Safety and efficacy of early thromboembolism chemoprophylaxis after intracranial hemorrhage from traumatic brain injury

Clinical article

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Object. Patients with traumatic brain injury (TBI) are at risk for development of thromboembolic disease. The use of chemoprophylaxis in this patient group has not fully been characterized. The authors hypothesize that early chemoprophylaxis in patients with TBI is safe and efficacious.

Methods. In May 2009, a protocol was instituted for patients with TBI where chemoprophylaxis for thromboembolic disease (either 30 mg of Lovenox twice daily or 5000 U of heparin 3 times a day) was initiated 24 hours after an intracranial hemorrhage (ICH) was demonstrated as stable on head CT image. Two cohorts were evaluated: Cohort A included patients from May 2008 through April 2009 who had no routine administration of chemoprophylaxis, and Cohort B included patients from May 2009 through May 2010 after the protocol was instituted. The groups were compared, with the major outcomes being deep venous thrombosis (DVT), pulmonary embolism, and increase in size of ICH.

Results. Of the 312 patients with TBI who were seen during the study course, 236 patients met criteria for inclusion in the study: 107 patients in Cohort A and 129 patients in Cohort B. The DVT rate was 6 occurrences (5.61%) in Cohort A and 0 occurrences (0%) in Cohort B, which was a statistically significant difference (p = 0.0080). Pulmonary embolism was found in 4 patients (3.74%) in Cohort A and 1 patient (0.78%) in Cohort B, a difference that did not reach statistical significance (p = 0.18). Three instances (2.8%) in Cohort A and 1 instance (0.7%) in Cohort B of increased ICH occurred after starting anticoagulation for chemoprophylaxis; this was not statistically different (p = 0.33).

Conclusions. Use of chemoprophylaxis in TBI 24 hours after stable head CT is safe and decreases the rate of DVT formation.

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Key Words • deep venous thrombosis • traumatic brain injury • chemoprophylaxis • Lovenox • heparin

Thromboembolic events frequently complicate the course of hospitalized patients. Trauma patients with multisystem injuries have some of the highest rates of thromboembolic events, ranging from 0.22% to 58%.8 In particular, patients with traumatic brain injury (TBI) are independently at risk for the development of thromboembolic complications with a 3-fold to 4-fold increase in risk of development of thrombotic events.14 Even as chemoprophylaxis for prevention of venous thromboembolism (VTE) has become a mainstay for most nonsurgical and nontrauma patients in the hospital, use of chemoprophylaxis in neurosurgical patients and patients with TBI has been approached with some reticence. The preponderance of data in recent studies shows the effectiveness and safety of chemoprophylaxis in surgical and trauma patients. However, barriers to initiation of chemoprophylaxis in neurosurgical patients and patients with TBI remain due to concerns about the potential for increased risk of intracranial hemorrhage (ICH) with prophylactic anticoagulation; studies suggest that such risk of prophylaxis exceeds its potential benefit.13

Previous studies have shown that subcutaneous heparin reduces the risk of deep venous thrombosis (DVT) without an increase in hemorrhagic complications in neu-
Early chemoprophylaxis for DVT after TBI

Rosurgical patients from 16% to 9% when given 24 to 48 hours postoperatively. Alternatively, enoxaparin has also been used in a selective postoperative neurological patient population within 48 hours after surgery, decreasing incidence of DVTs from 4.8% to 0% with no associated increase in ICH. Other studies have shown some efficacy of chemoprophylaxis in selected trauma patients with head injury. Based on these studies, our trauma center adopted a new clinical protocol to initiate VTE chemoprophylaxis 24 hours following injury after demonstration of stable ICH verified by CT scan. We hypothesized that on review of our outcomes we would appreciate a decrease in the rate of DVT and pulmonary embolism (PE) without progression of ICH or development of a new hemorrhage on CT scan after implementation of the protocol.

