Middle ear gas exchange in isobaric counterdiffusion

C. W. DUEKER, C. J. LAMBERTSEN, J. J. ROSOWSKI, AND J. C. SAUNDERS
Institute for Environmental Medicine, Department of Otorhinolaryngology and Human Communication, and Department of Anesthesiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104

DUEKER, C. W., C. J. LAMBERTSEN, J. J. ROSOWSKI, AND J. C. SAUNDERS. *Middle ear gas exchange in isobaric counterdiffusion.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 47(6): 1239–1244, 1979.—Nitrous oxide entry into the middle ear gas space was studied in cats in relation to anesthesia and the vestibular dysfunction caused by isobaric inert gas counterdiffusion in diving. A catheter implanted in the auditory bulla was used for direct gas sampling and pressure measurements. Experiments were designed to evaluate the participation of the eustachian tube, mucosal blood vessels, and tympanic membrane in middle ear gas exchange. The eustachian tube did not contribute to N_2O entry and the mucosal blood supply only contributed about one-third of the total N_2O accumulation. Diffusion across the tympanic membrane accounted for most of the N_2O entering the middle ear from ambient and respiratory environments containing N_2O.

inert gas uptake; nitrous oxide; anesthesia; diving

THIS STUDY OF MIDDLE EAR gas exchange was prompted by the occurrence of incapacitating vestibular dysfunction in men breathing nitrogen-helium-oxygen or neon-helium-oxygen mixtures while surrounded by helium (5, 8, 9). These symptoms have now been identified, along with dermal gas lesions (9) and continuous venous gas embolization (7), as part of the isobaric counterdiffusion phenomenon, which is particularly important as a hazard in manned undersea activity. The process of inert gas counterdiffusion, though without such severe consequences, also occurs in gas inhalation anesthesia.

Whether vestibular dysfunction induced by counterdiffusion is caused by gas flux across the membrane of the round window, resulting in damaging gas phase development in the fluid of the inner ear (9), is not known. It is conceivable that the dysfunction may also be caused by gas embolization produced by transcutaneous isobaric counterdiffusion (7, 9). Middle ear gas exchange is also a relevant factor in general anesthesia for open ear surgery because nitrous oxide may cause elevated middle ear pressure (7, 11, 16).

Gas exchange in the middle ear can occur in three ways: gas can diffuse across the tympanic membrane, enter or leave via the eustachian tube, or diffuse between mucosal blood vessels and the middle ear cavity. Ingelstedt and Jonson (6) reported that middle ear ventilation depends primarily on eustachian tube function. More recently, Elner (4) used a technique similar to that used by Ingelstedt and Jonson to evaluate gas absorption from the middle ear indirectly.

Studies of gas transfer across the tympanic membrane in vitro (3) and with radioactive xenon (16) have suggested that the tympanic membrane, in spite of its extremely thin character (10), contributes very little to middle ear gas exchange. These studies, however, used indirect techniques or in vitro preparations. None of them was concerned with the exchange of gas after a shift in the respired and/or ambient gases.

The present experiments were designed to study the dynamics of gas exchange in the middle ear of living animals by means of direct sampling techniques. Three different experimental designs permitted determination of the respective contributions of the eustachian tube, tympanic membrane, and mucosal blood vessels to middle ear gas exchange.

GENERAL METHODS

Adult male cats were used. The auditory bulla of the cat provides a convenient site for gas sampling and connects directly with the middle ear space. After induction of anesthesia with ketamine (avg dose 20 mg/kg), tracheal intubation was performed via the mouth. Ketamine provided maintenance anesthesia as needed; incremental doses up to a maximum of 60 mg/kg were given. The bulla was exposed by using a ventral approach modified from that of Paparella and Hohmann (13). After drilling a hole into the bulla, a 16-gauge polyethylene vascular catheter was inserted into the bulla. An attached plastic flange fixed the catheter tip 2 mm into the bulla cavity. The flange was attached to the bulla with fast-drying dental acrylic cement; the flange and exposed bulla were then covered with acrylic filler and the incision was closed in layers. To facilitate visualization of the tympanic membrane, a 1-cm incision was made in the tragus; each side of this incision was maintained with wire suture. The cat was then allowed to recover from surgery.

