Increased ICP is a potentially life-threatening condition that can be caused by primary brain insult or can occur secondary to trauma, metabolic derangement, neoplasia, seizures, and other conditions in humans\(^1\) and animals.\(^2,3\) Normal ICPs for dogs and cats range between 5 and 12 mm Hg.\(^2\) In general, recommendations for human head trauma patients are to maintain ICP $< 20$ mm Hg.\(^2\)

Increased ICP causes ischemic and hypoxic injury to neuronal cells. As a result of this injury, multiple changes can occur at the cellular level in neuronal cells, including increased metabolism and use of ATP.\(^3\) These metabolic derangements promote abnormal calcium and sodium ion influx into the neurons, leading to cellular edema and reactive oxygen species formation.\(^3,4\) Concurrent inflammation causes disruption of the blood-brain barrier and nitric oxide release. Together, these processes can lead to devastating consequences such as brain herniation and possibly death.\(^2,5\) Preventing the development of these injuries by identifying and controlling increases in ICP provides the best chance for a patient’s recovery.\(^6\)

In humans, invasive devices are routinely used for continuous and reliable measurement of ICP.\(^7\) There is no gold standard method to measure ICP in small animal patients in either clinical or research settings, but it is assumed that an intraparenchymal system would likely be the most precise in animals.\(^2\) An inexpensive and easy method to measure ICP was described in cats\(^8\) by use of an EICPMS; the epidural pressure was
equivalent to and changed in parallel with ICP in cats. Thus, measuring epidural pressure was found to be a reliable alternative to the more invasive and expensive fiberoptic intraparenchymal ICP monitoring system in that species. The human literature similarly supports that epidural pressures change in parallel with invasively monitored ICP.9

At this time, invasive devices are not typically used to monitor ICPs in small animal patients outside of a research setting. Advanced imaging modalities such as MRI or CT can be used in humans to assess increases in ICP,2,10 but utility of these modalities is limited because the results represent only a single moment in time. Although CT and MRI are becoming more readily available for use with small animal patients, it may be cost prohibitive to use these modalities singly or serially to assess or predict ICP. Ultrasonographic measurement of the ONSD has been suggested as a possible method to evaluate changes in ICP in humans.11–13 The optic nerve is surrounded by a sheath composed of an inner and an outer layer, which are continuations of the dura mater, arachnoid, and pia mater that surround the brain.14 The space between the inner and outer layers of the optic nerve sheath is filled with CSF that is continuous with the CSF in the subarachnoid space around the brain.15 The optic nerve sheath is distensible in the retrobulbar region and will expand when there are increases in CSF.16 The resulting change in ONSD as the ICP increases can be appreciated ultrasonographically in humans.11–13 In 1 study,18 ultrasonography was used to identify and measure the ONSD in clinically normal dogs.

The objective of the study reported here was to evaluate the association between ultrasonographically measured ONSD and acute increases in ICP as measured by an EICPMS in healthy dogs. Our hypotheses were that the ONSD would be positively associated with acute increases in ICP above baseline (measurement obtained immediately after placement of the monitoring device) as indicated by EICPMS and that the degree of increase in ONSD would be greater during the initial ICP increase from the baseline value than at the higher-magnitude ICP increase.

Materials and Methods

Animals

Six purpose-bred sexually intact 6-month-old female Bloodhounds weighing between 15 and 19 kg were included in the study. The dogs were selected from a group of laboratory dogs undergoing terminal surgical procedures as part of the veterinary school curriculum. The dogs were determined to be healthy on the basis of a complete physical and neurologic evaluation performed by one of the investigators (LAI) on the day of the study. A thorough ophthalmologic examination, including intraocular pressure measurements with an applanation tonometer and fundic examination, was performed by a board-certified ophthalmologist prior to the study. The study protocol was approved by the Purdue Animal Care and Use Committee (approval No. 1111000308).

