Different hematologic responses to hypoxia in Sherpas and Quechua Indians

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WINSLOW, ROBERT M., KEITH W. CHAPMAN, CARTER C. GIBSON, MICHELE SAMAJA, CARLOS C. MONGE, EUGENE GOLDWASSER, MINGMA SHERPA, F. DUANE BLUME, AND RAIMONDO SANTOLAYA. *Different hematologic responses to hypoxia in Sherpas and Quechua Indians.* J. Appl. Physiol. 66(4): 1561–1569, 1989.—Previous studies of the erythropoietic response to hypoxia in high-altitude natives suggest that the hematocrit and hemoglobin values in Himalayan natives (Sherpas) are lower than expected for the altitude, perhaps because of a genetic adaptation. However, differences in sampling techniques and experimental methods make comparisons difficult. Our studies were carried out to compare the erythropoietic response with the same altitude in age-matched natives of the Himalayas and Andes by the same experimental techniques. Healthy male subjects were selected in Ollagüe, Chile (n = 29, 27.3 ± 5.9 yr) and in Khunde, Nepal (n = 30, 24.7 ± 3.8 yr). Both of these villages are located at 3,700 m above sea level. Hematologic measurements confirmed lower hematocrit values in Nepal (48.4 ± 4.5%) than in Chile (52.2 ± 4.6%) ($P < 0.003$). When subjects were matched for hematocrit, erythropoietin concentrations in Chile were higher than in Nepal ($P < 0.01$). Detailed measurements of blood O_2 affinity in Nepal showed no differences in shape or position of the O_2 equilibrium curve between Sherpas and Western sojourners. Our results indicate that although Quechua Indians have higher hematocrits than Sherpas living at the same altitude, nevertheless they may be functionally anemic.

high altitude; hematocrit; erythrocytes; oxygen affinity; erythropoiesis; erythropoietin

HEMOGLOBIN CONCENTRATION is known to vary in normal humans, but whether it is subject to genetic control, except in disease states, has never been shown. If genetic mechanisms do exist, high-altitude natives would seem an ideal model for study, because generations of exposure to hypoxia might select for the degree of erythropoiesis that optimizes O_2 transport.

Although it has been known for over a century that erythrocytosis occurs at high altitude, its importance in acclimatization is still debated. Although an increase in hemoglobin concentration augments the blood O_2-carrying capacity, it also increases bulk viscosity of blood and may impose a circulatory burden. Some authors have argued that erythrocytosis is an essential feature of adaptation, whereas others believe that those natives who are best adapted have the lowest hematocrit (19).

The literature reporting the degree of erythrocytosis in high-altitude natives is conflicting. Two studies by Hurtado et al. (11, 12) gave discrepant results in natives of Peru. Cosio (7) showed very different hematocrit values in natives of neighboring Peruvian towns that are situated at nearly the same altitude. Garruto and Dutt (10) found hematocrits in southern Peru were lower than those in mining towns at similar altitudes in northern Peru. Beall reviewed published data and found hemoglobin values in natives of Nepal were lower than those reported for Andean natives (4). Beall believed these data support the hypothesis that Himalayan natives have evolved a genetically different erythropoietic response to hypoxia by virtue of their much longer exposure to altitude.

Differences in hematocrit between two populations could have many possible explanations. Some of them are not of genetic or physiological interest, such as nutritional deficiencies or endemic diseases that cause anemia. Nutritional causes for the lower hematocrits found in the Himalayas have not been identified (1, 2, 5). Differences in the mean altitude of exposure for the two populations could also occur. However, if such explanations cannot be established, then differences in O_2 transport or the erythropoietic response to hypoxia remain.

If genetic adaptation to hypoxia occurred in humans it will provide a unique opportunity to observe human evolution in progress. Our studies were initiated to investigate this possibility. Our first step was to detect differences, if any, between the hematologic response to hypoxia of these two groups. Because the literature on this point is so contradictory, we chose to begin our studies with a set of measurements carried out by stand-

ard procedures, done by the same personnel using the same instruments in the two geographic areas.

METHODS

The Andean studies were done in Ollagüe, Chile (21.12° south, 70.29° west, 3,700 m altitude, barometric pressure 493 Torr) located on the Andean altiplano near the Chile-Bolivia border. The subjects were either employees of the railway or were farmers or other types of laborers.

The Himalayan studies were done in Khunde, Nepal (27.49° north, 86.43° east, 3,700 m altitude, barometric pressure 481 Torr) located in the Khumbu region. The work pattern of the residents of Khunde is typical of Sherpas, and follows the seasons. In the pre- and post-monsoon season, they work as porters and guides. During the monsoon season, they remain in their native villages.

