Pathogenesis of Impending Myocardial Infarction and Acute Myocardial Infarction: Clinical and Angiographic Evaluation of Coronary Thrombosis as a Precipitating Factor

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In order to investigate the role of coronary thrombosis as a precipitating factor of acute myocardial infarction (AMI), we examined coronary angiographic findings in 89 patients with AMI taken within 24 hours of the onset and in 42 patients with prolonged angina attack of impending myocardial infarction (impending MI) taken within 50 hours of the last angina attack. Furthermore, in the patients with impending MI, the effects of intracoronary and intravenous thrombolytic therapy and anticoagulant therapy used to prevent impending MI from developing into AMI, were also studied.

(1) In 72 of 89 patients (81%) with AMI, coronary thrombi were detected angiographically. The thrombi were detected most frequently (88%) in angiographs taken within 3 hours of onset. (2) In 23 of 42 patients with impending MI, coronary thrombi were detected angiographically. In 6 patients with coronary thrombi who underwent intracoronary thrombolysis during angina attack, occlusive coronary thrombi in ischemia-related vessels were the observed, and recanalization by thrombolysis with intracoronary urokinase infusion relieved chest pain and improved ECG changes. (3) The incidence of AMI in 42 patients with impending MI who were treated with intracoronary and intravenous thrombolytic therapy and anticoagulant therapy was significantly less than in the conventional therapy group (80 patients) (11.9% vs. 27.5%; p < 0.05). In 4 of 5 patients with developing AMI, coronary thrombi were detected angiographically in the acute phase of impending MI.

These results indicate that coronary thrombosis plays an important role not only in the precipitation of impending MI but also in the development of impending MI to AMI.

Although evidence relating to proposed mechanisms of precipitation of acute myocardial infarction (AMI), such as coronary thrombosis and abrupt progression of coronary arterial narrowing with atheromatous plaque rupture and hemorrhage, platelet aggregation and coronary spasm has been reported, the mechanisms that actually lead to AMI remain controversial because of variability in development to AMI and limitations of methodology in pathological and clinical studies.

Recently, with the prevalence of intracorono-
nary thrombolysis therapy for AMI, it has been clarified\textsuperscript{9,10} that a high incidence of occlusive coronary thrombi is observed angiographically soon after the onset of AMI. Therefore, the role of coronary thrombosis has again come under scrutiny.

However, it is uncertain whether coronary thrombosis is a precipitating factor of AMI or a complicating factor. Accordingly, in order to investigate the role of coronary thrombosis as a precipitating cause of AMI, we examined the findings of coronary angiographs in the active phase of impending myocardial infarction (impending MI) and AMI, and the effects of thrombolytic and anticoagulant therapy on prevention of development of impending MI to myocardial infarction.

MATERIALS AND METHODS

1. Selection of patients:
   (A) Study of AMI
   Eighty-nine patients with AMI admitted to our coronary care unit within 24 hours of the onset of AMI from April, 1982 to December, 1984 were studied.

   (B) Study of impending MI
   Two hundred and two consecutive patients with impending MI admitted to our hospital within 48 hours of the last angina attack from January, 1981 to December, 1984 were studied.

   We defined impending MI as follows: (1) new onset of angina or recently worsening angina (within the past 4 weeks), either rest angina (RA) or angina on effort (EA) and (2) duration of attack > 30 minutes with a decreased responsiveness to nitrates (prolonged angina) or frequency of attacks > 3 times/day (frequent angina). In same cases the serum CPK level was normal or rose only minimally (under 200 IU/L), but electrocardiograms did not show new Q waves. Patients who developed AMI immediately after admission were excluded.

   Patients with impending MI were subdivided as follows:
   - impending MI (202 pts.)
     - frequent angina group (80 pts.)
       - prolonged angina group (122 pts.)
         - conventional therapy group (80 pts.)
         - intracoronary thrombolysis group (42 pts.)
   - prolonged angina group
   - patients with frequent angina and no prolonged angina.

   patients with prolonged angina.

   conventional therapy group -
   - patients treated with medical therapy except thrombolytic therapy i.e., nitrates β-blockers, Ca antagonists and so on.

   intracoronary thrombolysis group -
   - patients treated with medical therapy and intracoronary and intravenous thrombolysis therapy.

