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## **Sensitivity and specificity of fluid-blood levels for coagulopathy in acute intracerebral hematomas.**

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# Sensitivity and Specificity of Fluid-Blood Levels for Coagulopathy in Acute Intracerebral Hematomas

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**PURPOSE:** To characterize the imaging features of intracerebral hemorrhages in patients with coagulopathies that alter prothrombin time or partial thromboplastin time. **METHODS:** A fluid-blood level was defined as a horizontal interface between hypodense bloody serum layered above hyperdense settled blood. The prevalence of fluid-blood levels in acute intracerebral hemorrhages was determined on third-generation CT scans in 32 patients with elevation in prothrombin time or partial thromboplastin time. This was compared with the frequency of fluid-blood levels in 185 patients with intracerebral hemorrhage in which there was no laboratory evidence of coagulopathy. **RESULTS:** The probability of finding a fluid-blood level in an intracerebral hemorrhage of a patient with abnormal prothrombin time or partial thromboplastin time was 59% (sensitivity). The probability that there will be no fluid-blood level in a patient with a normal prothrombin time and partial thromboplastin time was 98% (specificity). **CONCLUSION:** Fluid-blood levels in acute intracerebral hemorrhage are moderately sensitive to the presence of coagulopathy (ie, abnormal prothrombin time and partial thromboplastin time) and highly specific for this condition. Thus, an intracerebral hemorrhage with a fluid-blood level should prompt a thorough search for coagulopathy because early treatment of this condition may improve the 40% mortality in these patients. Caution should be used to distinguish the horizontal interface of a fluid-blood level from a clot with a flat top. A decubitus CT is useful in these rare instances.

**Index terms:** Cerebral hemorrhage; Brain, computed tomography; Anticoagulants; Hematoma, intracerebral

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Bleeding disorders have varied causes, which can be divided into two groups: vascular-platelet defects and coagulation defects. Coagulation defects can be caused by rare inherited deficiencies of one or more of the 10 coagulation factors. More commonly, coagulation disorders are acquired. They may be caused by disorders of liver function (ie, secondary to diseases of hepatocytes or lack of vitamin K), increased destruction or clearance of coagulation factors (ie, disseminated intravascular coagulopathy or loss of coagulation protein in the urine), or specific circulating anti-

bodies to a coagulation factor. This study concentrated on patients who had an intracerebral hemorrhage secondary to a coagulopathy that prevented clot formation or lysed the coagulum once it was formed. Patients with only vascular platelet defects were excluded.

Several small studies have reported finding fluid-blood levels in intracerebral hemorrhage patients with coagulopathy (1-5). The present study was undertaken to determine sensitivity and specificity of this finding. These data have clinical significance, because patients with coagulopathies require special care and have been reported to have markedly worse prognoses (5, 6). The data concerning the morphology of in vivo acute clots are also expected to be helpful in unraveling the complicated magnetic resonance (MR) patterns seen in intracerebral hematomas.

## Materials and Methods

This study was assembled in two independent stages. First, 36 consecutive patients seen over a 5-year period

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with the discharge diagnosis of intracerebral hemorrhage and coagulopathy were identified with a computer search of medical record discharge codes. From this group 17 were excluded because an initial head computed tomographic (CT) scan was not available (usually done at an outside institution), and one was excluded because an intracerebral hemorrhage was not identified (only a subdural hematoma was seen). The initial head CT scans of the remaining 18 patients were independently assessed by two authors (M.J.P. and L.A.H.). Subsequently, 324 consecutive patients seen over a 2-year period with the discharge diagnosis of intracerebral hemorrhage were identified with a computer search of medical record discharge codes. Ninety-one patients from this group were excluded because an admitting head CT scan was not available, and 34 were excluded because the initial CT scan did not reveal intracerebral hemorrhage. One author (M.J.P.) reviewed the initial head CT scan of the remaining 199 patients without the knowledge of the clinical history or laboratory data. The medical records of all 217 patients were reviewed by one author (E.P.H.). All CT scans were performed on a third-generation unit (either GE 9800, GE Sigma Medical Systems, Milwaukee, Wis, or Siemens DRH, Siemens, Erlangen, Germany).

