Rate of uptake of carbon monoxide at different inspired concentrations in humans

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JONES, HAZEL A., J. C. CLARK, E. E. DAVIES, R. E. FORSTER, AND J. M. B. HUGHES. *Rate of uptake of carbon monoxide at different inspired concentrations in humans.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 52(1): 109–113, 1982.—The rate of uptake of carbon monoxide (CO) in the lungs of normal subjects was measured at inspired concentrations of <1, 300, and 3,000 ppm (<0.0001–0.3%) using radioactive CO (^{11}CO). In nine subjects the rate of uptake was monitored at the mouth during rebreathing. At inspired CO concentrations of approximately 1, 300, and 3,000 ppm and a mean alveolar O_2 fraction of 0.15, the mean lung diffusing capacity was 25.8, 26.4, and 25.3 $ml \cdot min^{-1} \cdot Torr^{-1}$, respectively. In seven subjects the measurements were repeated after a period of O_2 breathing, giving a mean alveolar O_2 fraction of 0.78. The calculated membrane diffusing capacity was 31.9, 33.7, and 32.0 $ml \cdot min^{-1} \cdot Torr^{-1}$ at <1, 300, and 3,000 ppm inspired CO. We conclude that there is no difference in the rate of uptake of CO over the range of concentrations studied in these experiments. No evidence for the presence of a facilitated transport system for CO in the normal human lung was found.

lung diffusing capacity for CO; membrane diffusion for CO; facilitated transport; radioactive CO; rebreathing techniques

CARBON MONOXIDE (CO) is generally considered to diffuse across the pulmonary membrane between alveolar gas and capillary blood and across the placental membrane between maternal and fetal capillary blood at a rate proportional to the difference in partial pressure of CO. However, variations in the proportionality constant (the diffusing capacity) have led various authors to propose facilitated transport of CO in the placenta of sheep and dogs (1, 5, 7). Following Longmuir et al. (9), Gurtner and Burns (6) have suggested that cytochrome P_{450} may act as a carrier for O_2 and CO in the placenta.

A similar mechanism has been proposed for the lung (2, 12) and evidence for the presence of such a system in dogs and sheep has been put forward on the basis of a differential rate of uptake of CO with varying inspired concentrations. If the transfer of CO is purely passive, the rate of uptake will be independent of initial concentration, but if the transfer is facilitated by any means, for example by a cytochrome carrier, the rate of uptake will be higher at low concentrations than at concentrations high enough to saturate the carrier mechanism (9).

Recently, confirmation of the claim that pulmonary diffusing capacity varies systematically with the inspired concentration of CO has been sought using isotopic techniques (8, 13). Meyer et al. (13) used the stable isotopes, $^{12}C^{18}O$ and $^{13}C^{18}O$ and a mass spectrometer, and we used the radioactive isotopes, $^{11}C^{16}O$ and $^{12}C^{15}O$. In neither study was any dependence on inspired concentration found. In this paper, we report a further series of measurements in which the membrane diffusing capacity for CO has been measured in addition to the pulmonary diffusing capacity, over a 3,000-fold range of CO concentration.

METHODS

The rate of uptake of CO was studied by a rebreathing method in nine normal male subjects, whose anthropometric data are shown in Table 1. All gave informed consent; the maximum radiation dose to each subject (70 mrads) had been approved by the Health Services Division of the Department of Health and Social Security. We were able to make measurements at very low concentrations, less than 1 ppm by the use of ^{11}C-labeled CO a positron (β^+) emitting isotope of CO with a half-life of 20 min. The ^{11}CO was produced in the Medical Research Council cyclotron, London, using an N_2 target (3). The ^{11}CO was free from stable CO and had no radioactive contaminants. The ^{11}CO was dispensed into a syringe in stable N_2. The concentration at this low level was measured as less than 1 ppm using an Ecolyser CO analyzer (Energetics Science). Monitoring was carried out on a gas radiochromatograph to ensure that no radioactive contaminants were present.