Nitrous oxide was used as the experimental gas because its effects on middle ear pressure have been reported (11, 15, 18).

The experiments were performed either in air or in a glove box filled with N_2O and oxygen. A pump circuit provided temperature and humidity control for the glove box. Carbon dioxide expired by the animals was removed by alkali absorbent. An infrared gas analyzer (Beckman) measured N_2O concentration for continuous recording. Oxygen partial pressure was measured by a paramagnetic oxygen analyzer (Servomex).

Before the experiment, each cat was anesthetized. Air

was injected into the bulla catheter, and the motion of the tympanic membrane was then observed to verify system tightness. A low-dead-space three-way stopcock was then attached to the bulla catheter. Continuous middle ear pressure determinations were made with a water-filled strain gauge transducer (Statham) and recorded.

Gas samples were withdrawn from the catheter into 100-μl gas-tight syringes (Precision Sampling Pressure-Lok series A-2) at about 1, 3, 6, 9, 12, and 15 h after the experiment began. An initial sample of 100 μl was withdrawn to remove the dead-space gas trapped in the catheter, and a second sample was then drawn for analysis. The first sample was then reinjected into the bulla to minimize ear volume changes. Each sample was analyzed for CO_2, N_2O, O_2, and N_2 with a gas chromatograph (Varian Aerograph 1420). Peak areas of the chromatogram were digitally integrated (Hewlett-Packard 3700A) and the resulting values were converted to gas percent volumes.

To minimize the effect of slight changes in inspired or ambient N_2O, bulla N_2O concentration was expressed as a fraction of the inspired N_2O or the ambient N_2O. The mean inspired or ambient concentration over the hour preceding each bulla sample was used in calculating this ratio.

Three experimental situations were studied: *I*, cats breathing N_2O-O_2 while surrounded by N_2O-O_2; *II*, cats breathing N_2O-O_2 while surrounded by air; and *III*, cats breathing air while surrounded by N_2O.

Situation I. N_2O Breathing in N_2O Atmosphere

Procedures. This situation was designed to measure maximal entry of gas into the middle ear. Seven cats breathed 80% N_2O-20% O_2 while surrounded by 75% N_2O-25% O_2.

Each cat was studied in a closed plastic box large enough to accommodate two cats. Rubber gloves mounted in the side of the box allowed access to the animals. The animals breathed spontaneously. Anesthesia, gas sampling, and pressure measurements were performed in accordance with procedures described in GENERAL METHODS.

Results. Figure 1*A* illustrates the course of N_2O entry into the middle ear for five of these animals. After a rapid rise to about 80% of inspired N_2O within the 1st h, the rate of increase slowed with time and reached a plateau of 90% of the inspired gas at 6 h. A long balloon catheter was placed in the nose of one cat (Fig. 1*A*, *expt 7*) and inflated with water to obstruct the orifice of the eustachian tube almost completely. The extent of the eustachian tube seal was verified by injecting air into the bulla and showing by the pressure traces that the eustachian tube could not completely vent the increased middle ear pressure. Gas entry in this cat did not differ detectably from that in the cats with patent eustachian tubes (Fig. 1*A*). To assess the effect of sampling per se on gas equilibrium, gas was not sampled in two cats until 8 h after the experiment began, at which time equilibrium between middle ear and ambient N_2O had been achieved.

Figure 1*B* shows sequences from a typical middle ear pressure tracing from one animal in *situation I*. During the period of rapid N_2O entry, pressure rose by as much as 9 cmH_2O in some animals, and then fell to ambient. These decreases in pressure probably accompanied eustachian tube opening because pressure tracings from the cat with the obstructed eustachian tube did not show the marked changes seen in animals with patent tubes. Maximum bulla pressure in *situation I* slowly decreased over