For statistical analysis, this data pool of 217 patients was subdivided into two groups. Group I (185 patients) included patients without a coagulopathy. Group II (32 patients) comprised the 18 patients with a known coagulopathy, as well as 14 patients from the unselected group of 199 who were shown to have an abnormal prothrombin time or partial thromboplastin time by review of the medical record. Patients from either group who had a fluid-blood level were independently analyzed as a separate subset (Tables 1 and 2).

For purposes of this paper a CT fluid-blood level was defined as a region in the intracerebral hemorrhage that had the following features: 1) upper compartment hypodense to brain; 2) lower compartment hyperdense to brain; and 3) a sharply defined *horizontal* interface between upper and lower compartments (Fig 1). Other properties that can be seen in fluid-blood levels include: 1) the interface remains horizontal after the positional changes (Fig 2); and 2) fluid-blood levels may appear during the CT study (Fig 3).

The size of each intracerebral hemorrhage was graded as small (<2 cm), moderate (2–5 cm), or large (>5 cm). The location of each intracerebral hemorrhage was recorded (cerebral lobe, basal ganglia, thalamus, brain stem, or cerebellum). The presence or absence of associated extraaxial hemorrhage (ie, intraventricular, subarachnoid, and/or subdural spaces) was assessed. Each patient's age, sex, and presumed cause of the intracerebral hemorrhage was recorded, as well as the time interval between the patient's symptoms and the head CT scan. Special attention was devoted to detecting the presence of specific coagulopathies by evaluating pertinent laboratory values (prothrombin time, partial thromboplastin time, and fibrinogen and fibrin split products), medications (warfarin, heparin, and tissue plasminogen activator) and medical history

**TABLE 1: Summary of clinical and radiographic data in 217 patients with 232 intracerebral hemorrhages**

	Number of Patients (Number with intracerebral hemorrhage)		Patients with Fluid-Blood Level
	Group I No Coagulopathy	Group II Coagulopathy	
Totals	185 (197)	32 (35)	22 (25)
Cause			
Hypertension	79 (82)	4 (4)	1 (1) <sup>a</sup>
Infarct	24 (28)	4 (4)	2 (2) <sup>a</sup>
Arteriovenous malformation	17 (18)	2 (2)	
Trauma	7 (8)	3 (5)	2 (4)
Aneurysm	6 (6)	1 (1)	
Unknown	34 (37)		2 (2) <sup>a</sup>
Other	18 (18)		
Coagulopathy		18 (19)	15 (16)
Coumadin		7 (7)	4 (4)
Liver failure		4 (4)	4 (4)
Diffuse intravascular coagulation		4 (5)	4 (5)
Other		3 (3)	3 (3)
Time interval (hours) onset until CT			
0–6	38 (40)	12 (14)	10 (12) <sup>a</sup>
6–12	35 (36)	4 (4)	3 (3) <sup>a</sup>
12–24	38 (40)	3 (3)	1 (1) <sup>a</sup>
24–48	3 (3)	4 (4)	2 (2)
>48	18 (20)	3 (3)	
Unknown	53 (58)	6 (7)	6 (6)
Sex and age			
Male/average age	104/55.9	19/58.3	12/58.5
Female/average age	81/56.7	13/62.5	10/65

<sup>a</sup> One patient in this group had a fluid-blood level, and documented coagulopathy was not found.

**TABLE 2: Correlation between size, presence of associated extraaxial hemorrhage (AEAH), and mortality in 217 patients**

	Small	Medium	Large	Total
Group I (No coagulopathy)				
Patients	66	65	54	185
Patients with AEAH	15	26	35	76
Died with AEAH	2	16	24	42
Died without AEAH	6	3	8	17
Group II (Coagulopathy)				
Patients	3	12	17	32
Patients with AEAH	1	5	11	17
Died with AEAH	1	2	9	12
Died without AEAH			1	1
Patients with fluid-blood level				
Patients		5	17	22
Patients with AEAH		3	9	12
Died with AEAH		1	7	8
Died without AEAH			1	1

Note.—For the 15 patients with two intracerebral hemorrhages the largest hematoma was used for classification in this table.



