Hemolysate-Induced Contraction in Smooth Muscle Cells of the Guinea Pig Basilar Artery

SHIGERU FUJIWARA, M.D., AND HIROSI KURIYAMA, M.D., D. PHIL.

SUMMARY The hemolysate (10^{-5}-10^{-2} times dilution; original hemoglobin concentration was 0.83 ± 0.10 \times 10^{-3}M) evoked the contraction in a dose dependent manner, and this contraction was composed of low and high sensitive responses as estimated from the Eadie-Hofstee's plot. Indomethacin (10^{-7}-10^{-5}M) inhibited the latter component in the hemolysate-induced contraction. The membrane potential of smooth muscle cells was —50 mV and the cell was electrically quiescent. The hemolysate (>10^{-2} times dilution) produced the contraction with no change in the membrane property. Carbocyclic thromboxane A_2 (cTXA_2; 2.8 \times 10^{-10}M) produced the contraction without depolarization of the membrane, yet the TXA_2 synthesis inhibitor, OKY-1581 (10^{-3}M), had no effect on the hemolysate-induced contraction. PGE_1, PGE_2, and PGF_2_\alpha (2.8 \times 10^{-10}M) produced the contraction with no change in the membrane property. The contraction evoked by 2.8 \times 10^{-8}M PGF_2_\alpha corresponded well with that evoked by 3 \times 10^{-3} times dilution of the hemolysate. Removal of the endothelium by mechanical rubbing modified the hemolysate-induced contraction. Under the assumption that OKY-1581 is a selective inhibitor for TXA_2 synthesis, the major part of the contraction (the indomethacin sensitive component) of the basilar artery is postulated to be due to synthesis of the primary PG rather than TXA_2 by the hemolysate, yet the hemolysate itself, has to some extent a direct action in evoking the small contraction.

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CEREBRAL VASOSPASM has a grave influence on the prognosis of patients with subarachnoid hemorrhage following ruptured cerebral aneurysms. ¹ ² The underlying mechanism is related to a complex of multiple factors, e.g. the hemolysate extracted from the subarachnoid clot, especially oxyhemoglobin (oxy Hb), plays an important role in the genesis of chronic vasospasm.³ ⁴ and frequent associations of vasospasm with the presence of subarachnoid clot have been verified by computed tomography.⁵ Toda et al⁶ reported that the Hb containing solution released vasoconstrictive substances from the canine cerebral artery, and thus the contraction evoked by this solution was inhibited when aspirin was added to the bath in vitro. However, the relaxation of the cerebral vascular tissue induced by aspirin was incomplete. Not only aspirin but other nonsteroid anti-inflammatory agents which possess a prostaglandin (PG) synthesis inhibiting action suppressed the hemolysate-induced cerebrovascular contraction, and differed in the actions were quantitative.⁷ ⁸ On the other hand, activations of the arachidonic cascade related to generation of a vaso-
spasm through the free radical reaction induced by oxy Hb have been discussed. Superoxide scavenger and superoxide dismutase, which modify phosphatidyl inositol and other phospholipids contributing to the arachidonic cascade, had no effect on the Hb-induced vasospasm.

The membrane and contractile properties of the guinea pig and canine basilar arteries have been extensively investigated and in the present experiments we attempted to clarify the mechanism of hemolysate action on the guinea pig basilar artery, in vitro. We found that PGs, especially PGF$_{2\alpha}$, play an important role in the hemolysate-induced contraction. The underlying mechanism, in relation to clinical cerebral vasospasm was given attention.

Methods and Materials

Guinea pigs of either sex weighing 300–350 g were decapitated, and the basilar artery carefully dissected under a binocular microscope. The diameter of this artery was between 0.2–0.3 mm. The basilar artery (10 mm in length) was mounted in an organ bath with a capacity of 1.0 ml and a temperature of 35–36°C. In superfusion with Krebs solution was carried out at the rate of 2 ml/min, for recording the electrical and mechanical responses. With this procedure, the bath solution could be replaced completely within 30 sec.

To record the membrane potential, conventional glass capillary microelectrodes filled with 3 M KC1 (the resistance of the electrode was 50–80 MΩ) were used. The microelectrode was inserted from the outer layer of the artery. To record electrotonic potentials, application of electrical stimulation was made by the partition stimulating electrode method by Abe and Toida, and a current pulse of 1–2 seconds in duration was applied in the longitudinal direction of the vessel.