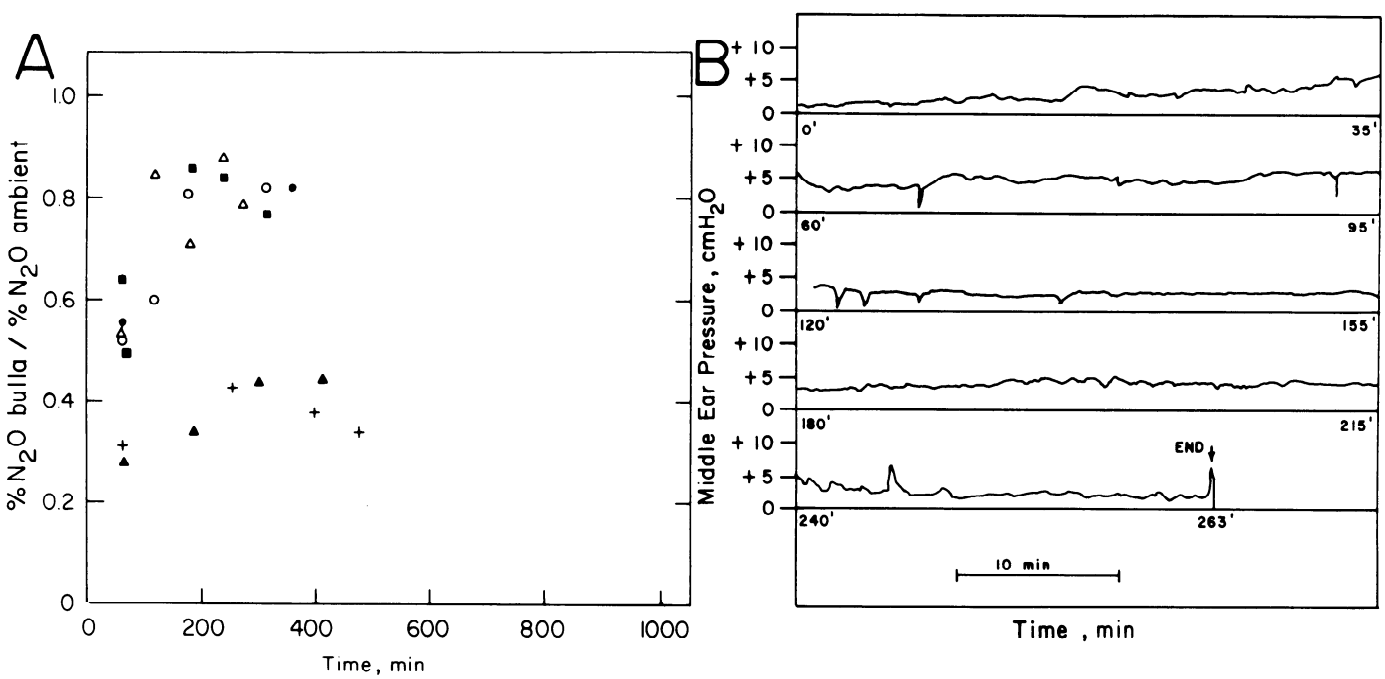

FIG. 1. N_2O breathing-N_2O ambient situation (*I*). *A*: attainment of near-equilibrium between middle ear and inspired N_2O concentrations; results represent essentially exponential increases from initial middle ear N_2O value of zero. Five experiments: *1*, ●; *2*, +; *3*, ▲; *4*, ■; *7*, ○. *B*: 5 traces, each lasting 35 min showing time course of pressure changes in middle ear during approximately 10 h of exposure. *Rise*: entry of gas; *abrupt fall*: venting via eustachian tube (*expt 1*).

time and returned to a control level within 8 h after initiation of the experimental procedure.

Situation II. N_2O Breathing in Air Atmosphere

Results from *situation I* demonstrated a rapid rise of N_2O concentration in the bulla cavity when the eustachian tube was both blocked and unblocked, indicating that the eustachian tube does not contribute to this uptake. *Situation II* was designed to study the contribution of a single pathway, the mucosal blood vessels, to middle ear gas exchange.

Procedure. Five cats were anesthetized according to procedures outlined in GENERAL METHODS. Four were prepared by endotracheal intubation via the mouth; one of these four (*expt 12*) also had its eustachian tube blocked. The cuff of the tube was inflated until positive-pressure ventilation resulted in no leakage around the tube. One cat (*expt 11*) inhaled N_2O through an oronasal breathing mask, rather than through an endotracheal tube.

