SUMMARY To investigate the relationships between gastric change accompanying patients with acute stroke and the function of the autonomic nervous system and pituitary-adrenal system, studies on the gastroendoscopic technique and biochemical observations were done in 122 patients.

The mean urinary noradrenalin and adrenalin excretions were elevated in patients with acute gastric changes, especially in patients with multiple erosions and acute ulcers.

ACUTE CHANGES of the gastrointestinal tract in association with cerebral disease have been recognized since the first half of the nineteenth century. This subject has received much attention more recently, and a number of clinical and experimental studies on patients with various cerebral diseases and concomitant gastrointestinal changes have been reported. These studies suggested that such gastrointestinal changes were induced by the accelerated function of the autonomic system and/or pituitary-adrenal system due to a lesion of the hypothalamus or its centrifugal tracts. But, in spite of considerable clinical and experimental work, the role of the autonomic nervous system and hypothalamic-pituitary-adrenal system in the production of acute gastrointestinal changes still remains unclear.

In the present study, in order to investigate the relationship between acute gastric change accompanying cases of acute stroke and the function of the autonomic nervous system and pituitary-adrenal system, studies using the gastroendoscopic technique, and analyses of urinary nor-adrenalin excretion, urinary adrenalin excretion, serum gastrin concentration and urinary 17-OHCS excretion were done on 122 patients with acute stroke.

Methods

One hundred twenty-two patients who were admitted to the Research Institute of Brain and Blood Vessels, Akita, Japan, from May 1973 to October 1974 were studied, including 50 with cerebral hemorrhage, 40 with cerebral infarction, and 32 with subarachnoid hemorrhage. In all patients positive results of these cerebral lesions were found by carotid and/or vertebral angiography, and stroke patients with a normal angiogram were excluded. There were 89 men and 33 women, age 29 to 80 years (mean age, 56.7 ± 10.9 years). Most patients were admitted within three days after the onset of stroke (85%), and all within 18 days after stroke.

The first gastroendoscopic examination (Olympus GTF S-2) was done on the majority of patients within one week after the onset and on all within two to three weeks. On 44 patients the gastroendoscopic examination was done only once, and on the rest of the patients the examination was done several times within six weeks after the onset.

Measurement of the urinary noradrenalin and adrenalin was done 222 times, that of fasting serum gastrin concentration was done 228 times, and that of urinary 17-OHCS excretion was done 272 times.

The classification of the gastroendoscopic findings was done similarly to the previous study. There were acute ulcers in nine patients, multiple erosions in six, petechiae in 48, erosion showing fibrin nets in eight and no acute gastric change in 51, as shown in table 1.

Measurement of urinary catecholamines was done with ethylenediamine method (Yoshinaga's modification). The patients' 24-hour urine samples were collected in a bottle into which a solution of HCI concentration (10 ml) was added to preserve the urine acid. These urine samples (100 ml) were stored in a refrigerator (2° to 4°C), until the measurements were done.

Serum fasting gastrin concentration was measured with CIS-GASK which is based on radioimmunoassay. Blood was taken at 6 A.M. after overnight fasting and the separated serum was stored in a refrigerator (−20°C).

Measurement of urinary 17-OHCS was done with the analysis of Porter-Silber chromogen (Kanbegawa's modified method). The urine was collected and stored in the same way as for the urinary catecholamines.

The means of patient controls for urinary noradrenalin, adrenalin and 17-OHCS excretion were obtained from the values of those which were measured after more than four weeks from the onset of stroke in 30 patients with normal gastroendoscopic findings and with alert consciousness. Therefore, the patient control values in the present study might approximate normal control values, and the mean of patient controls for serum gastrin concentration were obtained from 19 similar patients.

The comparison of biochemical values was done between the patient controls and the groups of each gastroendoscopic findings in four periods (in the first, second, third and fourth to sixth week after stroke). When the numbers of data of a respective group were less than four, statistical studies were not performed.
Results

Urinary Noradrenalin Excretion (Table 2)

The mean of patient controls of urinary noradrenalin excretion in our Institute was 20.5 ± 11.8 µg per day (mean ± SD).

The mean urinary noradrenalin excretion in the first and second week after stroke was elevated in almost all groups including the group with no acute gastric change compared with that of patient controls. Especially, the elevation was found to be significant in patients with multiple erosions and acute ulcers.

In the patients with acute ulcers, the increase of urinary noradrenalin excretion was found in all periods, from the first to the fourth to sixth weeks. The urinary noradrenalin excretion was higher in patients with acute ulcers than in patients with no acute gastric change in all four periods (first week: p < 0.005, second week: p < 0.05, third week: p < 0.005, fourth to sixth weeks: p < 0.01).