The β^+ emissions from this isotope were detected using the apparatus shown in Fig. 1. This detector consists of a plastic scintillator $2 \times 2 \times 0.4$ cm^3 in a thin light-tight stainless steel envelope that projects into the rebreathing apparatus at the same point as the tip of a sampling line from a mass spectrometer (Centronics MGA 200). The plastic scintillator emits light when bombarded by positrons. The light is converted into an electronic signal and amplified in a photomultiplier tube. Counts proportional to the amount of ^{11}CO present are relayed to a computer (Digico μ 16) simultaneously with signals of flow and volume. The response of the detector was linear well beyond ranges of count rates achieved. These signals are all delayed to synchronize with signals coming from the

mass spectrometer, which lag the other signals due to transit time down the sample line. The rebreathing apparatus is shown in Fig. 2. This consists of a 1-liter bag in a bottle connected via a pneumotachograph to a wet spirometer for the measurement of flow and volume. The test gas consisted of 10% He, 10% SF_6, and 30% O_2 in Ar with either no CO, 0.03% CO, or 0.3% CO. The ^{11}CO at a concentration of <1 ppm was added to all these mixtures to give total CO concentrations of <1, 300, and 3,000 ppm. The bag was filled with 0.65 liter of one of the test gas mixtures. The subject was switched into the rebreathing system at end expiration and asked to empty and fill the bag completely 15 times at a rate of 1 breath/s, set by a metronome. During the rebreathing maneuver the concentrations of all gases, N_2, O_2, Ar, CO_2, He, and SF_6 measured in the mass spectrometer and ^{11}CO monitored by the β^+-detector were sampled 50 times/s together with signals of flow and volume. The computer printed out the time and volume of each breath, followed by the flow-weighted mean concentrations of all the gases for each inspiration. Paired measurements were made at inspired CO concentrations of <1, 300, and 3,000 ppm in random order. In seven subjects three additional measurements, one at each inspired concentration, were made after an initial period of breathing 100% O_2 for 5 min.

TABLE 1. *Anthropometric data for the subjects*

Subj	Age, yr	Ht, m	Wt, kg	VC, liters (BTPS)	FEV_1, liters (BTPS)	Smoking History
SC	33	1.68	74	4.3	3.7	Exsmoker
MH	44	1.69	63.5	5.0	3.9	Nonsmoker
AS	30	1.85	82	5.6	5.0	Smoker
RC	23	1.83	68	5.5	4.3	Nonsmoker
MT	30	1.81	75	5.8	4.6	Nonsmoker
LN	29	1.63	57.6	3.9	3.4	Pipe smoker
ED	44	1.77	85	4.6	3.3	Pipe smoker
EE	40	1.85	75	6.3	5.4	Nonsmoker
RA	31	1.73	71	4.6	3.5	Nonsmoker

VC, vital capacity; FEV_1, forced expired volume at 1 s.

The rate of uptake of CO (K_{CO}) was calculated as the exponential slope of the fall in radioactivity in the gas sampled at the mouth once the initial mixing phase had passed, as shown by the equilibration of the He and SF_6. The diffusing capacity (D_{LCO}) in $ml \cdot min^{-1} \cdot Torr^{-1}$ was calculated as $(K_{CO} \times Vs \times 60 \times 0.826)/713$, where K_{CO} is the rate constant for CO uptake (s^{-1}), Vs the system volume, i.e., the end-expiratory volume plus the bag volume in ml (BTPS) calculated from insoluble gas dilu-

