History of the Development of Anesthesia for the Dolphin

A Quest to Study a Brain as Large as Man's

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ABSTRACT

It is important for academic-minded human anesthesiologists to have an interdisciplinary perspective when engaging in cutting-edge research as well as the practice of human anesthesiology. This was a philosophy promoted by Dr. Robert Dripps, former pioneering Chairman of the Anesthesiology Department at the University of Pennsylvania (Philadelphia, Pennsylvania). Many human and veterinary anesthesiologists as well as biomedical engineers and neuroscientists benefited from Dr. Dripps's constructive outlook personified in the quest to develop dolphin anesthesiology.

The motivation to anesthetize dolphins came from the fact that scientists and physicians wanted to study the brain of the dolphin, a brain as large as man's. Also, investigators wanted to develop anesthesia for the dolphin in order to study the electrophysiology of the dolphin's highly sophisticated auditory system, which facilitates the dolphin's amazing echolocation capability.

Dolphin anesthesia involves a complex matter of unique neural control, airway anatomy, neuromuscular control of respiration, and sleep behavior. **(ANESTHESIOLOGY 2018; 129:11-21)**

THE motivation to anesthetize dolphins first came from the fact that scientists and physicians were excited about the prospect of studying the brain of a dolphin, an animal with a brain on average 10% larger than man's. For a complete review of dolphin body and brain weights, see Ridgway *et al.*[1] See figure 1 for a dolphin to human brain comparison photograph. Also, scientists wanted to develop anesthesia for the dolphin in order to study the electrophysiology of the dolphin's highly sophisticated central and peripheral auditory system, which facilitates the dolphin's amazing echolocation capability. In addition, the need to develop comprehensive medical and surgical care of dolphins was a paramount consideration.

The odyssey to develop dolphin anesthesiology to accomplish mapping of the dolphin's large brain, plus electrophysiologic study of the dolphin's very advanced auditory system, involved contributions from a neurology/psychiatry physician, Dr. Orthello Langworthy at the Johns Hopkins Medical School (Baltimore, Maryland); another physician, Dr. John Lilly, with a background in neuroscience at the National Institutes of Health (Bethesda, Maryland) and a biomedical background from the California Institute of Technology (Pasadena, California); a human anesthesiologist at the University of Miami (Miami, Florida), Dr. Eugene Nagel; several world-class neurophysiologists, including Drs. Jersey Rose, Vernon Mountcastle, and Lawrence Kruger from Johns Hopkins Medical School, plus Drs. Clinton Woolsey and J. Hind from the University of Wisconsin (Madison, Wisconsin), Dr. Karl Pribram from the Institute of Living (Hartford, Connecticut), and Dr. Leonard Malis from Mt. Sinai Hospital (New York, New York); Dr. Sam H. Ridgway, a pioneer marine mammal veterinarian and neuroscientist with the U.S. Navy (San Diego, California); a neuroscientist, Dr. James G. McCormick, from Princeton University (Princeton, New Jersey) and Wake Forest University School of Medicine (Winston-Salem, North Carolina); Dr. Lawrence Soma, the former Chief of Veterinary Anesthesiology at the University of Pennsylvania (Philadelphia, Pennsylvania); and an engineer and medical scientist, Dr. Forrest Bird, of the Bird Respirator Company (Palm Springs, California), who developed both human and veterinary respirators and anesthesia machines.

Dr. Bird and Dr. Soma both benefited from study and collaboration under the legendary interdisciplinary influence of the Chair of Human Anesthesiology at the University of Pennsylvania, Dr. Robert Dripps. Dr. Francis M. James III, former Professor and Chair of Anesthesiology at Wake Forest University School of Medicine and anesthesiology resident of Dr. Dripps, related to Dr. McCormick in November 2017, as an example of Dr. Dripps's interdisciplinary philosophy, how Dr. Dripps invited Dr. Soma to do a year of human anesthesiology residency with Dr. Dripps. Dr. James went on

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to note that both sides of this collaboration benefited greatly. Previously, in 1967, when Dr. McCormick was meeting with Dr. Soma for advice on the 1967 dolphin anesthesiology manuscript published in *Science* by Drs. Ridgway and McCormick,[2] Dr. Soma expressed to Dr. McCormick admiration for the wonderful collaborative bent of Dr. Dripps.

The 90-yr venture to develop a safe, humane surgical anesthesia procedure for the dolphin personified the interdisciplinary philosophy of Dr. Dripps. Failures and successes were all important. Scientists, engineers, and human and veterinary anesthesiologists all participated.

History of the Development of Dolphin Anesthesiology

The first effort to study the electrical activity of the large brain of the dolphin was attempted by Dr. Langworthy of Johns Hopkins School of Medicine in 1928 on the coast of North Carolina. Attempting to accomplish this, Langworthy tried to anesthetize stranded dolphins using an ether cone, which resulted in respiratory failure deaths. However, as a result of this effort, Langworthy was able to publish exceptional pen-and-ink drawings of the gross anatomy of the dolphin's cortical and subcortical brain structures.[3] The next attempt to study the dolphin brain was in 1955. Neurophysiologists and physicians attempted to anesthetize dolphins using intraperitoneal Nembutal (brand name for pentobarbital; produced by Lundbeck, Denmark), which resulted in respiratory failure deaths.[4] It became clear that intubation and controlled respiration were necessary for anesthetization of the dolphin, and in 1964, Forrest Bird of the Bird Respirator Company modified a Bird Mark 9 Respirator so it could mimic the natural apneustic plateau breathing pattern of the dolphin.

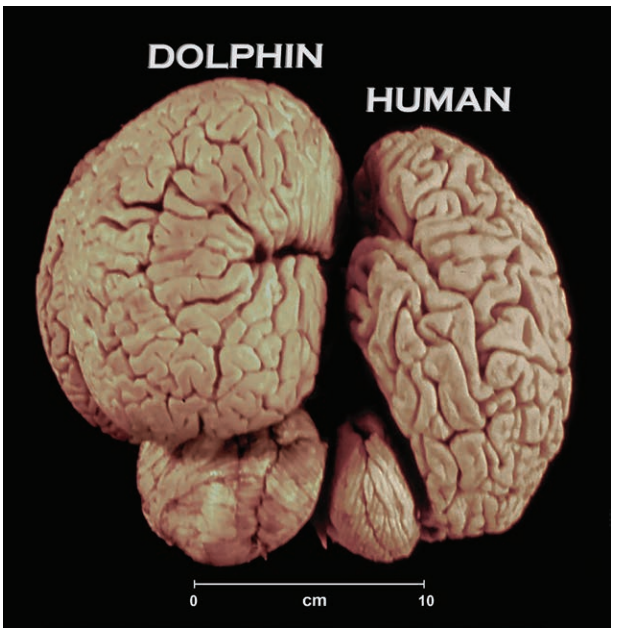

Fig. 1. The dolphin brain is a *Tursiops truncatus (T.t.)*, a genus and species of dolphin with one of the largest brains. The dolphin brain weighs 1,789 g, and the human brain weighs 1,250 g. Both these brains are within normal limits, but the average weight of a *T.t.* dolphin brain is 1,549.9 g,[1] and the average weight of a human brain is 1,450 g.[4] The dolphin brain came from a 200-kg dolphin, and the human brain came from a human weighing approximately 70 kg.