Procedures

Each dog was premedicated with hydromorphone hydrochloride (0.1 mg/kg, IV) and acepromazine maleate (0.02 mg/kg, IV) approximately 15 minutes prior to IV catheter placement in a cephalic vein. Propofol (6.0 mg/kg, IV) was administered for anesthetic induction, an endotracheal tube was placed, and the dog was connected to an anesthesia machine. Isoflurane was administered to effect for maintenance of anesthesia. A balanced electrolyte solution was administered IV to each dog at ≥5 mL/kg/h, with rates determined on the basis of the patient’s blood pressure and other vital signs. With dogs under anesthesia, noninvasive blood pressure, ECG, end-tidal CO2, and oxygen saturation via pulse oximetry were continuously measured with a multiparameter monitor. Respiratory rate, heart rate, and rectal temperature were monitored manually and intermittently. Veterinary students performed various surgical procedures on the dogs (including splenectomy, cystotomy, enterotomy, and forelimb amputation) prior to initiation of the present study. The dogs were under general anesthesia for approximately 8 hours before the present study began. Hydromorphone was administered at the described dose, IV, every 4 to 6 hours.

When the present study began, each anesthetized dog was placed in sternal recumbency. Hair over the skull was shaved, and the site was aseptically prepared for a surgical approach. Baseline intraocular pressure and baseline ultrasonographic images for ONSD measurements were obtained prior to instrumentation of each dog with the EICPMS.

Ultrasonographic evaluation of the optic nerves was performed by placing the transducer directly over the closed eyelid of each eye without exerting pressure on the eye. During the first experiment, a 5- to 8-MHz curvilinear ultrasound transducer was used but resulted in technical difficulties in obtaining optic nerve images and determining subsequent measurements. Thus, for the remaining 5 dogs, a 5- to 12-MHz linear transducer was used. For each dog, 3 images of each optic nerve sheath were recorded with the ultrasound transducer held in position to image the transverse plane through the optic nerve sheath (parallel to the ground). Sagittal images were obtained as well; these images were not used in the statistical analysis because it was subjectively easier to distinguish the borders of the optic nerve on the transverse images, facilitating measurement. Imaging was performed by a board-certified radiologist (HGI), and images were saved for later review.

To facilitate creation of the EICPMS, a dorsal midline incision was made through the skin and subcutaneous tissue extending from the level of the medial canthi to approximately 2 to 3 cm caudal to the occipital protuberance. Both temporalis muscles were reflected. A burr hole (approx 4 mm in diameter) was
created in the left and right parietal bones, 3 to 5 cm lateral to midline, by use of an electric drill with a 4-mm-diameter round burr. Care was taken to make the burr hole perpendicular to the dura mater, rather than perpendicular to the skull, to allow good contact between the ICP measuring device and the dura mater. The burr hole extended through the skull, but the dura was left intact. The EICPMS was then created by inserting a 3-way stopcock that was prefilled with sterile saline (0.9% NaCl) solution a distance of 2 to 3 mm into an arbitrarily selected burr hole until it contacted the dura mater. The portion of the stopcock inserted through the skull was the same diameter as the burr hole that had been created, allowing a tight fit that immobilized the stopcock. The stopcock was secured by application of tissue adhesive and was connected to a saline solution–filled, disposable, noncompliant tubing-transducer set placed at the level of the lateral canthus. The transducer was connected to an invasive blood pressure monitor to generate a continuous epidural pressure waveform. The transducer was zeroed to atmospheric pressure, and then the monitor was inspected for the presence of an epidural pressure wave that corresponded to the dog’s heart rate. The monitor displayed a measurement of the area under the epidural pressure waveform (ie, the mean pressure), which was recorded as the ICP. A baseline measurement of ICP as indicated by EICPMS was recorded prior to any further instrumentation.

A 22-gauge IV catheter was then placed through the contralateral burr hole into the brain parenchyma. A small amount of tissue adhesive was placed around the catheter to help prevent dislodgement. This catheter was used for injection of autologous blood into the brain parenchyma.

A 26.5-mL autologous blood sample was obtained from a saphenous vein and was mixed with 3.5 mL of acid-citrate dextrose anticoagulant solution. To increase ICP, 0.5 to 2 mL of the anticoagulated blood was injected via the intraparenchymal catheter at 4-minute intervals. The ICP as indicated by EICPMS was recorded at each injection time point (ie, immediately after the injection was completed). Successive injections were made until the Cushing reflex was detected (defined as a heart rate < 40 beats/min combined with a systolic arterial blood pressure > 140 mm Hg or until an ICP plateau was noted > 60 mm Hg above baseline) for 3 consecutive injections. This plateau point was selected because ICPs > 60 mm Hg above baseline were considered to be incompatible with life.