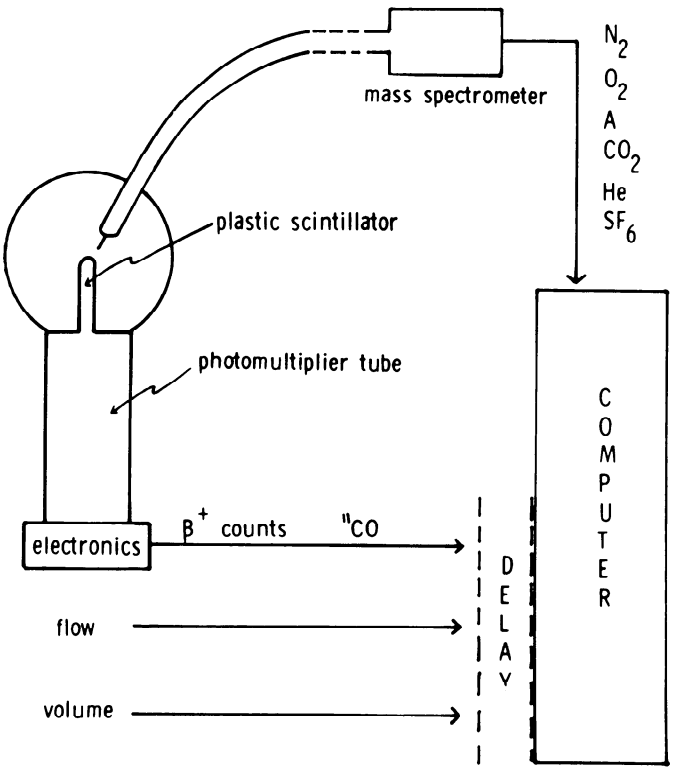

FIG. 1. Diagram of detector used for monitoring ^{11}CO, showing its position relative to other detection systems and computer. *Circle* represents cross section of tube (2.5 cm ID) connecting mouthpiece to rebreathing bag.

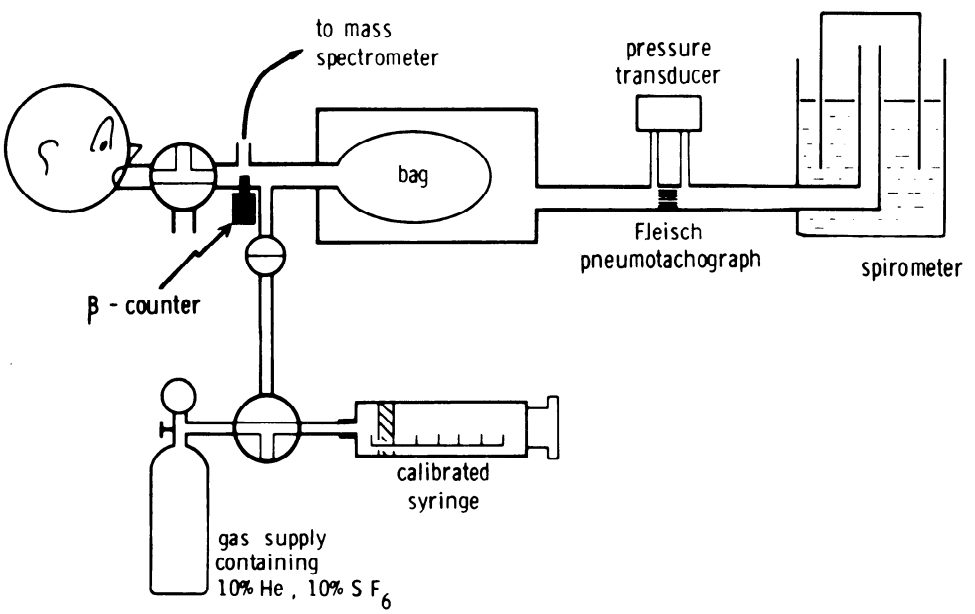

FIG. 2. Diagram of whole rebreathing apparatus.

