Pathogenetic role of no-reflow phenomenon in experimental subarachnoid hemorrhage in dogs

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The real pathogenetic role of no-reflow phenomenon in clinical situations such as the acute stage of subarachnoid hemorrhage (SAH) is not yet known. To study this problem, we carried out the following experiment in dogs: SAH was induced by withdrawing a needle previously inserted into the internal carotid artery through a small craniectomy in the lateral base of the skull. Complete dural repair and cranioplasty was done to avoid cerebrospinal fluid leakage. Cortical cerebral blood flow (CBF) changes, measured by a double-needle type thermocouple, intracranial pressure (ICP), electroencephalogram (EEG), and sensory evoked response were monitored under controlled ventilation for 3 hours after SAH. At the end of the experiment, the brain was perfused with carbon black solution at a pressure of 120 mm Hg. The 32 episodes of SAH thus induced yielded two basic patterns of ICP changes which simulated those previously reported with human SAH. In the first pattern, reactive hyperemia was always observed, followed by complete or incomplete recovery of cerebral function. Perfusion defects were frequently seen in the thalamus, basal ganglia, and parieto-occipital cortex symmetrically. In the second pattern, prolonged elevation of ICP resulted in failure of recovery of both CBF and EEG. Carbon black filled only the pial arteries and the rest of the brain was totally unperfused. From the results, the pathogenetic role of the no-reflow phenomenon in the acute stage of SAH as influencing the prognosis is strongly suspected.

Key Words: cerebral aneurysm • cerebral anoxia • cerebral blood flow • intracranial pressure • subarachnoid hemorrhage • cerebral vasospasm

As has been emphasized in many clinical reports, the prognosis of subarachnoid hemorrhage (SAH) due to rupture of a cerebral aneurysm depends largely on the neurological condition of the patient in the acute stage. Also it is known that the better the level of consciousness, the better is the operative result. Although this fact enables us to select those patients in good condition for operative treatment, the other patients are left without any treatment that has proved really effective. Since ischemia is undoubtedly the major cause of brain damage, as shown in autopsy studies, cerebral vasospasm has been regarded as the determining factor of the prognosis of SAH due to rupture of intracranial aneurysms. However, recent studies on the correlation between vasospasm and cerebral blood flow (CBF) in clinical and experimental materials have revealed that reduction of CBF does not necessarily follow the presence of angio-
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graphically recognized vasospasm.44,50,55,58 Therefore, in addition to angiography of cerebral vasospasm, more integrative investigations on the pathophysiological mechanism, such as interrelationships between intracranial pressure (ICP), CBF, cerebral functions, edema, and the status of cerebral microcirculation, are definitely required for the understanding of the true nature of the brain lesion in the acute stage of SAH. Although clinical monitoring offers some information, the data hitherto obtained are limited in number and quality because of the practical difficulty in performing multiple examinations in critically ill patients.11,17,24,41

As knowledge concerning the pathophysiology of SAH in the acute stage seems to be essential for determining the timing of operation and producing a better form of therapy, we used an experimental SAH model in dogs that was designed to simulate human SAH as closely as possible. In this model, we monitored ICP, CBF, electroencephalogram (EEG), sensory evoked response (SER), and studied the status of cerebral microcirculation in the acute stage of SAH. The data suggest the pathogenetic role of the no-reflow phenomenon (NRP) in influencing the prognosis of SAH.

Materials and Methods

Production of Subarachnoid Hemorrhage

Although various techniques have been devised to produce SAH in experimental animals,8,15,46,56 the kinetic aspect of SAH due to rupture of aneurysms (that is, an arterial bleeding in a closed cavity), has been accurately simulated in very few.6,8,21 To simulate this kinetic aspect in the study of pathological physiology of SAH, the authors designed the model described below, using adult mongrel dogs.