Later in 1964, another group attempted to surgically anesthetize dolphins utilizing the Bird Mark 9 Dolphin Respirator with nitrous oxide supplemented with succinylcholine muscle relaxant[5]; however, Ridgway and McCormick tested this nitrous oxide preparation in 1967 without the use of succinylcholine so that dolphin reflexes could be measured to evaluate the plane of anesthesia with nitrous oxide, and found nitrous oxide to be inadequate for major surgery.[2] In addition, since Nagel *et al.*[6] reported that the dolphin does not have plasma cholinesterase, which is needed for the metabolism of succinylcholine, it is important to note that succinylcholine is contraindicated in the dolphin. Ridgway and McCormick went on to describe perfection of successful halothane surgical anesthesia for the dolphin with IV thiopental induction.[2,7] This work of Ridgway and McCormick was a follow-up comprehensive study based in part on the first successful halothane anesthesia for the dolphin by Ridgway in 1965.[8] McCormick, in 1969 and 2007 explained that dolphin anesthesia is a complex matter of unique neural control, airway anatomy, neuromusculature control of respiration, and sleep behavior.[9,10]

The dolphin anesthesia work of Ridgway, McCormick, and others involved a large number of successful cases for surgical medical care and electrophysiologic studies of the dolphin peripheral auditory sensory cells and central auditory nervous system.[11–23] Bullock and his group[21–23] accomplished auditory central nervous system recordings from the brain of the dolphin, using the successful dolphin surgical anesthesia procedure perfected by Ridgway and McCormick.[2,7]

The U.S. Navy Office of Naval Research (Arlington, Virginia) recently funded an interdisciplinary team consisting of human anesthesiologists, veterinary anesthesiologists, neurophysiologists, and engineers to design and build a new dolphin respirator for anesthesiology (Anesthesia Ventilator for Atlantic Bottlenose Dolphins and California Sea Lions, Navy STTR FY2014A – Topic N14A – T015). The authors of this article are two members of the Navy Office of Naval Research team. A recent Office of Naval Research Dolphin Respirator planning and construction meeting took place in San Diego, California, at the U.S. Navy Marine Mammal Facility, February 14 to 16, 2017, with McCormick and Ridgway as the introductory speakers.

Dolphins are born in water and live their whole lives in water. Living exclusively in water imposed many necessary adaptations in form, physiology, and anatomy. The most critical consideration for anesthesiology in the dolphin is the fact that the animal exclusively breathes with an apneustic plateau. Whereas humans normally breathe continuously in and out, with pneumotaxic and apneustic brain centers opposing each other in sequence, the dolphin holds an apneustic plateau for 20 to 50 s between expiration-inspiration periods.[9]

The natural apneustic breathing adaptations of the dolphin have required the development of anesthesia procedures based on the need for intubation and controlled respiration with a respirator capable of apneustic breathing. Ridgway and McCormick documented that due to the collapsible nature of the dolphin lungs, coupled with a collapsible chest and collapsible alveoli that prevent nitrogen going into the circulation during diving to help mitigate decompression sickness from diving (fig. 2), it is especially necessary to use positive pressure apneustic ventilation of the dolphin to maintain normal blood gas values and heart function with proper inflation of the alveoli for gas exchange.[7] This principle was further clearly illustrated both in a gas exchange diving study on open ocean dolphins by Ridgway and Howard[24] and in a dolphin deep diving study by Ridgway *et al.*[25]

In addition to protection against nitrogen gas decompression sickness by the dolphin's dive-induced collapsing lung, the dolphin does not have contact clotting factor 12 in his blood. The activation of thrombosis by gas bubbles in decompression sickness *via* clotting factor 12 has been demonstrated and discussed by Hallenbeck and Andersen,[26] and McCormick *et al.* demonstrated the thrombogenic action of bubbles in decompression sickness as the etiology of inner ear deafness from decompression sickness.[27–29]

Control of Respiration in the Dolphin and Implications for Anesthesiology

McCormick examined the special theory of Lilly that respiration in the dolphin is based on altogether voluntary control.[9] McCormick concluded that respiration in the dolphin can be automatic or can be brought under voluntary control, just as in other mammals. He reported that oxygen–carbon dioxide respiratory control in a *Tursiops truncatus* dolphin is similar to that of other mammals, except that tolerance to carbon dioxide in the blood is greater due to increased buffering capacity.[9] Normal exhaled carbon dioxide for *Tursiops* is 6 to 9%. With presentation of controlled mixtures of carbon dioxide, oxygen, and nitrogen to a *T. truncatus* dolphin, it was determined that concentrations of 5% carbon dioxide or greater caused an increase in respiration rate. At 5% carbon dioxide, the rate of respiration was double that measured with ambient air breathing. This held true even when oxygen was concurrently increased to 40%. Decreasing the oxygen to 9 or 10% while holding the carbon dioxide at ambient concentration also caused a respiration rate double that measured in ambient air for the awake dolphin.[9]

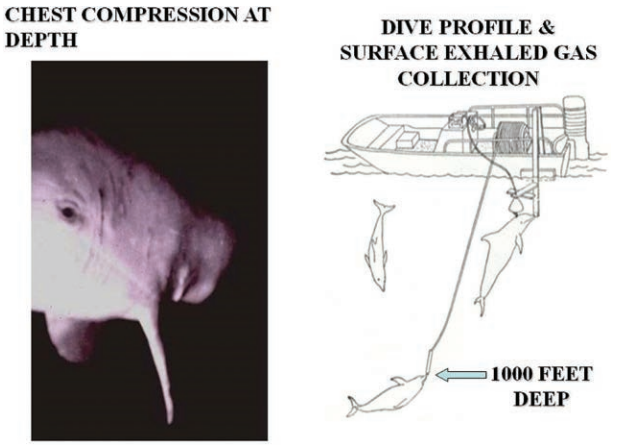

Fig. 2. Chest collapse in the dolphin documented by Ridgway and Howard[24] and Ridgway *et al*.[25] in a diving *Tursiops truncatus* dolphin photographed at 1,000 feet deep in the open ocean. Adapted from Ridgway *et al*.[25]

McCormick further noted that when one observes the natural respiratory pattern of the awake dolphin,[9] as described by Irving *et al*.,[30] there can be no doubt that the dolphin has an apneustic respiratory mechanism that operates differently from the pons apneustic center of man.[31] As explained in the beginning of this article, whereas man normally breathes continuously in and out, with pneumotaxic and apneustic brain centers opposing each other in sequence, the dolphin holds an apneustic plateau for 20 to 50 s between expiration-inspiration periods. Differences between man and dolphin respiration and other key factors of dolphin anesthesiology *versus* man are summarized in box 1.