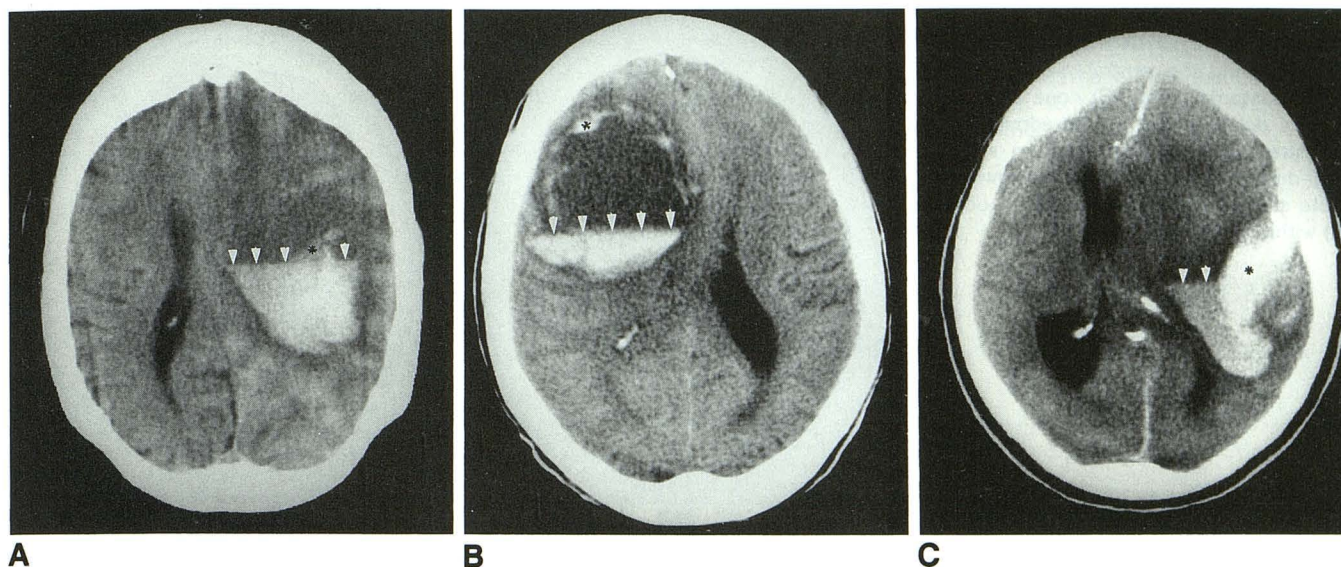


Fig. 1. A–C, Fluid-blood level in an intracerebral hemorrhage in three patients (A, B, and C), all of whom were taking coumadin. Arrowheads indicate the horizontal interface between hyperdense settled blood and the hypodense bloody serum above. Note the presence of irregular hyperdense regions (\*) within the fluid cavities. These presumably represent clumps of hyperdense red blood cells.

