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978-1-009-43629-8 — A Practical Guide to Portable Pupillometry
Merlin D. Larson
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A Practical Guide to Portable Pupillometry

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"Merlin Larson is the world's authority on pupils and anesthesia and has spent his life studying this fascinating and underappreciated window into the brain. In this monograph, Professor Larson presents an engaging non-technical history of the pupil and clearly explains how pupillary measurements have improved our understanding of anesthesia. It is well worth reading!"

Daniel I. Sessler, MD, Professor and
Michael Cudahy Chair, Outcomes Research Consortium,
Cleveland Clinic

"Merlin Larson absolutely nails this practical guide to portable pupillometry, setting the tone and capturing the reader with the fascinating history of thoughts on the pupil as a window to the soul, the heart, and the brain. Professor Larson brings his decades-long journey, in the fashion of his former colleague, John Severinghaus, to describe how he and others have created this important tool and its many practical applications in perioperative and critical care medicine. The large majority of this book provides fundamental concepts of anatomy, circuitry, physiology, and pharmacology, which are presented in an easy-to-understand manner without talking down to the reader. The book succeeds in being extremely up to date while taking pains to include how this tool is likely to evolve in the near future. As a researcher who utilizes desktop pupillometry on a regular basis, I learned much from this book and wish it had been available when I first started study of this fascinating structure."

James C. Eisenach, M.D., F.M. James, III Professor
of Anesthesiology,
Wake Forest University School of Medicine,
Winston-Salem, North Carolina

"Portable pupillometry is increasingly being used as a diagnostic tool in clinical practice and holds tremendous promise to further expand our abilities to monitor central nervous function. However, until now, this tool was missing a guidebook that would inform the interested practitioner about the underlying science. Few users of infrared pupillometry are aware about its diagnostic possibilities and limitations, or know about its many established – and potential future – clinical applications. *A Practical Guide to Portable Pupillometry* closes this gap, serving both as an introduction to the field and as a reference for the experienced clinician or researcher using pupillometry."

Merlin Larson established himself during his long scientific career as the leading expert in the field of portable pupillometry. His pioneering work laid the foundations of pupillometry use in anesthesia, pain management, and resuscitation. *A Practical Guide to Portable Pupillometry* gives the reader access to Dr. Larson's vast knowledge in an exciting, expanding field of clinical care and scientific exploration."

Matthias Behrends, MD, Health Science Clinical Professor,
and Medical Director of Inpatient Pain Services,
Department of Anesthesia and Perioperative Care,
University of California, San Francisco (UCSF)

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Merlin D. Larson
University of California, San Francisco

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About the Author

The author studied at the National Institutes of Health and Stanford University. Following his anesthesia training, he was Chairman of the Department of Anesthesia at French Hospital, San Francisco and Clinical Instructor at the University of California, San Francisco. In 1989, he joined the full-time faculty at the University of California, San Francisco and is now Professor Emeritus of Anesthesiology and Peri-Operative Medicine. He served as Chief of the Acute Pain Service at Mount Zion Hospital in San Francisco from 2013 to 2019. He has studied pupillary behavior during anesthesia for over 40 years and has published extensively on the topic. In 2001, he hosted the International Pupil Colloquium at Asilomar, California.

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Preface

As a medical student, I wanted to study neurotransmission in the brain. At the time, in 1965, this was an emerging new science based on how neurons communicated with each other. It was an exciting time because John Eccles had recently detected acetylcholine-mediated transmission in the spinal cord, and various amino acids were also candidates as central neurotransmitters (1, 2).

The Chair of the Pharmacology Department at the University of Kansas, Edward J. Walaszek, was attracted by my interest because of his research on the cataleptic bulbocapnine. He accepted me into a summer project to study how alterations in brain catecholamine levels changed the cataleptic response to bulbocapnine. My research went through two summers and the data was later published in manuscripts by Drs. Walaszek and John Chapman (3). The tentative conclusion that bulbocapnine interfered with dopamine neurotransmission has more recently been studied by other investigators (4).