In the patients with multiple erosions, the mean urinary noradrenalin excretion was increased in the first and second week only. The excretion was also significantly higher in patients with multiple erosions than in patients with no acute gastric change in the first (p < 0.005) and second weeks (p < 0.005).

In the third week, the excretion in patients with petechiae was higher than that in the patients with no acute gastric change (p < 0.05). However, even in the patients with no acute gastric change the excretion was increased in the first and second weeks compared with that of patient controls.

Urinary Adrenalin Excretion (Table 3)

The mean of the patient controls of urinary adrenalin excretion in our Institute was 5.1 ± 4.2 µg per day (mean ± SD).

In the patients with acute ulcers, a significant increase of the mean urinary adrenalin was found in all four periods as compared with that of the patient controls. Further, the mean excretion was higher in patients with acute ulcers than in patients with no acute gastric change in the first (p < 0.01), the second (p < 0.05) and the fourth to sixth weeks (p < 0.05).

In the patients with multiple erosions and petechiae the urinary adrenalin excretion was increased extremely in the first and second weeks as compared with that of patient controls. The mean excretion was higher in the patients with multiple erosions than in the patients with no acute gastric change in the first and second weeks (p < 0.005).

The excretion was slightly increased in the patients with erosion showing fibrin nets and no acute gastric change compared with that of the patient controls.

Fasting Serum Gastrin Concentration (Table 4)

The mean of the patient controls of serum gastrin concentration in our Institute was 46.9 ± 29.4 pg per milliliter (mean ± SD).

Compared with the patient controls the elevation of the mean fasting serum gastrin concentration was found in the patients with acute ulcers and no acute gastric change. The mean concentration was higher in the patients with acute ulcers.
ers (p < 0.005) and no acute gastric change (p < 0.005) than in the patients with petechiae in the first week. In the patients with multiple erosions, petechiae and erosion showing fibrin nets, the mean serum gastrin concentration was almost within the patients' control value.

Urinary 17-OHCS Excretion (Table 5)

The mean of the patient controls of urinary 17-OHCS excretion in our Institute was 7.3 ± 3.2 mg per day (mean ± SD).

Compared with the patient controls the mean urinary 17-OHCS excretion was increased in the patients with multiple erosions, petechiae and acute ulcers in the first and second weeks. There were significant differences in the mean urinary 17-OHCS excretion between the patients with erosion showing fibrin nets and the patients with multiple erosions in the first week (p < 0.01).

Interval Between Onset of Stroke and the Most Severe Gastric Complication in Each Patient

Multiple erosions and petechiae were produced mainly in the first week after the stroke; acute ulcers and erosion showing fibrin nets were found mainly in the second week as seen in table 6.

In figure 1, the time course of urinary noradrenalin and adrenalin excretion, serum gastrin concentration and urinary 17-OHCS excretion in a 48-year-old man with cerebral hemorrhage of combined type is shown. On the first gastroendoscopic examination (the fourth day after the onset), only a few petechiae were found with increases in serum gastrin concentration and urinary 17-OHCS excretion, but on the second examination (the eleventh day after the onset) acute ulcers were found with increases in urinary noradrenalin and adrenalin excretion. Thereafter, the acute ulcers become cured with the normalization of the level of urinary noradrenalin and adrenalin excretion and serum gastrin concentration.

Discussion

The relationship of accelerated function of the sympathetic nervous system to the occurrence of acute gastric changes has been demonstrated by experimental studies. The relationship of urinary catecholamine excretion and acute gastric changes in association with cerebral diseases, however, has not been explained in these articles. On the contrary, Nyman and Wahlberg reported that a patient with pheochromocytoma showed a high increase in catecholamines and vanilmandelic acid excretion and died due to gastrointestinal bleeding; at autopsy, the gastric mucosa showed atrophic gastritis with mucosal necrosis.

In the present study, the mean urinary noradrenalin and mean adrenalin excretion were increased in all groups in the acute stage of stroke. The increase was marked in the patients with acute ulcers and multiple erosions. On the other hand, in patients with no acute gastric change the increase was slight and not prolonged.

