Pulmonary Gas Exchange in Nonnative Residents of High Altitude

F. C. Cerny, J. A. Dempsey, and W. G. Reddan

From the Pulmonary Physiology Laboratory, Department of Preventive Medicine and Community Health, University of Wisconsin Medical School, Madison, Wisconsin 53706

ABSTRACT This study represented an initial attempt, by means of cross-sectional investigation, to determine the effects of chronic exposure to high altitude on pulmonary gas exchange. Single-breath D_{LCO} and its components were determined at rest and during muscular work in two groups of healthy, non-smoking, sea level natives who had initiated 1–16 yr of residence at 3,100 m altitude either during physical maturation (at age 10±4 yr) or as adults (at age 26±4 yr). The relative degree of acclimatization achieved in these lowland residents was assessed through their comparison both with normal sea-level values and with two additional groups of short-term sojourners and natives to 3,100 m. D_{LCO} at rest and work was significantly elevated above normal and above sojourner values in both groups of resident lowlanders at 3,100 m. The high D_{LCO} in the native to 3,100 m was closely approximated in the younger resident lowlander at rest, but only during exercise in the adult resident lowlander. The high D_{LCO} at rest and during exercise in the resident lowlanders was not attributable to differences in Hb concentration or in alveolar lung volume; and was accompanied primarily by an increased estimated Dm_{CO} and to a lesser extent by an expanded Vc. The interpretation and implications of these findings were limited by the low quantitative capability of Vc and Dm_{CO} estimates and by the cross-sectional nature of the study. Nevertheless, the higher than normal D_{LCO} and Dm_{CO} in the non-native, long-term resident of 3,100 m was substantial, highly significant statistically, and consistent over a wide range of metabolic rates at rest and work. These data provide, then, a reasonable rationale upon which longitudinal experiments may be based to determine the true effects of chronic hypoxia on pulmonary gas exchange in man.

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INTRODUCTION

A higher than normal alveolar-capillary diffusion for CO (D_{LCO}) [1] has been observed consistently in healthy humans native to high altitude (3,100–4,200 m) (1–4). This elevated D_{LCO} has been associated with a high pulmonary capillary blood volume (Vc) and/or so-called membrane diffusing capacity (Dm_{CO}) (1, 2), an altered lung structure (5), and during exercise in ambient hypoxia, was reflected in a narrowed alveolar to arterial P_{O_2} difference (1).

This study was directed to the question of postnatal adaptability of the lung to hypoxia in the native lowlander. Several studies have shown negligible or relatively minor alterations in D_{LCO} in the native lowlander as a result of short-term (< 3 mo) sojourn to high altitude (1, 2, 6, 7). On the other hand, we have reported data on a limited number of subjects which suggested that the native lowlander who began long-term residence at 3,100 m during early maturation was characterized by a higher than normal D_{LCO} (1). The present study extends these previous preliminary observations and represents an initial attempt, by means of cross-sectional investigation, to answer two specific questions concerning the effects of chronic high altitude exposure on alveolar gas exchange in healthy man. Can the healthy, nonnative, long-term resident of high altitude acclimatize in a manner approaching that of the native to high altitude? Is the completeness of his adaptation dependent upon the stage of physical maturation present at the initiation of residency at high altitude?

To these ends, D_{LCO} and its components were determined at rest and during muscular work in two groups of sea level natives who had initiated long-term residence at

[1] *Abbreviations used in this paper:* D_{LCO}, alveolar-capillary diffusion for CO; Dm, membrane diffusing capacity; CI, confidence interval; P_B, barometric pressure; P_{IO_2}, pressure of inspired oxygen; P_{O_2}, pressure of oxygen; TLC, total lung capacity; Vc, pulmonary capillary blood volume.

3,100 m altitude either during or following physical maturation. The relative degree of acclimatization achieved in the lowlander residents of 3,100 m was assessed through their comparison both with normal sea level values and with two additional groups of sojourners and natives to 3,100 m altitude.