These questions about neurotransmission in the central nervous system remained on my mind during my internship year at the Hospital of the University of Pennsylvania. My mentors that year promoted my continued involvement in this topic and gave me recommendations to continue my studies at the National Institutes of Health under the direct supervision of Drs. G. C. Salmoiraghi, Forrest Weight, and Floyd Bloom. Dr. Salmoiraghi had perfected a method of recording electrical potentials inside central neurons while giving drugs through a glass pipette on the outside of the same neuron (5).

My initial mentor in that lab was Forrest Weight, who was recording electrical potentials inside the large motoneurons of the cat spinal cord. Because anesthetics interfere with drug effects in the brain, his studies were performed without anesthesia. Cats were anesthetized with ether and a mid-collicular *cerveau isole* was electrolytically performed on the anesthetized animal. When the ether was discontinued, these animals would tolerate the surgical procedure of exposing the spinal cord without distress. Our reassuring sign was an animal with tightly constricted pupils who was not responsive to surgical stimulation. Failing that, we would abandon the case or attempt another mid-collicular *cerveau isole* preparation. The papers by F. Bremer from the 1930s (6) pointed to an area in the reticular formation below the nucleus of the third cranial nerve as the target of our electrolytic lesions that resulted in favorable conditions for our experiments without anesthetic agents.

In 1966, Dr. Weight left the laboratory for a two-year sabbatical in Sweden. I continued the same feline study by myself, but with a question regarding the neurotransmitters that excite and inhibit the motoneuron. The motoneuron was inhibited by a feedback mechanism. Strychnine blocked the inhibition, but how it did so was not known. These experiments showed that strychnine blocked the inhibitions elicited by glycine, but not those elicited by GABA (7) (Figure 0.1), lending support to the theory that the convulsant action of strychnine was brought about by antagonizing glycine inhibition. Because glycine is located predominantly in the spinal cord, the convulsions are primarily in the limbs, and the subjects are often awake during the convulsion. The studies at NIH introduced me to the phenomena of inhibitory mechanisms in the brain, a topic that has continued to interest me throughout my career.

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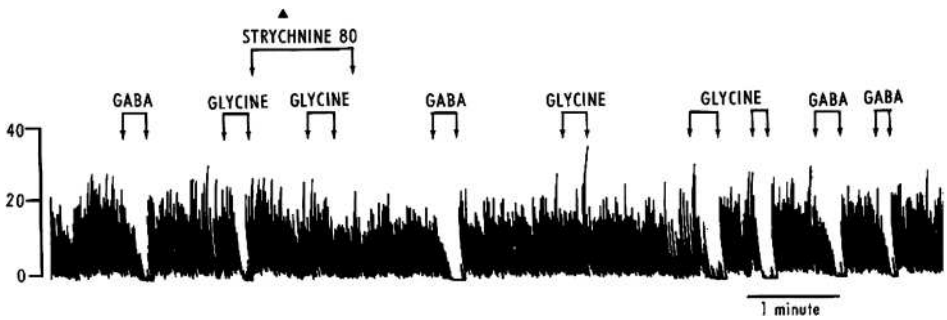

Figure 0.1 Iontophoretic application of GABA and glycine onto a motoneuron in the cat spinal cord. Note that strychnine blocked the inhibition of glycine, but not the inhibition of GABA (7). The following pages will explain how inhibitory transmission in the mesencephalon plays a major role in the control of pupil size and reactivity. Permission from Elsevier to reproduce image, License Number: 5593111219239.

My final project at NIH was to measure the effect of a barbiturate, hexobarbital, on the recurrent inhibitory process that is produced by activation of the Renshaw cells. My colleague Mitchell Major and I observed an intensification of this inhibition and published it in a short report in *Brain Research* in 1969. This observation led us to speculate that anesthetics might act partially by intensifying inhibition in the CNS (8).

The management of performing surgical procedures on cats without any anesthetic agents was challenging. The portions of the brain stem that required ablation for the *cerveau isole* preparation led me into thinking about the neurophysiology of anesthesia. John Bunker was Chair of the anesthesia department at Stanford and had similar interests. He recruited me into the anesthesia residency at Stanford University Hospital in 1968. We both felt that pursuing the questions surrounding inhibitory processes in the brain had implications for the mechanisms of anesthesia.