To avoid large spikes in the ICP, it was initially decided to inject 0.5 mL of autologous blood every 4 minutes. However, injection of this volume during the first experiment (in the first study dog) led to minimal increases in ICP and lengthened the experiment time by 2 hours. Therefore, for the remaining 5 dogs, the amount of autologous blood injected was doubled after 8 consecutive injections (ie, 0.5 mL of autologous blood was administered 8 times, and then the amount of blood injected was increased to 1 mL). After 4 consecutive 1-mL injections, the volume was doubled again, and blood was delivered in 2-mL volumes until the end of the experiment.

The ICP as indicated by EICPMS at baseline was predetermined as normal. For subsequent measurements, an ICP ≤ 20 mm Hg above baseline was considered mildly increased, an ICP 21 to 40 mm Hg above baseline was considered moderately increased, and an ICP > 40 mm Hg above baseline was considered severely increased.

Ultrasonographic imaging of the optic nerves was performed as described at each injection time point (every 4 minutes) for 5 of the 6 dogs. For the first dog that underwent the procedure, the images were obtained every 6 minutes (with image acquisition starting immediately after each injection was completed). The time needed for image acquisition for the first dog was longer to give the ultrasonographer (HGH) time to obtain the needed images before the next injection was made. For the remaining 5 dogs, the period between successive injections was shortened to 4 minutes. The radiologist who obtained the images was aware that ICPs were increasing as time progressed. The ultrasonographic images were saved to be reviewed at a later date.

A second radiologist (HCL) reviewed all ultrasound images during a single sitting (by use of 1 viewer) and performed the ONSD measurements (Figure 1). This individual was not present when the images were obtained and was not aware of ICP data when making the measurements. However, the images were reviewed and measured in the same order as the images were viewed at a later date.
der in which they were collected. The ONSD\textsubscript{max} was measured once on each image, and the mean of the 3 values for each eye at each injection time point was used in the statistical analysis. The exact distance of the ONSD\textsubscript{max} caudal to the globe was not measured but was consistently judged between 1 and 5 mm. The ONSD\textsubscript{5mm} was also measured as previously described,\textsuperscript{18} and the mean of the 3 values for each eye was recorded.

At the conclusion of the study, all dogs were euthanized via IV administration of pentobarbital solution.\textsuperscript{9} The brains of all dogs were then removed for gross evaluation.

**Statistical analysis**

A commercially available statistical software package\textsuperscript{7} was used for statistical analysis. Numeric data were assessed for normality by means of the Shapiro-Wilk test. Because of nonparametric distributions and the small sample size, all data are reported as median and range.

The ONSD at the 2 anatomic locations was measured 3 times at each time point, including baseline, and the mean of the 3 measurements was determined. These mean measurements for left and right eyes (in the same dog and time point) were compared by Wilcoxon signed rank test for paired data.

The relationship (linear versus nonlinear) between ONSD and ICP was examined by regression modeling of overall mean ONSD values (1/dog/measurement time) and the corresponding ICP measurements. A fractional polynomial regression model was used to compare goodness of fit for linear versus various polynomial models of the data points by use of a programmed predefined set of powers (-2, -1, -0.5, ln, 0.5, 1, 2, and 3)\textsuperscript{19} of x (ICP), where ln is the natural log of the measured value. Values of P ≤ 0.05 were considered significant.

**Results**

Data from 2 dogs were excluded from statistical analysis owing to technical difficulties with the experimental model and data collection. During the first ex-