The zygomatic arch and coronoid process of the mandible were removed and the lateral base of the skull exposed medially until the orbital fissure was identified. Then a small craniectomy of about 1 x 1 cm in diameter was carried out. Under an operating microscope with x 20 magnification, the dura was incised and cerebrospinal fluid (CSF) was aspirated. By this approach, the intracranial portion of the internal carotid artery was easily visualized with minimal brain retraction, and destruction of the normal anatomical relationship between the arachnoid membrane and the artery was avoided. Then a 4-0 atraumatic needle was inserted into the internal carotid artery between the origin of the posterior communicating artery and the carotid bifurcation. This caused no bleeding from the artery, although transient arterial spasm was usually observed. A thread attached to the needle was then brought out through the incision and the dura was approximated with several stitches reinforced with Gelfoam. The bone defect was filled with small pieces of Gelfoam and covered with a silver plate which was fixed to the surrounding skull with tissue adhesive. The wound was tightly closed in layers. Leakage of CSF was completely prevented by the above method in most animals. Those cases in which pooling of CSF was later confirmed in the wound were excluded from the result. At 2 or 3 hours after the above preparation, SAH was induced by pulling the thread.

Experimental Model

Forty adult mongrel dogs weighing 8 to 12 kg were used. Of these a complete recording was obtained in 32. The other eight dogs were excluded from the experimental results because of unsuccessful cerebral perfusion with carbon black, or CSF pooling in the operative wound.

The skull was fixed in a stereotaxic holder. Each dog was immobilized by intravenous drip of gallamine and artificially ventilated throughout the experiment. The arterial pCO₂ was measured by the Astrup method every 30 minutes and the stroke volume was controlled to maintain the level of pCO₂ between 30 and 40 mm Hg. The body of the dog was covered with an electric blanket to keep the rectal temperature at 37°C. In several dogs, the systemic arterial pressure (SAP), monitored in the abdominal aorta, cisterna magna pressure (CMP), epidural pressure (EDP), regional cerebral blood flow (rCBF), and venous outflow (VOF) were recorded continuously on a polygraph recorder.*

*Polygraph recorder RM150 manufactured by Nihon-Koden, 1-31-4, Nishiochiai, Shinjuku-ku, Tokyo, Japan.
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Fig. 1. Simultaneous monitoring of cerebral blood flow by venous outflow technique (VOF) and the thermocouple (rCBF). Left: Response to inhalation of 5% CO₂. Right: Response to cisternal infusion of 60 mm Hg saline (upper) coupled with inhalation of 5% CO₂ (lower). Note the instantaneous and parallel changes of both parameters. SAP = systemic arterial pressure; CMP = cisterna magna pressure; EDP = epidural pressure.

Fig. 2. Correlation between heat clearance and H₂ clearance methods. In four dogs, the thermocouple and H₂-sensitive platinum electrode were implanted in the symmetrical points of the parietal cortex to the same depth (2 to 3 mm from the brain surface). In H₂-clearance method, CBF was calculated by tₘ₉ method after inhalation of 10% to 20% H₂ gas mixture according to the method of Pasztor, et al. (see text). The abscissa denotes percentage changes of CBF thus calculated. The zero point refers to the initial CBF value at a pCO₂ of 40 mm Hg (mean CBF = 50.8 ml/100 gm/min + 2.7 SE). The ordinate denotes the relative changes of the output of the thermocouple to a fixed calibration voltage in all the measurements. Drug-induced hyper- or hypotension was employed to vary CBF.
Measurement of Regional Cerebral Blood Flow

A double-needle type thermocouple probe was implanted in the right parietal cortex 2 to 3 mm from the brain surface. As this device has no compensating circuit for temperature shifts,\textsuperscript{45,54} such changes were maximally avoided by covering the whole head with a thick cotton pad and warming it with an electric lamp. The probe was inserted through a pair of small holes made in the skull overlying the parietal cortex and was fixed in a stereotaxic holder. The reliability of this thermocouple was tested in the preliminary experiments in several dogs, in which the value of the thermocouple was compared with that of the torcular outflow technique.\textsuperscript{46} As shown in Fig. 1, the two methods gave parallel changes of CBF. We then compared this method with the hydrogen clearance method,\textsuperscript{47} and found that good correlation exists between these two methods (Fig. 2).

From these data, it was concluded that this thermocouple can provide a satisfactory qualitative estimate of local CBF. There are two advantages to this device: it is a simple technique, by which excessive manipulations of the torcular outflow technique can be avoided, and the thermocouple reflects rapid changes of CBF which are overlooked in ordinary gas clearance techniques. Although we are aware of the inherent defects of the heat clearance technique,\textsuperscript{48} the above advantages and the relative reliability demonstrated in the preliminary experiments made us decide to employ this method.