Mechanical responses were recorded by the method described by Suzuki and Casteels; briefly, a pair of L-shaped stainless rods, sharpened by electrolysis, was inserted into a ring segment of about 0.2 mm width. One of the rods was fixed to a manipulator and another was connected to a tension recorder (TB-612T, Nihon-Kohden). Hemolysate was prepared by the following procedures, i.e. heparinized whole blood (100 units of heparin for each 10 ml of blood) of the guinea pig was spun at 3,000 r.p.m. for 30 minutes, and the supernatant and buffy coat were removed. The lower layer of packed erythrocytes was pipetted off and washed three times with three to five volumes of cold saline. With these procedures, contamination by platelets could be ruled out. The washed erythrocytes were lysed with the addition of the same volume of distilled water, using an electric blender. The lysed erythrocytes were spun at 15,000 r.p.m. for 30 minutes, and the supernatant was used as the original hemolysate. The final concentration of the hemolysate in the bath was expressed from a dilution of the original hemolysate with Krebs solution, i.e. the dilution ratio $10^{-2}$ times means the concentration of hemolysate of $10^{-2}$ times the original hemolysate. The original hemolysate contained 0.83

± 0.10 × 10$^{-3}$M Hb, as measured by the cyanmethemoglobin method. Krebs solution served as the control solution, and was of the following composition (mM): Na+, 137.4; K+, 5.9; Mg$^{2+}$, 1.2; Ca$^{2+}$, 2.5; Cl$^{-}$, 134.0; H$_2$PO$_4$-, 1.2; HCO$_3$-, 15.5; and glucose, 11.5. The solution was bubbled with 97% O$_2$ and 3% CO$_2$, and the pH was kept at 7.2–7.3. Excess [K]$_o$ solution was prepared by replacing NaCl with equimolar KC1 isotopically.

The following drugs were used at concentrations (molar concentrations) described in the results; indomethacin (Sigma), phen tolamine and mepryramine (Tokyo Kasei), methysergid (Sandoz), atropine (Daichi), theophylline and quinidine (Ishizu), apamin (Serva), carbocyclic throm boxane A$_2$ (cTXA$_2$), OKY-1581 (Ono) and prostaglandins F$_{2\alpha}$, E$_1$, E$_2$ (Ono), diltiazem (Tanabe) and EGTA (Dozin).

Obtained values are expressed as the mean ± standard deviation (S.D.). Statistical significances were determined using Student’s t-test, and probabilities of less than 5% ($p < 0.05$) were considered to be significant.

Results

Effects of Hemolysate on the Mechanical and Electrical Properties of the Guinea Pig Basilar Artery

The hemolysate, ($10^{-2}$ times dilution) evoked the contraction of smooth muscle cells in the basilar artery. The amplitude was about 0.77 times the 39.2 mM K$_o$-induced contraction (fig. 1). The hemolysate-induced contraction was composed of an initial phasic and then tonic responses. To avoid alternations in the pH and in the constitution of the perfusate, we used $10^{-2}$ times dilution of the hemolysate, as the maximum concentration. The minimum concentration of hemolysate required to evoke the contractions was $10^{-2}$ times dilution and the contraction increased, in a dose-dependent manner. Following pretreatment with indomethacin (IND) for 40 min, amplitudes of the hemolysate-induced contraction were decreased, yet this agent had no effect on the 39.2 mM K$_o$-induced contraction. The inhibition of the hemolysate-induced contraction was given attention.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Contractions evoked by application of 39.2 mM [K]$_o$ or the diluted hemolysate ($10^{-4}$, $10^{-3}$ and $10^{-2}$ times) and the effect of $10^{-8}$M indomethacin (IND) on these contractions. $10^{-8}$M indomethacin was pre-treated for 40 minutes. Horizontal bars indicate the application of various agents.
contraction by IND depended on the time of exposure and the maximum inhibition was observed after 40 min (after 5 min: 0.92 ± 0.11 times, 20 min: 0.77 ± 0.05 times, 40 min: 0.55 ± 0.10 times, 60 min: 0.55 ± 0.05 times the control observed in 39.2 mM [K]o). Therefore, in the following experiments, pretreatment with IND on tissues was over 40 minutes. Even with a high concentration of IND (10^{-3} M) given as a pretreatment, the hemolysate-induced contraction was not completely blocked, and a small amplitude of sustained contraction remained in any given concentration of the hemolysate (>3 × 10^{-4} times dilution). Figure 2 A shows the dose-response relationship of the hemolysate-induced contraction, and the effect of various concentrations of IND on the hemolysate-induced contractions. In concentrations over 10^{-3} times dilution, the hemolysate evoked the contraction, dose-dependently, however, with application of the hemolysate (>10^{-3} times dilution), a slope of the dose-response relation curve became steeper. Figure 2 B shows the relationship as determined by the Eadie-Hofstee’s plot. Two components of the contraction were revealed. The inhibitory effect of IND on higher concentrations (10^{-3} times dilution) of the hemolysate-induced contraction was prominent, while with applications of lower concentrations (<3 × 10^{-4} times dilution) of hemolysate, IND had no effect on the contraction. Thus, it indicated that the hemolysate-induced contraction was composed of two responses, i.e. IND-sensitive and IND-less sensitive responses.