At both sites, electrical power was supplied by the same self-contained gasoline-fueled generators (EM3000X and EM1800X, Honda) to ensure that there were no differences in the operation of the electrical equipment.

Subjects. Experimental subjects in Chile were recruited from the local residents of Ollagüe and surrounding villages. We paid the subjects to remain in the laboratory for 2 full days and 1 night. Extensive histories were taken from all potential subjects and physical examinations were performed. We chose only nonsmoking males between 20 and 30 years of age for the complete set of studies. Others participated in certain portions of the protocols. We did not accept subjects who had visited lower altitudes in recent months, who used tobacco or drugs, or who reported or demonstrated evidence of significant illness of any kind. Blood was also obtained from four residents of Amincha, Chile (5,950 m). These subjects worked intermittently in the mine at the summit of Aucanquilcha (6,300 m).

In Nepal we used the same criteria for acceptance of subjects into the studies. However, a trekking company (Nepal Himal) contracted the subjects in advance of the expedition to provide adequate numbers of candidates. The Nepal phase of the study was carried out at the beginning of the monsoon, which ensured that the maximum number of potential subjects would be in their native villages. It was virtually impossible to obtain detailed information about the altitude exposure in the months just before the studies. However, because the subjects worked as porters, they had been intermittently exposed to altitudes slightly higher than their altitude of residence. If this influenced our results, it would give the impression of elevated erythrocyte production. Blood was also obtained from expedition members and was used as controls for some of the measurements.

Protocol. In most of the cases, the studies were performed over 2 days. On the first, we obtained histories, electrocardiograms, and chest X-rays and performed physical examinations. Also on the first day we obtained venous blood for routine hematologic measurements. We performed exercise and other tests of ventilatory drives in the afternoon of the first day and sleep studies during the night. We carried out tests of water balance on the morning of the second day and obtained additional blood for analysis of oxygen affinity, 2,3-diphosphoglycerate (2,3-DPG), and, in many cases, arterial blood gases. Samples of blood or separated plasma were frozen in liquid N_2 to return to the United States for special analysis such as measurements of electrolytes, hormones, and erythropoietin. This basic protocol was varied in many cases to accommodate the needs of individual volunteers, the team members, or the load of work to be done.

General evaluation. Native physicians took histories in the subjects' native language. They paid special attention to questions relating to symptoms of polycythemia, intolerance to altitude, recent descent to lower altitude, therapeutic phlebotomy, or respiratory symptoms. We selected for study only subjects who did not work underground.

Native physicians also performed physical examinations; they had extensive experience with high-altitude medical problems. We obtained anterior and lateral photographs of most of the subjects, and supine and erect blood pressures and we recorded standard 12-lead electrocardiograms. We did not obtain chest X-rays in Nepal because of lack of equipment there.

Routine hematology. Venous blood was obtained without stasis and immediately placed into evacuated tubes containing heparin. Microhematocrits were measured by centrifugation at 3,000 rpm for 10 min using a Clay-Adams microhematocrit centrifuge. In control experiments, we verified that longer centrifugation times did not give lower hematocrit values, even with samples with very high hematocrits.

We measured hemoglobin concentration by the Drabkin's method by using kits obtained from Becton-Dickinson and by the method of Rossi-Bernardi et al. (13). In Chile a Perkin-Elmer model 35 spectrophotometer was used for the hemoglobin concentration measurements, whereas in Nepal, a Hewlett-Packard model 8451A diode array spectrophotometer was used. Although the same kits and procedures were used in both sets of studies, the Hewlett-Packard instrument lends itself to more accurate work because of precise wavelength selection and the possibility to use standard cuvettes. The Perkin-Elmer instrument uses an analog wavelength selection and the cuvettes are test tubes whose optical quality is variable.

Kits from Becton-Dickinson were also used for erythrocyte counts, white blood cell counts, reticulocyte counts, platelet counts, and osmotic fragility. We made blood films of each sample and examined them later in the United States after staining.

Erythropoietin. Fresh blood samples were placed into evacuated tubes that contained no anticoagulant. After the clot formed, the serum was separated by centrifugation and frozen in liquid N_2. These samples were kept frozen and shipped to Chicago where erythropoietin measurements were made according to methods described previously (15). These measurements were made within 6 wk of the respective expeditions. Laboratory personnel were not aware of the sample sources or of the hematologic values associated with them. We considered this procedure superior to assaying all samples in one

batch, because, in that case, one set of samples would be 1 yr older than the other.