Measurement of Intracranial and Systemic Arterial Pressures

An epidural pressure transducer\textsuperscript{†} was inserted into the left epidural space over the parietal region through a burr hole. Before insertion, it was calibrated by sinking it to variable depths in water warmed to 37°C. Both SAP and CMP were measured with diaphragm-type pressure transducers.\textsuperscript{‡} The initial reading of EDP was set to equal CMP before induction of SAH. Dissociation of these two values was observed in a few dogs, in which there were sustained prolonged elevations of ICP.

Measurement of EEG and Serial Evoked Response

In all the dogs, EEG was monitored in both hemispheres with the use of epidural silver-ball electrodes. In several dogs, SER of the right posterior sigmoid gyrus to electrical stimulation of the left sciatic nerve was also monitored. In 10 dogs in SAH Pattern 1, the EEG index (mean dominant frequency) was calculated according to the manual analysis method of Sulg.\textsuperscript{59}

Cerebral Perfusion with Carbon Black

At the termination of the experiment (3 hours after SAH), the thoracic cavity was opened while artificial respiration was continued. The abdominal and the ascending aorta at the origin were clamped simultaneously. Then a cannula 3 mm in diameter was inserted into the thoracic aorta as quickly as possible and perfusion was immediately started with mixture of equal volumes of 10% formalin and carbon black solution. The carbon black solution was previously filtered with a No. 2 filter paper\textsuperscript{w} and both solutions were warmed to 37°C. To avoid particle formation, the perfusion was started with formalin alone and then carbon black solution was added. The external jugular veins previously exposed were transected. At a pressure of 120 mm Hg, 500 ml of the mixture could be infused within a few minutes. The degree of perfusion was checked by observing the blackening of the back of the tongue and the conjunctiva. Then the brain was removed and fixed in 10% formalin for a week. The status of the cerebral microcirculation, as revealed by perfusion defect, was evaluated in coronal slices in three different planes, R-15, -20 and -25, according to the atlas of Lim, et al.\textsuperscript{61} Microscopic examination of the microcirculation was done with sections 100 μ thick; histological exam-

\footnotesize{\textsuperscript{†}Epidural pressure transducer MH-AC manufactured by ST-Laboratory Company, 4-17-3, Sumiyoshi-cho, Hoya-city, Tokyo, Japan.}

\footnotesize{\textsuperscript{‡}Diaphragm-type pressure transducers TMI-BLH, MPU-0.5 manufactured by Toyo-Baldwin Company, 7-Banchi, Sakuragawa-Chō, Nishikubo, Shiba, Minatoku, Tokyo, Japan.}

\footnotesize{\textsuperscript{w}Filter paper No. 2 manufactured by Toyo Roshi Kaisha Ltd., 3-7, Nihonbashimoto, Chuoku, Tokyo, Japan.}
inination with hematoxylin and eosin; cresylfast violet, and luxol-fast blue stains were also used.

**Results**

The representative patterns of ICP and CBF are shown in Fig. 3. In Pattern 1, ICP rose abruptly to nearly the level of the arterial diastolic pressure and stayed there for several minutes. Then it gradually fell to a level slightly higher than the original level. On the other hand, rCBF fell rapidly, with severe depression or flattening of EEG. As ICP fell, CBF rapidly recovered, followed by an overshoot (reactive hyperemia). In Pattern 2, ICP elevation was prolonged and rCBF and EEG did not recover at all.

![Fig. 3. Representative polygraphic recordings showing Patterns 1 (left) and 2 (right).](image)

**Fig. 3.** Polygraphic recording in Pattern 1. Sequential electroencephalogram (EEG) and serial evoked response (SER) are also shown. The analysis time of SER is 250 msec to 32 repetitive stimuli. Analysis was done by computer.
The polygraph record of Pattern 1 with EEG and SER is shown in Fig. 4. Electroencephalogram activity disappeared within a few minutes after SAH while the initial negative wave of SER was retained. Appearance and recovery of EEG activity was always preceded by reactive hyperemia. In the total of 32 dogs, 26 demonstrated Pattern 1 and the other six Pattern 2. Figure 5 shows the time course of ICP, rCBF, and the EEG index of 10 dogs with Pattern 1 recordings. This pattern is characterized by the gradual fall of ICP to near the normal value, always accompanied by the overshoot of rCBF.