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**Figure 2**—Scatterplot representations of ONSD\textsubscript{max} (A and B) and ONSD\textsubscript{5mm} (C and D) measurements from the right and left eyes of 4 healthy female Bloodhounds under general anesthesia. Anticoagulated autologous whole blood was injected into the brain parenchyma at 4-minute intervals; ICP was measured with an EICPMS and optic nerve images were obtained by ultrasonography at each injection time point. The mean ONSD\textsubscript{max} and ONSD\textsubscript{5mm} measurements from 3 images/time point for each eye were plotted against the corresponding ICP. Experiments continued until the Cushing reflex was detected or until an ICP plateau was noted ≥ 60 mm Hg above the baseline ICP measurement for 3 consecutive injections; thus the number of measurements per dog varied. Data for right eyes (OD) are shown in panels A and C; data for left eyes (OS) are shown in panels B and D.
periment, various technical difficulties were encountered. This resulted in use of a different ultrasound transducer for ONSD measurements as well as differences in blood volume administration for this dog versus the remaining dogs. Thus, all data from the first dog in the study were excluded. Data for another dog were excluded because an epidural hematoma developed under the tip of the stopcock, which affected the accuracy of the ICP measurement by dampening the ICP waveform. This finding was suspected during the experiment and confirmed at necropsy. Proper placement of the EICPMS without a hematoma between the tip of the stopcock and the dura mater was confirmed on necropsy of the remaining 4 dogs.

In 2 other dogs, the EICPMS waveform also became dampened during the course of the study, but this was easily corrected by flushing the 3-way stopcock with 0.5 mL of saline solution as previously described.8 In 1 dog, the intraparenchymal catheter kinked where it exited the skull; this was corrected by manually holding the catheter in extension. Data from these 3 dogs were retained in the analyses. The experimentally determined baseline values as measured by EICPMS for the 4 study dogs were 32, 23, 17, and 17 mm Hg, respectively, while the final cutoff values at the end of experiments were 108, 78, 72, and 125 mm Hg, respectively.

Sagittal and transverse images of optic nerves were easily obtained with the linear ultrasound transducer. The ONSD max was located between 1 and 5 mm caudal to the globe on the transverse images for all dogs before and during ICP increases. There was no observed difference between the left and right eyes.

Figure 3—Mean ONSD max (for both eyes) and corresponding mean ICPs for the same 4 dogs as in Figure 2. Data for individual dogs (A–D) and for all 4 dogs (E) are shown. In panels A through D, lines represent the sequential mean ONSD max with their accompanying mean ICP values as measured with an EICPMS. In panel E, the solid line represents a fitted fractional polynomial regression line; dotted lines indicate upper and lower limits of the 95% confidence interval.
The increase in ONSD max was greater than ONSD measurement; the mean of 3 measurements/eye was used to generate the mean ONSD measurements of both eyes per dog. The median injection. The ICP was measured, and optic nerve images (3 images/eye) obtained by ultrasonography during this time period were recorded for each dog.

<table>
<thead>
<tr>
<th>Increase from baseline ICP (mm Hg)</th>
<th>No. of measurement intervals (No. of eyes measured)</th>
<th>Median (range)</th>
<th>No. of measurement intervals (No. of eyes measured)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20</td>
<td>4 (8)</td>
<td>2.27 (1.95–3.08)</td>
<td>3 (6)</td>
<td>1.65 (1.50–1.72)</td>
</tr>
<tr>
<td>21–40</td>
<td>14 (28)</td>
<td>2.99 (2.12–4.44)</td>
<td>12 (24)</td>
<td>1.82 (1.53–2.92)</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>59 (118)</td>
<td>3.47 (2.48–4.28)</td>
<td>58 (116)</td>
<td>1.84 (1.47–2.80)</td>
</tr>
<tr>
<td>Total</td>
<td>77 (154)</td>
<td>——</td>
<td>73 (146)</td>
<td>——</td>
</tr>
</tbody>
</table>

Anticoagulated autologous whole blood was injected into the brain parenchyma at 4-minute intervals (to allow for image acquisition after each injection). The ICP was measured, and optic nerve images (3 images/eye) obtained by ultrasonography during this time period were recorded for ONSD measurement; the mean of 3 measurements/eye was used to generate the mean ONSD measurements of both eyes per dog. The median values for each group are summarized.

— = Not applicable.

for either ONSD5mm or ONSDmax over the range of all ICPs (n = 72 for each comparison; Figure 2). Median ONSD5mm for the right eye was 1.77 mm (range, 1.27 to 3.07 mm), and that for the left eye was 1.77 mm (range, 1.20 to 2.77 mm; P = 0.420). Median ONSDmax for the right eye was 3.35 mm (range, 1.50 to 4.60 mm), whereas that for the left eye was 3.43 mm (range, 1.67 to 4.27 mm; P = 0.251).