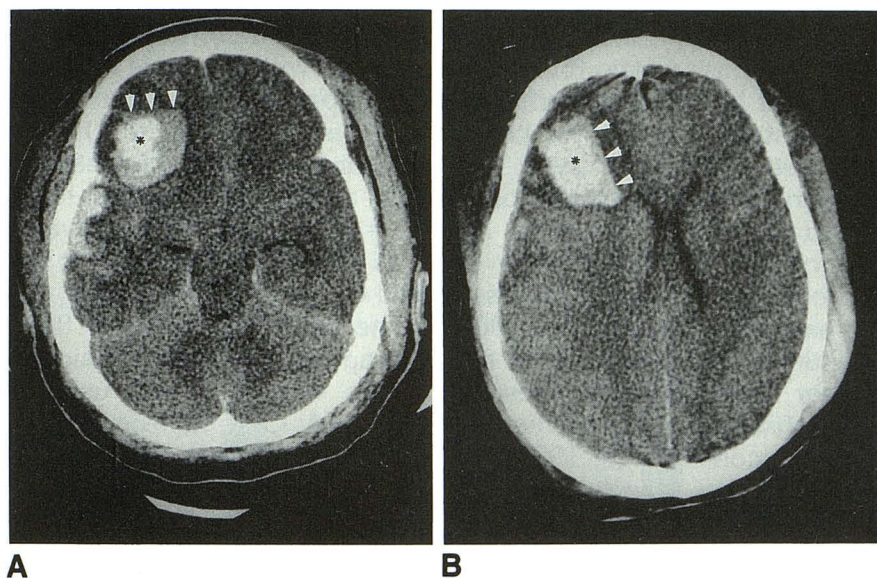


Fig. 2. A and B, CT scans in supine (A) and right lateral decubitus (B) show a change in the position of the fluid-blood interface (arrowheads). Note it remains horizontal as the patient's position changes. Without the comparison decubitus view the hypodense fluid seen at the nondependent (upper) aspect of the intracerebral hemorrhage could be mistaken for brain edema. Note clumps of hyperdense red blood cells (\*) within the cavity.

(ie, liver disease or renal dialysis). Finally, the outcome of each patient was recorded.

## Results

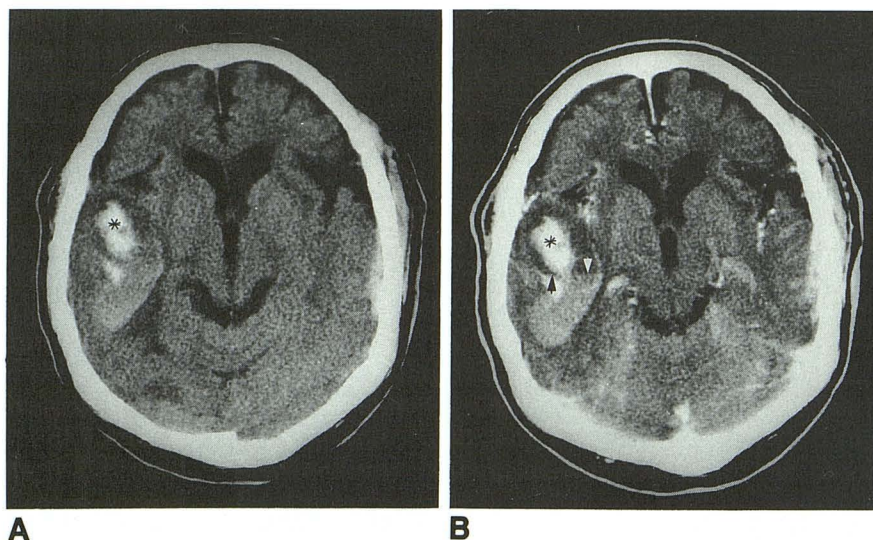
Group I contained 185 patients with 197 intracerebral hemorrhages. There were 104 men (average age 55.9 years) and 81 women (average age 56.7 years). Fluid-blood levels were noted in three of the intracerebral hemorrhages in this group (these are marked with an asterisk in Table 1). Group II contained 32 patients with 35 intracerebral hemorrhages. There were 19 men (av-

erage age 58.3 years) and 13 women (average age 62.5 years). From this group, 19 patients with 22 intracerebral hemorrhages were noted to have a fluid-blood level of which 12 were in men (average age 58.5 years) and 10 were in women (average age 65.0 years).

The probability of finding a fluid-blood level in an intracerebral hemorrhage of a patient with the specified coagulopathy (sensitivity) was 59.4% (95% confidence interval: 40.6% to 76.3%). The probability that there will be no fluid-blood level in a patient with normal prothrombin time/partial thromboplastin time (specificity) was



Fig. 3. A and B, Initial CT scan (A) of intracerebral hemorrhage show a gradient of density along the ventral-to-dorsal axis of the hematoma. Scan (B) done after a 20-minute delay caused by the administration of intravenous contrast medium shows a well-defined fluid-blood level (arrowheads). Note clumps of hyperdense red blood cells (\*) within the cavity.



98.4% (95% confidence Interval: 95.3% to 99.7%). Eighteen of the 22 patients with a fluid-blood level had a large intracerebral hemorrhages (5 cm or greater).

