dioisotope. As our two sets of experiments differed only in the nature of the tracer that was used and the technique used to measure its concentration, we attribute the different transport rates to the Pb^{2+} daughter product created during the diffusion of the radiotracer (*6*).

Figure 2 compares the data for stable and radioactive Tl diffusion in a different way. The least-squares fit to the temperature dependence of the diffusion coefficient for stable Tl was taken to represent the "true" tracer diffusion coefficient (that is, proportional to the native vacancy concentration). Against this value we plot the apparent radiotracer diffusion coefficient, D^*_{app}, obtained in each radioisotope experiment. All data points lie well above the line $D^*_{app} = D^*$. To test the ability of our model (*1*) to qualitatively account for the discrepancy we then calculated the expected magnitude of D^*_{app}, using the true D^* and the actual experimental conditions (time, specific activity, and native cation vacancy concentration as inferred from the "knee" temperature or the enthalpy for Schottky defect formation) of each experiment. The model contains a disposable defect generation parameter, g, to account for the effectiveness of internal vacancy sources in maintaining electroneutrality; $g = 1$ corresponds to complete neutralization of the aliovalent daughter, whereas $g = 0$ represents a situation in which no vacancies are created and every daughter creates space charge. The vertical line drawn through each data point in Fig. 2 represents the range of apparent diffusion coefficients computed for $0 < g < 1$. (The maximum and minimum values for D^*_{app} do not obtain for the extreme limits of g.) In each case the range of computed values includes the observed value for D^*_{app}. Given an appropriate value of g, the model is thus capable of satisfactorily predicting the magnitude of the transmutation effect. The best agreement between theory and experiment was obtained for $g = 1$ for the high-temperature data. That is, internal sources and sinks are fully effective in producing vacancies to maintain electroneutrality and no space charge is developed. At the lowest temperatures that were examined, the best fit obtained for $g = 0.8 \pm 0.1$. This result suggests, not unreasonably, that the reduced rates of vacancy formation or migration have resulted in the accumulation of a slight space charge.

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7. This report is based on a thesis (G.C.T.W.), Massachusetts Institute of Technology (1976). Work was supported by the U.S. Atomic Energy Commission under contract AT(11-1)-2390.
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Ammonia in the Human Airways: Neutralization of Inspired Acid Sulfate Aerosols

Abstract. *In the human being, expired ammonia concentrations from 7 to 520 micrograms per cubic meter are controlled by the last airway segment traversed by the air, and such concentrations are higher in the mouth than nose. Inspired submicrometric sulfuric acid aerosol at a mass concentration of 600 ± 100 micrograms per cubic meter was found to be an ammonium salt with an average ammonium to sulfate molar ratio of ≥1, when sampled within 0.5 second after exhalation.*

We hypothesize that gaseous ammonia which is released into the respiratory system of the human being can neutralize inhaled acidic aerosols and may potentially alter or mitigate their toxicity. To support this hypothesis we present (i) measurements of NH_3 in expired air following several breathing procedures designed to identify the sources and sinks of NH_3, and (ii) evidence that inhaled acid sulfate particles which remain airborne and are subsequently exhaled undergo a change in molecular form during passage.

A persistent sulfate aerosol, submicrometric in diameter, has been observed in the lower troposphere over the eastern and midwestern United States and northern Europe (*1*). The aerosol consists of sulfuric acid (H_2SO_4) plus its products of neutralization with ammonia, that is, NH_4HSO_4, $(NH_4)_3H(SO_4)_2$, and $(NH_4)_2SO_4$ (*2, 3*). Surface measurements near St. Louis (*2*) have shown concentrations ranging from 10 to 20 $\mu g/m^3$.

The recent CHESS report (*4*) of the Environmental Protection Agency concluded that ambient levels of "sulfate aerosol" in the concentration range found near St. Louis may affect health adversely. The report did not specify the molecular composition nor size-distribution of the aerosol, ambiguities that limit the value of the conclusions, particularly with respect to policy on air quality standards.

Evidence has also been adduced that sulfate aerosols with comparable mass concentrations and size-distributions may differ in toxicity depending on their molecular form. For example, H_2SO_4 is reported to cause greater impairment of pulmonary function in guinea pigs than does $ZnSO_4$ which, in turn, is reported to be more irritating than $(NH_4)_2SO_4$ (*5*). The relative irritancy of these compounds in human subjects has not been reported.