Anatomy of Dolphin Related to Intubation for Controlled Respiration and Anesthesia

Figure 3 depicts the anatomy of the dolphin (*T. truncatus*) related to intubation and anesthetization. For most mammals during the induction of anesthesia, the control of the intercostal muscles involved in breathing is lost before the loss of diaphragm control, and diaphragm control alone is sufficient to maintain respiration without the work of the intercostals.[32]

In contrast, McCormick, based on his experience with dolphin anesthesia induction in 35 dolphins, noted that dolphins must utilize their intercostal muscles to maintain respiratory excursions. The dolphin must also have control of his larynx and blowhole to help maintain the air in the lungs during the apneustic plateau.[9] McCormick went on to say that when an induction agent like sodium thiopental is administered intravenously as a preliminary to intubation of the dolphin, it is necessary to wait for the cessation of breathing. Before breathing stops, the dolphin has extremely good control of the closure of his epiglottis, and can deliver a rather painful pinch should a finger be inserted in the larynx before it is completely relaxed. As the thiopental takes effect, the epiglottis relaxes (fig. 3) and air escapes from the larynx, and concurrently the intercostal muscles may go into a momentary spasm of contraction. The problem of moving the intercostal muscles for the apneustic plateau is compounded for the dolphin by the added weight of the body when removed from the water. In recovery from anesthesia, the blowhole is the last element of the respiratory system to regain function.[2,9]

Box 1. Dolphin Anesthesia Differences from Man

Dolphin anesthesiology requires the use of intubation and controlled respiration with a respirator capable of apneustic breathing, which is necessary for maintenance of normal blood gas values and heart function, given the fact that the dolphin has collapsible alveoli and a collapsible chest designed to mitigate nitrogen going into the circulation during the pressure of diving[7,24,25] (fig. 2).

The dolphin has an apneustic respiratory mechanism that operates differently from the pons apneustic center of man.[31] Man normally breathes continuously in and out, with pneumotaxic and apneustic brain centers opposing each other in sequence. The dolphin holds an apneustic plateau for 20 to 50 s between expiration-inspiration.

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Dolphins must be continuously cooled with water during anesthesia to avoid overheating. Dolphins normally live in water, which takes up heat much faster than air. Anesthesiology of dolphins should be performed with the dolphin in a temperature-controlled water immersion tank to provide buoyancy support of pulmonary and cardiac function.[11] (fig. 9).

Dolphins have a unique list of reflexes to check for monitoring induction of anesthesia, including body movement reflexes related to similar motions during sleep in dolphins.[2,9,10] See text section "Clinical Signs of Induction and Recovery in Dolphin Anesthesia."

Succinylcholine is contraindicated in dolphins due to the fact they do not have plasma cholinesterase for metabolism of succinylcholine.[6]

The *Tursiops truncatus* dolphin has the capability to have unihemispheric brain protection against suppression from the pharmacologic agent diazepam. General surgical anesthesia suppresses both hemispheres of the dolphin brain.[2,7,9,10]

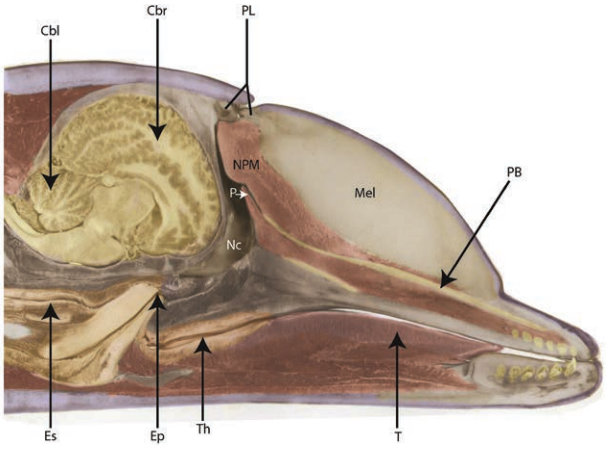

Fig. 3. Section through the head of a bottlenose dolphin (*Tursiops truncatus*) outlining major anatomical areas of interest for anesthetization. Cbl = cerebellum; Cbr = cerebrum; Ep = epiglottis; Es = esophagus; Mel = melon; Nc = nasal cavity; NPM = nasal plug muscle; P = premaxillary sacs; PB = premaxillary bone; PL = phonic lips; T = tongue; Th = throat. Photo labels and color modification courtesy of Katie Van Alstyne.

As noted in figure 3, the epiglottis protrudes up in the middle of the throat and is normally inserted into the passageway up to the blowhole in the top of the dolphin's head. The dolphin has very good control over the closure of the epiglottis. This control is important both for regulating the dolphin's apneustic plateau and for control of air passed up the passage to the blowhole in the top of the head. In this passage to the blowhole, the air from the larynx as controlled by the epiglottis is directed to echolocation sound-producing structures. The large fatty melon of the dolphin, located just anterior to the air passageway to the blowhole, operates as an acoustic lens to beam the dolphin's sonar pulses out into the water environment for echolocation. The outgoing echolocation pulses do not mask the returning echoes analyzed by the dolphin's hearing, since the ears of the dolphin are acoustically isolated from the skull.[11–13,19]

Clinical Signs of Induction and Recovery in Dolphin Anesthesia

Ridgway and McCormick outlined the reflexes that can be used to indicate the presence or absence of good anesthesia for surgery in the dolphin[2]: "(i) eyelid reflex, contraction or closure of the eyelid induced by tapping on the inner canthus of the eye; (ii) corneal reflex, contraction of the eye muscles or lids when the cornea is touched; (iii) gag reflex, contraction of the throat muscles when the hand is inserted into the pharynx; (iv) tongue reflex, contraction or pulling away of the tongue when it is pulled forward; (v) anal reflex, reflex movements of any body parts when the anus is distended; (vi) swimming reflex, movements of the tail up and down in a swimming motion"—a reflex only seen with slower gas induction as opposed to faster IV induction with an agent like sodium thiopental (fig. 4). On recovery from anesthesia, the dolphin will slowly start to produce the same swimming

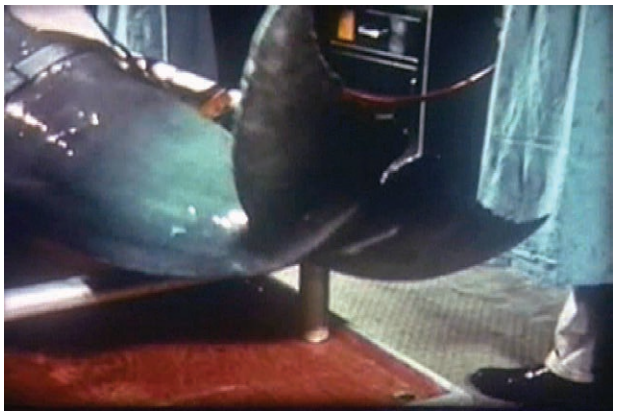

Fig. 4. Swimming reflex movements of the dolphin observed when going under gas anesthesia, and again on recovery from anesthesia.[10] See explanation in "Clinical Signs of Induction and Recovery in Dolphin Anesthesia." Reproduced with permission from McCormick.[10]

motion of his tail seen in induction (fig. 4)[10]: "(vii) pectoral scratch reflex, movements of the pectoral flippers in response to a pinprick or scratch of the chest or axillary region; (viii) blowhole reflex, movements of the blowhole when the finger is inserted into the nares of the vestibular sacs; (ix) vaginal or preputial reflex, movements of the vagina or penis or other body parts when the vagina or prepuce is distended by insertion of the fingers or other instruments."[2]