The cats spontaneously breathed 80% N_2O-20% O_2 supplied through an unvalved nonrebreathing system at a flow rate of 1 l/min. Ambient gas was room air. Respiratory N_2O and O_2 concentrations were measured continuously, as described in GENERAL METHODS, with a catheter placed in the endotracheal tube connector or under the mask. Middle ear pressure measurements and gas sampling also followed the procedures described in GENERAL METHODS.

Results. Figure 2*A* shows N_2O in the bulla as a ratio of inspired N_2O in the five cats. In the 1st h, this ratio reached 20%; it leveled off at about 35% after 5 h. The cat that breathed through the mask (Fig. 2*A*, *expt 11*) had a gas entry equivalent to that of the intubated cats.

If retrograde gas flow from nasopharynx to middle ear contributed to N_2O exchange, the masked cat (nasopharynx exposed to respired N_2O) would have shown a faster rise in middle ear N_2O. This was not the case, and to evaluate eustachian tube retrograde flow further, a nasal balloon was placed in one of the intubated cats (eustachian tube exposed to ambient air) as in *situation I* (Fig. 2*A*, *expt 12*). This procedure did not affect N_2O entry into the middle ear.

Figure 2*B* shows a representative pressure tracing from one animal in this experimental situation. Pressure elevations of as much as 20 cmH_2O began promptly with N_2O breathing, and were followed by eustachian tube venting. The pressure shifts continued and showed only a slight decrease over time. This was in marked contrast to the pressure tracings of animals both breathing and surrounded by N_2O (*situation I*) (Fig. 1*B*). Blockage of the eustachian tube in one cat resulted in a persistent positive pressure without cyclic rapid pressure falls attributable to eustachian tube venting.

Situation III. Air Breathing in N_2O Atmosphere

Breathing N_2O while surrounded by air did not account for the full entry of N_2O shown in the total (respiratory and ambient) N_2O exposure of *situation I*. This third study was therefore conducted to determine the contribution to gas entry into the bulla by diffusion through the tympanic membrane itself.

Procedure. Six cats were anesthetized and intubated. After intubation, they were placed in the glove box and spontaneously breathed air delivered from outside the box through an unvalved nonrebreathing apparatus. The exhaust from the breathing bag was vented outside the box. A sampling line in the endotracheal tube connector