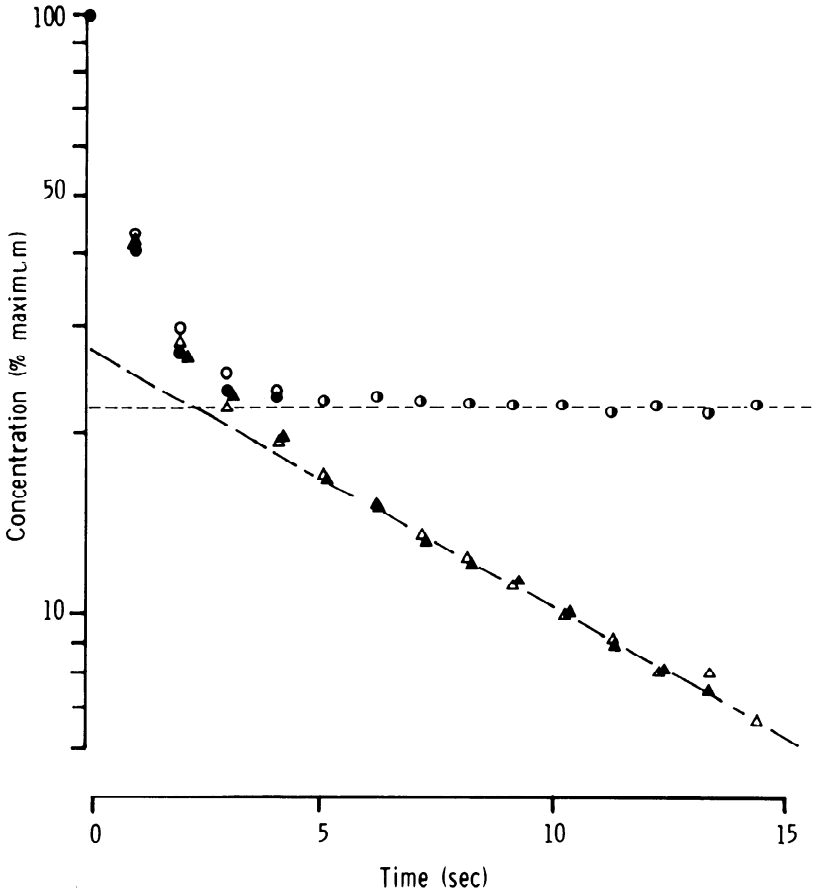

FIG. 3. Semilogarithmic plot of breath-by-breath He (●), SF_6 (○), and ^{11}CO(Δ) concentrations (as percent of maximum) against time, in *subject SC*, rebreathing a high (3,000 ppm) CO mixture. ^{11}CO values at low concentration (▲) have been added for comparison. Insoluble gas dilution was identical for both measurements.

tion, 60 the conversion from s to min, 0.826 the conversion from BTPS to STPD, and 713 the barometric pressure minus water vapor pressure.

The membrane diffusing capacity (Dm) and the capillary blood volume (Vc) were calculated graphically from the relationship described by Roughton and Forster (14)

$$\frac{1}{D_L} = \frac{1}{Dm} + \frac{1}{\theta Vc}$$

θ, the rate of reaction of CO with hemoglobin, was calculated from the mean alveolar O_2 concentration during the post-mixing part of the rebreathe, measured by the mass spectrometer.

$$\frac{1}{\theta} = (\alpha + \beta \cdot P\bar{c}_{O_2})/[Hb] \cdot (1 - S\bar{c}_{CO})$$

We followed Cotes (4) in using values of 0.34 and 0.006 for the coefficients α and β. $P\bar{c}_{O_2}$ is the mean partial pressure of O_2 in the plasma of the alveolar capillaries, [Hb] is the hemoglobin concentration as a fraction of normal, and $S\bar{c}_{CO}$ the mean fractional saturation of hemoglobin with CO (11).

The backpressure of ^{11}CO was measured by repeating the rebreathing maneuver with a bag filled with air immediately after the final measurement.

RESULTS

Figure 3 shows data obtained in one subject (*SC*) rebreathing high and low concentrations of CO after air breathing. After five breaths mixing has been established as shown by the constant He and SF_6 concentrations; the uptake of CO is monoexponential after this point. For all subjects the regression coefficients of the 75 calculated slopes were never less than 0.687 with a mean of 0.959 ± 0.062 (SD). The accumulated data for all the studies is shown in Table 2. Each number is the mean of two measurements made at each inspired concentration. A two-tailed paired *t* test of significance was carried out on the individual values between the high and medium concentrations and the high and low concentrations, yielding *P* values of 0.51 and 0.55, respectively. For all

TABLE 2. *Vs, KCO, and DLCO for all subjects at high, medium, and low inspired CO concentrations*

Subj	Approximate Inspired Concentration, ppm								
	3,000	300	<1	3,000	300	<1	3,000	300	<1
	Vs(BTPS), liters			K_{CO}, %·s^{-1}			D_{LCO}, ml·min^{-1}·Torr^{-1}		
SC	2.99	2.94	2.99	10.12	10.05	10.18	20.92	20.53	21.13
MH	3.95	4.10	4.19	8.94	8.67	8.76	24.52	24.75	25.53
AS	4.64	4.85	4.92	8.42	8.72	8.52	27.21	29.41	29.12
RC	4.26	4.14	4.36	10.77	11.88	11.65	31.88	35.10	35.07
MT	4.43	4.47	4.45	9.91	11.05	8.61	30.47	34.20	26.66
LN	3.64	3.68	3.41	7.43	7.21	7.49	18.66	18.28	17.77
ED	4.11	3.55	3.82	8.07	8.66	7.04	23.07	21.40	18.69
EE	5.68	6.39	6.23	7.69	6.73	6.84	30.29	29.77	29.50
RA	3.31	3.61	3.49	11.02	9.49	10.03	25.18	23.80	24.37
Mean	4.11	4.20	4.21	9.15	9.16	8.79	25.80	26.36	25.32

Values are means of 2 measurements. Mean alveolar O_2 fraction is 0.15. Vs, system volume i.e., bag plus end-expiratory lung volume; K_{CO}, rate constant for CO uptake; D_{LCO}, pulmonary diffusing capacity.