METHODS

Subjects. A total of 24 residents of 3,100 m altitude (Leadville, Colo. $P_B \sim 530$ mm Hg) were studied, all of whom were natives of < 500 m altitude. 11 of the lowlanders had initiated their residence at 3,100 m after 20 yr of age. They ranged in length of residence from 1 to 11 yr and in age from 27 to 51 yr. The remaining 14 subjects had moved to 3,100 m before 15 yr of age. They ranged in length of residence from 0.5 to 16 yr and in age from 12 to 19 yr. All subjects lived almost exclusively between 3,000 m and 3,300 m, spending an average of 2–3 wk annually at lower altitudes.

All subjects had normal rest and exercise ECG, normal chest X rays and had no previous history, evidence, or symptoms of cardiopulmonary disease. The adult residents of 3,100 m were recruited from a variety of occupations, but most were office workers in the employ of private industry and government. All adolescent residents of 3,100 m were high school students. None of the subjects were smokers, nor had they been employed in underground mining operations. No subjects could be classified, in terms of habitual activity levels, as either extremely sedentary or as endurance athletes.

Measurement techniques and procedures. Rest and exercise $D_{L_{CO}}$ and Dm_{CO} and Vc were determined by the single-breath method (8) as previously described (1). All were obtained at lung volumes above 90% of total lung capacity (TLC) with the subject in an upright position (sitting or walking). Breathholding time varied between 8 and 12 s at rest and work. For resting values, four to six determinations were averaged, while only a single measurement per subject was obtained at each exercise level. All measures of $D_{L_{CO}}$ were corrected for CO back pressure (1, 9). Reproducibility of $D_{L_{CO}}$ between days, at both rest and work, showed no systematic variation and a random variation of no more than 5% of the absolute mean values. Estimations of Dm_{CO} and Vc, were made from measurements of $D_{L_{CO}}$ at ambient (~ 100 torr) and high (~ 380 or 480 torr) inspired P_{O_2}. $1/\theta$ values were derived from estimated $P\bar{c}_{O_2}$ and arterialized Hb concentration (1, 10, 11). Quantitative estimates of Vc and especially Dm_{CO} are critically affected by small errors in the measurement of $D_{L_{CO}}$ (10). Therefore, present considerations of Vc and Dm were limited to a qualitative assessment of group differences in the plotted slope and position of the $1/D_L - 1/\theta$ relationships at rest and work.

Minute ventilation and oxygen consumption were determined under steady-state conditions at rest and during exercise (1). Under conditions of constant $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ simultaneous collections of mixed expired gas and "arterialized" blood (12) were completed over a 30–40 s period. Mixed expired O_2 and CO_2 concentrations were analyzed volumetrically in a Lloyd-Gallenkampf apparatus. Hemoglobin concentration was determined by the cyanmethemoglobin technique.

Two testing sessions were required for most subjects. At the first session, all resting measurements were completed and subjects walked on a treadmill at several grades in order to select work loads of "light," "moderate," and in some cases, "hard" intensity. The exercise tests were conducted at a second session and consisted of treadmill walking at constant speed, at two or three predetermined grades. A series of measurements were obtained over a 15 min walk at each grade, using the following protocol: (*a*) ECG, $\dot{V}_E$, and end-tidal CO_2, O_2, and N_2 were measured throughout; (*b*) mixed expired gases and arterialized blood were sampled between the 5th and 6th min, followed immediately by a single-breath $D_{L_{CO}}$ measurement ($P_{I_{O_2}} \sim 100$); (*c*) inspired P_{O_2} was raised to ~ 380 or 480 torr from the 7th to 11th min, followed by repeat determinations of $D_{L_{CO}}$ and estimation of CO back pressure.