During induction with halothane gas anesthesia, the swimming movements of the dolphin disappeared just after the loss of strong corneal and eyelid reflexes. All other reflexes noted above, except the anal reflex, are not present during periods of surgical anesthesia. Recovery from anesthesia is first noted when the swimming reflex reappears. Extubation can be safely performed after the blowhole reflex returns and the dolphin starts to buck the endotracheal tube connected to the ventilator tube.[2,7]

McCormick[9,10] observed a form of water surface sleep in the dolphin *T. truncatus* similar to the tail swimming motion of the dolphin during gas anesthesia induction. As noted in figure 5 showing dolphin surface sleep, "Respiration is automatic in nature with a tail kick reflex synchronized to the respiration cycle so that the blow hole of the dolphin is always raised just above the surface to breathe."[10] As shown in figures 6 and 7, if the dolphin is in calm water and left undisturbed, the tail kick linked to the respiration cycle will eventually stop and lead to motionless floating at the surface with both eyes closed and the blow hole just above the water surface, providing safe breathing.[10] In this motionless state, the dolphin does not respond to the presence of other dolphins in his tank, and does not wake up when a flash camera is set off in front of his face. Thus, dolphin brain bihemispheric suppression appears to take place both in surgical anesthesia and water surface sleep under safe, calm conditions.

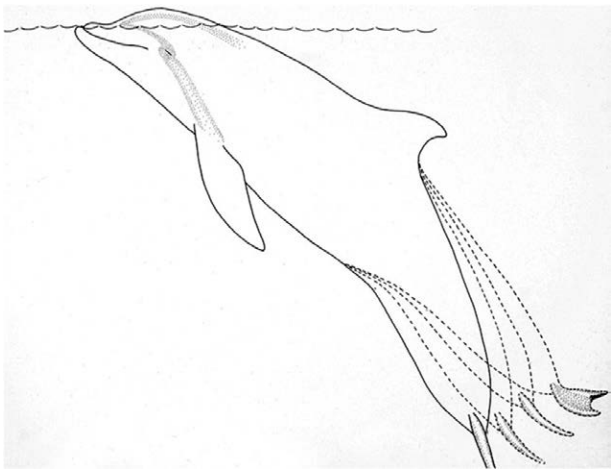

Fig. 5. "Drawing depicting the behavior observed with *Tursiops truncatus* dolphin surface sleep. Respiration is automatic in nature with a tail kick reflex synchronized to the respiration cycle so that the blowhole of the dolphin is always raised just about the surface to breathe." Reproduced with permission from McCormick.[10]

Fig. 6. Photograph shows two *Tursiops truncatus* dolphins surface-sleeping with their eyes closed. If the dolphins are undisturbed in quiet water, the surface sleep tail kick shown in figure 5 can subside and lead to motionless hanging at the surface with both eyes closed. The surface of the water is at the top of the picture, and the dolphins are floating with their blowholes just above the surface to breathe. Reproduced with permission from McCormick.[10]

According to Ridgway *et al.*,[11] after induction of anesthesia in the dolphin, the heartbeat, rather than following its normal respiratory bradycardia with the hold of the apneustic plateau, becomes steady at approximately 80 to 120 beats per minute depending somewhat on the size of the animal (larger specimens having slower rates). On recovery from anesthesia, the normal respiratory rhythm of the dolphin returns (fig. 8).

Necessary Support of the Dolphin for Anesthesia

Ridgway and McCormick[2] pioneered using a compliant surgical stretcher and, later, a more advanced surgical water immersion tank (fig. 9) to provide better, more physiologic pulmonary and cardiac support to the dolphin during anesthesia.[11] Total submersion of the dolphin in the temperature-controlled water tank except for the surgical site was possible due to the fact that the dolphin was always intubated with a strong inflatable cuff seal for positive pressure apneustic respiration.

Bird Mark 9 Dolphin Apneustic Control Respirator

As mentioned in the beginning of this article, in 1964, Forrest Bird of the Bird Respirator Company modified a Veterinary Bird Mark 9 Respirator so it could mimic the natural apneustic plateau breathing pattern of the dolphin. Figure 10 is a schematic of the key components of a Bird Mark series ventilator, which are all pneumatically powered and controlled. Of these components, there are two diaphragm valves that control the majority of the ventilator functionality. The first is the servo

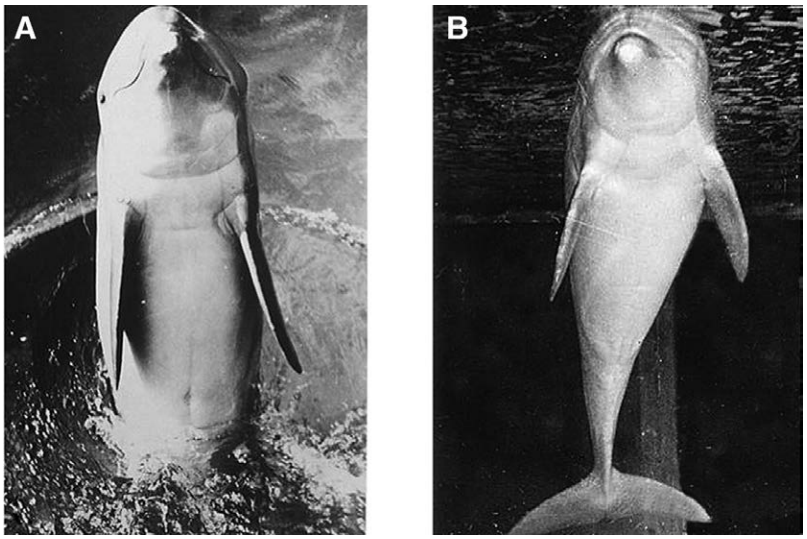

Fig. 7. (*A*) For comparison, a dolphin is shown fully awake posing above the surface. (*B*) This *Tursiops truncatus* dolphin was observed resting at the surface, virtually immobile, with both eyes closed and breathing in an automatic fashion for more than 1 h. The animal did not respond to the flash of the camera, and did not respond to another dolphin that gently bumped up against him. The dolphin is floating motionless with his blow hole positioned continuously just above the surface at the top of this photograph. Reproduced with permission from McCormick.[10]

cartridge, which senses the lung pressure (*via* its diaphragm) and initiates and terminates the inspiration mode. This valve is fairly complex, including magnetic clutches to throttle flow and aid in sensing negative pressures for assisted breathing. When this valve senses zero pressure (or a negative pressure for assisted breathing), it opens, allowing gas to flow into the lungs through the gated venturi. As with all of the Bird Mark series ventilators, a major advantage of the Mark 9 system is gas delivery to the lungs *via* a gated venturi that acts as an air dilutor, increases the gas flow capability, and acts as a pneumatic clutch during inspiratory flow. In this mode, the servo cartridge also supplies gas to the apneustic plateau cartridge pilot (177 in fig. 10), opening it to supply gas to the nebulizer and to the exhalation valve to keep it closed.