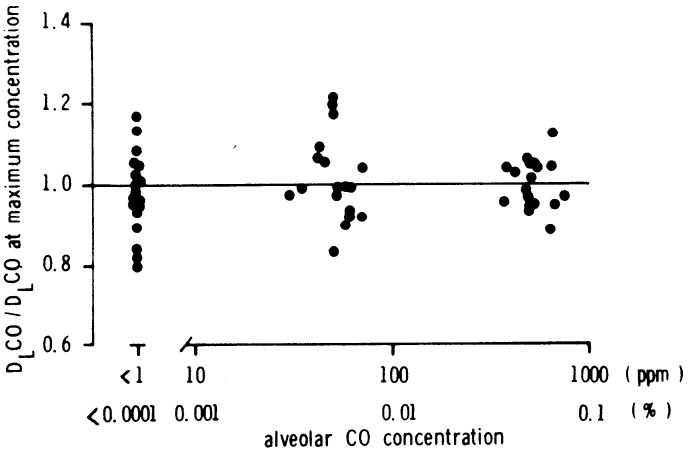

FIG. 4. Lung diffusing capacity for CO (D_{LCO}) at different alveolar concentrations. Each point represents a single measurement, and all are plotted as fraction of mean of two measurements at highest inspired concentration. No concentration-linked difference is apparent.

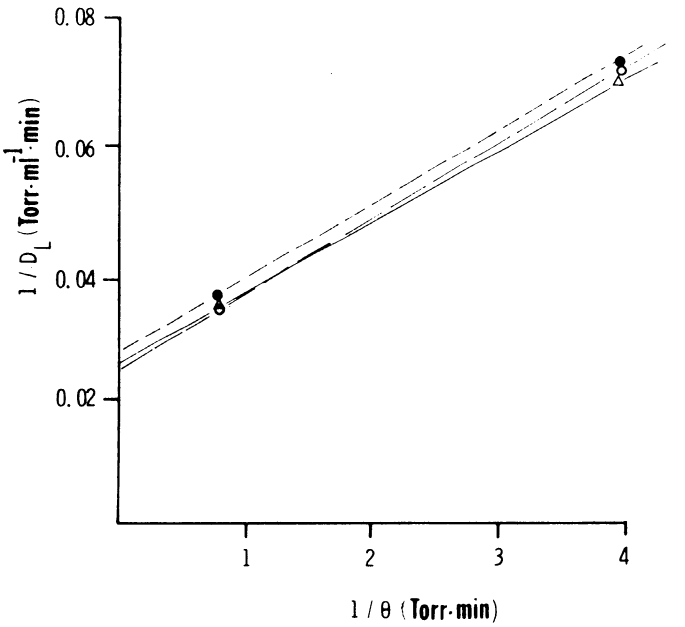

FIG. 5. Graphic analysis of Dm and Vc. $1/D_L$ is plotted against $1/\theta$ for high (●), medium (○), and low (Δ) inspired concentrations. High values for $1/\theta$ were obtained by O_2 breathing. Intercept on y-axis represents 1/Dm and slope of lines 1/Vc.

subjects the individual values for D_{LCO} are plotted against the calculated initial alveolar concentration for CO (Fig. 4). The points are all shown as a fraction of the mean D_{LCO} at the highest concentration. Thus values greater than 1.0 would indicate an increased CO uptake. Despite the expanded scale there appears to be no such increase at the intermediate or low levels.

Figure 5 shows the graphical analysis for Dm and Vc on one subject (*AS*); 1/Dm obtained from the intercepts on the y-axis did not vary with concentration, nor did 1/Vc obtained from the slopes of the lines. The results for Dm and Vc are shown in Table 3. A two-tailed paired t test of significance gave P values of 0.25 for Dm between high and medium and 0.95 between high and low concentrations. The individual results for Dm at differing alveolar CO concentrations are shown in Fig. 6, each point being plotted as the fraction of the value at the highest CO concentration. There appears to be no influence of CO on the membrane diffusion as all points at the medium and low concentrations lie around the line of unity.