Assessment of $D_{L_{CO}}$ in the resident lowlander. The relative status of the resident lowlander was assessed by two types of comparisons. *First,* the resident lowlander's data were compared with normal sea level values through the use of published regression equations. The selected equations showed good predictability for most variables in a sample of healthy young adult males measured in our laboratory at 250 m altitude.[2] *Secondly,* the relative degree of acclimatization in resident lowlanders was assessed through comparison with two other groups at 3,100 m, who represented short-term and life-long exposure to high altitude; namely, 19 natives of < 300 m altitude with 3–8 wk sojourn at 3,100 m and 15 first to third generation natives of Leadville (Table I). Data for these two groups were obtained both from a previously reported study from our laboratory (1) and from additional subjects who were tested at the time of the present study. $D_{L_{CO}}$ was measured by the same technique in all subjects.

Normal (sea level) "predicted" values for total lung capacity and for resting $D_{L_{CO}}$ and its components were computed for all groups. TLC was predicted from standing height using separate equations for the adult and adolescent groups (13, 14). Dm and Vc were predicted from TLC after Bucci, Cook, and Barrie's data (15) which included a wide age range (7–40 yr). A predicted normal resting $D_{L_{CO}}$ value was calculated using each subject's calculated $1/\theta$ together with his predicted Vc and Dm ($1/D_L = 1/Dm + 1/\theta \cdot Vc$). A predicted normal value of $D_{L_{CO}}/V_A$ was then calculated by dividing each subject's predicted $D_{L_{CO}}$ by his observed V_A. This value allowed comparisons among different groups based on the percent of predicted D_L/V_A which took into consideration any intergroup variations in both lung volume and in $1/\theta$ values (i.e. Hb and $P\bar{c}_{O_2}$) existing at the time of measurement.

Comparison of resident lowlanders with sojourner and native groups at 3,100 m was achieved by two means. First, all groups were compared on the basis of the percent of predicted D_L/V_A criterion, as described above. The use of this standard permitted a meaningful comparison of the adolescent resident lowlander group with adult groups at 3,100 m. Secondly, evaluation of the exercise $D_{L_{CO}}$ and of Dm_{CO} and Vc at rest and work in the adult resident lowlander, was accomplished through comparing the observed values in the three adult groups at 3,100 m.

Data were computed using a PDP-8 LINC computer. Statistical probability of differences among means was determined using conventional analysis of variance techniques (16), and $P \leqq 0.05$ was accepted as the level of statistical

[2] N = 19; age = 23–43 yr; Hb = 14–15.5 g/100 ml; mean values for percent of predicted = 103% $D_{L_{CO}}$; 104% D_L/V_A; 108% Vc; 138% Dm_{CO}; and 95% TLC.

TABLE I

Physical Characteristics of Resident Lowlanders, Sojourners, and Natives at 3,100 m

		Ht	Wt	Age	Time at 3,100 m	TLC	Hb	$1/\theta$
		cm	*kg*	*yr*		*liter*	*g/100 ml*	
Sojourners at 3,100 m	Mean	176	73.9	29.8	36 days	6.51	15.5	1.158
(N = 19)	±95% CI	6	6.9	5.3	10	0.41	0.8	0.09
Natives of 3,100 m	Mean	177	70.1	23.5	1–3	6.34	16.0	1.143
(N = 15)	±95% CI	9	7.7	4.8	Generations	0.29	1.1	0.02
Adult resident lowlanders	Mean	178	79.9	31.3	4.9 yr	6.67	16.8	1.123
(N = 11)	±95% CI	4	6.5	4.7	1.9	0.45	1.1	0.04
Adolescent resident lowlanders	Mean	165	53.4	15.7	5.5 yr	5.00	15.9	1.176
(N = 13)	±95% CI	7	8.1	5.9	3.9	0.81	0.9	0.04

±95% CI refers to the confidence interval for the mean values.

significance. 95% confidence intervals for group mean values were determined using "small sample" statistical criteria (17).

RESULTS

The D_{LCO} at rest in resident lowlander groups, together with their comparison with predicted sea level normal values, are shown in TABLES II and III. In the 11 resident lowlanders who had moved to 3,100 m as adults (TABLE II) D_{LCO} was higher than predicted in all subjects. The mean increase was + 12.5 ml/min per mm Hg or + 34%, with a range of + 11 to + 60% of normal predicted D_{LCO}. In the adolescent resident lowlander group (TABLE III) D_{LCO} was increased 15.3 ml/min per mm Hg or 56% above predicted on the average with a range of + 28 to + 79%. Total lung capacity was not significantly different from predicted in either group of residents.