The resting membrane potential of smooth muscle cells of the guinea pig basilar artery was -51.6 ± 2.3 mV (n = 60 measured from 10 preparations), this value being roughly the same as previously reported but the value was much lower than that observed in most of the muscle cells, and the spike potential was generated during the transient peak depolarization. The amplitude of spike potential was not in an "all or none manner", and during repolarization of the membrane, generation of the spike potentials finally ceased in the presence of hemolysate.

Table 1 showed the effects of various antagonists for the known receptors on the hemolysate-induced contraction. The results indicated that the generation of the

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**Figure 2. The effects of indomethacin (10^{-3} M-10^{-4} M) on the dose-response relationship of contractions obtained by application of various concentrations of hemolysate. A. The effects of indomethacin on contractions evoked by the hemolysate. The effects of 3 different concentrations of indomethacin on the relationship between the amplitude of hemolysate-induced contraction and concentration of hemolysate (10^{-2} to 10^{-3} times dilution) were observed. The amplitude of the 39.2 mM [K]o-induced contraction before application of the hemolysate in each experiment was registered as a relative tension of 1.0. Vertical bars indicate S.D. or 2 × S.D., *p < 0.05, **p < 0.01 in comparison to the control. n = 5-10 preparations. B. Eadie-Hofstee plot of the hemolysate-induced contraction. The line was drawn by least square method.
hemolysate-induced contraction (the IND-sensitive and less sensitive components) was not due to activations of α-adrenoceptor, 5-hydroxytryptaminergic receptor, histaminergic H1 receptor, acetylcholine receptor and purinergic P1 and P2 receptors.

**TABLE 1. Effects of Various Chemical Agents on the Hemolysate-induced Contraction of the Guinea Pig Basilar Artery.**

<table>
<thead>
<tr>
<th>Diluted hemolysate (10^{-2} times)</th>
<th>Relative tension ± S.D. (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreated with</td>
<td></td>
</tr>
<tr>
<td>Phentolamine 10^{-6} M</td>
<td>0.43 ± 0.09 (7)</td>
</tr>
<tr>
<td>Methysergide 10^{-6} M</td>
<td>0.42 ± 0.15 (7)</td>
</tr>
<tr>
<td>Mepyramine 10^{-6} M</td>
<td>0.47 ± 0.12 (6)</td>
</tr>
<tr>
<td>Atropine 5 × 10^{-6} M</td>
<td>0.48 ± 0.13 (6)</td>
</tr>
<tr>
<td>Theophylline 10^{-6} M</td>
<td>0.48 ± 0.10 (5)</td>
</tr>
<tr>
<td>Quinidine 10^{-6} M</td>
<td>0.50 ± 0.15 (5)</td>
</tr>
<tr>
<td>Apamine 10^{-7} M</td>
<td>0.50 ± 0.13 (3)</td>
</tr>
</tbody>
</table>

39.2 mM [K]_o induced contraction was registered as 1.0.