The duration of reactive hyperemia was variable, ranging from several minutes to more than 3 hours. Recovery of cerebral functions, as estimated from EEG and SER, took place gradually after the appearance of reactive hyperemia, although it was not complete in the majority of animals at the time of sacrifice, 3 hours after SAH.

In 20 of 26 dogs with a Pattern 1 recording, perfusion defects were recognizable (Fig. 6 B). The extent of non-filling of the 20 brains is shown in Fig. 7. The most frequent locations of non-filling were thalamus, basal ganglia, and parietooccipital cortex. The upper portion of the midbrain was sometimes involved. Characteristically, the lesions were symmetrically distributed in all cases. In microscopic sections, non-filling was most prominent in the fine capillary networks while the larger penetrating arterioles remained patent (Fig. 6 C and D). These patches of non-filling were scattered in the macroscopically recognized areas of defective perfusion. The hypothalamus, hippocampus, brain stem, and cerebellum were spared in most cases. Ischemic cell changes, as described by Brierley, et al., were seen sporadically in the pyramidal cell layers of poorly perfused areas. No significant ischemic changes were detected in the ganglion cells of the thalamus, basal ganglia, and hippocampus.

The courses of ICP and rCBF of the six dogs with Pattern 2 recordings are shown in Fig. 8. During the observation period of 3 hours, neither reactive hyperemia nor recovery of cerebral function was observed. Carbon black perfusion revealed total non-filling of the cerebral hemispheres (Fig. 9), sparing the relatively large pial arteries and the infratentorial portion of the brain. Microscopic sections showed complete obliteration of the intraparenchymal capillary networks while the pial and relatively large penetrating arteries were partially filled with carbon. Ischemic changes of cortical neurons were more frequently seen than in Pattern 1, but were not evident in other parts of the brain.

Discussion

Validity of the SAH Model

There have been only a few clinical reports concerning ICP changes immediately after SAH. According to Nornes, ICP changes after SAH are divided into two basic patterns, ischemic-edematous and hematomatous. In both patterns, the initial elevation of ICP reached systemic diastolic pressure. The subsequent elevations of ICP were thought to be dependent on the presence of intracerebral hematoma or cerebral edema. The similarity between the above ICP patterns and those of the present model is believed to prove that the basic mechanism of ICP elevation due to rupture of an aneurysm was satisfactorily simulated in this experiment.
FIG. 6. Coronal sections of the brain at the level of R-15. A: Control. B: Perfusion defect is evident bilaterally in the thalamus and parietooccipital cortex. The upper part of the midbrain including the deep tegmental gray is also involved. C and D: Microscopic sections of the same brain (100 µ thick), taken from the areas marked in the figure. In both specimens, fine capillary networks are almost completely obliterated except for the relatively large penetrating arterioles. × 40.

FIG. 7. Patterns of the no-reflow phenomenon in 20 Pattern 1 dogs. R-15, R-20, R-25 = coronal slices on different planes according to Lim’s atlas. Macroscopically recognized areas of non-filling are dotted black.
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The initial elevation of ICP up to the systemic diastolic pressure, which is about the same as the intraarterial pressure of the main trunks of intracranial arteries, is sufficient to cause temporary cessation of blood flow to the brain, accompanied by suppression of cerebral function. In Pattern 1, this initial suppression of cerebral function, either complete or incomplete, lasted from several minutes to a considerably longer period, although it showed a tendency to recover. In Pattern 2, the initial suppression of both EEG and rCBF lasted as long as ICP remained elevated. In most of the experimental studies of SAH previously reported, the effect of this initial global ischemia has been negated since these studies were mainly concerned with the production of vasospasm. Considering the profound effect of the initial ICP elevation as demonstrated in our experiment, it may be said that not only the introduction of blood into the subarachnoid space but also the accompanying ICP changes must be simulated in the experimental study of SAH. In this respect, our model seems to be an appropriate one, although further refinement is possible.