In Fig. 1, the resident lowlander groups are compared with sojourners and natives to 3,100 m on the basis of percent of (sea level) normal predicted values for D_{LCO}/V_A. (*a*) The mean D_{LCO}/V_A in the adult resident lowlander was 135±12% of predicted. This was significantly greater than the mean D_L/V_A in the sojourner (116±6%; $P < 0.01$) and significantly lower than that in the native of 3,100 m (161±14%; $P < 0.02$). Of the 11 adult resident lowlanders studied, percent of predicted D_L/V_A in nine exceeded the upper 95% confidence limit of the sojourner group and four of these subjects were within the limits of the highlander native group. (*b*) The mean D_L/V_A in the adolescent resident lowlander was 150±15% of predicted. This was significantly greater than the mean value in the sojourner ($P < 0.01$) and similar to that in the native ($P > 0.05$). Seven of these 13 resident lowlanders were within the 95% confidence

TABLE II

Physical Characteristics and Resting Pulmonary Function of Adult Native Lowlanders with Long-Term Residence at 3,100 m (N = 11)

				Residence at 3,100 m		TLC		D_{LCO}		D_{LCO}/V_A		
Subject	Ht	Wt	Age	Duration	Age at arrival	Observed	Predicted	Observed	Predicted	Observed	Predicted	Hb
	cm	*kg*	*yr*	*yr*		*liter*		*ml/min per mm Hg*				*g/100 ml*
L. E.	168	71.3	33	5.7	27	6.67	6.08	48.2	36.8	8.0	6.1	17.5
W. P.	188	88.6	31	6.0	25	5.78	7.81	47.1	32.1	9.5	6.5	17.0
E. V.	170	70.5	27	1.3	25	6.57	6.25	52.1	35.5	9.4	6.4	16.8
P. W.	173	68.2	28	4.0	24	5.67	6.51	40.0	31.6	8.4	6.6	17.1
J. P.	179	90.9	27	1.2	25	6.67	7.03	47.0	36.6	8.4	6.5	16.3
R. R.	175	88.6	27	6.8	21	6.43	6.68	56.1	35.0	9.3	5.8	17.4
D. C.	185	95.5	30	4.2	26	7.92	7.55	50.6	41.5	7.2	5.9	17.0
L. F.	173	70.5	29	8.0	21	6.35	6.51	45.0	34.4	8.3	6.3	17.0
H. N.	180	81.8	51	1.8	49	7.63	7.12	44.8	40.3	6.6	5.9	17.0
R. S.	183	81.8	30	4.0	26	6.65	7.38	49.6	40.3	8.8	7.1	17.4
G. K.	179	71.8	31	10.5	21	7.04	7.03	59.0	38.3	9.7	5.6	16.8
Mean	178	79.9	31	4.9	26	6.67	6.90	49.1	36.6	8.5	6.3	16.8
±95% CI	4	5.5	5	1.9	4	0.45	0.34	3.6	1.9	0.7	0.3	1.1
P	—	—	—	—	—	>0.10		<0.001		<0.001		

Prediction equation for sea level normal values: TLC = 8.67 ht(meters) − 8.49 (reference 13); D_{mco} = 11(TLC) + 3; V_c = 9.3(TLC) + 16.5; $1/D_{LCO}$ = 1/pred. D_{mco} + $1/\theta\cdot$pred. V_c (reference 15); Pred. D_{LCO}/V_A = D_{LCO}(pred.)/V_A(observed).