Methods

Chemoprophylaxis Protocol

On May 1, 2009, our trauma center initiated a protocol to begin VTE chemoprophylaxis after ICH. The intent of the protocol was to initiate chemoprophylaxis at 24 hours postinjury for all patients, only delaying initiation for progression of hemorrhage on routine follow-up brain imaging, presence of coagulopathy, or active systemic hemorrhage (Fig. 1). All trauma center patients, including patients undergoing craniotomy or intracranial pressure monitoring, were intended to be managed according to this protocol. All patients received follow-up head CT approximately 24 hours or the next calendar day after their initial admission head CT; this follow-up head CT preceded any chemoprophylaxis. If a neurosurgical procedure was performed, a CT of the head was obtained 24 hours following the procedure. If no new hemorrhage was noted, chemoprophylaxis was initiated. Chemoprophylaxis was not started on those patients with progression of hemorrhage noted on follow-up head CT (Fig. 2). Patients were started on low-molecular-weight heparin or unfractionated heparin following the guidelines (Table 1) depending on patient comorbidities, such as renal insufficiency, age, and weight/body mass index. After initiation of chemoprophylaxis, a routine CT of the head was obtained 48–72 hours later to evaluate for progression of ICH. Subsequent imaging was performed based on clinical indications. Any radiology report indicating hemorrhage progression was also reviewed immediately by the senior authors (S.B. and N.S.L.) at the time of the report. Deep vein thrombosis and PE surveillance was performed only when clinically indicated with duplex ultrasound, CT PE protocol, or ventilation-perfusion scan. Routine surveillance for DVT or PE was not performed before or after protocol initiation. Prior to initiation of the protocol, the use of chemoprophylaxis was intermittent and not standardized and left to the discretion of treating physician. At the time of protocol initiation, patients were managed utilizing the Practice Management Guidelines of the Eastern Association for the Surgery of Trauma (www.east.org/resources/treatment-guidelines).

Patient Inclusion

A retrospective analysis was performed on adult trauma patients (age ≥ 15 years) entered into the University of Missouri Trauma Registry between May 1, 2008, and May 1, 2010. Patients selected for analysis had TBI with ICH. Patients were excluded if they died of their injuries or were discharged within 24 hours of admission. The study was approved by the University of Missouri Health Sciences Institutional Review Board.

Two cohorts of patients were compared. Cohort A included patients treated from May 1, 2008, to April 30, 2009, prior to initiation of the chemoprophylaxis protocol (pre-protocol group). Cohort B included patients treated with the protocol from May 1, 2009, to April 30, 2010 (post-protocol group). A survey of the electronic medical record was performed on all patients, including a review of all radiological interpretations of CT scans of the head to evaluate for progression of ICH. In addition, as part of our retrospective review, all head CT scans were once again reviewed by a senior neurological resident (B.H.) during data analysis who was blinded to the radiologist’s report to evaluate for time to stability and for any signs of hemorrhage progression. Intracranial hemorrhage progression was defined as any new hemorrhage or any increase in size of a preexisting acute hemorrhage (epidural, subdural, intraparenchymal, or subarachnoid) on a CT scan of the head (Fig. 2). Evolution of an acute hemorrhage to a subacute or chronic hemorrhage was not considered progression. Progression of hemorrhage was denoted as either present or absent; no gradation of the degree of progression was determined.

Data Collection

Data collected include patient age; admission Glasgow Coma Scale (GCS) score; Injury Severity Score (ISS); and Abbreviated Injury Scale (AIS) score (head, face, chest, abdomen, extremities, and external). Mechanism of injury was defined, and trauma admission status was determined as either a full trauma team admission, neurosurgery admission with or without trauma consult, or admission to trauma and subsequent transfer to neurosurgery. Hospital length of stay (LOS), ICU LOS, and ventilator days were also determined.

The primary outcome measured was rate of DVT and PE. A secondary outcome was defined as time to initiation of chemoprophylaxis.