These findings suggest that the accelerated functions of

### Table 3: Time Course of Urinary Adrenalin Excretion After Onset of Stroke

<table>
<thead>
<tr>
<th>Gastroendoscopic findings</th>
<th>1 (µg/day)</th>
<th>2 (µg/day)</th>
<th>3 (µg/day)</th>
<th>4 to 6 (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ulcers</td>
<td>19.3 ± 8.7**</td>
<td>21.9 ± 16.2*</td>
<td>16.0 ± 12.3</td>
<td>16.6 ± 10.5***</td>
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<td></td>
<td>n = 8</td>
<td>n = 9</td>
<td>n = 7</td>
<td>n = 8</td>
</tr>
<tr>
<td>Multiple erosions</td>
<td>30.6 ± 5.0***</td>
<td>32.5 ± 14.3***</td>
<td>10.7 ± 7.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 6</td>
<td>n = 7</td>
<td>n = 0</td>
<td>n = 3</td>
</tr>
<tr>
<td>Petechiae</td>
<td>13.6 ± 9.4†††</td>
<td>12.3 ± 7.5†††</td>
<td>4.6 ± 3.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 32</td>
<td>n = 17</td>
<td>n = 5</td>
<td></td>
</tr>
<tr>
<td>Erosion showing fibrin nets</td>
<td>12.3 ± 9.2</td>
<td>11.4 ± 6.3†††</td>
<td>9.4 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>No acute fibrin nets</td>
<td>9.9 ± 8.5†††</td>
<td>10.6 ± 10.2</td>
<td>5.1 ± 2.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 49</td>
<td>n = 22</td>
<td>n = 11</td>
<td>n = 5</td>
</tr>
</tbody>
</table>

1. Differences from patient controls, *p < 0.05, †p < 0.01, ‡‡‡p < 0.005.
2. Differences from group with no gastric change, *p < 0.05, **p < 0.01, *** p < 0.005.
3. Mean values of patient controls (5.1 ± 4.2 SD Mg/day).

### Table 4: Time Course of Serum Gastrin Concentration After Onset of Stroke

<table>
<thead>
<tr>
<th>Gastroendoscopic findings</th>
<th>1 (pg/ml)</th>
<th>2 (pg/ml)</th>
<th>3 (pg/ml)</th>
<th>4 to 6 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ulcers</td>
<td>187.2 ± 166.4†††</td>
<td>130.9 ± 90.0††</td>
<td>67.3 ± 27.1</td>
<td>48.8 ± 20.1</td>
</tr>
<tr>
<td></td>
<td>n = 7</td>
<td>n = 9</td>
<td>n = 7</td>
<td>n = 7</td>
</tr>
<tr>
<td>Multiple erosions</td>
<td>52.5 ± 24.9</td>
<td>67.6 ± 34.1</td>
<td>106.7 ± 25.7</td>
<td>60.0 ± 10.0</td>
</tr>
<tr>
<td></td>
<td>n = 6</td>
<td>n = 5</td>
<td>n = 3</td>
<td>n = 3</td>
</tr>
<tr>
<td>Petechiae</td>
<td>54.6 ± 24.0</td>
<td>60.4 ± 52.4</td>
<td>34.1 ± 22.1</td>
<td>54.5 ± 27.0</td>
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<td></td>
<td>n = 40</td>
<td>n = 8</td>
<td>n = 2</td>
<td>n = 3</td>
</tr>
<tr>
<td>Erosion showing fibrin nets</td>
<td>33.1 ± 14.9</td>
<td>67.9 ± 42.0</td>
<td>74.0 ± 5.7</td>
<td>31.8 ± 21.1</td>
</tr>
<tr>
<td>No acute fibrin nets</td>
<td>122.9 ± 89.9†††</td>
<td>113.2 ± 103.0††</td>
<td>49.2 ± 47.7</td>
<td>71.7 ± 57.6</td>
</tr>
<tr>
<td></td>
<td>n = 44</td>
<td>n = 16</td>
<td>n = 10</td>
<td>n = 10</td>
</tr>
</tbody>
</table>

1. Differences from patient controls, †p <0.01, ‡‡‡p <0.001.
2. Mean values of patient controls (46.9 ± 29.4 SD pg/ml).
ACUTE GASTRIC CHANGES IN PATIENTS WITH ACUTE STROKE. 2/Kitamura et al. 467