TABLE III

Physical Characteristics and Resting Pulmonary Function of Adolescent Native Lowlanders with Long-Term Residence at 3,100 m (N = 13)

Subject	Ht.	Wt.	Age	Residence at 3,100 m: Duration	Residence at 3,100 m: Age at arrival	TLC: Observed	TLC: Predicted	DLco: Observed	DLco: Predicted	DL/VA: Observed	DL/VA: Predicted	Hb
	cm	*kg*	*yr*	*yr*		*liters*		*ml/min per mm Hg*				*g/100 ml*
S. H.	159	49.1	15	0.9	14	4.75	4.22	34.3	25.7	8.1	6.1	15.0
P. B.	163	53.2	17	5.7	12	4.77	5.64	48.6	26.8	11.8	6.5	16.0
B. H.	173	72.7	16	0.9	15	6.39	5.31	44.3	35.4	8.3	6.5	17.3
R. P.	181	65.5	14	1.0	13	5.63	6.01	43.8	31.3	9.3	6.6	16.1
F. B.	178	63.6	19	16.6	3	6.31	6.94	62.8	35.0	11.7	6.5	17.6
V. O.	146	37.3	14	1.0	13	3.27	3.34	26.9	19.1	10.4	7.3	12.7
R. J.	188	66.3	18	2.7	15	7.24	7.81	64.0	38.8	10.3	6.2	17.0
T. M.	138	35.0	12	2.0	10	2.92	2.87	25.4	17.4	10.8	7.4	15.5
E. B.	173	56.0	17	15.8	2	5.03	6.51	44.8	28.0	10.7	6.7	15.6
D. W.	159	35.7	14	1.2	13	3.39	4.22	25.0	19.5	9.0	7.0	15.9
R. M.	175	66.1	19	16.5	3	6.99	6.68	62.9	32.3	10.7	5.5	16.9
K. W.	149	33.6	12	0.5	11	3.41	3.53	24.4	20.4	8.9	7.5	14.9
E. P.	177	59.1	17	7.0	10	5.08	6.86	48.6	28.4	9.0	5.3	16.6
Mean	165	53.4	15.7	5.5	10	5.00	5.38	42.8	27.5	9.9	6.6	15.9
±95% CI	7	8.1	5.9	3.9	4.1	0.75	0.88	8.7	4.8	0.7	0.4	0.9
P	—	—	—	—	—	>0.10		<0.001		<0.001		

Prediction equations: TLC = 1.19 ht $^{2.73}$ (height in meters) (reference 14). Other prediction equations as in Table II.

limits and five of the seven exceeded the mean value for the highlander native. The six adolescent resident lowlanders who fell clearly below the highlander's 95% confidence limit were those with the shortest duration of residence at 3,100 m (i.e. 0.6–1.5 yr). (*c*) Group mean percent of predicted DL/VA in the adolescent resident lowlanders was numerically greater than the adult resident lowlander (135% vs. 150%), but these differences were not statistically significant ($P > 0.05$).

The effects of steady-state exercise on DLco are shown in Fig. 2. DLco in the adult resident lowlander during mild to moderately heavy exercise was essentially similar to that in the native and consistently exceeded that in the sojourner to 3,100 m. The smaller lung volume, body size, and $\dot{V}O_2$ in the adolescent resident lowlander complicate any comparison of their absolute DLco with the adult groups. It is of interest, however, that DLco in these younger residents equaled or exceeded that achieved by the adult sojourner at comparable $\dot{V}O_2$ during exercise.

Average resting values describing $1/DL$ vs. $1/\theta$ relationships (i.e. Vc and Dmco) for each resident lowlander group are plotted in Fig. 3*A*; and compared both with normal sea level predicted values and to absolute values in the sojourner and native to 3,100 m. The adult resi-

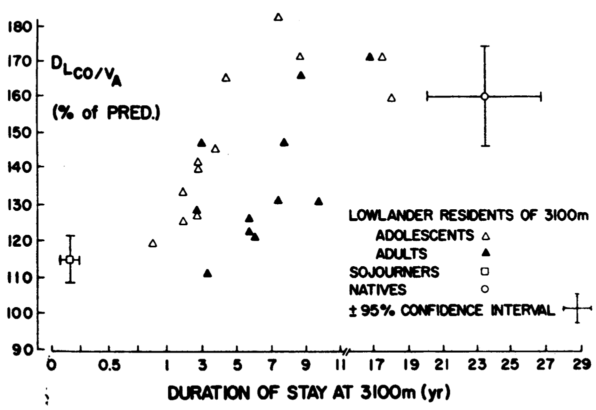

FIGURE 1 DLco/VA as a percent of (sea level, normal) predicted values vs duration of residence at 3,100 m, in adult (N = 11) and adolescent (N = 13) resident lowlanders, and in native highlanders (N = 15), and sojourners (N = 19) at 3,100 m.