Statistical Analysis

All statistical analyses were performed using SAS (version 9, SAS Institute, Inc.). The chi-square test was used to compare qualitative data, such as admission status and etiology of trauma, between the cohorts; the nonparametric Wilcoxon rank-sum test was used to compare the numeric outcomes, such as age, LOS, GCS score, ISS, and AIS score. Deep vein thrombosis, PE, and hemorrhage size increase were compared using the Fisher exact test because of the low numbers of each event.

Results

Two hundred thirty-six patients meeting the inclusion criteria were included in the study: 112 patients in the pre-protocol group and 124 in the post-protocol group. Data were collected prospectively, and all patients meeting inclusion criteria were entered into the study. The study was approved by the University of Missouri Health Sciences Institutional Review Board.

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Results

Two hundred thirty-six patients meeting the inclusion
criteria for the study were analyzed. Cohort A (the pre-protocol cohort) contained 107 patients and Cohort B (the post-protocol cohort) contained 129 patients.

**Comparison of Cohorts at Admission**

The admission data acquired from the trauma database are outlined in Table 2. The mean ages of Cohort A and Cohort B were similar at 53.3 ± 23 years and 57.4 ± 23 years, respectively (p = 0.12), with 61% male in Cohort A (71 of 107) and 58% male in Cohort B (75 of 129). Admission GCS scores and AIS scores of head, face, chest, and external were also similar (Table 2). The external AIS scores were more severe in Cohort B compared with Cohort A (0.39 ± 0.5 and 0.19 ± 0.4, respectively, p = 0.001), but the overall ISS was worse for Cohort A than for Cohort B (12.42 ± 13.2 and 7.56 ± 7.6, respectively, p = 0.002).

**Mechanism of Injury**

Mechanism of injury was determined at the time of admission for all patients and a comparison of the two groups is shown in Table 3. There were no significant differences in the etiology of the trauma (p = 0.31).

**Comparison of Hemorrhages**

Types of ICH (Table 4) were also similar, with the exception of subdural hematomas, which were more common in Cohort B (p = 0.004). In Cohort A, epidural hematoma was present in 6 patients, subdural hematoma in 40 patients, subarachnoid hemorrhage in 62 patients, and intraparenchymal hemorrhage in 55 patients. In Cohort B, epidural hematoma was present in 2 patients, subdural

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**Fig. 1.** University of Missouri TBI DVT prophylaxis protocol. aPTT WNL = activated partial thromboplastin time within normal limits; INR = international normalized ratio; plts = platelets; PT = prothrombin time; SCD = sequential compression device.

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**Fig. 2.** A and B: CT scans obtained in a patient with a subarachnoid hemorrhage (large arrow), contusion (small arrow), and punctuate hemorrhage (open arrow). C and D: CT scans obtained 24 hours after admission with progression of contusion (small arrow) and punctuate hemorrhage (open arrow), delaying initiation of chemoprophylaxis.
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**TABLE 1: Summary of chemoprophylaxis guidelines**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal serum creatinine (creatinine clearance &gt;30 ml/min)</td>
<td>Lovenox 30 mg SQ BID; if ideal body weight &lt;60 kg Lovenox 0.5 mg/kg SQ BID†</td>
</tr>
<tr>
<td>abnormal serum creatinine (creatinine clearance &lt;30 ml/min)</td>
<td>heparin 5000 U SQ TID</td>
</tr>
<tr>
<td>BMI &gt;35</td>
<td>heparin 5000 U SQ TID</td>
</tr>
<tr>
<td>age &lt;15 yrs</td>
<td>no protocol</td>
</tr>
</tbody>
</table>

* Age ≥ 15 years, ideal body weight > 60 kg, BMI < 35. Protocol excludes pediatric patients; Lovenox dosing is based on body weight for patients with ideal body weight to avoid overdosing; if BMI > 35, Lovenox absorption becomes variable, thus necessitating the use of heparin instead. BID = twice a day; BMI = body mass index; SQ = subcutaneously; TID = three times a day.