2. Coronary angiography (CAG) and intracoronary thrombolysis:
   Coronary angiography using standard Judkin’s or Sones’ techniques was performed within 50 hours of the last angina attack in 42 patients with prolonged angina of impending MI and within 24 hours of the onset in 89 patients with AMI. Subsequently, nitroglycerine, 300 μg, was infused into the ischemia related coronary vessels, and then intracoronary urokinase was infused by positioning a standard coronary catheter. Urokinase was infused at a rate of 24,000 units/min for the first 40 minutes. Mean total urokinase dose was 480,000 ± 125,000 IU (mean ± SEM) with a range of 240,000 to 960,000 IU in patients with impending MI and 640,000 ± 108,000 (mean ± SEM) with a range of 240,000 to 1200,000 IU in patients with AMI. Coronary angiography was repeatedly performed at 10 minute intervals during urokinase infusion on the projection best demonstrating the obstructive lesions.

   Follow-up CAG was performed 4 weeks after intracoronary thrombolysis therapy in the 34 patients in intracoronary thrombolysis group of impending MI.

   To assess angiographic findings suggestive of thrombus and the response to thrombolysis, two experienced angiographers reviewed all angiographs separately without knowledge of clinical findings.

3. Therapy after intracoronary thrombolysis:
   In patients with both AMI and impending MI or whom intracoronary thrombolysis was performed, heparin was infused continuously at a rate of 15,000–20,000 units/day intravenously for 3 days after intracoronary thrombolysis and accelerated coagulating time was controlled at one and a half times the normal range. Urokinase was also infused intravenously for 3
days at 480,000 units/day (1st day), 240,000 units/day (2nd day), and 120,000 units/day (3rd day). Three days later, warfarin was administered and thrombo test was controlled at 20% of normal value. For recurrent prolonged angina after intracoronary thrombolysis, 960,000 units of urokinase was infused intravenously over 30 minutes.

Nitrates, Ca antagonists and β-blockers were administered as in the conventional therapy group.

4. Angiographic definition of intracoronary thrombus:
The angiographic definition of intracoronary thrombus required one of the following according to Terrosu's criteria:11

- Presence of endoluminal filling defects
- Lengthening of the patent tract or regression of filling defects by urokinase administration
- Persistent staining of intraluminal material
- Abrupt occlusion with frayed border or convex dye outline

We attached special importance to endoluminal filling defects since they represent the negative image of the thrombus itself. Figure 1 shows typical angiographic features of coronary thrombi in impending MI.

5. Statistical analysis:
The results are given as mean values ± standard error of mean. Observed differences were tested for significance with the use of chi-square tests. Differences were considered to be

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Fig. 2. Coronary narrowing and incidence of coronary thrombi in infarct related vessels detected at intracoronary thrombolysis therapy in patients with acute myocardial infarction (n = 89).

![Graph showing coronary narrowing and incidence of coronary thrombi](image)

**Frequent angina group (n = 80)**

- New onset
- RA
- EA

- MI developed

**Prolonged angina group (n = 80)**

- New onset
- RA
- EA

- Frequent attack (>3 time a day, 3 days)
- Prolonged attack (duration >30 min and poor response to nitrates)

Fig. 3. Occurrence rate of myocardial infarction in conventional therapy group (160 pts.) with impending myocardial infarction during a 4-week follow-up period.

significant if p < 0.05.

**RESULTS**

(A) Study of acute myocardial infarction:

1. Coronary thrombi in early phase of acute myocardial infarction:

   In 89 patients with acute myocardial infarction (AMI), intracoronary thrombolytic therapy was performed within 24 hours of onset. Stenotic grade and frequency of occurrence of coronary thrombi in infarct vessels on baseline coronary angiography (CAG) are shown in Fig. 2. Patients were subdivided into three groups according to the interval between the onset of AMI and CAG.

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   In 81% of all patients, coronary thrombi were detected angiographically and in 85%, partial or total obstruction of the infarct vessels was observed. The incidence of coronary thrombi was highest in the group undergoing CAG within 3 hours of onset of AMI. Thus, coronary thrombi were found most commonly immediately after the onset of AMI.