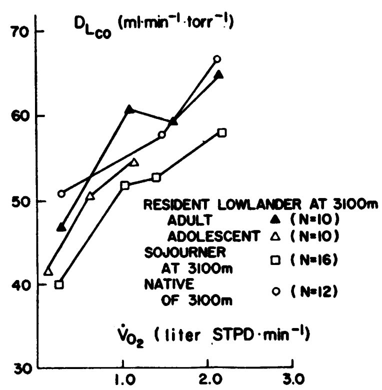

FIGURE 2 Effects of steady-state exercise on DLco. Group mean values in residents, sojourners, and natives at 3,100 m. All mean values for DLco were corrected to the average $1/\theta$ and Hb concentration in the sojourner.

dent lowlander had a mean Dmco which was ~ 2.2 times predicted ($P < 0.01$), was significantly greater than the sojourner ($\sim 1.3 \times$ predicted), and was significantly less than the highlander native ($\sim 3.1 \times$ predicted). His estimated group mean Vc was within 10% of normal predicted values, as were those of the native and sojourner groups. The adolescent resident lowlander had a mean Dmco which was ~ 2 times predicted ($P < 0.01$). Vc was also greater than predicted in this group ($\sim 1.3 \times$) but not significantly so ($P > 0.05$).

The effects of moderate exercise on Vc and Dmco in the three adult groups at 3,100 m are shown in Fig. 3*B*. Exercise effected an increase in Vc above resting values in all groups, but no change in Dmco. In the adult resident lowlander exercise Vc was greater than that in the sojourner and similar to that in the native to 3,100 m.

DISCUSSION

The findings have demonstrated that the apparent diffusing capacity for CO was significantly elevated above normal in the lowlander who initiated long-term residence at 3,100 m altitude either during or following physical maturation. This observed elevation in DLco applied when either predicted sea level values or values obtained in the short-term sojourner at 3,100 m were used as the "normal" criterion with which to assess the status of the resident lowlander. Furthermore, it was shown that while the elevation in DLco was not significantly different between adolescent and adult resident lowlander groups, the younger resident more closely approximated the high resting DLco observed in the native to 3,100 m. DLco in the adult resident lowlander was comparable to that in the highlander native only under conditions of mild to moderately heavy exercise. Finally, it was observed that the high DLco in the resident lowlander was not attributable to variations in hemoglobin concentration or alveolar lung volume. Estimates of the components of diffusion revealed that a high estimated Dmco contributed most to the resident lowlander's elevated DLco.

It is important to point out the limitations which are imposed on the application of present findings to the question of long-term hypoxic exposure effects on pulmonary exchange and its determinants. These limitations are discussed below with particular reference to experimental methods and design.

First, it appears that our experimental design and application of the measurement techniques permit the conclusion that DLco in the resident lowlander of 3,100 m was substantially greater than normal; and that under resting and/or exercise conditions approached that of the highlander native. Three points support this conclusion: (*a*) The reproducibility of single-breath DLco measurements between days or within test sessions was