To the extent that the acidity of sulfate aerosol may contribute to toxicity, any chemical change that reduces this acidity following inhalation should be mitigating. We hypothesize that acidity may be reduced in two ways: (i) by dilution resulting from the hydration of the aerosol following inhalation and (ii) by neutralization with NH_3 (*6*). Neutralization with NH_3 is the potentially more significant way in which acidity may be changed. Just as NH_3 may regulate the molecular form of acid aerosols in ambient air (*7*), we propose that NH_3, normally present in the respiratory system, reacts with these aerosols in the gas phase to reduce their acidity before they become deposited on tissue surfaces.

Ammonium ion (NH_4^+) is a normal constituent of a variety of body fluids including those lining the respiratory tract (*8*). Ammonia, a highly soluble and diffusable gas, is likely to be present in air passing over these fluids. Concentrations ranging from 37 to 102 $\mu g/m^3$ have been reported in expired air collected from tracheostomized dogs [see (*9*); we report here concentrations at 25°C and 1 atm]; a concentration of about 120 $\mu g/m^3$ has been reported in the expired air of dogs breathing by mouth (*10*). In human subjects, concentrations ranging from 210 (*11*) to about 700 $\mu g/m^3$ (*10*) have been found in expired air collected during quiet mouth breathing.

We measured gas phase NH_3 with a chemiluminescent nitric oxide (NO) analyzer that was equipped with a stain-

Table 1. Measurements of NH_3 in human airways. The breathing procedures are described in the text. The total number of 16 subjects included nine males aged 25 to 63 years and seven females aged 23 to 41 years; the subgroups were all male.

Breathing procedure	No. of subjects	No. of measurements	NH_3 ($\mu g/m^3$)*	
			Median	Range
		Mouth traversed last		
M↔TB↔A	16	38	170†	29 to 520
M↔TB	3	5	130	42 to 270
N→M	5	10	210	38 to 520
		Nose traversed last		
N↔TB↔A	5	9	25	13 to 46
N→N	5	11	21	7 to 33
M→N	5	6	27	13 to 62
		Upper airway bypassed		
TB↔A	1	1	29	

*At 25°C and 1 atm. †Mean, 157; standard error, 27.

less steel converter for oxidizing NH_3 to NO (Thermo Electron Corporation model 14 B). The analyzer was calibrated by means of a wet-chemical indophenol blue method for measuring NH_4^+ (*12*). A comparison of the two analytical methods confirmed that we measured NH_3 in exhaled air rather than oxides of nitrogen (NO_x) or other interfering compounds.

Two methods of sample collection were used. (i) A Rudolph respiratory valve was mounted between two 50-liter Teflon bags, one bag for supply and the other for collection. The valve was heated to prevent condensation of exhaled moisture and absorption of NH_3 by the condensate. The supply bag contained 12 liters of dry NH_3 and NO_x-free air (relative humidity < 10 percent; $NH_3 + NO_x \leq \mu g/m^3$ as total nitrogen); the collection bag initially contained 24 liters of the same air. The subject breathed quietly for about 1 minute until all supply air was transferred to the collection bag; analysis of this air followed immediately. A correction was made to account for dilution of the exhaled gas. (ii) Alternatively, direct continuous measurements were made of expired NH_3 with a probe inserted in the nasal antrum or mouth. The exhaled gas was immediately heated above 37°C. A portion of this gas was sampled, diluted with a known flow of dry, clean air to avoid condensation, and analyzed.

We used one or both sampling methods to measure the NH_3 concentration in the expired air of 16 human subjects who breathed quietly by mouth. Potentially, these measurements reflect sources and sinks of NH_3 in the mouth (M), tracheobronchial system (TB), and alveoli (A) (the term "mouth" includes the oral cavity and oropharynx). To simplify reporting, this breathing procedure is referred to as M↔TB↔A; the underlined symbol identifies the last segment traversed by the gas and the arrows indicate the direction of air flow, whether unidirectional or bidirectional. Additional breathing procedures in five of the 16 subjects included (i) either direct sampling or batch sampling during quiet nose (N) breathing: N↔TB↔A; and (ii) direct sampling during three procedures, each of which involved a deep inspiration followed by breath-holding with the glottis closed. In the first procedure, N→M, a heated tube (inner diameter $\simeq$ 2 cm) was placed between the lips, and suction was applied to the tube producing a continuous flow of 0.5 liter/second into the nose and out of the mouth. The flow rate through each nostril was assumed to equal 0.25 liter/sec. Sampling from the tube was made as close to the lips as possible. Depending on the degree of equilibration across the gas-liquid interface, the level of NH_3 in this sample should reflect the contribution of the mouth alone or of the mouth and nose combined. In the second procedure, M→N, one nostril was closed and suction was applied to the other intubated nostril producing a continuous flow of 0.25 liter/second into the mouth and out of the nose. The NH_3 concentration in this sample should represent the contribution of the nose alone or of the nose and mouth combined. In the third procedure, N→N, the mouth was closed and suction was applied to one intubated nostril producing a continuous flow of 0.25 liter/sec into the opposite nasal passage and out of the intubated side. Ammonia sampled at the exit should be purely nasal in source.