Once the servo cartridge senses that the peak pressure is achieved (pressure set by tensioning the valve spring), it closes, ending the inspiration mode. At this point, the apneustic plateau cartridge pilot is no longer being fed gas, but there is still a small amount remaining that keeps this valve open, which in turn keeps the exhalation valve closed and the nebulizer running. The duration that the apneustic plateau control cartridge remains open after the inspiration mode terminates is

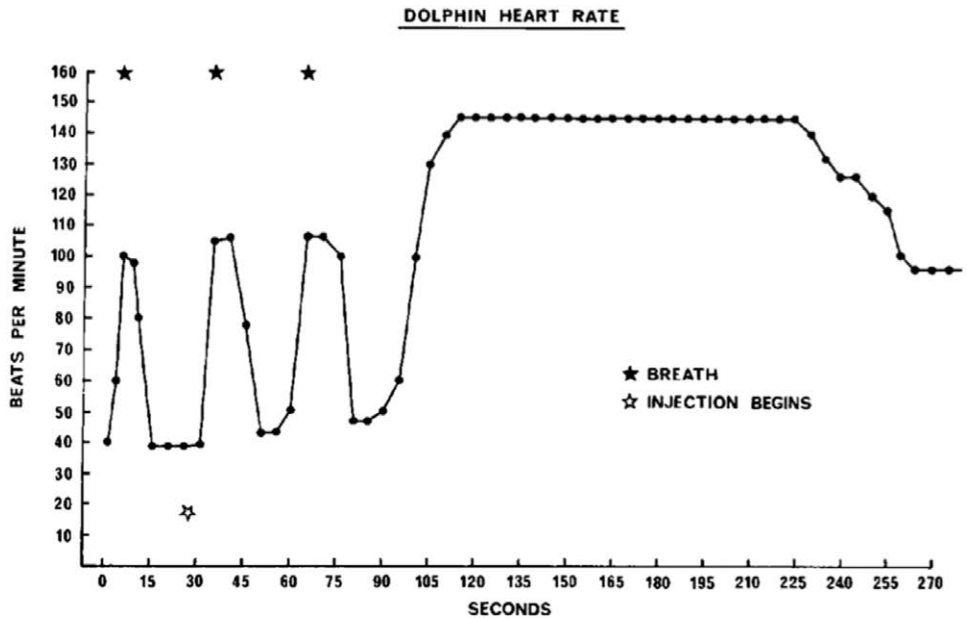

Fig. 8. Graph of heart rate in *Tursiops truncatus* just before and after intravenous injection of pentothal. Preanesthetic atropine was not given. Reproduced with permission from Ridgway *et al*.[11]

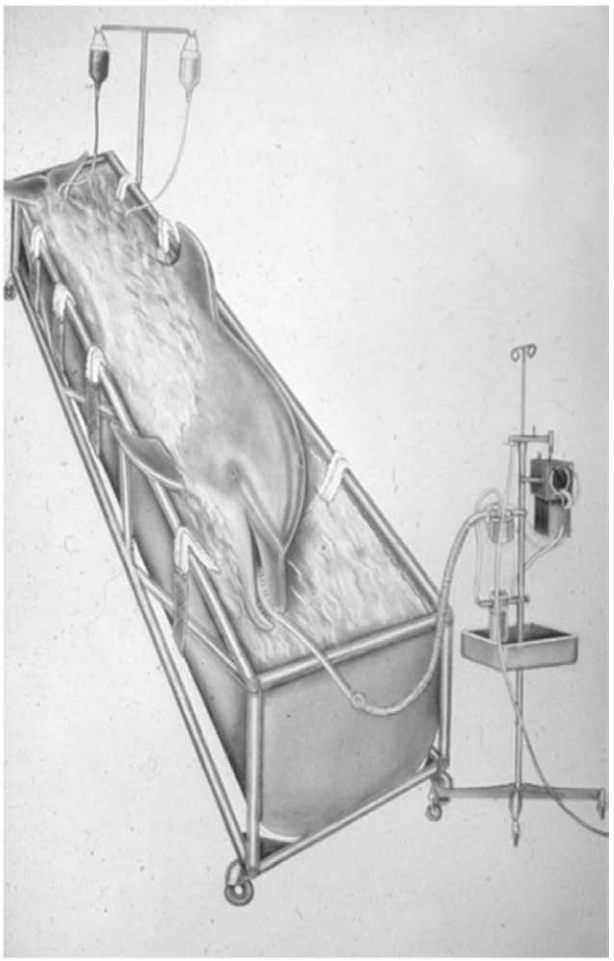

Fig. 9. Surgical tank with a dolphin in the customary position used for ear surgery. The Bird Mark 9 Respirator with apneustic control unit is also shown. Reproduced with permission from Ridgway *et al*.[11]

determined by the apneustic plateau control valve (*upper right*, fig. 10), which limits the flow from the apneustic plateau cartridge pilot (bleed-out time = apneustic plateau). Once the gas in the pilot is sufficiently bled out, the apneustic plateau cartridge closes, stopping the nebulizer and opening the exhalation valve. As can be seen in figure 10, during the apneustic plateau (*blue arrows*), this bleed-out gas is slowly fed to the dolphin along with anesthesia from the nebulizer, enhancing the volume of gas and the distribution of gas in the patient's lungs to mitigate ventilation-perfusion mismatch. As built, all of the components in a Bird Mark series ventilator are purely mechanical with manual controls relying on diaphragms to sense pressures.

Importance of Humidification of Dolphin Ventilator Gases

In human and terrestrial mammal animal anesthesiology, whenever the natural humidification of the nasal-sinus system is bypassed with intubation, to maintain a good physiologic preparation, the loss of humidification must be artificially replaced by some kind of humidifier in the anesthesia machine circuit. The use of a humidification nebulizer with the Dolphin Bird Mark 9 Respirator is noted in figure 9.[11] Coulombe *et al*. documented the respiratory water exchange in two species of dolphins.[33]

Respirator Apneustic Plateau Control Pressures and Cycle Times for the Dolphin

Ridgway and McCormick established physiologic apneustic pressure and cycle time regulation for anesthesia in the dolphin based on intrasurgical monitoring of arterial P_{O_2}, partial pressure of carbon dioxide, and pH blood gases; electrocardiogram; expired oxygen; and expired carbon dioxide monitoring in 35 dolphin anesthesia cases.[2,7,9] Frequency and pressure of apneustic respiration were controlled in response to blood gas measurements taken at intervals of 15 to 30 min from the central artery of the tail fluke or from one of the caudal arteries running along the tail stock. Venous and arterial blood samples were taken from the tail fluke at intervals of 15 to 30 min for determination of P_{O_2}, pH, and partial pressure of carbon dioxide. Arterial values were maintained as follows: P_{O_2}, 95 to 120 mmHg; pH 7.2 to 7.4; partial pressure of carbon dioxide, 30 to 45 mmHg.