As I progressed through residency, the thought of the miotic pupil of the *cerveau isole* preparation resurfaced. But measuring the pupil during anesthesia presented a problem. Seventy-five years ago, there were many comments about the size of the pupil and its reactivity to light in books relating to anesthesia and critical care (9). Noticeably lacking were any actual numbers that documented the changes that were said to occur. For example, the original papers of Guedel (9), Gillespie, Poe (10), Clement, and others demonstrated charts that showed black circles that were supposed to represent the changes that were brought about by anesthetics, pain, and analgesics. Cullen and others positioned a mm rule next to the orbit, and this method provided a crude measure of pupil size, but did not measure the dynamic reflexes of constriction and dilation (11). The classic book by Plum and Posner on coma had extensive discussions on the pupil, but they did not include quantitative measurements (12).

On the other hand, Irene Loewenfeld had precisely measured pupillary reactivity relating to drugs and to critical events in animals and humans. These precise measurements were taken with a new technology using infrared light, thus avoiding the confounding effects of visible light on the pupil. The Loewenfeld records documented that the mechanism of pupillary reflex dilation was brought about through different mechanisms in the awake compared to the anesthetized animal (13). A discussion of reflex dilation will be presented in later chapters. The only academic work on the effect of

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anesthetics and opioids on the pupil in humans at that time had been performed by measuring the pupil with calipers or a mm rule (11, 14).

None of these prior discussions of pupillary reactivity would fit with what was observed during a typical anesthetic that was being used during the early 1970s. The newer halogenated agents like halothane did not produce the same changes in the pupil as had been described for ether. It seemed like a simple project to measure the pupil during the typical anesthetic of meperidine, thiopental, halothane, nitrous oxide, curare, neostigmine, and atropine. However, a pupillometer was not a device that was available in anesthesia departments. Frederic Hewitt (1857–1916) had made a crude pupil gauge and Cullen and others had used a mm rule positioned next to the eye (11). I was motivated to make a simple dot comparison pupillometer with an attached magnifying glass to evaluate the size and light reaction during induction of anesthesia with thiopental. Initial studies with this device were published in *Anesthesiology Review* (15) and attracted the attention of three retired executives of the DuPont Company who were interested in the detection of opioid abuse with pupillometry. They suggested that I help them construct a portable infrared pupillometer that would be an objective measure of pupillary size and pupillary reactions. Their company was named Fairville Medical Optics after the location near the DuPont mansion in Fairville, PA. The Fairville pupillometers went through several iterations and eventually were developed into an instrument that was able to measure and record without requiring a connecting laptop computer. These instruments will be discussed in more detail in Chapter 6.

In 1989, Peter Brock, the director of Fairville Medical Optics, visited me in San Francisco and we showed the Fairville pupillometer to Larry Stark at the University of California, Berkeley. Dr Stark was the expert in measuring the pupil with infrared light (16), but he had not considered the idea of developing a portable instrument. A new company later built on the idea of a portable instrument and invented the Neuroptics pupillometers, which became available in 1995.

These developments led to the idea of using accurate pupillary measurements in the areas of anesthesia and critical care. Consequently, I attended several sessions of the "Pupil Colloquium" where the experts on the pupil from various disciplines meet to discuss the clinical applications of pupillary measurements. At these meetings, I became acquainted with Irene Loewenfeld, Stan Thompson, Elemer Szabadi, Stuart Steinhauer, Barbara Wilhelm, Helmut Wilhelm, Paul Gamlin, Dion Bremner, Steven Smith, and Randy Kardon. In learning about the effect of anesthetics on the pupil, I became aware of how little was known about the pupil by the average physician.

In 1989, the hospital where I practiced closed and I was able to secure a position as an attending physician in the Anesthesiology Department at the University of California, San Francisco. This change in employment initiated a series of studies on the pupil that have continued to this day. I conducted several studies between the years 1990 and 2000 in collaboration with Daniel Sessler, who was studying the effect of anesthetics on thermoregulation (17). It was easy to devise a pupillary project to integrate into these studies. The questions at that time were related to the effects of hypnotics and analgesics on three separate parameters: pupil diameter (PD), pupillary light reflex (PLR), and pupillary reflex dilation (PRD). With the use of the Fairville pupillometer, we documented that the dilation of the pupil that followed a nociceptive stimulus was more robust than the hemodynamic measures that responded to the same stimulus (18).