The cumulative sampling period for each breath-holding procedure was about 5 minutes; the subject withdrew from the probe to take several deep breaths every 30 to 40 seconds.

In addition, bag samples were collected from three of the five subjects during mouth-panting. Panting was intended to minimize "contamination" from alveolar gas and to provide an estimate of the contribution of the anatomic dead space to expired NH_3, that is, M↔TB. The effectiveness of the maneuver in excluding alveolar gas was gauged with a fast-responding CO_2 analyzer (Beckman medical gas analyzer) connected by a sampling probe to the mouthpiece: expired gas was found to contain less than 0.5 percent CO_2. The procedure took about 5 minutes, with alternating half-minutes of panting and recovery.

A procedure that bypassed the NH_3 sources and sinks of the nose and mouth was also used in one subject: TB↔A. An 8-mm (outer diameter) polyethylene endotracheal tube was inserted through the subject's nose into the trachea following application of a topical anesthetic (lidocaine hydrochloride, 4 percent). The tube was then attached to the heated Rudolph respiratory valve, and a bag sample was collected.

We made no attempt to control the subjects' diet prior to obtaining the NH_3 measurements, or the interval between the last meal and the measurement.

The data, summarized in Table 1, cluster into two distinct groups. One group includes measurements obtained with the M↔TB↔A, N→M, and M↔TB procedures, that is, circumstances in which the mouth was the final pathway; the other includes measurements obtained with the N↔TB↔A, M→N, and N→N procedures, in which the nose was the final pathway. The results demonstrate that the concentration of NH_3 in expired gas is determined largely by the last segment of the respiratory system traversed. It is reasonable to infer that this would also apply to inspired gas as it moves through the system. The concept of an anatomic dead space for NH_3, such as applies to O_2 and CO_2, is not supported by the results.

The NH_3 concentration resulting from the TB↔A procedure was close to the estimated range of alveolar NH_3 concentrations. The latter, based on published values for blood NH_4^+, is about 10 to 25 $\mu g/m^3$ (*13*). This result, if one assumes that the test subject's blood NH_4^+ lay within this range, suggests that the tracheobronchial region is not a major NH_3 source.

The findings also indicate that the mouth is a larger source of NH_3 than the nose. This NH_3 has been attributed to bacterial decomposition of salivary urea (*14*). We found the concentration of NH_3 in the mouth to be an inverse function of ventilatory flow rate, as shown in Fig. 1, suggesting that less NH_3 may be avail-

able for reaction with acid aerosols during hyperpnea, as in exercise.

To test whether the NH_3 released by the upper airways can neutralize inhaled acid particles which are still airborne, we have made preliminary observations on one subject who was exposed to H_2SO_4 aerosol while breathing quietly by mouth (M↔TB↔A). The extent to which the aerosol reacted with NH_3 was measured 0.5 second after exhalation by thermal analysis of the exhaled aerosol (*15*). This technique can distinguish particles with NH_4^+/SO_4^{2-} molar ratios of less than one (H_2SO_4 or mixtures of H_2SO_4 and NH_4HSO_4) from particles with NH_4^+/SO_4^{2-} molar ratios greater than or equal to one [NH_4HSO_4 or mixtures of NH_4HSO_4 and $(NH_4)_2SO_4$]. The NH_4^+/SO_4^{2-} molar ratio of less than one can be quantified if one assumes that the aerosol is in equilibrium (that all particles have the same NH_4^+/SO_4^{2-} molar ratios).

Stoichiometrically, 1 μg of NH_3 per cubic meter can convert 5.8 μg of H_2SO_4 per cubic meter to NH_4HSO_4 (NH_4^+/SO_4^{2-} molar ratio = 1). Thus the resultant molar ratio of NH_4^+/SO_4^{2-} in the equilibrated aerosol equals 5.8 times the mass concentration ratio of NH_3 to H_2SO_4 initially present. Since in one subject, for example, the expired NH_3 concentration was 100 ± 25 $\mu g/m^3$ at the time of exposure to a concentration of 1200 ± 200 μg of H_2SO_4 per cubic meter (*16*), the theoretical equilibrium NH_4^+/SO_4^{2-} molar ratio of the expired aerosol is $5.8 \times [(100 \pm 25)/(1200 \pm 200)] = 0.5 \pm 0.2$. In two exposures, the measured molar ratio was 0.5 and 0.6, respectively, implying that the particles were about an equal molar mixture of NH_4HSO_4 and H_2SO_4. When a lower concentration of 600 ± 100 μg of H_2SO_4 per cubic meter was administered, a ratio greater than or equal to one was observed; the theoretical ratio should have been 1.0 ± 0.4. We emphasize that our procedure did not determine how much neutralization of H_2SO_4 occurred during inspiration before any particles became deposited, during expiration, or within 0.5 second after expiration.