TABLE 3. *D_{LCO}, Dm, and Vc for 7 subjects at high, medium, and low CO concentrations*

Subj	Approximate Inspired Concentrations, ppm								
	3,000	300	<1	3,000	300	<1	3,000	300	<1
	D_{LCO}, ml·min^{-1}·Torr^{-1}			Dm, ml·min^{-1}·Torr^{-1}			Vc, ml		
SC	12.2	12.2	12.1	25.8	24.6	21.7	85	98	98
MH	13.2	13.0	11.9	30.7	32.2	34.8	90	83	72
AS	13.7	14.0	14.4	37.1	40.3	39.1	87	88	91
RC	14.0	17.2	18.6	45.2	44.6	44.6	80	111	125
MT	17.9	16.6	18.2	35.9	45.2	40.3	148	103	140
LN	10.1	8.5	9.4	22.9	25.5	22.9	74	49	61
ED	16.2	15.6	14.2	25.8	23.8	20.6	171	174	170
Mean	13.9	13.9	14.1	31.9	33.7	32.0	105	101	109

Mean alveolar O_2 fraction is 0.78. D_{LCO}, pulmonary diffusing capacity; Dm, membrane diffusing capacity; Vc, capillary blood volume.

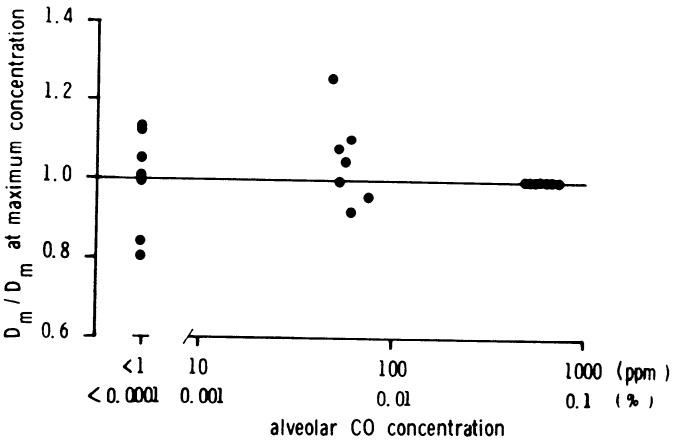

FIG. 6. Membrane diffusing capacity (Dm) for CO at different alveolar concentrations. Each point represents a single measurement as fraction of that at highest inspired concentration.

DISCUSSION

The use of radiolabeled ^{11}CO enabled us to measure CO uptake accurately at very low concentrations. The CO backpressure poses a significant problem in experiments not using tracers of CO, but no backpressure of ^{11}CO was detected at any time.

The rate of uptake of CO is influenced by the state of inflation of the lung (10). The variation in the lung volumes at which our measurements were made, shown in Table 2, was not large enough nor in the appropriate range of the vital capacity to affect the results.

The rate of uptake during air breathing is also dependent on the capillary blood volume. The studies carried out after O_2 breathing were designed specifically to study the properties of the alveolar membrane in which the proposed carrier resides. At high O_2 levels the θVc term is reduced fourfold and the Dm term dominates. Under these conditions CO uptake was again not dependent on inspired concentration.

It is possible that there may be a carrier present in

human lungs whose O_2 half saturation pressure (P_{50}) is at a CO concentration that we did not study. Even were this so, we would have expected to find a slightly increased uptake for at least one of the concentrations studied, as the influence of a carrier should be apparent up to 10 times above its P_{50} concentration and below it to a lesser extent (12).

The presence of a carrier for CO and O_2 in the placenta has been suggested (1, 7); in this situation, where diffusion distances are significant, there is at least a physiological role for a carrier to enable the fetus to obtain an adequate supply of O_2. In contrast, the diffusion distances across the alveolar membrane in the lung are extremely small, approximately 1.7 μM (15). In certain diseases the membrane does become thickened, but these conditions are relatively rare and the thickening usually occurs at a late stage in the disease process. Thus the evolutionary pressure required to develop a facilitated transport system in the lung is not strong.

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