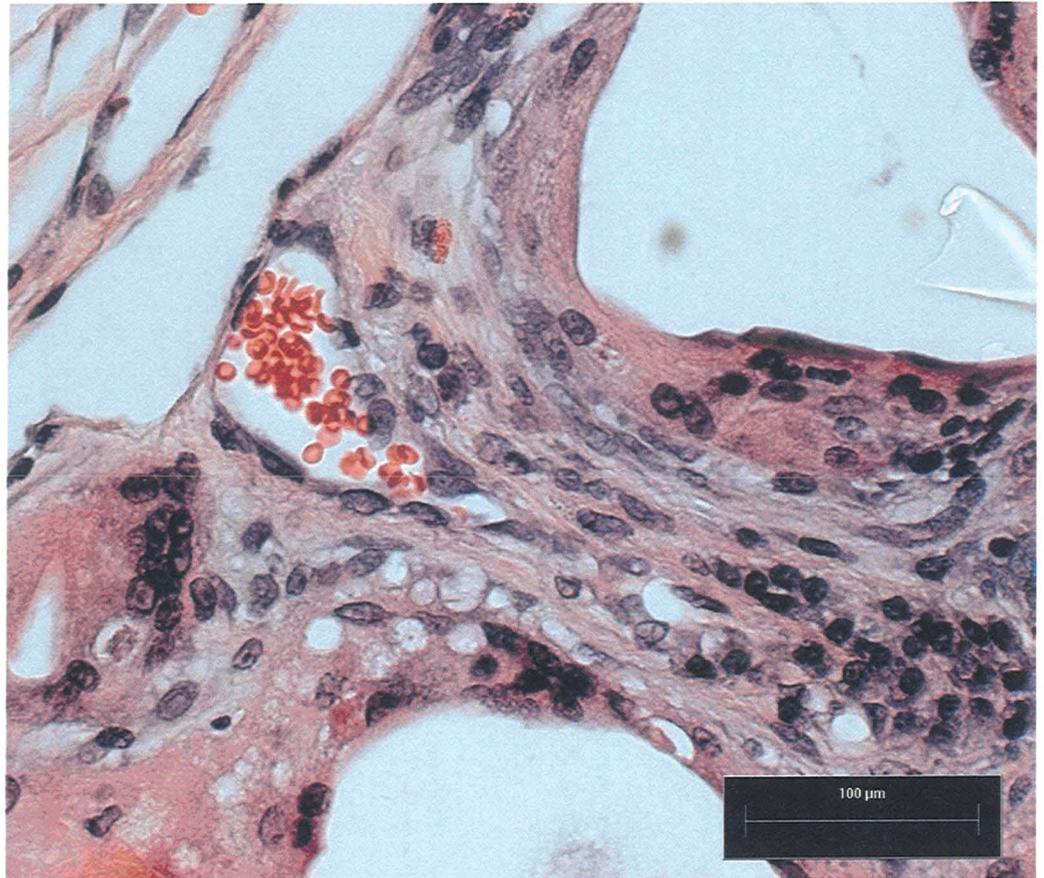


Figure 4.10: In-growth at 12 months in the Matrix (3.5 mm). CVS (blood vessel) seen at high magnification. Dense, space filling in-growth is observed.

4.3.5.3.3. Conclusions; [REDACTED]

At six months the highest in-growth scores were achieved by the 3.5 mm Matrices. This was due to the lower blood vessel counts of the [REDACTED] Matrices and higher inflammatory cell counts for both [REDACTED] matrices. By 12 months, the differences between the different length Matrices had disappeared and all scores were basically equivalent. It appears that any of these lengths of Matrices could be used to cause tubal occlusion in the dye test and good in-growth. At twelve months, all had good vascular supply, minor inflammation and negligible necrosis.

The primary objective of pregnancy prevention in all implanted tubes and determining in-growth characteristics of porous silicone Matrices implanted in rabbit fallopian tubes for 6 and 12 months was accomplished. No rabbits became pregnant. All 28 implanted matrices were recovered at explant and all tubes were occluded as determined by passing the dye pressure test.

All three Matrices, differing in length only, were successful in occluding the fallopian tube with stable, space filling in-growth, which successfully prevented pregnancy at up to one year.

4.3.5.4. Overall Conclusions -Animal Fertility Study

In these two studies, both methods of sterilization and all three different matrix lengths resulted in occlusion of the fallopian tube as measured by the dye pressure test. Moreover, pregnancy was prevented in all animals.

In analyzing the results for the current Adiana system, which uses 3.5mm matrices and steam sterilization, there were a total of 19 such matrices which were implanted in these two studies, 9 for six months and 10 for twelve months. All 19 tubes were found to be not pregnant after mating with proven bucks. Dye patency tests showed 9 of 9 tubes occluded at six months and, in a different group of animals, 9 of 10 tubes occluded at twelve months. At 12 months there was one tube which was found to be patent. Subsequent histologic examination revealed this Matrix was missing, most likely due to technical difficulty at the time of initial implant.

The method for scoring tissue in-growth into the Matrix in the Adiana procedure is based upon our mechanism of action. To permanently occlude the fallopian tube, it is desired that the in-growth be space filling and have long-term biocompatibility. Long-term stability will be achieved through a benign host integration of the Matrix. Several characteristics are required for complete integration of the Matrix: It is necessary that the epithelium be removed expose the underlying tissue to the Matrix architecture, that there be an adequate blood vessel support to maintain healthy tissues, and that the Matrix not trigger a chronic foreign body inflammatory response which could lead to encapsulation or walling off.

The in-growth was judged to be very good at the 12 week time point observed. It was a space filling in-growth in the pores of the matrix which was generally observed to reach the solid core. It consisted of a vascularized in-growth with the absence of a fibrotic capsule. Only mild amounts of necrosis were observed and inflammation was not felt to be significant. It consisted primarily of lymphocytes in the in-growth. It is believed that this indicates the in-growth is stable which should last indefinitely.

4.3.6 CONCLUSIONS

In summary, the In Vitro human extirpated uterus studies and the rabbit implant studies showed the following:

- The current catheter/electrode configuration could safely deliver RF energy to the fallopian tube
- That the selected RF parameters lead to appropriate lesion geometry.
- Lesion creation had a repeatable geometry, and achieved adequate cell destruction
- That the combination of RF energy and Matrix implantation led to tissue in-growth and tubal occlusion in the rabbit
- That the combination of RF energy and Matrix implantation followed by tissue in-growth resulted in tubal occlusion and long term pregnancy prevention in the rabbit.

As discussed previously, additional studies (in the Pre- and Peri-Hysterectomy patient populations) were utilized to verify these conclusions in a human population. Acute safety (in terms of serosal tissue temperature as a result of RF delivery, as well as lesion extent) were investigated in the Peri-Hysterectomy studies. Additionally, the ability to achieve tissue ingrowth and fallopian tube occlusion were investigated in the Pre-Hysterectomy studies. These studies will be provided in Module 4: Clinical.

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