Blood O_2 affinity. In most of the subjects in Chile, we collected blood from the radial artery into heparinized syringes. The blood was kept on ice (4°C) until the partial pressure of O_2 (P_{O_2}) and CO_2 (P_{CO_2}) and pH were measured. In Chile, we used a Radiometer BMS-3-MK2 pH meter and in Nepal a Corning model 168 instrument. In each case, we calibrated the electrodes according to the instructions provided by the manufacturer using buffers obtained from the manufacturer.

In Nepal, our subjects did not allow us to draw arterial blood. We therefore equilibrated venous blood with gases (Matheson) of known composition in a tonometer (Instrumentation Laboratories, model 237) for ~20 min. We then measured P_{CO_2}, P_{O_2}, and pH using the Corning blood gas analyzer.

In Nepal, continuous whole blood O_2 equilibrium curves were obtained with the instrument described previously (22). According to this method, samples of venous blood (2.5 ml) were equilibrated in an IL model 237 tonometer for 15–20 min with N_2 containing 6.86% CO_2 (P_{CO_2} 29.7 Torr). We then transferred the blood anaerobically to the reaction cuvette which was flushed with the N_2-CO_2 gas mixture and thermostatted to 37°C. We added 10 μl of a catalase suspension (Sigma Chemical) and then oxygenated the blood by the addition of 0.45 M H_2O_2 (Parke-Davis) from a 10-μl Hamilton syringe driven by a stepping-motor drive. The pH was held constant by the manual addition of 0.4 M NaOH from a second Hamilton syringe mounted in a micrometer drive. An analog-to-digital converter (Digital Equipment) converted P_{O_2} and P_{CO_2} signals to digital values every 3 s and displayed them on a graphic terminal of a computer (Professional 380, Digital Equipment). We made definitive calculations of saturation according to equations detailed previously (22). We estimated Adair parameters by curve-fitting techniques which were also described previously (23). In this case we implemented the programs on a MicroVax II computer (Digital Equipment), using a Fortran program, after returning to the United States.

In both Chile and Nepal, barometric pressure was measured with an anaeroid barometer (Wallace and Tiernan model FA185300D, Belleville, NJ).

2,3-DPG. Fresh samples of venous blood were deproteinized by addition to ice-cold 6% perchloric acid. The extracts were neutralized with K_2CO_3 and the precipitates were removed by centrifugation. We measured 2,3-DPG in these neutral extracts within 1–2 h with kits obtained from Boehringer-Mannheim. The absorbance measurements were made in Chile with a Perkin-Elmer model 35 spectrophotometer and in Nepal with a Hewlett-Packard model 8451A spectrophotometer.

Statistical methods. Normalcy of distributions was evaluated using the Wilk-Shapiro test. After analysis of variances, group means were compared using either a pooled variance t test (equal variances) or unpooled t test (unequal variances). Differences were accepted as significant when $P < 0.05$.

RESULTS

Subjects. Table 1 presents some characteristics of the study populations. The Chilean subjects were slightly older ($P = 0.05$), shorter ($P = 0.03$), and heavier ($P = 0.003$). The detailed anthropometric data for these subjects were reported elsewhere (6).

Hematology. Table 2 summarizes the hematologic results. The most significant difference between the two groups is in hematocrit ($P = 0.003$), the values in Nepal being lower. Hemoglobins are also lower in Nepal ($P = 0.012$). It is of interest that there is no statistical difference in erythrocyte counts between the two groups. This implies that the average erythrocyte in Sherpas is smaller and contains less hemoglobin than those in Quechuas. Mean cell volumes, mean cell hemoglobin concentrations, and mean cell hemoglobin contents calculated from these primary measurements, however, are not statistically different between the two study groups.

Figure 1 shows the hematocrit distributions in Nepal and Chile. Except for one case, the hematocrits in Nepal are distributed normally around a mean of 48.4%. The single exception was a Sherpa whose hematocrit was 63.5%. He had recently worked as a high-altitude porter. He had no symptoms associated with excessive polycythemia. In contrast, the hematocrit values in Chile are skewed toward higher values with a mean of 52.2%. Nevertheless, the medians (50.8% in Chile, 47.7% in Nepal) are still significantly different.

In Chile, one subject who volunteered for our studies had typical symptoms of chronic mountain sickness,

TABLE 1. *Characteristics of the study subjects*

	Chile	Nepal	P
Age, yr	27.3±5.9 (29)	24.7±3.8 (30)	0.05
Height, cm	162.2±4.4 (28)	165.0±5.1 (30)	0.03
Weight, kg	60.4±8.8 (28)	54.5±4.5 (30)	0.003

Values are means ± SD for no. of subjs shown in parentheses.