(B) Study of impending MI:

1. Prognosis of impending myocardial infarction in the conventional therapy group:

   Figure 3 shows the incidence of development to AMI in the conventional therapy group (160 pts.) during a 4-week follow-up period. The occurrence rate of myocardial infarction was
TABLE I  FINDINGS OF CORONARY ANGIOGRAMS IN THE INTRACORONARY THROMBOLYSIS GROUP (42 PATIENTS) (No. of patients)

<table>
<thead>
<tr>
<th>CAG findings</th>
<th>Coronary thrombus (+)</th>
<th>Coronary thrombus (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasm</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No lesion</td>
<td>0</td>
<td>48.0</td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>12.4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>23</th>
<th>2</th>
<th>3</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attack-CAG interval mean (hrs.)</td>
<td>10.0</td>
<td>0</td>
<td>48.0</td>
<td>12.4</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>2</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>−12</td>
<td>10</td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>−50</td>
<td>7</td>
<td></td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of involved vessels</th>
<th>0VD</th>
<th>1VD</th>
<th>2VD</th>
<th>3VD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: CAG = coronary angiography; VD = vessel disease

TABLE II  CLINICAL FEATURES AND FINDINGS OF CORONARY ANGIOGRAMS IN THE ACUTE PHASE IN THE INTRACORONARY THROMBOLYSIS GROUP OF IMPENDING MI (No. of patients)

<table>
<thead>
<tr>
<th>CAG findings</th>
<th>Coronary thrombus (+)</th>
<th>Coronary thrombus (−)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasm</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>No lesion</td>
<td>0</td>
<td>48.0</td>
<td></td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>12.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Age</th>
<th>Male 24</th>
<th>Female 18</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35–80 years old (mean 62.3 years old)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>ECG changes during attack</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST ↑</td>
<td>13</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>ST ↓</td>
<td>6</td>
<td></td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Underfined</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Type of angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New onset</td>
<td>15</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>RA worsening</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>EA worsening</td>
<td>6</td>
<td></td>
<td>9</td>
<td>15</td>
</tr>
</tbody>
</table>

Abbreviation: MI = myocardial infarction; RA = rest angina; EA = angina on effort

significantly higher in the prolonged angina group (27.5%) than in the frequent angina group (3.8%) (p < 0.05).

2. Coronary angiographic findings in the acute phase in the intracoronary thrombolysis group of impending myocardial infarction:

Coronary thrombi in ischemia-related vessels were detected in 23 of 42 patients (55%) (coronary thrombus group). Of 19 patients without angiographic evidence of coronary thrombi, coronary spasm was observed in 2 patients during angina attack, and severe stenosis in ischemia-related vessels in 14 patients (severe stenosis group). No significant lesion was detected, in the remaining 3 patients (Table I). The grade of coronary narrowing in all patients with coronary

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thrombi was not reduced by intracoronary nitroglycerin administration.

Coronary angiography was performed at mean times of 10.0 hours after the last angina attack in patients with coronary thrombi and 16.7 hours in patients without coronary thrombi. In all patients in whom coronary spasm was observed angiographically, coronary angiography was performed during the angina attack.

While 19 of 23 patients with coronary thrombi had single vessel disease, 10 of 14 patients in whom severe stenosis was observed with no angiographic evidence of coronary thrombi in the ischemia related vessels had multiple vessel disease.

3. Clinical features and coronary angiographic findings in the acute phase in the intracoronary thrombolysis group:

The relationship between coronary angiographic findings and clinical features (type of impending MI, ECG findings during angina attack and previous myocardial infarction) was investigated in the intracoronary thrombolysis group (Table II).

The type of impending MI was new onset angina in 21 of 42 patients (50%), EA worsening in 15 patients (36%) and RA worsening in 6 patients (14%). Coronary thrombi were detected in 15 of 21 patients (71%) with new onset angina, in 6 of 15 patients (40%) with EA worsening and in 2 of 6 patients (23%) with RA worsening. Thus, coronary thrombi were detected most frequently in the new onset angina group. Coronary spasm was observed in 2 patients with new onset angina and no significant lesion in one patient with new onset angina and 2 patients with RA worsening.

Severe stenosis without angiographic evidence of coronary thrombi in the ischemia related vessels was found in 9 patients with EA worsening, 2 patients with RA worsening and 3 patients with new onset angina.

Regarding ECG findings during angina attack, ST elevation in the leads corresponding to the ischemia related vessels was more frequently observed in the coronary thrombus group than in the severe stenosis group (57% vs. 21%).

4. Changes in coronary narrowing before and after intracoronary thrombolysis and at follow-up of impending MI cases with intracoronary thrombi: (Fig. 4)

In all patients with coronary thrombi, intracoronary thrombi and coronary narrowing regressed immediately after intracoronary urokinase infusion.

In the follow-up study, regression of coronary narrowing was found in 4 of 20 patients (20%) and progression in 8 patients (40%). In 4 patients who developed AMI during the 4-week follow up period, progression of the ischemia related vessels was observed and in 3 of those 4 patients, total obstruction was found.