Some surgical anesthesia cases by Ridgway and McCormick with their colleagues[2,7,12] lasted as long as 18 h. The usual pressure used on the dolphin Bird Mark 9 Respirator ranged from 18 to 24 mmHg with a cycle time averaging one per 20 s. The Bird Mark 9 Dolphin Respirator operates as a "pressure"-regulated system, which mitigated calculation of tidal volume.[2]

Tidal volume ranged from 5.5 to 10.0 l in the *Tursiops* dolphin of 145 to 170 kg measured by Irving *et al*.[30] Therefore, lung volume of these dolphins ranged from 49 to 71 ml/kg. Ridgway and Howard[24] measured tidal volume of 51 ml/kg in a 138-kg *Tursiops* and 55 ml/kg in a 200-kg dolphin. These findings suggest that, although tidal volume in coastal *Tursiops* is five or six times that of humans, total lung volume is similar to that found in average terrestrial mammals. On the other hand, larger offshore *Tursiops* dolphins exhale larger breaths, 91 ml/kg, with a larger vital capacity.[34] Thus, these differences in lung volume and vital capacity must be considered for ventilation. Piscitelli *et al*. recently contributed "A Review of Cetacean Lung Morphology and Mechanics,"[35] and Fahlman *et al*. authored an article on "Lung Mechanics and Pulmonary Function Testing in Cetaceans."[36]

Anesthesia Agents Currently Used for the Dolphin

In 1967, Ridgway and McCormick perfected induction and intubation of the dolphin with sodium thiopental administered intravenously, followed by maintenance with halothane.[2] Currently for dolphins, induction is by IV propofol, and maintenance is with isoflurane or sevoflurane. A detailed explanation of access to arterial and venous blood in dolphins is given by Dold and Ridgway[37]: "Venipuncture is performed with needles longer and larger than those used for fluke vessel venipuncture in the same animal. Eighteen to 21 g, 4 to 5 cm (1.5–2 inch) needles and larger may be required. The site can

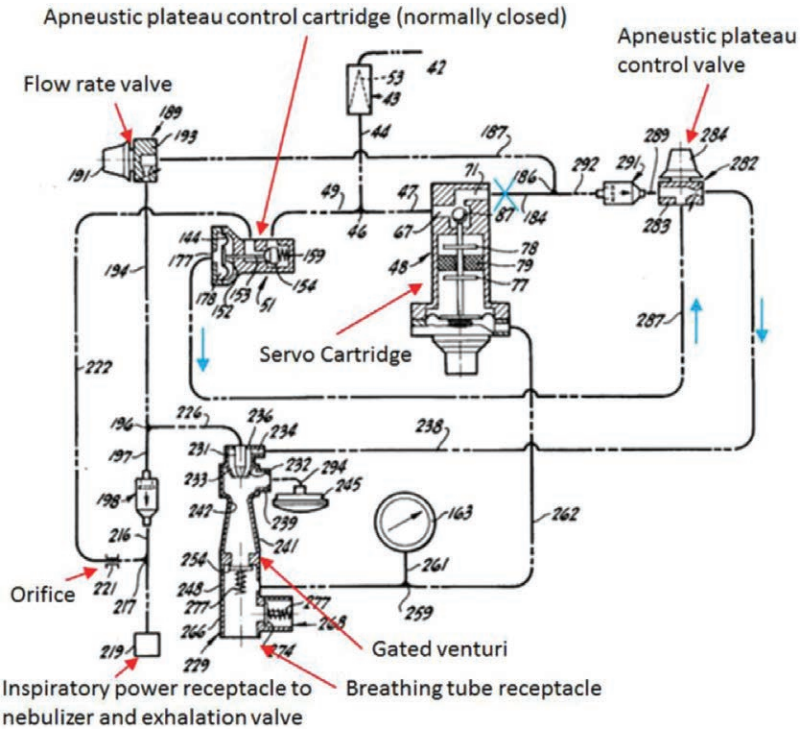

Fig. 10. Schematic of the key components of a Bird Mark series ventilator. Reproduced from Google Patents with dolphin apneustic plateau modifications. Bird FM. Ventilator. US 3915164, Patent Application Filed: August 22, 1974. Public domain material.

be accessed from voluntary fluke presentations by animals out of the water for examinations and procedures. The larger arterial diameter at this site allows for rapid collection of large volumes of arterial and arterial-venous admixed blood. It also mitigates some of the challenges encountered with fluid and drug administration at other sites, making it appropriate for IV injection. Assuming appropriate positioning and if necessary restraint of the flukes, the needle may be left indwelling during longer procedures for constant rate infusion of fluids, as well as repeat blood samples for arterial blood gases."

Overview of Dolphin Surgical Anesthesia Procedures in a National Institutes of Health, National Library of Medicine Movie by Ridgway and McCormick

Ridgway and McCormick produced a comprehensive color sound movie, *Anesthesia for Major Surgery in Porpoises* (this movie can be viewed in the online version of this article).[38] The words *porpoise* and *dolphin* are used interchangeably to specify the same animal. The movie was published in the National Institutes of Health, National Library of Medicine, in 1968, back when halothane was the anesthetic of choice, before the perfection of IV induction of the dolphin, and before the development of the water immersion surgery tank for the dolphin shown in figure 9. However, the movie gives a very good overview of halothane gas anesthesia induction and recovery in the dolphin, including explanation of the reflexes monitored in the dolphin during surgical anesthesia, as well as blood sampling from the dolphin for arterial blood gas analysis during anesthesia.

Of special note, the movie produced by Ridgway and McCormick presents an illustration of endotracheal intubation on a dissection of a dolphin that died from stranding.[38] This depiction in the movie greatly expands the explanation of dolphin intubation illustrated with the figure 3 cross-section of the dolphin in this article in the section "Anatomy of Dolphin Related to Intubation for Controlled Respiration and Anesthesia."

Future Advancements and Study Needed

As noted by Westhorpe and Ball in July 2012,[39] the Bird Mark series of respirators was originally designed as respiratory therapy and intensive care patient machines. Thus, these respirators were designed to be operated as open systems.