TABLE 2. *Hematology*

	Chile	Nepal	P
Hct, %	52.2±4.6 (24)	48.4±4.5 (30)	0.003
Hb, g/dl	18.0±1.8 (24)	16.9±1.2 (30)	0.012
RBC, $\times 10^6$/mm^3	6.14±1.29 (21)	5.84±1.01 (30)	NS
MCHC, g/dl	34.5	34.9	NS
MCV, fl	85.0	82.9	NS
MCH, pg/cell	29.3	28.9	NS
Plat, $\times 10^3$/mm^3	253±85 (23)	265±68 (39)	NS
WBC, $\times 10^3$/mm^3	6.40±2.4 (24)	6.53±2.1 (39)	NS
EPO, mU/ml	9.6±4.3 (21)	8.4±7.1 (30)	NS

Values are means ± SD for no. of subjs shown in parentheses. Hct, hematocrit; Hb, hemoglobin; RBC, erythrocyte count; MCHC, mean cell hemoglobin concn; MCV, mean cell volume; MCH, mean cell hemoglobin; Plat, platelet count; WBC, white blood cell count; EPO, erythropoietin.

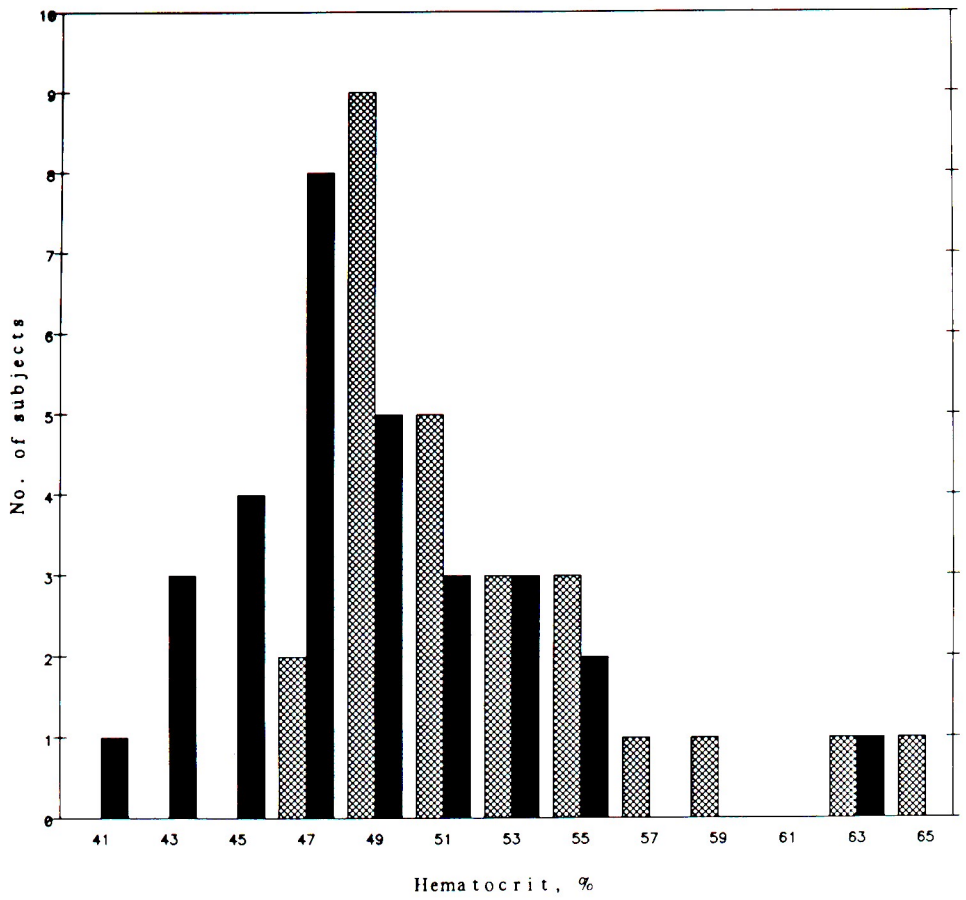

FIG. 1. Hematocrit distributions in Nepal and Chile. Closed bars, Nepal; cross-hatched bars, Chile.

although his hematocrit was only 57.5%. These symptoms included headache, confusion, and sleeplessness. On physical examination he appeared cyanotic and his conjunctivae were markedly erythremic, as is commonly seen in subjects with chronic mountain sickness. This subject is not included in the comparative analyses because his age was 55 yr, outside the range used in the study. In Nepal, no subject reported symptoms of chronic mountain sickness, regardless of hematocrit. Furthermore, a physician who had worked in Khunde for 2 yr had not encountered any case of chronic mountain sickness in his practice there.