TABLE 2: Patient demographics at time of admission to hospital

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-Protocol (Cohort A, n = 107)</th>
<th>Post-Protocol (Cohort B, n = 129)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (yrs)</td>
<td>53.30 ± 22.8</td>
<td>57.37 ± 22.5</td>
<td>0.126</td>
</tr>
<tr>
<td>AIS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>head</td>
<td>3.68 ± 0.6</td>
<td>3.81 ± 0.6</td>
<td>0.101</td>
</tr>
<tr>
<td>face</td>
<td>0.31 ± 0.7</td>
<td>0.34 ± 0.7</td>
<td>0.669</td>
</tr>
<tr>
<td>chest</td>
<td>1.28 ± 1.5</td>
<td>1.24 ± 1.5</td>
<td>0.804</td>
</tr>
<tr>
<td>abdomen</td>
<td>0.27 ± 0.7</td>
<td>0.53 ± 1.1</td>
<td>0.033</td>
</tr>
<tr>
<td>extremity</td>
<td>0.88 ± 1.2</td>
<td>0.82 ± 1.1</td>
<td>0.679</td>
</tr>
<tr>
<td>external</td>
<td>0.19 ± 0.4</td>
<td>0.39 ± 0.5</td>
<td>0.002*</td>
</tr>
<tr>
<td>overall</td>
<td>3.71 ± 0.6</td>
<td>3.87 ± 0.6</td>
<td>0.039</td>
</tr>
<tr>
<td>ISS</td>
<td>12.42 ± 13.2</td>
<td>7.56 ± 7.6</td>
<td>0.002*</td>
</tr>
<tr>
<td>GCS total</td>
<td>10.2 ± 5.5</td>
<td>11.2 ± 5.4</td>
<td>0.057</td>
</tr>
</tbody>
</table>

* Statistically significant difference between Cohort A and Cohort B.

**TABLE 3: Mechanism of injury**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Pre-Protocol (Cohort A, n = 107)</th>
<th>Post-Protocol (Cohort B, n = 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>fall</td>
<td>32</td>
<td>51</td>
</tr>
<tr>
<td>MVC</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>MCC</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>pedestrian</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>other</td>
<td>9</td>
<td>14</td>
</tr>
</tbody>
</table>

* No statistically significant difference in mechanism of injury between Cohort A and Cohort B (p = 0.037). MCC = motorcycle collision; MVC = motor vehicle collision.

The DVT rate of 5.6% (n = 6) in Cohort A was significantly higher than the 0% (n = 0) rate in Cohort B (p = 0.008) (Table 7). The rate of PE in Cohort A was 3.74% (n = 4) and 0.78% (n = 1) in Cohort B, which was not significantly different (p = 0.18). Progression of ICH was not significantly different between the 2 groups (n = 3 in Cohort A and n = 1 in Cohort B, p = 0.33). One of the 3 patients in Cohort A required a craniotomy following progression of hemorrhage, at which point in time the patient was receiving therapeutic Lovenox for a DVT found 19 days after admission; this event therefore fell outside of the premise of this analysis.

The average time from admission to initiation of chemoprophylaxis was significantly shorter in Cohort B compared with Cohort A (60.8 ± 48.4 hours and 159 ± 107.9 hours, respectively, p = 0.001). In Cohort A, 64 patients (59.8%) were treated with chemoprophylaxis, while in Cohort B 83 patients (64.3%) had chemoprophylaxis initiated during their hospitalization. This difference was not significant (p = 0.48).

Of the 47 patients in whom chemoprophylaxis was not initiated after protocol implementation, 23 were admitted to the neurosurgery service, 11 were on the trauma service, and 13 were transferred to the trauma surgeons following admission (Table 8). The admission disposition was then simplified to include only initial admission to the trauma service or the neurosurgery service (Table 9). Patients admitted initially to the neurosurgery service were less likely to receive chemoprophylaxis than other patients (p = 0.037).