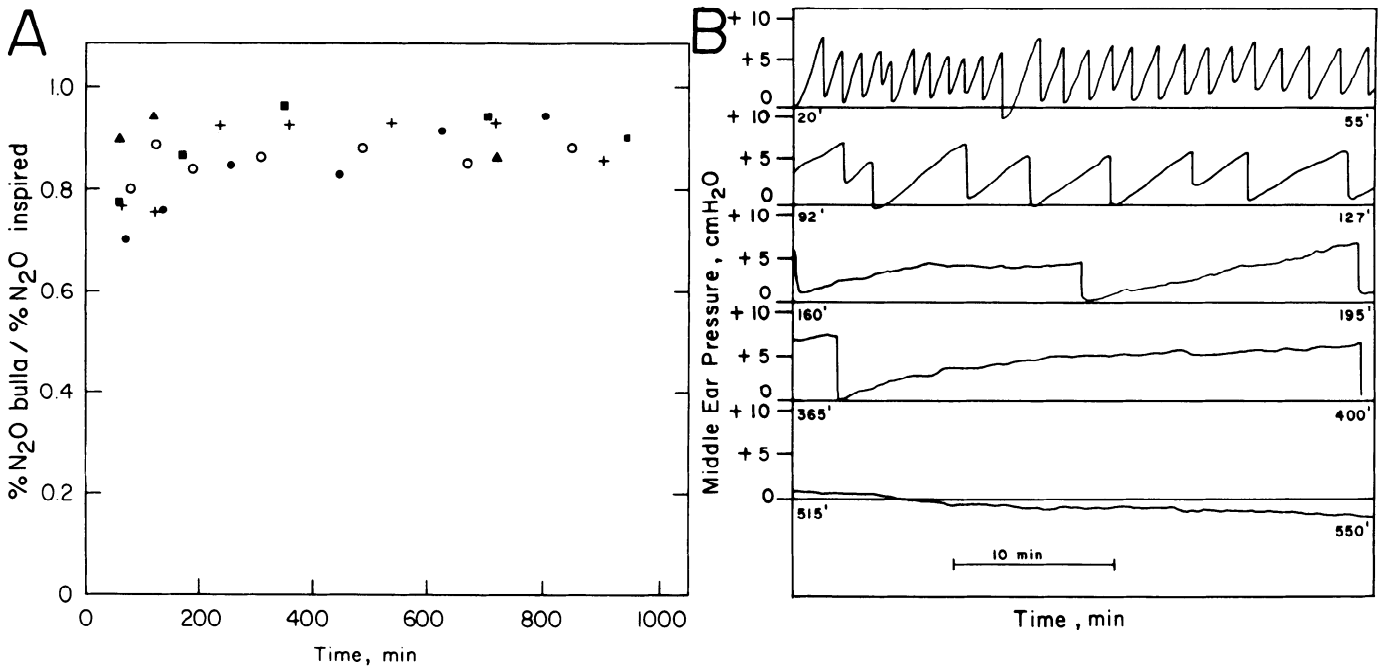

FIG. 2. N_2O breathing-air ambient situation (*II*). *A*: relatively low equilibrium values for composite effects of N_2O entry (via respiratory gas) and N_2O loss (via tympanic membrane). Five experiments: *8*, ●; *9*, +; *10*, ▲; *11*, ○; *12*, ■. *B*: representative time course of middle ear pressure changes (*expt 8*). Repeated rises and falls indicate continuous entry of N_2O throughout experiment despite low stable-state N_2O concentrations shown in *A*.