5. Changes in coronary lesion of impending MI cases with coronary thrombi undergoing intracoronary urokinase administration during angina attack:

In order to examine the mechanisms of acute coronary insufficiency and development to AMI, the effect of intracoronary urokinase was analysed in 6 patients with coronary thrombi undergoing coronary angiography during angina attack: (Fig. 5).

During angina attack, partial obstruction in the ischemia related vessels was found in 5 of 6 patients and total obstruction in one. Three of the former had intermediate collateral in the ischemia related vessel and intermittent obstruction was observed during angina attack in the latter.

Regression of the ischemia related vessels was
not observed in any of the patients with intracoronary nitroglycerin infusion. After intracoronary urokinase administration, however, recanalization with thrombolysis was observed. Simultaneously, chest pain disappeared, and ST deviation on ECG was restored.

At follow-up, total obstruction in the ischemia-related vessels was found in 2 patients with development to AMI during the follow-up period. In these patients, infarct size was small and good collateral circulation was observed in the infarct vessels.

6. Prognosis and effect of thrombolytic therapy and anticoagulant therapy in impending MI cases with prolonged angina:

Though anticoagulant therapy with heparin and warfarin was carried out in the intracoronary thrombolysis group, recurrent prolonged angina occurred during a 4-week follow-up period in 11 of 23 patients (48%) with coronary thrombi and in 2 of 19 patients (11%) with no angiographic evidence of coronary thrombi (Table III). In 9 of 13 patients with recurrent prolonged angina, 960,000 units of urokinase were infused intravenously during angina attack. While intravenous urokinase infusion was effective in relieving prolonged chest pain in these patients, 4 of 9 patients developed small myocardial infarction. One of 4 patients without intravenous urokinase administration developed nontransmural myocardial infarction.

As a result, 4 patients in the coronary thrombus group and one patient in the severe stenosis group developed myocardial infarction. Thus, during a 4-week follow-up period, the occurrence of myocardial infarction in the intracoronary thrombolysis group (42 pts.) was significantly lower than that in the conventional therapy group (80 pts.) (11.9% vs. 27.5%; p < 0.05).

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Table III: Prognosis in the Intracoronary Thrombolysis Group during a 4-Week Follow-Up Period

<table>
<thead>
<tr>
<th></th>
<th>(+)</th>
<th>(−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent prolonged AP</td>
<td>11/23</td>
<td>2/19</td>
</tr>
<tr>
<td>Intravenous infusion of UK 96 x 10^4 iu.</td>
<td>8/11</td>
<td>1/2</td>
</tr>
<tr>
<td>Prognosis</td>
<td>TMI 2</td>
<td>NTMI 1</td>
</tr>
</tbody>
</table>

Abbreviations: AP = angina pectoris; UK = urokinase; TMI = transmural in fraction; NTMI = nontransmural infarction.
DISCUSSION

Various authors have reported on the incidence of coronary thrombus in patients with transmural myocardial infarction, subendocardial myocardial infarction, and sudden coronary death. Because the subjects and the incidence of coronary thrombus in these previous reports varied and patients were identified mainly at necropsy, the role of coronary thrombosis in ischemic heart disease remained controversial.

Recently with the advent of intracoronary thrombolysis therapy, the incidence of coronary thrombus in patients with AMI has been examined angiographically in a clinical setting. These examinations indicated that immediately after the onset of AMI, coronary thrombi commonly exist in infarct vessels.

Studies at necropsy and/or after onset of AMI, however, cannot clarify the cause and effect relationship of coronary thrombosis in AMI.

Thus, to clarify the role of coronary thrombosis, study of the state developing into AMI is necessary. Accordingly, we analyzed angiographic findings during angina attacks and response to anticoagulant and thrombolytic therapy in impending MI.

1. Coronary thrombus immediately after onset of AMI:

Spain et al. reported from pathological examinations of coronary sudden death cases that frequency of coronary thrombosis increased with increasing time between the onset of acute ischemic symptoms and death and so they maintained that thrombosis occurs as a result of infarction. On the other hand, Bough et al. emphasized the importance of coronary thrombosis as a precipitating factor of AMI because of the high incidence of coronary thrombi in their pathological study. Recent angiographic studies done shortly after onset of AMI support this conclusion. Namely, many authors have reported that occlusive coronary thrombi are found angiographically in the infarct vessels and early recanalization with thrombolysis arrests the evolution of AMI and improves clinical state. Also, in our present study, occlusive coronary thrombi were detected in 88% of patients who underwent coronary angiography within 3 hours after onset of AMI.