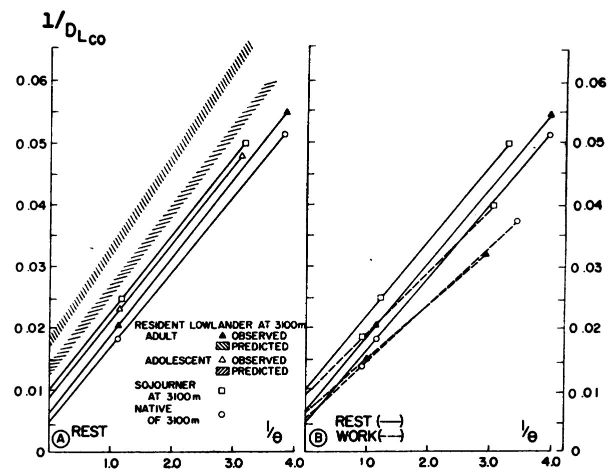

FIGURE 3 $1/D_{Lco}$ vs. $1/\theta$ relationships at 3,100 m (slope = Vc, intercept = Dmco). (*A*) Resting values in all groups. Number of subjects per group as in Fig. 1. Prediction equations are listed in Table II. The predicted $1/D_L$ vs. $1/\theta$ in the adult natives and sojourners to 3,100 m closely approximated that shown for the adult resident lowlander group. (*B*) Effects of steady-state exercise (mean $\dot{V}o_2 = 1.9$–2.1 liters/min) on $1/D_L$ vs. $1/\theta$ in the three adult groups at 3,100 m. Number of subjects per group as in Fig. 2.

without significant systematic or random variation. (*b*) The use of sojourners and natives to 3,100 m for comparative purposes permitted fairly precise definition of the relative status of DLco in the resident lowlander. These intergroup comparisons of DLco were facilitated both through the use of identical measurement techniques and by the finding that variation among adult groups in VA and Hb concentration could account for a maximum of 8–10% of the observed differences in DLco. (*c*) Finally, the findings were highly consistent in support of the conclusion, in that DLco in most resident lowlanders clearly exceeded the confidence limits of normal values and the differences among groups were consistent over a wide range of metabolic rate at rest and work.

On the other hand, the methods used do not permit a definitive explanation for this elevated DLco in the resident lowlander; and in fact the results obtained with the partitioning of DLco appear to be inconsistent with most reasonable interpretations. Numerous explanations for the elevated DLco are theoretically possible (*2, 18*) and include factors which might influence either the effective alveolar-capillary surface area and/or a change in one or more sites of resistance along the length of the diffusion pathway. Accordingly, previous studies have shown that long-term hypoxia produces an increase in alveolar number and/or volume in sea-level animals (*19, 20, 21*); and in man limited cross-sectional data point to an increase in pulmonary blood volume after approximately 6 mo to 1 yr of exposure to high altitude (*22, 23*).

Present findings indicate that an approximate 70% increase in estimated D_{mco} above normal[3] was the dominant factor underlying the resident lowlander's elevated D_{Lco}. Any contribution from an expanded Vc was limited to the working state in the adult resident lowlander and to a relatively small extent at rest in the adolescent resident lowlander. One interpretation of the increased D_{mco} would be that the effective alveolar-capillary surface area was greatly expanded (18). However, it is difficult to envision how the estimated increase in Dm could be achieved without an increment in alveolar volume or capillary blood volume. If indeed the suggested increase in surface area for gas exchange was achieved through an increased alveolar number and alveolar septal growth—as has been demonstrated in the native to high altitude (5)—one would have also expected an associated increase in pulmonary capillary blood volume. An alternative explanation for the resident lowlander's high D_{mco} may be found in an abnormal θ value, secondary to altered red cell kinetics or to a systematic discrepancy between systemic and pulmonary capillary red cell concentration (18). A minimum reduction of $\sim 40\%$ in the assumed θ value would have been required to account for the superior D_{Lco} in the resident lowlander at rest or work. Finally, it is important to reemphasize the limitations placed on the validity and hence the quantitative capability of the D_{mco} estimate, become of its high susceptability to small errors in the measurement of D_{Lco} (10, 18, 3). In view of these various limitations in methods and interpretation, we are unable to provide any definitive explanation for the residents' elevated resting D_{Lco}; and can only refer to the consistent observation of a coincident elevation in estimated D_{mco}.