Table 1 gives a detailed comparison of the presumed cause of the intracerebral hemorrhages in each patient as well as the time interval between symptom and CT scan. There is a strong and statistically significant association between time interval and the three groups shown in Table 1. The group with no coagulopathy had 20.5% of scans in 0 to 6 hours, 37.5% of the group with coagulopathy also had scans within 6 hours, and 45.5% of the fluid-blood level patients had scans in 0 to 6 hours. The  $P$  value for the entire table is .0045 as determined using the Fisher Exact Test as implemented in StatXact (Cytel Software, Cambridge, Mass, 1992). These results are consistent with the association of coagulopathy, the time of a scan, and the severity of injury in the head trauma data. Patients with more severe injuries are more likely to be scanned early.

Table 2 gives the size of each intracerebral hemorrhage, the number of patients with associated extraaxial hemorrhage, and the number of patients who died during the hospitalization for intracerebral hemorrhages. These data demonstrate that the mortality rate of patients in group I (without a coagulopathy) was 32%, and 66% of those who died had associated extraaxial hemorrhage. In the coagulopathy patients of group II 40% died, and 12 of the 13 patients (92%) had associated extraaxial hemorrhage (Table 2 and Fig 4). From these data analyses were performed on the relationship of coagulopathy, fluid-blood level, size of intracerebral hemorrhages, and pres-

ence of associated extraaxial hemorrhage to mortality. The final results were that the size of the intracerebral hemorrhages and the presence of associated extraaxial hemorrhage were both significantly associated with outcome. The odds ratio for death associated with the large intracerebral hemorrhages compared with a small intracerebral hemorrhages is 6.0 ( $P < .001$ ); that associated with a medium intracerebral hemorrhages as opposed to a small intracerebral hemorrhages is 1.95 ( $P = .155$ ). The overall  $P$  value for the size effect is .0002. The odds ratio for having an associated extraaxial hemorrhage was 6.0 ( $P < .0001$ ). The effect of having a fluid-blood level and a coagulopathy was not significant. These estimates were obtained using a logistic regression (STATA, CRC, College Station, Tex, 1992) model. The model was fit using associated extraaxial hemorrhage, size, coagulopathy and fluid-blood level, with the nonsignificant variables removed in a step-wise manner. On a univariate basis, associated extraaxial hemorrhage and size were both highly associated with outcome ( $P < .0001$  for both); the association with coagulopathy and fluid-blood level were not significant ( $P = .333$  and .417, respectively).

In general, the greater the degree of abnormality in the prothrombin time or partial thromboplastin time, the higher the incidence of a fluid-blood level. However, about half of patients with mild laboratory abnormalities (less than two times greater than control) demonstrated a fluid-blood level (Fig 5).

An analysis similar to the outcome analysis was performed using the presence of a fluid-blood level as the dependent variable. These