**Discussion**

Our analysis demonstrated that use of an aggressive DVT chemoprophylaxis protocol in brain-injured patients is effective in preventing DVT and PE without progression of ICH. In addition, we show that starting early chemoprophylaxis is safe as evidenced by the rate of ICH progression in our 2 cohorts. These results are consistent with other recent reports, which demonstrate safety and efficacy of chemoprophylaxis.

These studies vary in severity of head injury, time to initiation of chemoprophylaxis, chemoprophylaxis agent, and indications for postinitiation follow-up head CT to assess for hemorrhage progression. Most of these other studies focus on head AIS scores of 2 or 3 and range in initiation of
chemoprophylaxis from 24 hours post injury up to 3 days after admission. In confirming the general principles described in these other studies, our study adds several elements. First, the protocol addresses chemoprophylaxis for patients with more severe TBI, manifested by AIS > 3. Second, the protocol is designed for earlier initiation of chemoprophylaxis—beginning 24 hours after injury or neurosurgical intervention when the head CT shows stability of ICH. Third, ICH progression is determined on head CT scanning in all patients, not just in those patients who have a change in the neurological examination findings. Fourth, we compared our protocol patients with a recent cohort of patients treated without the protocol to demonstrate the protocol’s efficacy. Fifth, we included patients who required neurological procedures, which allows the protocol to be used with all patients with TBI.

Similar to other studies, we found a relatively high rate of noncompliance with chemoprophylaxis (64.3% of patients in Cohort B received chemoprophylaxis) and common delay in its initiation (60.7 hours in Cohort B). These rates were still superior to those patients in our center treated before the protocol was initiated. Compliance rates in other studies range from 10% to 85%. Minshall et al. intended chemoprophylaxis to begin at 24 hours after injury as well but had mean times to initiation of 47 hours for low-molecular-weight heparin and 54.8 hours for unfractionated heparin. Fifty percent of patients were started on chemoprophylaxis later than the 24 hours intended by Saadeh et al. Minshall et al. intended chemoprophylaxis to begin at 24 hours after injury as well but had mean times to initiation of 47 hours for low-molecular-weight heparin and 54.8 hours for unfractionated heparin. Fifty percent of patients were started on chemoprophylaxis later than the 24 hours intended by Saadeh et al. In addition, Kim et al. and Depew et al. had 23% and 43% of patients, respectively, in whom chemoprophylaxis was initiated after their 72-hour protocol.

Several reasons are likely responsible for delays and/ or noncompliance. Delays are obviously inevitable in those patients who have progression of hemorrhage prior to initiation of chemoprophylaxis. Delays will also occur in patients who require surgical procedures; if multiple procedures are required by different services, those delays may be magnified. Noncompliance may result from concerns raised after observed preinitiation progression of hemorrhage, with physicians—frequently neurosurgeons—voicing strong objections to proceeding with chemoprophylaxis. As Saadeh et al. suggested, patients whose discharges were subsequently delayed may have had their chemoprophylaxis deferred. In addition, it is important to note that of the 47 patients in whom chemoprophylaxis was not initiated after protocol implementation, only 11 were on the trauma service at our institution. The remaining patients were either admitted directly to neurosurgery or transferred to the neurosurgery service after trauma surgeons delivered the initial care following admission. These data highlight the practice among neurosurgeons to be resistant to implementing DVT chemoprophylaxis. Also, the data suggest that involvement of a specialized trauma service for management of patients suffering from traumatic injuries helps to maintain streamlined and protocol-based systemic care of trauma patients, including those with TBI.

As with most studies, our study has a number of limitations. A larger study may be associated with greater number of ICH progressions, which would raise concerns about the safety of chemoprophylaxis. Our controls are not randomized but are historic (the year prior). Other changes made in the overall management of TBI patients by the trauma team could have affected patient outcomes. For example, in addition to less VTE, patients treated after initiation of the chemoprophylaxis protocol had shorter ICU LOS, hospital LOS, and fewer ventilator days. These improvements in care are likely related to other protocols begun in the same trauma/surgical ICU by the trauma/acute care surgery team at this time for management of traumatic injuries using Practice Management Guidelines from the Eastern Association for the Surgery of Trauma. The creation of this team streamlined the inpatient care that trauma patients received, which may have affected these other outcomes. Therefore, while this study was conducted to demonstrate the efficacy and safety of a chemoprophylaxis protocol for TBI patients, it also illustrates the benefits of adopting more standardization into critical care of patients with TBI. Compliance with trauma-specific processes of care happens the least with those for TBI, suggesting that a streamlined and trauma-centered approach could optimize management of this subset of patients. The benefit of standardization in TBI guidelines