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The neurophysiology of the pupil is complex. It is poorly understood by many physicians. It became apparent that writing articles about pupillary physiology would have little impact because of this lack of understanding. To propose ideas to the wider medical community it seemed necessary first to put together a monograph outlining the rationale for measuring the pupil. This book attempts to achieve that goal, but it is not intended to be the final word on any topic. To facilitate the ease of reading the text and economize on space, the author has omitted tables and statistical treatments. Tables and statistical data can be found by reading the referenced manuscripts. The book begins with a historical summary about the pupil and from there slowly builds a case for pupillary measurements to be used as a tool to impact clinical care. There will be mistakes in this narrative and the author would be delighted to receive comments on any aspect of the book (merlin.larson@ucsf.edu).

The author is not affiliated with or funded by commercial entities. The ideas are my own and will provoke controversy. But valid disagreements will ultimately lead to a more complete understanding of this new technology. With time, these discussions will clearly define the circumstances where pupillometry can be a useful addition to medical science.

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Glossary

Accommodation: Adjustment of shape of the lens to optimize vision.
ACLS: Advanced cardiac life support.
Adrenalin: Epinephrine.
Afferent: A nerve impulse carrying a signal toward another nerve.
Algiscan: A pupillometer made by ID Med located in Marseille, France, that can stimulate selected dermatomes.
Algorithm: An ordered set of computerized instructions.
Ambient light: Normal indoor lighting, from 250 to 450 lux.
Amine: An organic compound that is a derivative of ammonia.
ANI: Analgesia Nociception Index. A measure of nociception during general anesthesia.
Anisocoria: Difference in size between the right and left pupils.
AU: Pupillary unrest in ambient light (PUAL) is measured in arbitrary units (AUs). This value reflects both the frequency and amplitude of the fluctuations of the pupil when exposed to light.
Bilateral: On both sides of the body.
Blocked dermatomes: Dermatomes that lack sensation because of a regional block.
BMI: Body mass index, considered to be a rough measure of body fat.
Brain stem: Portion of the central nervous system between the thalamus and the spinal cord.
Camera obscura: A dark space containing a small hole through which an image can be projected on a screen.
Cataract: An opacity in the lens of the eye.
Catecholamine: An organic compound containing a catechol group. Some of the catecholamine neurotransmitters in the brain are epinephrine, norepinephrine, and dopamine.
Caudal: A neuraxial block by injection of local anesthetics into the sacral hiatus.
Cephalad: Toward the head.
Cerveau isole: An operation that transects the midbrain below the oculomotor nucleus.
CNS: Central nervous system.
Coma: A state of unresponsiveness with eyes closed and unresponsive to vigorous stimulation.
Consensual reflex: The constriction of the pupil when light is directed into the opposite pupil.
Contralateral: On the opposite side.
CPR: Cardiopulmonary resuscitation.
CSF: Cerebral spinal fluid.
CVP: Central venous pressure.
Delirium: A temporary disorder of mental faculties.
Denervation: Loss of nerve supply to an area of the body.
Dermatome: The sensory area innervated by one spinal segment.