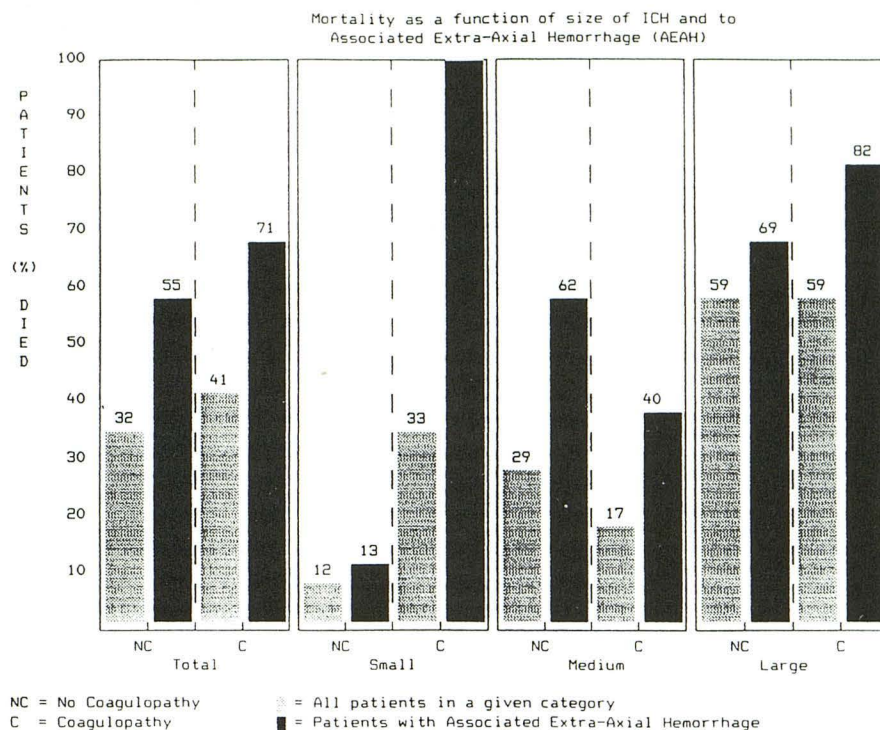


Fig. 4. Mortality as a function of size of intracerebral hemorrhage and associated extraaxial hemorrhage. Note that patients with associated extraaxial hemorrhage had a greater mortality in every category.

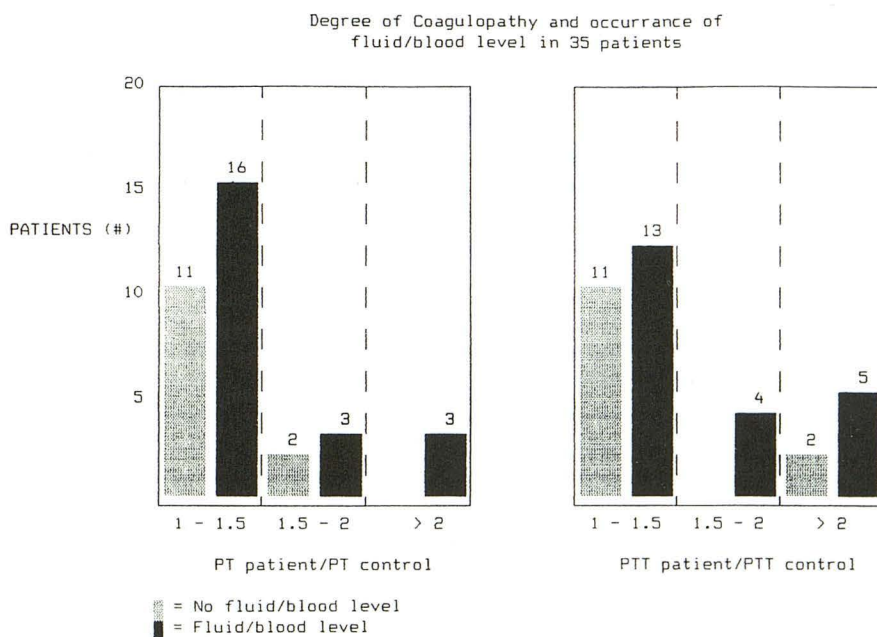


Fig. 5. Degree of coagulopathy versus the presence of fluid-blood level in 35 patients with 38 intracerebral hemorrhages. A, The patient's prothrombin time divided by the control prothrombin time value versus the number of intracerebral hemorrhages with a fluid-blood level. B, The patient's partial thromboplastin time divided by the control prothrombin time versus the number of intracerebral hemorrhages with a fluid-blood level. Note that there appears to be a threshold beyond which increasingly abnormal values do not increase the incidence of fluid-blood levels.

analyses indicate that, aside from coagulopathy, the only variable associated with the presence of a fluid-blood level is the size of the lesion ( $P < .0001$  for both). However, the coagulopathy effect is so strong that we would hesitate to use the logistic model. One can conclude that a fluid-blood level is significantly associated with coagulopathy and with the size of the intracerebral hemorrhages. Furthermore, the fluid-blood level's

absence strongly indicates that coagulopathy is not present.