Erythropoietin. The erythropoietin values ranged from almost undetectable (0.6 mU/ml in Nepal) to 45 mU/ml in the subject with chronic mountain sickness in Chile. All the values are plotted against hematocrit in Fig. 2 where the range for sea level normal subjects is shown for comparison (15). Hematocrit was chosen as the hematologic measurement for erythropoietin comparisons because we believed the hematocrit measurement was more accurate in the present experiments (see METHODS). That is, hemoglobin concentration was dependent on optical measurements (different spectrophotometers were used in the two locations) and erythrocyte counts were done manually.

The points for two expedition members measured after arrival at altitude in Nepal and again ~2 wk later are shown in Fig. 2 as connected points. These values show an appropriate decline in erythropoietin as erythrocyte production increases. The two notable exceptions, indicated in Fig. 2, are the Chilean subject with chronic mountain sickness and subjects who resided at Amincha (altitude 5,400 m) and worked at the summit of Aucalquilcha (altitude 6,300 m). In all of these subjects, the erythropoietin concentrations are significantly elevated, suggesting that the observed hematocrit does not compensate for hypoxia.

An initial comparison was made of the erythropoietin measurements in Chile and Nepal by using only the study subjects (Table 2). The distribution of erythropoietin values is normal in Chile but not in Nepal (Fig. 3); the medians of these samples are not different (P = 0.001). Although there is a definite relationship between erythropoietin and hematocrit, the correlation is not strong ($r = -0.54$ in Chile, $r = -0.40$ in Nepal). Correlations between erythropoietin and hemoglobin concentration ($r = -0.47$ in Chile, $r = -0.25$ in Nepal) and between erythropoietin and erythrocyte count ($r = -0.24$ in Chile, $r = -0.29$ in Nepal) are still weaker. These results are misleading, however, because the hematocrit means are different in the two populations.

An additional test of the differences was made using paired observations where hematocrit matching was possible (Table 3). In 13 cases, hematocrit could be matched in Chile and Nepal to within 1% (Table 3). A paired t test showed that the difference in erythropoietin in the two groups (Chile 10.5 ± 4.8 mU/ml, Nepal 6.1 ± 5.6 mU/ml) is still significant ($P = 0.02$). When cases were