After the 1955 anoxic intraperitoneal Nembutal deaths of several dolphins noted previously,[4] the neurophysiologists involved came to Forrest Bird primarily concerned with the need for development of a respirator capable of controlled apneustic breathing for the dolphin. The neurophysiologists, with no training in anesthesiology and accustomed to intraperitoneal anesthesia in lab animals like the cat, were not primarily concerned with administration of gas anesthetics to the dolphin. Thus, it was a natural jumping-off point for Forrest Bird to modify his Bird Mark series respirator to provide controlled respiration for the dolphin with apneustic plateau control. As noted by Westhorpe and Ball,[39] 1957 was

Fig. 11. The DolVent prototype dolphin respirator reproduced with permission from Innovative Veterinary Medicine, Inc. (USA) is shown, and it is anticipated that it will meet or exceed requirements specified in the original Office of Naval Research (Arlington, Virginia) request for proposal, Navy STTR FY2014A – Topic N14A-T015. It is a vision for a magnetic resonance imaging-compatible/conditional ventilator in a protective backpack design to simplify transport and withstand environmental extremes of humidity, salt water, temperature, ultraviolet light, sand, and dust. The removable user electronic interface with critical ventilation data would simplify use and enhance patient safety while maintaining magnetic resonance imaging conditional use when needed. Respiratory rates should be adjustable from 0 to 16 breaths per minute. The target tidal volume is 3 to 15 l. Inspiratory/expiratory volumes need to be adjustable to allow for variable rates of flow over time. Inspiratory volumes should be delivered in 0.5 to 4 s while expiratory volumes should be exchanged in 0.5 to 15 s. System requirements are that peak inspiratory pressures should range from 0 to 50 cm of water. The user interface should display the respiratory rate, inspiratory time, peak inspiratory/airway pressure, and inspiratory to expiratory ratio. The respirator should be able to deliver the normal apneustic plateau breathing pattern of the dolphin.

just the beginning of human anesthesiologists adopting controlled ventilation techniques.[39]

Ridgway and McCormick[2] then began using the Bird Dolphin Respirator as an open system. This was not only because it was originally designed as an open system. Given all the previous anoxic death failures in attempted dolphin anesthesiology, Ridgway and McCormick wanted to use the open system for maximum precision in control of the percent of halothane gas anesthesia for the dolphin. The Bird Mark 7 Respirator that led to the Bird Mark 9 Dolphin Respirator was powered by oxygen or compressed air and used as a nonrebreathing ventilator designed with the capability to deliver the driving gas with or without entrained air or anesthetic gas *via* a venturi.[39]

Ridgway and McCormick adapted their Bird Mark 9 Dolphin Respirator with a system of exhaust hoses and fans to remove expired anesthetic gases from the operating room, but this open system was of course an expensive use of halothane gas. Although the open system is more precise on percentage anesthetic gas delivered to the patient, there is some disadvantage in the control of temperature gained with a closed system. This was mitigated with the water immersion system of Ridgway *et al.* (fig. 9).[11] The water temperature around the dolphin during surgery was regulated according to a continuously monitoring dolphin rectal thermometer. The Bird Mark 9 Dolphin Respirator surgical experiments of Ridgway and McCormick, as previously noted,[2,9,12] provided good physiologic anesthesiology maintenance of the dolphin for up to 18 h.

In the future, Occupational Safety and Health Administration–compliant closed-loop dolphin anesthesia machines should be developed to take the place of the Bird Mark 9 Dolphin machine that is no longer in production. Replacing the Bird Mark 9 Dolphin anesthesia machine is no small order. As elucidated in this article, dolphins have unique respiratory anatomy and physiology. This makes adequate ventilation during anesthesia challenging. Among these challenges is the provision of adequate and physiologically appropriate ventilatory support secondary to severe respiratory depression that may be associated with anesthesia. There are commercially available mechanical ventilators designed for human and veterinary medicine. However, these ventilators have proven to be unsuitable for dolphins due to inadequate tidal volumes and apneustic plateau capability. With the possible exception of the currently out-of-production Bird Mark 9 Dolphin ventilator modified to include an apneustic plateau control used in early evolution of dolphin anesthesia, no other system has proven effective for ventilating dolphins. As dolphins age, the potential need for anesthetic procedures increases. As surgical procedures become more complex, longer anesthetic procedures will be required to be supported by a Bird Mark 9 Dolphin Respirator replacement. Thus, as noted previously, the current research underway supported by the Office of Naval Research to develop a new dolphin respirator is very important. A prototype picture of the Office of Naval Research–supported dolphin respirator, the DolVent, being made by

Innovative Veterinary Medicine, Inc. (USA), is depicted in figure 11.

Finally, one of the most intriguing recent findings for the dolphin's large brain function by Ridgway's group utilizing Bispectral Index monitoring and positron emission tomography and single photon emission computed tomography scanning is the fact that the *T. truncatus* dolphin can have unihemispheric brain protection against suppression from pharmacologic agents like diazepam—one side of the brain suppressed while the other is protected. In addition to the dolphin brain bihemispheric suppression that takes place both in surgical anesthesia and water surface sleep under safe, calm conditions,[2,7,9,10] unihemispheric pharmacologic function in the dolphin shown by Ridgway's laboratory has been extended, showing that the *T. truncatus* dolphin can maintain continuous auditory vigilance for 5 days with unihemispheric sleep.[40–42] The dolphin with its human-sized brain may provide insights into unihemispheric phenomena in man.

What We Have Learned from Dolphins for Human Anesthesiology

As noted in the beginning of this article, Dr. Robert Dripps, the former pioneering Chairman of the Human Anesthesiology Department at the University of Pennsylvania, promoted a philosophy of innovative interdisciplinary orientation between human anesthesiologists, veterinary anesthesiologists, engineers, and scientists. It is important for human anesthesiologists, especially in an academic setting, to remember and appreciate how an innovative interdisciplinary orientation can become the engine of cutting-edge advancements in science and medicine. The long interdisciplinary odyssey toward the perfection of dolphin anesthesiology during the past 90 yr personifies the ideals of Dr. Dripps.

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Competing Interests

The authors declare no competing interests.

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References

1. Ridgway SH, Carlin KP, Van Alstyne KR, Hanson AC, Tarpley RJ: Comparison of dolphins' body and brain measurements with four other groups of cetaceans reveals great diversity. Brain Behav Evol 2016; 88:235–57
2. Ridgway SH, McCormick JG: Anesthetization of porpoises for major surgery. Science 1967; 158:510–2
3. Langworthy OR: A description of the central nervous system of the porpoise *(Tursiops truncatus)*. J Comp Neurol 1932; 54:437–99
4. Lilly JC: Man and Dolphin. New York, Doubleday, 1961, pp 48–61
5. Nagel EL, Morgane PJ, McFarland WL: Anesthesia for the bottlenosed dolphin. Science 1964; 146:1591–3
6. Nagel EL, Morgane PJ, McFarland WL: Anesthesia for the bottlenosed dolphin and author's addendum. Vet Med Small Anim Clin 1966; 61:233
7. Ridgway SH, McCormick JG: Anesthesia of the porpoise, Textbook of Veterinary Anesthesia. Edited by Soma LR. Baltimore, Williams & Wilkins, 1971, pp 394–403
8. Ridgway SH: Medical care of marine mammals. J Am Vet Med Assoc 1965; 147:1077–85