## Discussion

CT plays a vital role in evaluating patients with acute intracerebral hemorrhages. In nontraumatic cases, the location and features of the hematoma can help the clinician determine the cause of the



bleeding. For example, hematomas caused by hypertension are usually located in the basal ganglia or thalamus. Bleeding caused by vasculitis is commonly subcortical. Aneurysmal intracerebral hemorrhages is associated with subarachnoid hemorrhage, and tumoral bleeding is often at the periphery of a mass that has a prominent halo of vasogenic edema (7). This study shows that more than half of patients with intracerebral hemorrhages caused by specific coagulopathies that either prevent the formation of a clot or lyse it have a characteristic fluid-blood level. This appearance is 98% specific for coagulopathy. We had three cases with a fluid-blood level in an intracerebral hemorrhage and no documented coagulopathy. In one case the timing of the prothrombin time/partial thromboplastin time probably prevented detection. This patient was on renal dialysis (which used anticoagulants) when the bleeding occurred, and the prothrombin time/partial thromboplastin time values for this patient were drawn several hours after dialysis. The other two cases did not have additional tests that could detect coagulopathies missed by screening prothrombin time and partial thromboplastin time examination.

The literature citing fluid-blood levels in intracerebral hemorrhage consists of small series and case reports which attribute this finding to a number of sources (ie, coagulopathy, tumors, and arteriovenous malformations). Systemic coagulopathy was noted in 12 patients (1–4). An additional three patients have been reported with fluid-blood level in an intracerebral hemorrhage within a metastatic focus (two of these were caused by melanomas, and one was a renal cell carcinoma) (9, 10). These findings probably reflect the presence of local agents that lyse the blood clot. These factors have been found within intracranial tumors (8). Four cases of fluid-blood level have been documented in patients with arteriovenous malformations who presumably bleed into a preexisting cavity (11, 12). None of the 17 patients with arteriovenous malformations in our study with normal prothrombin time and partial thromboplastin time values had fluid-blood levels (see Table 1).

There have been five patients reported with a *horizontal* fluid-blood level in an intracerebral hemorrhage without a documented coagulopathy or underlying lesion (12, 13). (Two patients from Ref 12 were omitted because the interface was *not* horizontal.) It has been suggested that a fluid-blood level in these cases may represent a hy-

peracute stage in the formation of intracerebral hemorrhage (12). This explanation is extremely unlikely because reported cases of *hyperacute* intracerebral hemorrhage have not demonstrated a fluid-blood level in patients with normal prothrombin time and partial thromboplastin time levels (14–16). Some of these cases even occurred while the patient was in the CT scanner (14, 15). Our study suggests that these five patients may have had occult coagulopathies not detected by their screening prothrombin time and partial thromboplastin time studies.

In vitro studies also support the hypothesis that an intracerebral hemorrhage fluid-blood level reflects the inability to either form or maintain a clot matrix. Phantom studies in the early 1980s have demonstrated that CT scans of blood are a simple measure of hemoglobin concentration. Bloody serum (with a hemoglobin concentration less than 15 g %) is hypodense to brain; settled red blood cells, which have a hemoglobin concentration greater than unclotted blood, are hyperdense to brain (17, 18). CT scans of heparinized and nonheparinized test tubes of blood demonstrate that it requires several minutes for a fluid-blood level to form (19). Therefore, the interval between positioning the patient in the scanner and actual time of the scan through the intracerebral hemorrhage is important. Figure 3 illustrates a delayed fluid-blood level which appeared when the patient was rescanned 20 minutes after the initial intracerebral hemorrhage demonstrated only a density gradient.

In summary, our study of 217 patients indicates that fluid-blood levels in acute intracerebral hemorrhage are moderately sensitive to the presence of coagulopathy and highly specific for this condition. Thus, an intracerebral hemorrhage with a fluid-blood level should prompt a thorough search for coagulopathy. If the screening examination (prothrombin time, partial thromboplastin time) is normal, specialized tests may be warranted (including tests for disseminated intravascular coagulopathy, fibrinogen, and fibrin split products, or tests for circulating inhibitor and specific coagulation factor assays). Previously published literature suggests that a preexisting cystic lesion (such as arteriovenous malformation) or metastatic lesion should also be considered.

#### Addendum

Since our presentation of this work at the ASNR meeting in June 1992, a paper has ap-



peared that supports our observation that fluid-blood levels are common in patients treated with fibrinolytic agents (20).

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