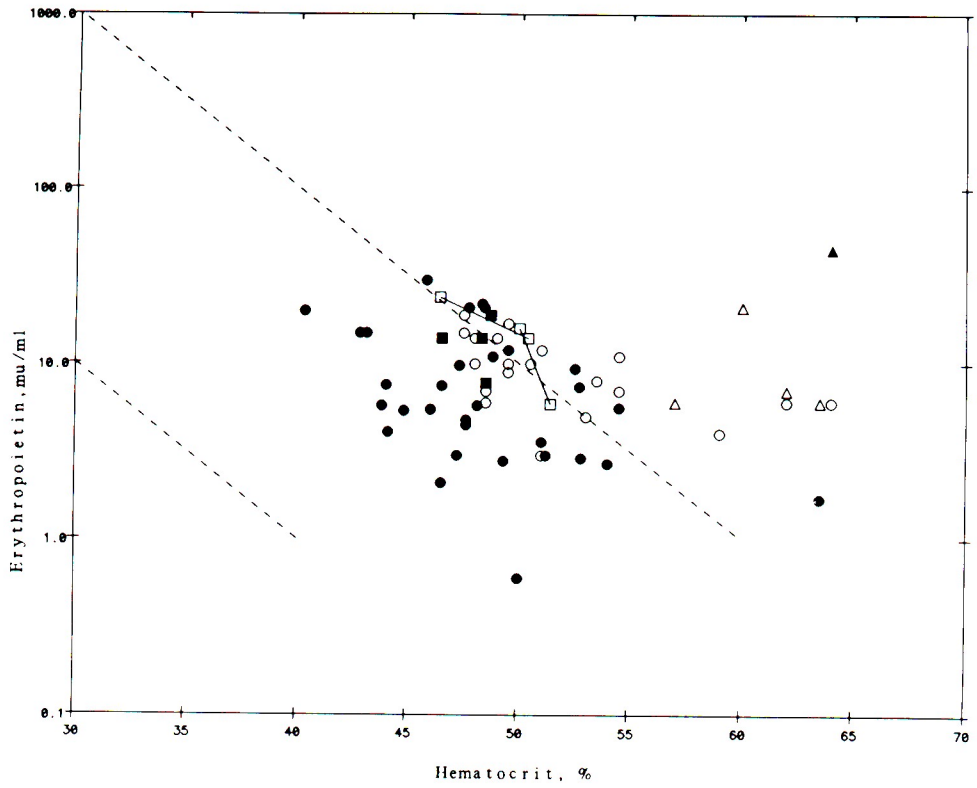

FIG. 2. Erythropoietin as a function of hematocrit for all subjects. Two Westerners (□) were studied immediately after arrival at 3,700 m altitude and again 2 wk later. They showed an appropriate suppression of erythropoietin as hematocrits rose. Dashed lines, sea level range of normal (9). ●, Nepal study subjects; ○, Chile study subjects; △, residents of Amincha (altitude 5,400 m); ■, low-altitude Sherpas, Nepal.

matched for hemoglobin concentration, the paired *t* test did not show a significant difference in erythropoietin concentration.

Erythrocyte osmotic fragility. To determine whether the erythrocytes of one of the populations may be more stable to lytic conditions, standard tests of osmotic fragility were performed and data from several controls are shown (Fig. 4). Although there does appear to be a small difference between the data for Quechuas and Sherpas, the curves still fall within the range of normal specified by the manufacturer of the test reagent and are very close to the curves measured for erythrocytes of two expedition members.

Whole blood O_2 equilibrium curves. At high altitude, even small shifts in the position of the whole blood O_2 equilibrium curves could significantly affect O_2 delivery to tissues and O_2 uptake in the lung. In Nepal, we used a method to measure the O_2 equilibrium curves that we have described previously (22) and which records the O_2 equilibrium curves over its full physiological range of P_{O_2}, 0–150 Torr, with pH, P_{CO_2}, and 2,3-DPG well-defined. We were not able to make the same measurements in Chile, but compared data for 14 Sherpas with those for 4 Westerners in Nepal who were well acclimatized to 3,700 m altitude.

The conditions for the measurements are shown in Table 4. All blood samples were equilibrated with 6.86% CO_2, giving a P_{CO_2} of ~29.7 Torr. Blood pH was measured in the deoxygenated condition.

The mean hematocrits and 2,3-DPG concentrations in the Sherpas and the Westerners selected for these studies are essentially the same.

The various parameters of the O_2 equilibrium curves for the two groups are virtually equivalent, including the four Adair constants, half-saturation O_2 concentration of hemoglobin (P_{50}), and Hill's parameter (n). P_{50} and n were also calculated by using predictive formulas for sea level residents (21). These predictions agree well with the observed values. The median ligand concentration is also very close to the observed P_{50}, suggesting that the curves are symmetrical (24).

These findings confirm the earlier findings of Samaja et al. (14) that there are no unusual factors controlling O_2 affinity of Sherpa blood. Taken together with our similar data in Quechuas (20), these results exclude the possibility that differences in erythrocyte O_2 transport mechanisms such as mutant hemoglobins or other effectors of hemoglobin function might explain differences between Sherpas and Quechua Indians.

Acid-base status. Table 4 compares the acid-base status of Sherpas, Quechua Indians, and several expedition members whose blood was taken after at least 3-wk acclimatization in Nepal. Our data do not permit comparison of P_{O_2} and P_{CO_2}, because arterial sampling was not possible in Nepal. Instead, the figures from Nepal are for blood samples equilibrated with N_2-6.86% CO_2. Base excess was calculated from the resulting pH by using the algorithms of Thomas (16) as modified by Winslow (18), which include consideration of the buffering of hemoglobin and the effect of hemoglobin saturation. The results show that the Sherpas are slightly more alkalotic than the Quechua Indians, but the base excess figures are very close. We believe these results indicate there is no essential difference in the acid-base response to hypoxia in the two populations.