When raw data points (mean ONSD5mm and ONSDmax measurements for left and right eyes at each ICP) for individual dogs were subjectively evaluated, all dogs had a rapid rate of ONSD increase with initial increases in ICP, followed by a slower rate of ONSD increase (Figure 3). In all dogs, the ONSD transiently decreased after its initial increase before rising again with increasing ICP. Review of the raw data points indicated that the relationship between ICP and ONSDmax was slightly nonlinear. A comparison of fractional polynomial regression models showed the relationship of ICP to ONSDmax was significantly (P = 0.006) better explained (i.e., with less deviance) by a fractional polynomial model incorporating the inverse of ICP (ONSDmax = 3.88 – 25.62 X ICP⁻¹) rather than raw ICP (ONSDmax = 2.72 – 0.01 X ICP).

Increases in ICP as indicated by EICPMS were nonlinear and positively associated with increases in ONSDmax as well as ONSD5mm (P < 0.001 for both comparisons). The increase in ONSDmax was greater than the increase in ONSD5mm (Table 1). In a linear model, the rate of ONSDmax increase was significantly (P = 0.004) greater for ICP ≤ 40 mm Hg above baseline (0.053± mm/1 mm Hg ICP increase) than for ICP > 40 mm Hg above baseline (0.0087 mm/1 mm Hg ICP increase).

### Discussion

In the present study, increases in ICP determined from an epidural pressure waveform generated by an EICPMS were nonlinear and were positively associated with ultrasonographically measured ONSDmax and ONSD5mm. In our study, the maximum size of the ONSD was found to be located ≤ 5 mm from the optic disk, which is similar to findings in human research studies. We suspect that the differences seen in ONSD at different distances behind the globe are attributable to the optic nerve anatomy; specifically, we suspect that the ONSD is more distensible closer to the optic disk rather than farther away.

Our study also found that measurement of ONSD5mm in these medium-sized dogs did not provide the greatest magnitude of change in the ONSD as the ICP increased from baseline (i.e., the value obtained immediately after placement of the EICPMS). On the basis of this information, we recommend measuring the maximum diameter of the ONSD rather than measuring it at 5 mm behind the optic disc in evaluation of ICP.

The data also showed that the degree of ONSDmax increase relative to the change in ICP was greater for ICPs ≤ 40 mm Hg above baseline than for ICPs > 40 mm Hg above baseline. In other words, the ONSDmax initially increased to a greater extent with rapid increases in ICP but after a certain point, the ONSD did not distend as much despite continued increases in ICP. We assume this was ascribable to the optic nerve sheath’s physical capacity to distend up to a point. Similarly, evaluation of raw data for each individual dog revealed that after the initial rapid increase in ONSDmax, the optic nerve sheath would transiently shrink prior to increasing in diameter again as the ICP increased. We believe this pattern is reflective of compensatory mechanisms that allow the optic nerve sheath to transiently decrease in size prior to increasing again. Individual variation in this general pattern was noted and was suspected to be caused by variability in each dog’s compensatory response to ICP.

Because the ONSDs measured in this study increased in general to a greater extent in the early stages of ICP increase, serial measurements may aid in detection of increased ICP at an early stage in clinical patients. It is also possible that the values measured in clinical patients could be decreasing at the time of measurement in response to an earlier rapid increase in ICP making serial measurements important. Conversely, if the patient has already undergone a severe increase in ICP (i.e., > 40 mm Hg above baseline as measured by EICPMS) prior to ultrasonographic measurement, ONSD increases may not be easily detected by ultrasonography. However, in the authors’ experience, when patients have a substantially increased ICP at initial evaluation, it is likely that clinical signs (e.g.,
Cushing reflex or altered mentation) can be used by the clinician to determine whether the patient is likely to have underlying high ICP. Whether the relationship described in this study is applicable to dogs that are not healthy, have conformation substantially different from that of dogs used in this study, or are not anesthetized remains to be proven.

Ultrasonographic measurements of ONSD have been found to correlate with clinical signs of high ICP in adults with traumatic brain injury, as well as in children with liver failure and hydrocephalus. In studies of traumatic brain injury, ultrasonographic examination of the ONSD was found to have a sensitivity of 100% and a specificity of 63% to 95% in diagnosing ICP increases when the optic nerve was measured 3 mm caudal to the optic disk; in each study, the ONSD was > 5 mm. Results of human research studies suggesting that the upper limit value of ONSD in patients with increased ICP is from 4.5 to 5.6 mm.