Cessation of Bleeding and Subsequent Course of Parameters

Judging from the pattern of ICP elevation immediately after bleeding, the cessation of hemorrhage seems to occur in the first few minutes when the ICP is maximally elevated and CBF is subsequently markedly reduced or nonexistent. As soon as hemostasis is completed, the pressure-buffering system begins to function, although its efficacy may be limited by the formation of cisternal hematoma or acute hydrocephalus. In Pattern 1, the fall of ICP, and conversely the increase of cerebral perfusion pressure (CPP = SAP – ICP), was invariably succeeded by rapid elevation of rCBF and reactive hyperemia. Functional recovery proceeded during the phase of reactive hyperemia, although the completeness of recovery did not seem to correlate with the duration of reactive hyperemia.

In several dogs in Pattern 1, prolonged and marked suppression of EEG was observed in spite of the occurrence of reactive hyperemia. This dissociation of CBF and EEG, apparently simulating the clinical observation of

![Fig. 8. Tracings of ICP and rCBF in six Pattern 2 dogs. The hump of ICP corresponds to the appearance of Cushing's reflex. In all the dogs, there was no recovery of EEG in the observed period.](image)

![Fig. 9. A representative pattern of non-filling in Pattern 2. Only the relatively large pial arteries are filled with carbon in the cerebral hemisphere, whereas the infratentorial portion of the brain is well perfused. Upper: External appearance of the brain. Lower: Coronal section at the level of R-20. The brain parenchyma is completely unperfused sparing a small portion around the hypothalamus.](image)
global luxury perfusion,\textsuperscript{21} is probably the result of cortical neuronal damage at the time of initial global ischemia, although participation of other factors, such as local circulatory disorder or damage to deeper brain structures, is also possible. The occurrence of acute brain swelling or temporary vasoparalysis may be suspected in these cases, but it is unlikely because no marked elevation of ICP was observed in the postischemic period suggesting the presence of these factors.

In human SAH, generalized slowing of EEG activity has been reported repeatedly and has been attributed mainly to the presence of cerebral vasospasm.\textsuperscript{87,42} It has become clear that the relationship between CBF and vasospasm is not so simple as was previously thought, and that CBF reduction in cases of severe vasospasm is mostly unilateral,\textsuperscript{24,44} so the generalized or symmetrical EEG slowing in both hemispheres cannot be explained by vasospasm alone, unless it is diffuse and severe. One possible explanation would be to assume the presence of symmetrical cortical or more deeply seated lesions involving the midbrain, thalamus, or brain stem, irrespective of the angiographically demonstrated spasm.\textsuperscript{29,45} As this problem seems to have a special clinical relevance in respect to the neurological status after SAH, it will be further discussed in the next paragraph in terms of cerebral microcirculatory disturbance. In any case, the patterns of ICP, CBF, and EEG changes in Pattern 1 showed good correlation with the results of experiments of acutely raised ICP.\textsuperscript{22,28,30} This also speaks in favor of the view that SAH, in its acute phase, is essentially a pressure-loading phenomenon capable of causing a considerable degree of cerebral ischemia.

\textbf{Cerebral Microcirculation}

Since Ames, \textit{et al.},\textsuperscript{9} demonstrated the no-reflow phenomenon (NRP) in a rabbit ischemia model, the occurrence of NRP in ischemic-anoxic models has been repeatedly confirmed.\textsuperscript{13,18} The causes of NRP are presently supposed to be the swelling of perivascular astrocytes, neuronal cells, and capillary endothelium, and aggregation of red blood cells.\textsuperscript{2} Reversibility of brain dysfunction after anoxic-ischemic insult, on the other hand, has been recently investigated especially with regard to energy metabolism.\textsuperscript{14,25,26} These studies have shown that the recovery of energy metabolism is almost complete even after 1 hour of complete cerebral ischemia.