DISCUSSION

Geographic and cultural differences restrict the selection of strictly comparable population samples in the

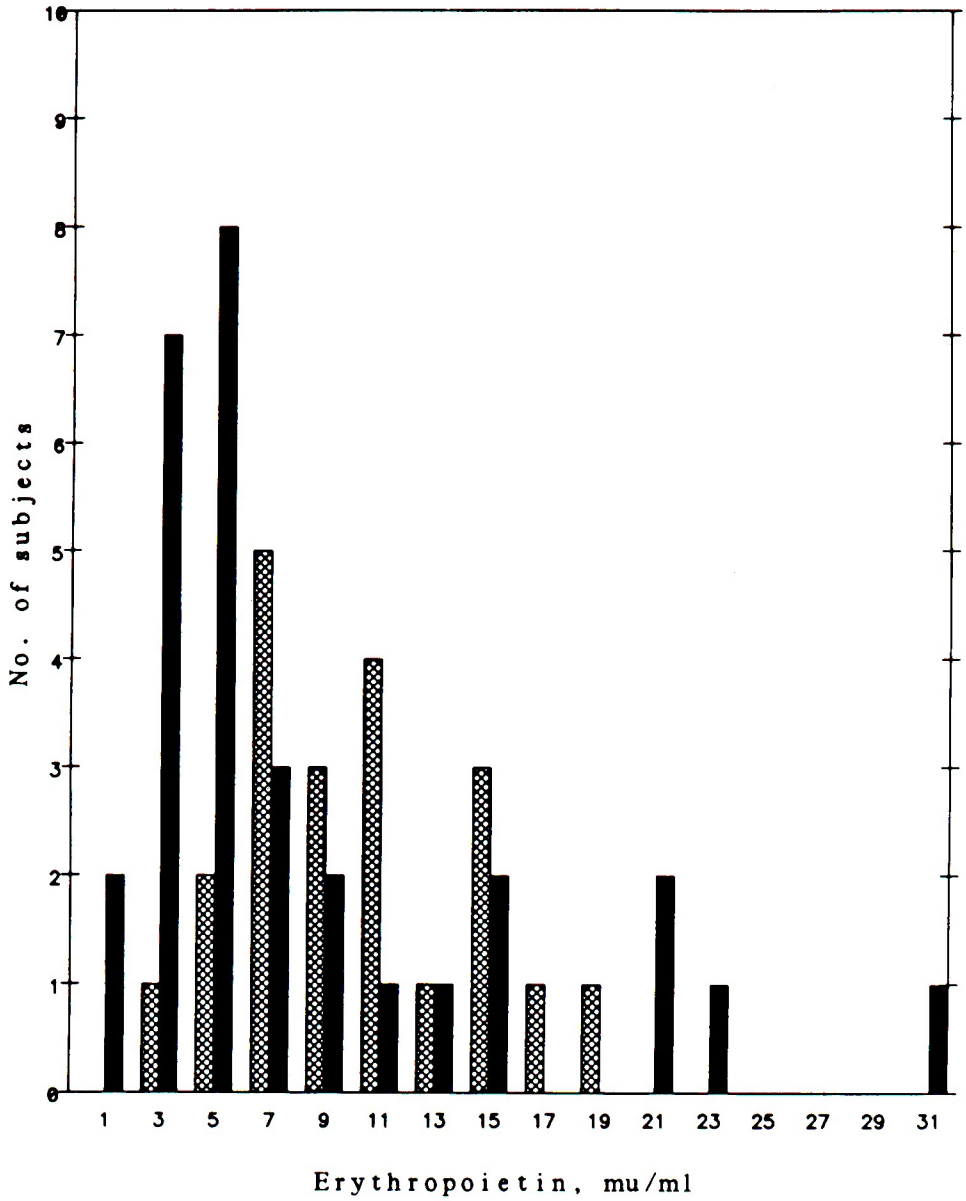

FIG. 3. Erythropoietin distributions in Nepal and Chile. Only study subjects are included. Closed bars, Nepal; cross-hatched bars, Chile.

TABLE 3. *Paired erythropoietin measurements*

Hct, %	Erythropoietin, mU/ml		
	Chile	Nepal	
47.5	19.0	21.0	
47.5	15.0	4.8	
48.0	14.0	4.5	
48.5	7.0	11.0	
48.5	6.0	5.8	
49.5	9.0	12.0	
49.5	17.0	2.8	
50.5	10.0	0.6	
51.0	3.0	3.6	
51.0	12.0	3.0	
54.5	7.0	5.6	
54.5	11.0	2.7	
64.0	6.0	1.7	
Mean±SD	10.5±4.8	6.1±5.6	$P < 0.02$

$n = 13$ subjs. Hct, hematocrit.

Andes and Himalayas. The climatic conditions in the Andean altiplano are extremely arid and constant over the year; the Himalayas are more vertical, with a marked seasonality. Therefore, although the study subjects were native to the same altitude, it is impossible to know the exact mean exposure to hypoxia. Our subjective impression was that native residents in Nepal are more likely to move vertically than those in the Andes, and they may have a more intermittent exposure to hypoxia.