In dogs, it is not possible at this time to suggest a similar cutoff to that used in human medicine, beyond which the ONSD indicates abnormally high ICP. We do not have sufficient information regarding the effects of body weight, age, sex, breed, or species on ONSDmax or ONSDmin in animals. A previous study evaluating ultrasonographic measurement of ONSDmin in 7 adult Yorkshire Terriers and 8 Maltese found no association between ONSDmin and sex, body weight, and age, but did indicate that ONSDmin varies with breed. The ONSD has also been found to vary with age in human patients. Further prospective studies are needed to generate normal values for ONSDs and assess the degree to which these measurements increase with increasing ICP in dogs of various body weights, ages, and breeds. However, although a specific ONSD measurement cannot currently be used to predict a degree of ICP, our data do imply that serial measurement of ONSDmax in individual patients might allow for a clinician to assess progression of that patient’s ICP.

Different techniques have been used to manipulate ICP in dogs. For our study, we elected to administer anticoagulated autologous blood into the brain parenchyma to simulate acute intracranial bleeding as described in a previous canine study. It remains unknown whether clinical patients with increased ICP for reasons other than intracranial bleeding will have similar changes in ONSD measured ultrasonographically. However, a recent study measuring ONSDmax from images obtained via MRI of canine patients suspected of having increased ICP from a variety of causes did show that ONSD was greater in patients with presumed increases in ICP than in those without. In that study, ICP was not measured; ICP was suspected as being increased on the basis of MRI findings (ie, lesions that compressed or displaced adjacent structures, substantial edema, or collapse of the ventricles).

One limitation of the present study was the prolonged anesthesia time prior to the start of the study. It is known that prolonged anesthesia can increase ICP by increasing cerebral blood volume. However, our results showed that we were able to increase the ICP as indicated by EICPMS from the baseline measurement in each dog and that measurable increases in ONSDmax and ONSD min resulted from increased ICP.

A second limitation to our study is the lack of a gold standard method of ICP measurement. To our knowledge, there is no gold standard method recommended to measure ICP of dogs in clinical settings. The EICPMS has been shown to be an accurate method for ICP measurement in cats, compared with an invasive fiberoptic intraparenchymal device. In our study, ICP determination was based on experimental measurement of epidural ICP by use of an EICPMS. This method provided a continuous pressure waveform, which increased with intraparenchymal autologous blood injections and varied with the dog’s heart rate, suggesting that the changes in values recorded were representative of the ICP. Use of the EICPMS allowed us to identify pressure increases from baseline in each dog and show that the ONSDmax and ONSDmin were positively associated with increasing ICP (P > 0.001).

The radiologist who obtained ultrasonographic images was not blinded to the value of ICP as indicated by EICPMS at the time of imaging, but given that individual’s role of capturing images at predetermined time points, this was likely to introduce little bias. However, although the radiologist who performed the ONSD measurements on these images was not aware of the specific ICP values, the images were reviewed in the order they were recorded rather than being randomized, and this was more likely to introduce bias.

Further prospective studies involving larger numbers of animals are needed to investigate ultrasonographic ONSD measurements in clinically normal dogs of various breeds and body weights as well as to evaluate the utility of ultrasonographic monitoring of the ONSDmax in clinical canine patients.

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**Footnotes**

a. Tono-Pen, Vet-Reichert Inc, Depew, NY.
b. West-Ward, Eatontown, NJ.
d. PropoFlo, Abbott Laboratories, North Chicago, Ill.
e. IsoFlo, Abbott Laboratories, North Chicago, Ill.
g. Datascopc, Passport 2, Datascopc Corp, Mahwah, NJ.
h. Philips IU22/microconvex Probe C 8-5, Philips Medical Systems, Bothell, Wash.
i. Philips IU22/Linear Probe L 1-2.5, Philips Medical Systems, Bothell, Wash.
k. Mida International Inc, Erlanger, Ky.
l. Gluture, Abbott Laboratories, Abbott Park, Ill.
m. Edwards Lifesciences LLC, Irvine, Calif.
References