TABLE 5  Time Course of Urinary 17-OHCS Excretion After Onset of Stroke

<table>
<thead>
<tr>
<th>Gastroendoscopic findings</th>
<th>Interval from onset, weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (mg/day)</td>
</tr>
<tr>
<td>Acute ulcers</td>
<td></td>
</tr>
<tr>
<td>n = 5</td>
<td>13.4 ± 9.8†</td>
</tr>
<tr>
<td>Multiple erosions</td>
<td></td>
</tr>
<tr>
<td>n = 7</td>
<td>16.7 ± 7.5††</td>
</tr>
<tr>
<td>Petechiae</td>
<td></td>
</tr>
<tr>
<td>n = 7</td>
<td>13.5 ± 9.4††</td>
</tr>
<tr>
<td>Erosion showing fibrin nets</td>
<td></td>
</tr>
<tr>
<td>n = 5</td>
<td>5.4 ± 2.9</td>
</tr>
<tr>
<td>No acute gastric change</td>
<td></td>
</tr>
<tr>
<td>n = 53</td>
<td>9.3 ± 7.5</td>
</tr>
</tbody>
</table>

1. Differences from patient controls. ††p <0.01, †††p <0.005.
2. Mean values of patient controls (7.3 ± 3.2 SD mg/day).

the sympathetic system may play a role in the production of gastric changes, particularly acute ulcers and multiple erosions accompanying acute stroke.

There have been several reports that showed the relationship between accelerated function of the parasympathetic nervous system and the elevation in serum gastrin concentration and in gastric secretion.11,12 Trudeau and McGuigan,13 Korman et al.14 and Hansky and Korman15 reported that the serum gastrin concentration was elevated in patients with peptic ulcer. Bowen et al.16 also reported that serum gastrin concentration was significantly higher after central nervous system injury than after non-central nervous system injury.

In the present study, the mean serum gastrin concentration was elevated in patients with acute ulcers in the first and second weeks after the onset of stroke. This observation led to the suggestion that the accelerated function of the parasympathetic systems had an effect on the occurrence of acute ulcers in association with acute stroke.

Meanwhile, in patients with no acute gastric change the mean serum gastrin was elevated too. However, in these patients an increase in the urinary catecholamine excretion was mild compared with patients with acute gastric change, and 17-OHCS was not increased. It is suggested that acceleration of the function of the parasympathetic nervous system alone could not produce the acute gastric changes in patients with stroke.

In recent papers a strong correlation between serum gastrin and the plasma adrenalin levels has been shown.18-20 In the present study, all the patients with an increase in urinary adrenalin excretion did not show an elevation of serum gastrin concentration. However, with reference to this relationship, further investigation may be necessary.

It is well known that administering steroid hormone induces acute gastric ulcer21,22 and the function of the pituitary-adrenal system has an influence upon the gastric secretion.3,11,23 Also, there are some reports that gastrointestinal lesions accompanying acute stroke may be induced by the increased excretion of steroid hormone.24

In this study, the mean urinary 17-OHCS excretion was increased in patients with multiple erosions, petechiae and acute ulcers in the first and second weeks. The mean urinary noradrenalin and the mean adrenalin excretion showed identical changes in the patients with petechiae and erosion showing fibrin nets. However, the mean urinary 17-OHCS excretion was increased in the former and was not increased in the latter.

From these results, it is suggested that adrenalin excretion, serum gastrin concentration and urinary 17-OHCS ex-

FIGURE 1. Time course of urinary noradrenalin excretion, urinary adrenalin excretion, serum gastrin concentration and urinary 17-OHCS excretion in a 48-year-old man with acute ulcers. Gastroendoscopic examination was done five times.
cretion have respectively different roles in the production of various types of acute gastric changes.

In the present study, the urinary noradrenalin and adrenalin excretion and serum gastrin concentration in patients with acute ulcers were increased significantly in the first and second weeks. On the other hand, the urinary 17-OHCS excretion was normalized in the second week, when acute ulcers would be induced. Therefore, it is inferred that acute gastric ulcer might be induced by the accelerated function of both sympathetic and parasympathetic nervous systems, but the role of accelerated function of the pituitary-adrenal system might be slight.

In the first week after stroke when multiple erosions and petechiae mainly would be produced, the urinary noradrenalin, adrenalin and 17-OHCS excretion were increased significantly in these groups. But the mean serum gastrin concentration and urinary noradrenalin excretion and serum gastrin concentration in patients with acute ulcers were increased significantly in the first and second weeks. On the other hand, the mean serum gastrin concentration was not elevated in these patients with multiple erosions or petechiae. It could be said that multiple erosions and petechiae would be induced by the acceleration of the sympathetic and pituitary-adrenal functions.

While in the patients with erosion showing fibrin nets a slight increase in urinary noradrenalin and adrenalin excretion was seen, the serum gastrin concentration and urinary 17-OHCS excretion remained normal until the fourth to sixth week. The complication of erosion showing fibrin nets might result from acceleration of only the sympathetic system.

Acknowledgment

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T Kitamura and K Ito

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