**Effects of Carbocyclic Thromboxane A2 (cTXA2) and Endothelium on the Hemolysate-Induced Contraction.**

TXA2 is most unstable and to be inactivated within one minute. Therefore, in the present experiments synthesized stable TXA2, cTXA2 were used. CTXAN (2.8 × 10^{-10}M) evoked the contraction in the guinea pig basilar artery. As shown in figure 4 A, 2.8 × 10^{-10}M cTXA2 evoked the contraction and the amplitude was roughly the same as that evoked by the hemolysate in the concentration of 10^{-2} times dilution. The cTXA2 induced oscillatory contractions were superimposed on the tonic contraction. To investigate the contribution of the TXA2 action on the hemolysate-induced contraction, we used OKY-1581, a thromboxane A2 synthetase inhibitor. When OKY-1581 (10^{-4}M) was treated for 20–40 minutes before application of the hemolysate, the subsequently evoked hemolysate-induced contraction was not affected (10^{-4} times dilution: 0.57 ± 0.11, n = 6 and following pretreatment with 10^{-4}M OKY-1581: 0.52 ± 0.08, n = 9 in comparison to the contraction evoked by 39.2 mM [K]_o (fig. 4 B).
HEMOLYSATE-INDUCED CEREBRAL VASOCONSTRICTION/Fujinara and Kuriyama

Figure 4. Contractions evoked by 39.2 mM \([K^+]_0\), 10^{-2} times diluted hemolysate and 2.8 \times 10^{-5}M carbocyclic thromboxane \(A_2\) (cTXA\(_2\)) (A), and the effects of 10^{-5}M OKY-1581 on the hemolysate-induced contraction (B). Horizontal bars indicate applications of the agent.

To investigate the contribution of endothelium to the hemolysate-induced contraction, the intimal surface was gently rubbed with a steel rod with a diameter of 0.1 to 0.2 mm that is equivalent to the lumen of the artery (histological observations were not made). As shown in figure 5, there was no marked difference in the amplitude of the phasic hemolysate-induced contraction between the tissues with and without an endothelium. The decay of the tonic response was slightly affected, i.e. the tissue with an intact endothelium evoked the phasic response and a gradual decay of the tonic response, while in tissue with an injured endothelium, the tonic response was retained (In 10^{-2} times dilution; 1.32 ± 0.14 times the control measured at 50% height of the tonic response, \(n = 5\)). Such sustained tonic response was occasionally seen during generations of the hemolysate-induced contraction. A rough manipulation of the tissue during the preparation may damage the endothelium, particularly in the small size of guinea pig basilar artery. These results show that the endothelium may play a minor role in the hemolysate-induced contraction.

Effects of Prostaglandins on the Membrane and Mechanical Properties of the Guinea Pig Basilar Artery

Figure 6 A shows the effects of prostaglandins (PGE\(_i\), E\(_i\), and F\(_{2\alpha}\)) on the smooth muscle cells. In concentrations below 2.8 \times 10^{-4}M, PGE\(_i\), PGE\(_i\), and PGF\(_{2\alpha}\) did not alter the membrane potential (control: 52 ± 2.0 mV, \(n = 20\), 2.8 \times 10^{-4}M PGF\(_{2\alpha}\): -51.6 ± 2.0 mV, \(n = 15\), 2.8 \times 10^{-4}M PGE\(_i\): -53.4 ± 1.8 mV, \(n = 15\), 2.8 \times 10^{-4}M PGE\(_i\): -51.4 ± 2.0 mV, \(n = 15\)) or the membrane resistance as measured from
amplitudes of the electrotonic potentials evoked by alternatively applied weak intensities of outward and inward current pulses. As shown in fig. 6 B, PGF$_{2a}$ (2.8 $\times$ 10$^{-6}$M) evoked the contraction which was slightly smaller than that induced by the hemolysate (10$^{-2}$ times dilution). PGE, and PGE$_2$ also evoked the contractions in the basilar artery, but these contractions were smaller than those evoked by equi-concentrations of PGF$_{2a}$. These results suggest that in concentrations below 2.8 $\times$ 10$^{-6}$M, PGF$_{2a}$ evokes the contraction in smooth muscles of the guinea pig basilar artery with no change in the membrane potentials, in the same manner observed in the hemolysate-induced contraction (below 3 $\times$ 10$^{-3}$ times dilution).