9. McCormick JG: Relationship of sleep, respiration, and anesthesia in the porpoise: A preliminary report. Proc Natl Acad Sci USA 1969; 62:697–703
10. McCormick JG: Behavioral observations of sleep and anesthesia in the dolphin: Implications for Bispectral Index monitoring of unihemispheric effects in dolphins. Anesth Analg 2007; 104:239–41
11. Ridgway SH, McCormick JG, Wever EG: Surgical approach to the dolphin's ear. J Exp Zool 1974; 188:265–76
12. McCormick JG, Wever EG, Palin J, Ridgway SH: Sound conduction in the dolphin ear. J Acoust Soc Am 1970; 48:1418–28
13. McCormick JG: Anatomical, electrophysiological, and histological studies of dolphin auditory system: Establishment of a theory of hearing for dolphins. J Acoust Soc Am 2008; 124:2464
14. McCormick JG, The Princeton University Auditory Laboratories: An ideal research environment, hearing and other senses: Presentations in Honor of EG Wever. Edited by Fay RR, Gourevitch G. Groton, Connecticut, Amphora Press, 1983
15. Wever EG, McCormick JG, Palin J, Ridgway SH: The cochlea of the dolphin, *Tursiops truncatus*: General morphology. Proc Natl Acad Sci USA 1971; 68:2381–5
16. Wever EG, McCormick JG, Palin J, Ridgway SH: The cochlea of the dolphin, *Tursiops truncatus*: The basilar membrane. Proc Natl Acad Sci USA 1971; 68:2708–11
17. Wever EG, McCormick JG, Palin J, Ridgway SH: The cochlea of the dolphin, *Tursiops truncatus*: Hair cells and ganglion cells. Proc Natl Acad Sci USA 1971; 68:2908–12
18. Wever EG, McCormick JG, Palin J, Ridgway SH: Cochlear structure in the dolphin, *Lagenorhynchus obliquidens*. Proc Natl Acad Sci USA 1972; 69:657–61
19. McCormick JG, Wever EG, Ridgway SH, Palin J: Sound reception in the porpoise as it relates to echolocation, Animal Sonar Systems. Edited by Busnel RG, Fish J. New York, Plenum Publishing Corp., 1980, pp 449–67
20. Medway W, McCormick JG, Ridgway SH, Crump JF: Effects of prolonged halothane anesthesia on some cetaceans. J Am Vet Med Assoc 1970; 157:576–82
21. Bullock TH, Grinnell AD, Ikezono E, Kameda K, Katsuki Y, Nomoto M, Sato O, Suga N, Yanagisawa K: Electrophysiological studies of central auditory mechanisms in cetaceans. J Physiol 1968; 59:117–56
22. Bullock TH, Ridgway SH: Evoked potentials in the central auditory system of alert porpoises to their own and artificial sounds. J Neurobiol 1972; 3:79–99
23. Bullock TH, Ridgway SH: Neurophysiological findings relevant to echolocation in marine animals, Animal Orientation and Navigation. Edited by Galler SR, Schmidt-Koening K, Jacobs GJ, Belleville RE. Washington, DC, NASA, 1972, pp 373–95
24. Ridgway SH, Howard R: Dolphin lung collapse and intramuscular circulation during free diving: Evidence from nitrogen washout. Science 1979; 206:1182–3
25. Ridgway SH, Scronce BL, Kanwisher J: Respiration and deep diving in the bottlenose porpoise. Science 1969; 166:1651–4
26. Hallenbeck JM, Andersen JC: Pathogenesis of the decompression disorders, The Physiology and Medicine of Diving, 3rd edition. Edited by Bennett PB, Elliott EH. London, Bailliere Tindall, 1982, pp 435–60
27. McCormick JG, Holland WB, Brauer RW, Holleman IL Jr: Sudden hearing loss due to diving and its prevention with heparin. Otolaryngol Clin North Am 1975; 8:417–30
28. McCormick JG, Philbrick T, Holland WB: The pathophysiology of diving induced sensory neural deafness as elucidated by beneficial prophylactic use of heparin, Proceedings of the International Symposium on Blood-Bubble Interactions in Decompression Sickness. Edited by Ackles KN. Downsview, Canada, Canada Defense Research Board, 1973, pp 272–91
29. McCormick JG, Philbrick T, Holland W, Harrill JA: Diving induced sensori-neural deafness: Prophylactic use of heparin and preliminary histopathology results. Laryngoscope 1973; 83:1483–501
30. Irving L, Scholander PF, Grinnell SW: The respiration of the porpoise, *Tursiops truncatus*. J Cell Comp Physiol 1941; 17:145
31. Comroe JH Jr.: Physiology of Respiration. Chicago, Year Book Medical Publishers Inc., 1966
32. Gillespie NA: The signs of anesthesia. Anesth Analg 1943; 22:275–82
33. Coulombe HN, Ridgway SH, Evans WE: Respiratory water exchange in two species of porpoise. Science 1965; 149:86–8
34. Kooyman GL, Cornell LH: Flow properties of expiration and inspiration in a trained bottle-nosed porpoise. Physiol Zool 1981; 54:55–61
35. Piscitelli MA, Raverty SA, Lillie MA, Shadwick RE: A review of cetacean lung morphology and mechanics. J Morphol 2013; 274:1425–40
36. Fahlman A, Loring SH, Levine G, Rocho-Levine J, Austin T, Brodsky M: Lung mechanics and pulmonary function testing in cetaceans. J Exp Biol 2015; 218(pt 13):2030–8
37. Dold, C. and Ridgway, S.H: Zoo Animal and Wildlife Immobilization and Anesthesia. Edited by West G, Heard D, Caulkett N. Ames, Iowa, Blackwell Publishing, 2007, pp 485–96
38. Ridgway SH, McCormick JG: Movie, Anesthesia for Major Surgery in Porpoises, Point Mugu, California, Naval Missile Center, Marine Bioscience Facility. For Loan by the National Institute of Health, National Library of Medicine, 1968, NLM Unique ID: 7600627A
39. Westhorpe RN, Ball C: The Bird ventilator. Anaesth Intensive Care 2012; 40:585
40. Ridgway S, Houser D, Finneran J, Carder D, Keogh M, Van Bonn W, Smith C, Scadeng M, Dubowitz D, Mattrey R, Hoh C: Functional imaging of dolphin brain metabolism and blood flow. J Exp Biol 2006; 209(pt 15):2902–10
41. Howard RS, Finneran JJ, Ridgway SH: Bispectral Index monitoring of unihemispheric effects in dolphins. Anesth Analg 2006; 103:626–32
42. Ridgway S, Carder D, Finneran J, Keogh M, Kamolnick T, Todd M, Goldblatt A: Dolphin continuous auditory vigilance for five days. J Exp Biol 2006; 209(pt 18):3621–8