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Desynchronized sleep: Sleep during which EEG resembles the awake condition.
Diplopia: Double vision.
Dot comparison pupillometer: A pupillometer consisting of different sizes of circular black dots.
Drug tolerance: A decrease in drug effect after prolonged use.
ECMO: Extracorporeal membrane oxygenation. A method to support the circulation and gas exchange in persons whose heart and lungs are unable to support life.
EEG: Electroencephalogram.
Efferent: A nerve impulse carrying a message away from another nerve.
EKG: Electrocardiogram.
Electromechanical dissociation: Lack of cardiac function with continuation of cardiac electrical activity.
Endoscopy: Insertion of a thin tube into the body to visualize an internal organ.
Epidural: A regional block produced by injection of agents into the epidural space.
Etiology: Pertaining to the cause of an event.
EW: Edinger Westphal nucleus. A region in the upper midbrain that contains the neurons that initiate the pupillary light reflex.
EWcp: The portion of the Edinger Westphal nucleus that projects centrally and is not involved in generating the pupillary light reflex.
EWpg: Preganglionic Edinger Westphal neurons that provide the nicotinic cholinergic input to the ciliary ganglion. These neurons generate the pupillary light reflex.
Extramission: The theory that vision is brought about by eye beams emitted from the eye.
Extubation: Removal of a tracheal tube.
FFT: Fast Fourier Transform. A mathematical operation that separates a fluctuating signal into frequency and amplitude components.
Fluctuation: An irregular chaotic change in the size of the pupil.
fMRI: Functional magnetic resonance imaging. An imaging method that demonstrates changes in brain metabolism.
Four Score: A 16-point scale that indicates the severity of neurological impairment.
GABA: Gamma aminobutyric acid. An inhibitory transmitter in the brain.
General anesthesia: An anesthetic that includes loss of consciousness.
Glasgow coma scale (GCS): A 15-point scale that indicates the severity of functional neurological impairment.
ICP: Intracranial pressure.
ICU: Intensive Care Unit.
Illumination: The intensity of light falling on a given surface. The Neuroptics PLR-3000 device provides the energy delivered to the LEDs in microwatts. Approximate illuminations are as follows: 10 microwatts: 80 lux, 50 microwatts: 410 lux, 121 microwatts: 1,000 lux, 180 microwatts, 1,500 lux. The NPi-300 and the Neurolight illuminate at approximately 1,000 lux.
Infrared: A type of electromagnetic radiation with a wavelength that is longer than visible light.
Inhibition: A type of neurotransmission in the brain that inhibits the activity of other neurons.
Intracranial: Within the cranium.

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Intraoperative: Occurring during an operation.
Intromission: The theory that vision is brought about by light rays entering the pupil.
ipRGCs: Intrinsic photosensitive retinal ganglion cells. Retinal ganglion cells that respond to light in the absence of rod and cone photoreceptors.
LC: Locus coeruleus. A brain stem nucleus in the pons containing norepinephrine.
Limbus: The junction between the cornea and the sclera of the eye.
LO: Light off. An abrupt change from brightness to darkness.
LSD: Lysergic acid diethylamide. A synthetic potent psychedelic drug.
MAC: Minimum anesthetic concentration, a measure of anesthetic potency.
Medulla: The lowest portion of the brain, which connects it to the spinal cord.
Midbrain: The uppermost portion of the brain stem.
Miosis: A small constricted pupil, below 3 mm in diameter in dim light.
Motoneuron: Large neurons in the spinal cord that innervate muscles to initiate movement.
MRI: Magnetic resonance imaging. A noninvasive process that produces detailed images of the body.
Near vision: Viewing objects close to the face.
Neuraxial block: A regional block by injecting local anesthetics into the neuraxis.
Neurolight: A pupillometer made by ID Med located in Marseille, France that is designed to measure the light reflex and PUAL.
Neuromuscular blocking agent: A drug like curare that paralyzes skeletal muscles.
Neuroptics: A company located in Laguna Hills, CA that makes pupillometers.
Neurotransmission: The process of transferring messages in the brain.
Neurotransmitter: A chemical that is released by a nerve to activate or inhibit another nerve or muscle.
NMDA antagonist: A drug like ketamine that blocks the N-methyl-D-aspartate receptor.
Nociception: The physiological response to activation of nociceptors.
Nociceptor: A specialized receptor that responds to intense stimuli that are potentially harmful.
NOL: Nociception Level. A monitor designed to objectively quantify pain and nociception.
NPi: Neurological Pupil index. An algorithm proposed by Neuroptics, Inc. to evaluate the quality of the pupillary light reflex.
NSAIDs: Nonsteroidal anti-inflammatory drugs. A non-opioid alternative for treatment of pain.
Ophthalmoscope: An instrument that permits visualization through the pupil into the interior of the eye.
Opioid: A natural or synthetic drug derived from opium.
Optic nerve: The second cranial nerve that transmits the visual sensation to the brain
PACU: Post-Anesthesia Care Unit
Pain: An unpleasant sensory and emotional response to real or imagined tissue injury.
Palpebral fissure: The open space between the upper and lower eyelids.
Parameter: A measurement that can be given a specific value.
Parasympathetic: That portion of the autonomic nervous system that arises from cranial and sacral nerves.
PCA: Patient controlled analgesia. The patient controls a pump that delivers analgesics.