**Ca Sources of Hemolysate-Induced and PGF$_{2a}$-Induced Contractions**

Figure 7 shows the contraction evoked by high concentrations of [K]$_o$, hemolysate (10$^{-2}$ times dilution) and 2.8 $\times$ 10$^{-6}$M PGF$_{2a}$ following treatment with Ca-free 2 mM EGTA containing solution, or 10$^{-4}$M diltiazem. As a Ca antagonist, the Ca channel blocker, diltiazem was used. With application of 39.2 mM [K]$_o$, 10$^{-2}$ times dilution of the hemolysate or 2.8 $\times$ 10$^{-6}$M PGF$_{2a}$ in the presence of 2.5 mM [Ca]$_o$, the phasic and subsequently generated tonic contractions were evoked. The amplitude of the phasic response differed with the agents (10$^{-2}$ times dilution of the hemolysate: 0.60 $\pm$ 0.08 (n = 10), 2.8 $\times$ 10$^{-6}$M PGF$_{2a}$: 0.44 $\pm$ 0.11 (n = 10), under the condition that the amplitude of 39.2 mM [K]$_o$-induced contraction was normalized as a relative tension of 1.0). In Ca-free 2 mM EGTA containing solution, the contraction produced by 39.2 mM [K]$_o$ was abolished within 1 min. Yet the phasic response remained, the tonic response was markedly inhibited in the hemolysate or PGF$_{2a}$-induced contractions. With application of 10$^{-4}$M diltiazem, the amplitude of the K-induced contraction was markedly reduced. The tonic but phasic responses of both hemolysate and PGF$_{2a}$-induced contraction were slightly inhibited. These results indicate that the main source of Ca in the production of contraction under conditions of excess [K]$_o$ was an influx of extracellular Ca rather than a release of Ca stored in the cell, while both the hemolysate and PGF$_{2a}$-induced contractions were mainly due to release of the Ca stored in the cell and only in part due to the influx of Ca.

**Discussion**

The present experiments showed that the hemolysate evoked contraction was not induced by the activation of known neurotransmitter receptors such as $\alpha$-adrenergic, cholinergic, histaminergic H$_1$, 5-hydroxytryptaminergic and purinergic receptors. This contraction was composed of two responses; indomethacin sensitive and less sensitive ones. The indomethacin sensitive response produced by the hemolysate was considered to relate to the synthesized prostaglandin, as indomethacin inhibits cyclooxygenase activity, the enzyme which acts on the first step of arachidonic cascade. Indomethacin strongly inhibited the hemolysate-induced contraction with no effect on the K- or PG-induced contractions. Furthermore, to inhibit the hemolysate-induced contraction, over 40 min superfusion of indomethacin was required. These results also indicate that a nonspecific action of indomethacin can be ruled out.

In the presence of high concentrations of indomethacin (>10$^{-4}$M), a small amplitude of contraction persisted (indomethacin-less sensitive response), and this contraction remained following pretreatment with antagonists of the neurotransmitters or autacoids. Therefore, the small contraction may be evoked by the hemolysate itself as reported by Tanishima and Sano. For clarification of the nature of the contraction-evoked substance, further detailed experiments are underway. The inconsistent observations of effects of the hemolysate-induced vasospasm, in relation to the action of anti-inflammatory agents, in vivo and in vitro, may relate to the concentrations of the hemolysate used.

The hemolysate (10$^{-5}$ - 3 $\times$ 10$^{-3}$ times dilution) evoked the contraction with no change in the membrane potential. Pharmacomechanical coupling may play a role in the generation of this contraction. In 10$^{-2}$ times dilution of the hemolysate, the membrane was depolarized with increase in the membrane ionic conductances. In the guinea pig basilar artery, as previously reported, there were a few cells with no rectifying property of the membrane. In these cells, depolarization of the membrane evoked a graded response or spike potential. The physiological significance of contraction of these two different types of cells remains to be clarified.

Thromboxane A$_2$ (TXA$_2$) is vasoconstrictor, and the potency of which was reported to be 100 to 1000 times stronger than primary PGs (PGE$_1$, E$_2$, F$_{2\alpha}$), in the canine basilar artery. In the guinea pig basilar artery, cTXA$_2$ evoked the contraction and the potency was 100 times larger than that evoked by an equi-concentration of PGF$_{2\alpha}$. Sasaki et al stated that the synthesis...
of TXA₂ plays an important role in the generation of chronic cerebral vasospasm following subarachnoid hemorrhage, and that OKY-1581 prevented experimentally-induced vasospasm in the dog.²⁶ In our experiments, OKY-1581 did not show any effect on the hemolysate-induced contraction in the guinea pig basilar artery. The endothelium seems to be capable of producing PG₁, as related to vascular smooth muscle relaxation.²⁷ Here, species differences are no doubt present. However Sasaki et al²⁸ and Maeda et al²⁹ examined prostaglandin synthetic activity in the canine basilar artery under conditions of experimentally-induced cerebral spasm, and found a diminution in the PG₁ synthesis in the artery caused by a subarachnoid injection of blood. In our experiments, the role of the endothelium in the hemolysate-induced contraction was not prominent, therefore clear differences in the amplitude of hemolysate-induced contraction between the intact and injured endothelium cannot be defined.