In this study as in previously reported studies of high altitude natives (1–4) the use of purely cross-sectional data imposes serious limitations on any attempt at cause-effect interpretation. That is, the question of natural selection, on the basis of one's "initial" status of D_{Lco}, precludes any conclusion of an apparent "effect" of hypoxic exposure. Does the tested resident population at 3,100 m merely represent those native lowlanders who chose to remain at high altitude because of a higher than average diffusing capacity; or were their observed differences from normal actually acquired as a result of hypoxic exposure? Present findings relate to these questions only indirectly through the substantial magnitude of the observed elevation above normal in D_{Lco} in the resident lowlanders. This finding merely suggests, on probability grounds, that the D_{Lco} observed in the resident lowlander at 3,100 m reflected some change beyond what might be expected to have been their pre-ascent status. Certainly, these cross-sectional data from a limited sample of the population do not prove this point, nor do they provide insight into the further possibility of individual differences in adaptability of the healthy lowlander's pulmonary system to chronic hypoxic exposure. It is clear, then that the question of acquired characteristics in the native lowlander may be answered conclusively only through longitudinal studies, initiated under pre-ascent sea level conditions and continued through long-term hypoxic exposure. To date, experimental studies of this type in man have been limited to periods of less than 3 mo sojourn at high altitude in the adult native lowlander, and all have shown a relatively small or negligible effect on D_{Lco} (1, 2, 4, 6, 7).

Related findings in the literature are limited in number and inconsistent concerning the question of a true effect of chronic hypoxia on alveolar gas exchange. Experimental studies in the rat support the concept of an adaptable lung structure during chronic hypoxic exposure in both the maturing and "adult" animal (19, 20, 12, 24). In young rats, exposure to $P_{I_{O_2}} \sim 90$–100 mm Hg beyond 21 days was characterized by an $\sim 15\%$ increase in alveolar-capillary surface area (18, 20, 21), which effected an estimated 20% increase in alveolar-capillary diffusion (20). Furthermore, in the adult rat exposed to higher altitudes ($P_{I_{O_2}} < 90$ mm Hg), significant increases above normal values in age-matched controls were observed in alveolar volume and/or number (18, 21). These animal studies would support, then, the concept of a true effect of hypoxia; but their application to man is limited by the fact that the rat lung continues to grow throughout life (20, 21). In apparent contradiction to this concept and to present findings, Guleria, Pande, Sethi, and Roy (4) reported near normal "predicted" D_{Lco} by the end-tidal steady-state technique in adult native lowlanders with "long-term" residence at 3,700 m altitude. However, both the methods used and the characteristics of the subjects employed in this study make the findings difficult to compare with present observations or to apply to the question of long-term hypoxic effects on D_{Lco} in native lowlanders. First, the end-tidal steady-state D_{Lco} measurements showed substantial variation between trials; as well as an unexplained sensitivity to small variations in tidal volume which varied markedly among the groups studied (4). In addition, single-breath and end-tidal steady-state D_{Lco} methods have been shown to differ significantly in their respective sensitivities to ventilation: perfusion distribution inequalities (18, 25). Secondly, the resident lowlander groups used in the respective studies differed in two important respects. In the earlier study (4) 35 of the 38 lowlanders studied were in continuous residence at 3,700 m for 1 yr or less (range 1–25 mo); whereas all but

[3] As explained in text the estimation of D_{mco} and to a lesser extent, Vc are highly susceptible to measurement error. Therefore, the most meaningful assessment of the resident lowlander's relative D_{mco} is achieved through use of the sojourner group, rather than published sea-level values, as the "normal" criterion.

three of the 24 lowlanders studied at 3,100 m were in residence greater than 1 yr (6 mo to 15 yr). Furthermore, more than three-fourths of the subjects studied at 3,700 m were chronic cigarette smokers—a practice which has been shown to have significant and individually variable effects on pulmonary gas exchange over a wide age range (*26–28*), and which may have served some negative role in determining the acclimatization process. Obviously, the only valid way that these discrepancies between findings may be resolved is through longitudinal study.

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