2. Clinical significance of coronary thrombosis in impending MI:

In the past, impending MI had been noticed as a prelude to AMI because of the clinical features and the high incidence of development to AMI. Therefore, many investigators have reported its pathological and clinical characteristics, particularly its clinical course. Previously, we reported that 23 of 128 patients (18%) with impending MI treated with conventional therapy but excluding thrombolysis therapy developed AMI and 90 of 250 patients (36%) with AMI had a history of impending MI immediately before onset.

Although the mechanisms contributing to precipitation of impending MI remain uncertain, progression of atherosclerosis, plaque rupture and hemorrhage, coronary thrombosis, platelet aggregation and coronary spasm have been noted as precipitating factors. In particular, many investigators have recently taken interest in the role of coronary thrombosis.

Falk suggested the relation between the ischemic event and coronary thrombosis in a pathological study of unstable angina with fatal outcome. Vetrovec and Mandelkorn and Capone reported that intracoronary thrombi were detected angiographically in 6.2%–85% of patients with unstable angina who underwent CAG in the acute or subacute phase. The reason for this variety in incidence of coronary thrombi is that unstable angina in these reports included many types of angina pectoris and pathogenesis may not be determinable by a single mechanism. Another reason is that the incidence of coronary thrombi decreases with increase in time from the last attack to CAG.

Therefore, we limited subjects to a prolonged angina group with intractableness for conventional therapy and high incidence of development to myocardial infarction, and performed CAG within 50 hours (11.5 ± 5.4 hours: standard error of mean). As a result, coronary thrombi were detected angiographically in 23 of 42 patients (55%) with impending MI. In 6 of 13 patients (46%) in whom CAG was carried out during the angina attack, occlusive coronary thrombi were detected and recanalization with intracoronary urokinase thrombolysis relieved the chest pain. Furthermore, in 11 of 23 patients with angiographic evidence of coronary thrombus, prolonged angina revived and urokinase intravenous injection was effective for these recurrent angina attacks.
These findings indicate that coronary thrombosis plays an important role as a causative factor in many cases of impending MI with prolonged angina.

3. Impending myocardial infarction and acute myocardial infarction:

Some investigators reported that the occurrence of AMI in unstable angina decreased with anticoagulant and/or thrombolytic therapy.²⁶,²⁷ In a randomized study of 214 patients on the effects of systemic heparin on intermediate coronary syndrome, Telford and Wilson²⁷ demonstrated a significantly reduced incidence of development to transmural myocardial infarction in the heparin and warfarin treated group compared to the group receiving placebo over a 6-month follow-up period, suggesting the important role of coronary thrombosis in the evolution of unstable angina to AMI.

In our study of patients with prolonged angina who were most intractable for conventional therapy and of patients with impending MI who developed AMI most frequently, the incidence of development to AMI was significantly less in the intracoronary thrombolysis group than that in the conventional therapy group. Furthermore, of 5 patients with development to AMI, 4 patients were in the coronary thrombus group and the remaining patient was in the severe stenosis group. In addition, coronary thrombi were detected with high frequency immediately after the onset of AMI.

These results indicate that coronary thrombosis plays an important role in the development of impending MI into myocardial infarction.

Concerning the confirmation of coronary thrombi in patients with impending MI, there is a question as to whether myocardial infarction had already developed at CAG in these cases. However, we can resolve this doubt for the following reasons: (1) None of these patients developed myocardial infarction immediately after intracoronary thrombolysis. (2) Of 22 patients with coronary thrombi, only 4 developed myocardial infarction during a 4-week follow-up period and in patients with development of AMI, recurrent prolonged angina developed into AMI.

Remarkably, coronary angiograms during angina attack showed residual flow in ischemic related vessels in all these patients (5 patients with subtotal obstruction, one patient with intermittent obstruction, 3 patients with intermediate collateral circulation). This indicates that residual flow and early recanalization with thrombolysis prevented these patients from developing AMI.

Only one of 19 patients with no angiographic evidence of coronary thrombi developed AMI. In these cases as well, the participation of coronary thrombi in development to AMI could not be disproved.

Though we restricted subjects in this study to prolonged angina patients with a high incidence of development to AMI and then could clarify the role of coronary thrombosis angiographically in many cases of impending MI by the various mechanisms of development to AMI are thought to be various. There is still uncertainty as to the role of other mechanisms such as coronary spasm, plaque rupture and hemorrhage with abrupt progression of coronary arterial narrowing, alteration in metabolism of prostanol, serotonin, histamine, platelet activating factor and so on.

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