Prostaglandins (PGÉ₁, E₂, F₂α) did not alter the membrane potential or the ionic conductance of the membrane, but did evoke a dose-dependent contraction. The potencies of the vasoconstrictive actions were in the order of PGF₂α >E₂ >E₁ in the guinea pig basilar artery. The pharmaco-mechanical coupling was evident in the PGs evoked contractions, as well as in the hemolysate-induced contractions (below 3 × 10⁻³ times dilution). The Ca sources in the evoked contraction were mainly release of Ca from the storage site in the cell membrane, and partly an influx of Ca in the presence of PGs or hemolysate. The influx of Ca seems to play a major role in the contraction evoked by either primary PGs or low concentrations of hemolysate (<3 × 10⁻⁴ times dilution) were apparent. Both agents produced the contraction in the guinea pig basilar artery with activations of the pharmaco-mechanical coupling mechanism, and the main source of Ca which evoked contractions was release of Ca from the storage site in the cell membrane and neuromuscular transmission in the guinea-pig membrane. Presumably due to influxes of Ca which in turn contract the cerebral artery. The contraction evoked by low concentrations of hemolysate (<3 × 10⁻⁴ times dilution) is an indomethacin-less sensitive component, and ceased in Ca-free EGTA containing solution. Presumably due to influxes of Ca activated by the hemolysate.

The present results indicate that in the guinea pig basilar artery, the hemolysate produces the contraction which is partly evoked by the hemolysate itself and mainly due to stimulation of the basilar artery to produce the primary PGs. The participation of thromboxane A₂ synthesis to the contraction and significant role of endothelium were not observed in this experiment. However, these may play roles in making worse of cerebral circulation following initial vasoconstriction as induced by the action of the hemolysate.

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References
A Two-Year Longitudinal Study of Post-Stroke Mood Disorders: Dynamic Changes in Associated Variables Over the First Six Months of Follow-Up

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SUMMARY We are prospectively studying a group of 103 stroke patients over the first 2 years after infarction to determine the variables which are associated with the development of depression. At both 3 and 6 months post-stroke, patients with left hemisphere infarcts showed a strong relationship between severity of depression and distance of the lesion on CT scan from the frontal pole. The strength of this association was unchanged from the immediate post-infarction period. In contrast, the correlation between degree of functional physical impairment and severity of depression steadily increased over the 6 month follow-up. The correlation between severity of depression and Mini-Mental score or between depression and social functioning score dropped between in-hospital and 3 months but then increased significantly between 3 and 6 months post-stroke. Age did not correlate with depression beyond the acute post-stroke period. Whether the increasing strength of the relationships between impairment and depression over the first 6 months post-stroke indicates that continued depression led to delayed recovery or whether continued severe impairments led to depression is not known, however, this issue will be addressed in further data evaluation from this prospective study.

DURING THE PAST SEVERAL YEARS we have been investigating mood disorders in stroke patients.1-9 We have reported that intrahemispheric as well as interhemispheric lesion location was important and that patients with left anterior strokes were significantly more depressed than patients with lesions of any other location.5, 6, 7 The importance of left anterior lesion location for depression held up even when we examined patients who had bilateral strokes6 and we have shown in several studies that the closer the lesion was to the frontal pole on CT scan, the more severe the depression.1, 5, 8

In addition to these studies of lesion location, we have been conducting a prospective study of stroke patients who were entered in the NINCDS Stroke Data Bank10 and have been following them over a two year post-stroke period. We have found that during the acute stroke period several variables were correlated with severity of depression, including anterior left hemisphere lesion location, the severity of impairment in activities of daily living, degree of cognitive impairment, the quality of available social supports and the patient's age.6

We have recently begun to analyze the follow-up data from this group of patients. During the six month follow-up, the prevalence of clinically significant depressions defined as meeting DSM III symptom crite-
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