This fact, together with the experimental demonstration of complete recovery of cerebral electrical function, calls special attention to the problem of postischemic recirculation. If the cerebral tissue can tolerate a greater degree of ischemia and anoxia than was previously thought, the reversibility of cerebral dysfunction will depend on the completeness of recirculation.\textsuperscript{2,26} Although NRP has been studied in ischemia models with strangulation or ligation of extra- or intracranial arteries, its occurrence has not been surveyed in raised ICP models until the recent study of Marshall, \textit{et al.}\textsuperscript{33-35} In this study of acutely raised ICP (150 mm Hg for 15 min) in rabbits, no perfusion defects were found. As the authors pointed out, however, it is known that the degree of NRP depends on the height of the postischemic perfusion pressure.\textsuperscript{15,58} Therefore, the absence of NRP in such an experimental model in which postischemic CPP was maintained artificially does not necessarily negate the occurrence of NRP in clinical situations.

Especially in the acute stage of SAH, the real perfusion pressure to the cerebral vascular bed is only inaccurately estimated from the CPP because considerable pressure drop along the major intracranial arteries is expected due to vasospasm. In our model of SAH, cerebral perfusion with carbon black coincided with the period when the early spasm frequently appeared.\textsuperscript{5,8,57} This vasospasm seems to be the cause of the extensive perfusion defect observed in our SAH model. However, there are some problems in regarding the early spasm as the sole cause of NRP in this model. First, the intensity of early spasm, as demonstrated in previous studies including our own, is not considered to be sufficient to cause any perfusion defect by itself.\textsuperscript{18} Second, the distribution of perfusion defects was always symmetrical, which is difficult to explain on the basis of vasospasm alone. Third, we know that the initial global ischemia immediately after SAH is in a range sufficient to cause NRP (about 5 minutes of total cessation of CBF, according to Ames, \textit{et al.}).\textsuperscript{3} In this respect, the symmetrical distribution of NRP in our SAH model, with predilection for locations in the thalamus,
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Fig. 10. Diagram summarizes hypothesis of the pathogenetic role of no-reflow phenomenon in acute subarachnoid hemorrhage.

Based on the above considerations, we speculate that the mechanism of genesis of NRP in the present SAH model is as described below. In Pattern 1 SAH, the initial rise of ICP causes severe global ischemia and anoxia of the whole brain with complete stasis of blood flow for several minutes or more. This is associated with the disturbance of the intraparenchymal vascular bed secondary to astroglial, neuronal, or endothelial swelling, or intravascular aggregation of red blood cells that subsequently causes increased vascular resistance. When hemostasis is accomplished in a short period and ICP falls smoothly to near the normal level because of the pressure-buffering system, reperfusion of the brain proceeds rapidly with recovery of deranged capillary networks because of the sufficient height of the pressure head. This is followed by reactive hyperemia and recovery of cerebral function. However, in such regions of the brain where the pressure head is relatively low, that is, the arterial boundary zones or the thalamus and basal ganglia where long penetrating arterioles terminate, reperfusion does not proceed as rapidly as elsewhere. The early spasm, which is known to be widespread in the circle of Willis, will further aggravate the situation. Thus, the perfusion defect is established in the above preferential regions which are the locus minoris of the brain in terms of the height of the pressure head at the time of reperfusion. In Pattern 2, in which elevated ICP persists, probably due to large cisternal hematoma in our model, recirculation is impossible. No-reflow of the whole brain continues as long as ICP is elevated, finally creating the clinical picture of brain death. The above hypothesis can explain not only the results of our experiment but also the wide distribution of the necrotic foci in human SAH seen at autopsy, that could not be ascribed to cerebral vasospasm. As discussed earlier, generalized slowing of the EEG is frequently observed in the acute stage of human SAH, combined
with a lowered level of consciousness. Since the prolonged suppression of EEG was associated with a pronounced perfusion defect in our model, it is possible to assume that the generalized slowing of EEG and lowered level of consciousness in human SAH are both related to disturbed cerebral microcirculation. In this respect, it is interesting that the thalamus and upper part of the mid-brain were frequently involved in our model as these areas are thought to have special relationship to the level of consciousness.

Although it is not possible to conclude that NRP does occur and plays an important role in human SAH from the above correlations, it may at least be said that the possibility of deranged cerebral microcirculation must always be borne in mind in planning the therapy of acute SAH. This hypothesis is summarized in Fig. 10. In the analysis of pathological physiology of human SAH, the recent developments of clinical monitoring and neuroradiology have made great contributions. But the state of cerebral microcirculation is still difficult to detect by conventional diagnostic methods. In the investigation of this problem, further experimental studies with models simulating human SAH will be required.

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