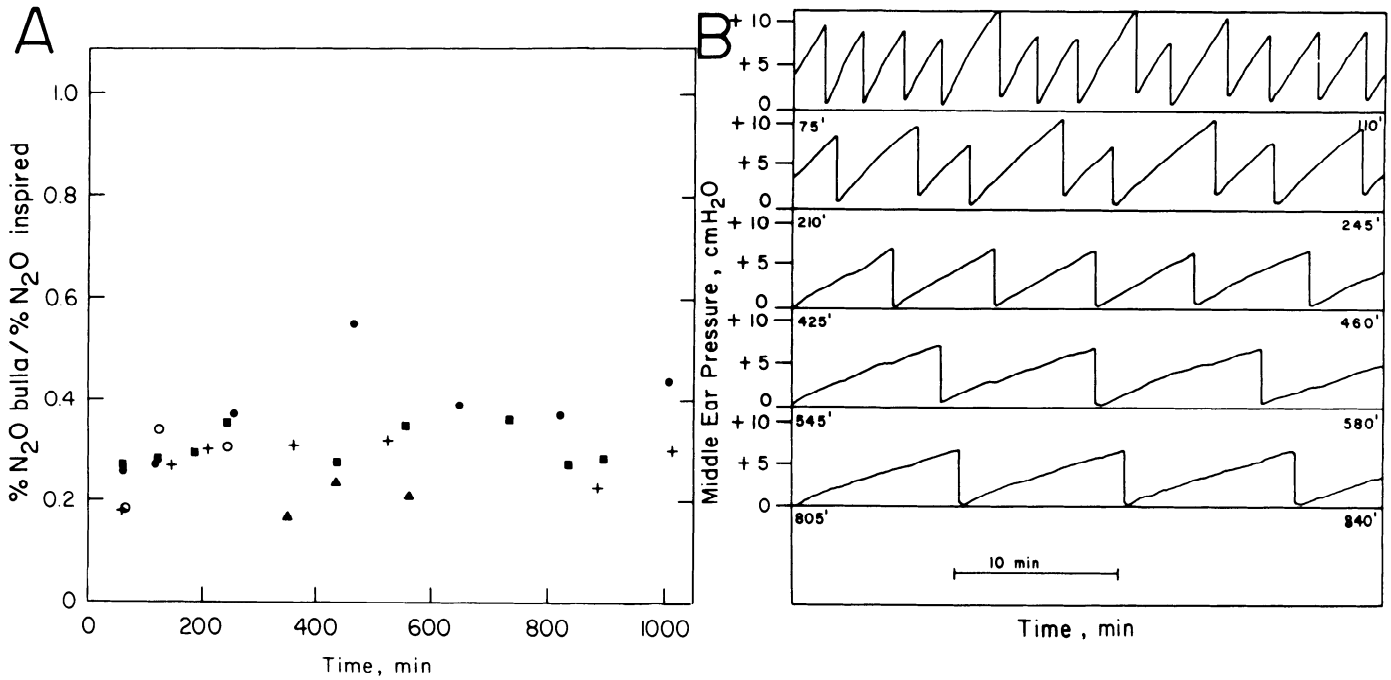

FIG. 3. Air breathing-N_2O ambient situation (*III*). *A*: rise in ratio from initial zero level indicating entry of N_2O via tympanic membrane. Six experiments: *13*, +; *14*, ▲; *15*, ○; *16*, ●; *17*, △; *18*, ■. *B*: tracing from representative experiment (*no. 15*) demonstrating absence of the pressure increases characteristic of N_2O breathing situations (see Figs. 1*B* and 2*B*).

was used to determine respired gas composition. As the cats breathed air, they were surrounded by a circulated atmosphere of 75% N_2O-25% O_2. Pressure measurements and gas sampling followed the methods described.

One cat was surrounded, except for his head, with a plastic bag flushed with air, to eliminate the possibility that some N_2O entry into the middle ear might have resulted from gas entering through the skin (1). Two cats had nasal balloons placed (as in *situations I* and *II*) to obstruct the eustachian tubes.

Results. Figure 3*A* shows middle ear N_2O concentration changes in cats breathing air while surrounded by N_2O. In this circumstance the ratio is expressed as bulla concentration/ambient N_2O. This experiment showed the widest range of N_2O concentrations. At 1 h, the ratios ranged between 30% and 65%; at 4 h, the range was 40–85%. The cat with no cutaneous exposure to N_2O also showed middle ear N_2O entry that fell within these ranges. Eustachian tube blockage did not affect N_2O level. Figure 3*B* shows the absence of the pressure fluctuations (from *expt 15*) characteristic of N_2O breathing situations.

DISCUSSION

During ordinary respiration of N_2O, all parts of the body give up N_2 as they take up N_2O. Diffusion rates into a gas-filled space like the middle ear depend on pressure gradients, area of diffusion surface, and length of diffusion path, as well as gas molecular weight and solubility. On the basis of gas permeabilities, N_2O should enter the middle ear space, by several pathways, 30 times faster than N_2 can leave.

During anesthesia with N_2O, the relatively large amount of N_2O entering closed gas spaces can cause dangerous increases in volume (distensible spaces) or pressure (rigid spaces). This has been reported in the middle ear (11, 15, 18) and the cranial vault (17), and in cases of intestinal obstruction (2), pneumothorax (2), and venous air embolism (12).

In semirigid spaces such as those of the middle ear, the imbalance between gas entry and loss causes a rise in pressure. The eustachian tube then opens to relieve pressure, venting the excess gas. The amount of gas vented approximates the net gas entry, that is, the difference between the amount of N_2O entering and the amount of N_2 leaving. If the volume of the middle ear is known, Boyle's law can be used to calculate the amount of gas exhausted at each eustachian tube opening.

Assuming a middle ear volume in the cat of 2 ml, cats in the N_2O breathing-N_2O ambient situation (*I*) had an uptake of 0.0088 ml/min in the 1st h, with a decrease to 0.0024 ml/min during the 2nd h. The entry rate of N_2O decreased as the middle ear approached equilibrium with the surrounding N_2O, lowering the pressure gradient for diffusion. As seen in Fig. 1*B*, middle ear pressure was equal to atmospheric pressure at the time corresponding to maximum middle ear N_2O concentration.

Cats breathing N_2O while surrounded by air (*II*) never achieved equilibrium between respiratory gas and the middle ear space (Fig. 2*B*). The initial rate of gas uptake, 0.0054 ml/min, was slower than that of *situation I* (0.0088 ml/min), but even after 9 h N_2O still entered at 0.0014 ml/min.