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PD: Pupil diameter.
PET scan: Positron emission tomography. An imaging technique that uses radioactive tracers to detect disease at an early stage of development.
Photopigment: A pigment in the retina whose chemical state depends on the degree of illumination.
Photoreceptor: Neurons in the retina that convert light into electrical neuronal signals.
PIPR: Post Illumination Pupillary Response. A sustained pupillary constriction following short wavelength light stimulation.
PLR: Pupillary light reflex.
Pons: That portion of the brain stem that lies between the medulla oblongata and the midbrain.
PPI: Pupillary Pain Index. A pupillometric technique designed to detect intraoperative analgesia.
PRD: Pupillary Reflex Dilation.
PUAL: Pupillary unrest in ambient light. The strength of the pupillary fluctuations in ambient light.
PUI: Pupillary Unrest Index. A long duration measurement of pupil size that is proposed to detect drowsiness.
Pupillometer: An electronic device that measures the pupil.
Pupillometry: The process of using pupillometers to measure the pupil and its reactions.
QPi: Quality of the pupillary light reflex. A number generated by the Neurolight pupillometers to gauge the quality of the pupillary light reflex.
Radial muscle: The radial muscle is the dilator muscle of the iris that is innervated by the sympathetic nervous system.
RAPD: Relative afferent pupillary defect. A relative defect in transmitting light excitation from the retina to the olivary pretectal nucleus as compared to the opposite side.
RASS: Richmond Agitation–Sedation Scale, a measure of sedation or agitation. Plus 4 is very combative and minus 5 is unarousable sedation.
Receptor: A specialized portion of a neuron that is activated by a neurotransmitter.
Regional block: Local anesthetic induced loss of sensation.
Reticular formation: A complex group of neurons in the brain stem that are crucial for maintaining a state of consciousness.
ROSC: Return of spontaneous circulation.
RR interval: The time elapsed between two successive R waves on the electrocardiogram.
Sensitivity: The ability of a test to correctly designate a person as positive for a condition such as disease state.
Smooth muscles: Involuntary muscles innervated by the autonomic nervous system in the hollow organs, the iris, and the walls of blood vessels.
Specificity: The ability of a test to give a negative result in a person who is actually negative for a condition.
SPI: Surgical Pleth Index. An objective measure of nociception that uses plethysmographic signals.

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Strabismus: A disorder of the extraocular muscles so that both eyes cannot fixate on the same object.
Subcortical: That portion of the brain that is below the cortex.
Supraspinal: The central nervous system above the spinal cord.
Sympathetic nervous system: A portion of the autonomic nervous system that arises from the first thoracic segment to the second lumbar segment.
Synapse: A specialized junction between two neurons that can be activated by a neurotransmitter.
Synchronized sleep: Slow-wave sleep.
TBI: Traumatic brain injury.
Tetanic stimulus: A painful electrical stimulus applied to the skin, typically stimulating at 50 to 100 Hz.
THC: Tetrahydrocannabinol. The principle psychoactive ingredient in cannabis.
TIVA: Total intravenous anesthesia. General anesthesia that is produced only via the intravenous route.
Toxic dose: A dose of a drug that is either lethal or nearly lethal.
Tracheal intubation: Insertion of a breathing tube into the trachea.
UCSF: University of California, San Francisco.
Ultrasound: A technique that uses high-frequency sound waves to make images of structures within the body.
Unilateral: One-sided.
Ventilation: Spontaneous or mechanically assisted breathing.
Vertex distance: The distance from the front surface of the cornea to the lens of the optical device.
Volatile anesthetic: An inhaled anesthetic that is a vapor.

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