### Table 4: Distribution of intracranial hemorrhages

<table>
<thead>
<tr>
<th>Hemorrhage Type</th>
<th>Pre-Protocol (Cohort A, n = 107)</th>
<th>Post-Protocol (Cohort B, n = 129)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>epidural hematoma</td>
<td>6</td>
<td>2</td>
<td>0.146</td>
</tr>
<tr>
<td>subdural hematoma</td>
<td>40</td>
<td>73</td>
<td>0.004*</td>
</tr>
<tr>
<td>traumatic subarachnoid hemorrhage</td>
<td>62</td>
<td>62</td>
<td>0.15</td>
</tr>
<tr>
<td>intraparenchymal hemorrhage</td>
<td>55</td>
<td>56</td>
<td>0.24</td>
</tr>
</tbody>
</table>

* Statistically significant difference between Cohort A and Cohort B.

### Table 5: Comparison of in-hospital parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-Protocol (Cohort A, n = 107)</th>
<th>Post-Protocol (Cohort B, n = 129)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS (days)</td>
<td>12.35 ± 13.5</td>
<td>7.36 ± 7.1</td>
<td>0.002*</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>9.24 ± 13.1</td>
<td>4.98 ± 7.6</td>
<td>0.001*</td>
</tr>
<tr>
<td>ventilator days</td>
<td>12.11 ± 15.9</td>
<td>7.61 ± 9.5</td>
<td>0.08*</td>
</tr>
</tbody>
</table>

* Statistically significant difference between Cohort A and Cohort B.

### Table 6: Admission status

<table>
<thead>
<tr>
<th>Status</th>
<th>Pre-Protocol (Cohort A, n = 107)</th>
<th>Post-Protocol (Cohort B, n = 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>neurosurgery admission</td>
<td>9</td>
<td>48</td>
</tr>
<tr>
<td>full trauma admission</td>
<td>43</td>
<td>37</td>
</tr>
<tr>
<td>trauma admission w/ transfer</td>
<td>55</td>
<td>44</td>
</tr>
</tbody>
</table>

* Statistically significant differences in admission status between Cohort A and Cohort B (p < 0.0001).
has been shown in several studies comparing Level I and Level II trauma centers and survival in TBI patients with regard to intracranial pressure monitoring in the setting of TBI.4,17 Of note, even though confounding variables are likely present in comparing the 2 epochs of patients in this study, none were related to evaluation or management of VTE, DVT, or PE. Therefore, the results seen with chemoprophylaxis in this study are unlikely related to these other variables and are the result of chemoprophylaxis itself. Standardization in VTE prophylaxis could similarly help to improve the quality of care given to these high-risk patients.

**Conclusions**

Initiation of a DVT chemoprophylaxis protocol at 24 hours postinjury in patients with TBI is safe and effective. Low-molecular-weight heparin or unfractionated heparin may be started 24 hours following injury or surgery with expectation for reduced rate of VTE and no increase in hemorrhage progression if follow-up head CT image shows no hemorrhage progression.

**Disclosure**

This work was supported by research funds from the Division of Neurological Surgery, University of Missouri–Columbia School of Medicine. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Litofsky, Hiser, Barnes. Acquisition of data: Farooqui, Hiser. Analysis and interpretation of data: Litofsky, Farooqui, Hiser. Drafting the article: Farooqui, Hiser. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Litofsky. Administrative/technical/material support: Litofsky, Barnes. Study supervision: Litofsky.

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