Role of Eustachian Tube

The results of this study do not support current concepts of middle ear gas exchange, which indicate that when a cat is surrounded by N_2O, flow up the eustachian

tube should hasten the increase of middle ear N_2O concentration (4, 6). Almost complete blockage of eustachian tubes under this condition failed to modify N_2O accumulation. It was considered possible that during endotracheal N_2O breathing while surrounded by air, the eustachian tube might allow air to enter the middle ear, diluting the N_2O. This was unlikely, considering the positive-pressure gradient from middle ear to nasopharynx. That it actually did not occur was shown by obstructing the eustachian tube almost completely. Similarly, breathing N_2O by oronasal mask would increase middle ear N_2O entry if N_2O could flow up the eustachian tube. However, the amount of entry was the same for the oronasal mask as for the endotracheal N_2O inhalation.

Ingelstedt and Jonson (6) calculated eustachian tube ventilation by measuring ear volume changes after inducing negative pressure within the middle ear. Elner (4) used similar calculations to estimate the amount of gas entering by way of the eustachian tube to replace the volume of gas absorbed from the middle ear into the mucosal vessels. In neither of these studies was eustachian tube function measured under conditions of variation in inhaled or ambient gas.

Role of Tympanic Membrane

Previous studies have concluded that the tympanic membrane contributes little to middle ear gas exchange. Elner (3) exposed cadaver tympanic membrane to CO_2 in a diffusion chamber; extrapolation of these results to O_2 and N_2 led to the report that diffusion across the tympanic membrane represented only 0.5–1.0% of the amount of gas venting through the eustachian tube. Riu et al. (16) has stated that transfer of radioactive xenon through the tympanic membrane was nonexistent or insignificant.

During N_2O breathing while surrounded by air (*II*), N_2O reaching the middle ear space arrived via the mucosal and tympanic membrane blood vessels. After 12 h, the blood concentration of N_2O should have been equivalent to that of the inspired mixture (80% N_2O). However, middle ear N_2O did not rise above 35%. Outward flow of gas through the eustachian tube did not alter the composition of middle ear gas, and there was no inward passage. Therefore, the failure in N_2O equilibrium was most probably caused by outward diffusion of N_2O through the tympanic membrane, accompanied by inward diffusion of nitrogen into the middle ear space through the tympanic membrane.

To measure the diffusion of N_2O across the tympanic membrane, air-breathing cats surrounded by N_2O were studied (*situation III*). The only available routes for N_2O entry were through the skin, around the endotracheal tube, up the eustachian tube, and across the tympanic membrane. Blocking the cutaneous route did not affect entry rate. Measurement of N_2O from all sources in the respiratory gas of the endotracheal tube showed that it was consistently less than 4%. The eustachian tube did not serve as a source of N_2O. Thus, N_2O reaching the middle ear in the air breathing-N_2O ambient situation (*III*) could only have come through the tympanic membrane.

The significant role played by diffusion across the tympanic membrane has been demonstrated in two ways. Outward diffusion markedly limited the extent of N_2O accumulation derived from mucosal blood supply, and inward diffusion resulted in a rapid increase of N_2O. Presumably, without loss of N_2O to the capillaries of the middle ear, there would be prompt gas equilibration between atmosphere and the middle ear of cats surrounded by N_2O.

Relation to Other Isobaric Counterdiffusion States

The aim of this study of nitrous oxide exchange in the middle ear cavity was to increase understanding of the process of isobaric inert gas diffusion among atmosphere, middle ear, and inner ear. The results indicate that nitrous oxide passes through the tympanic membrane more rapidly than had previously been believed. It is therefore likely that at high ambient pressures, very rapid movement of helium or other gases across the tympanic membrane occurs. An extension of the present study has led to a detailed mathematical model of middle ear gas exchange (14). Direct measurement of transtympanic diffusion of helium, nitrogen, and other respirable gases used at increased ambient pressure is necessary to relate these findings to the severe vestibular disruption associated with isobaric counterdiffusion in man.

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C. W. Dueker is presently with the Department of Anesthesiology, Palo Alto Medical Clinic, Palo Alto, CA.

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