The mouth, which is less efficient than the nose in scrubbing inhaled aerosols (*17*) and soluble gases such as SO_2 (*18*) and O_3 (*19*), may have a greater effect than the nose on the chemistry of acid aerosols. The range of oral NH_3 concentrations found in this study, 29 to 520 $\mu g/m^3$, has the potential for converting, per cubic meter, 84 to 1500 μg of H_2SO_4, a strong acid, to $(NH_4)_2SO_4$ which is a nearly neutral salt. The lower nasal concentrations of ammonia, 13 to 46 $\mu g/m^3$,

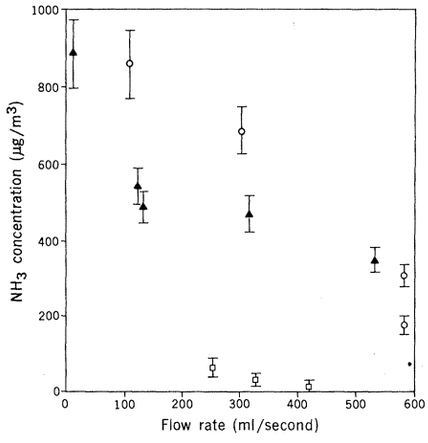

Fig. 1. The concentration of NH_3 plotted against flow rate for three subjects (□, ○, ▲) measured during the N→M procedure.

could convert 37 to 130 μg of H_2SO_4 to $(NH_4)_2SO_4$. Such concentrations of acid sulfate aerosol exceed those reported for ambient air (*3*), although it is possible that they do not exceed episodic levels, particularly in industrial environments (*20*). Based on a simplified diffusion calculation (*22*), H_2SO_4 particles at an ambient concentration of 20 μg per cubic meter with a diameter of 0.3 μm at 30 percent relative humidity should be completely neutralized after about 0.5 second in the nose, and after about 0.1 second in the mouth.

A particle of H_2SO_4 that is inhaled but not deposited may remain in the upper airways up to about 0.1 second before reaching the trachea. Our calculations suggest that this particle may not be fully neutralized before reaching the lower airways, particularly during quiet nose breathing, because of low local concentrations of NH_3, or during rapid mouth breathing because of a shortened residence time. The importance of these parameters can be tested empirically. Whether the biological changes attributable to exposure to the acid aerosols, in human populations or laboratory animals, are related to the levels of respiratory NH_3 can also be tested.

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6. The exact amount and rate of hygroscopic growth will depend on the initial size and chemical composition of the particle. A particle of H_2SO_4 initially 0.3 μm in diameter at 30 percent relative humidity will grow to about 1.2 μm at 99.5 percent relative humidity, and an 80-fold dilution, in less than 0.1 second. This dilution results in a droplet with $pH \simeq 1$; complete neutralization by NH_3 would result in an $(NH_4)_2SO_4$ droplet with $pH \simeq 5.5$. The ability of the droplet to absorb SO_2 would be increased significantly at the higher pH.
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21. This calculation makes the simplifying assumptions that the particles grow to their equilibrium size ($r = 0.8$ μm) at 99 percent relative humidity instantaneously and are exposed to an NH_3 concentration of 28 $\mu g/m^3$ in the nose and 140 $\mu g/m^3$ in the mouth. Further assumptions include: the diffusion of NH_3 to a spherical H_2SO_4 particle is at steady state; the rate of neutralization is limited by gas-phase diffusion; and the gaseous NH_3 concentration surrounding the drop is not significantly reduced. Neglected processes that would increase these times include depletion of gaseous NH_3, poor droplet mixing, and increases in ventilatory flow rate (decreases in NH_3 concentration). Processes that would decrease these times include particle growth caused by supersaturation and initial nonsteady state diffusion. Since the neutralization time per unit of aerosol mass is proportional to r^2, the effect of a distribution of particle sizes is to decrease the time to neutralize the mass fraction with $r < 0.15$ μm and increase the time for the fraction with $r > 0.15$ μm.

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