There are no roads for motor vehicles in the Khumbu region of Nepal. Natives travel by foot and loads are carried either by porters or by heavy domestic animals. Most of the natives are employed as porters, trekking guides, or as farmers. Heavy rains fall during the monsoon and natives tend to remain in their villages. Over the remainder of the year, trekking is very active, bringing not only income but, to an increasing degree, Western habits of living, eating, dressing, and Western values.

In contrast, Andean natives tend to remain at their

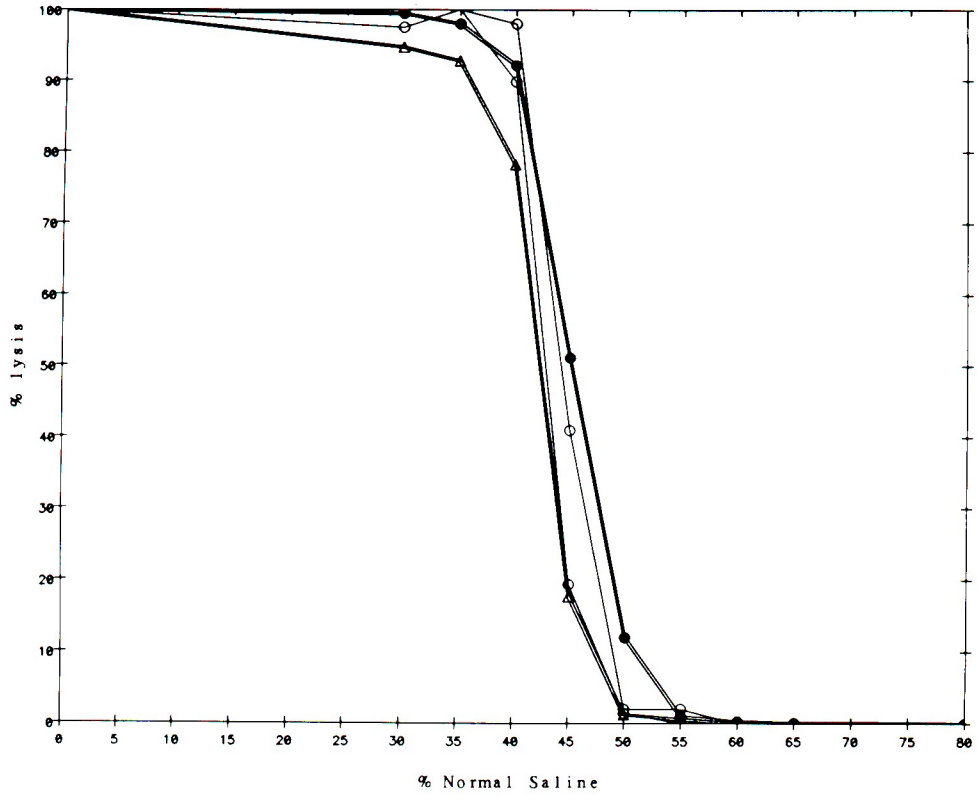

FIG. 4. Osmotic fragility of erythrocytes. All measurements fall within normal limits specified by manufacturer of test reagents. ○, Western expedition members; ●, Chile subjects; △, Nepal subjects.

TABLE 4. *Blood oxygen affinity and acid-base status at 37°C*

	Quechuas	Sherpas	Westerners in Nepal
n	20	14	4
Hct, %	52.2±4.6	49.2±3.2	48.7±2.0
P_{CO_2}, Torr	29.8±3.3	29.7±0.1	29.7±0.1
pH	7.399±0.021	7.431±0.060	7.448±0.020
P_{O_2}, Torr	57.3±4.9	0	0
BE, meq/l	−5.3	−6.5	−5.4
2,3-DPG/Hb, mol/mol		1.010±0.205	1.035±0.147
a_1, $\times 10^{-2}$		1.64±0.82	1.73±0.59
a_2, $\times 10^{-3}$		1.14±0.32	1.00±0.19
a_3		0	0
a_4, $\times 10^{-6}$		1.61±0.34	1.50±0.28
P_{50}, Torr			
Observed		29.81±1.88	30.34±1.21
Predicted		28.46±1.95	28.47±1.19
N			
Observed		2.55±0.12	2.58±0.07
Predicted		2.64±0.04	2.65±0.02
Pm, Torr		28.23±1.88	28.64±1.26

Values are means ± SD, except Adair parameters (a_1–a_4), which are means ± SE. Hct, hematocrit; BE, base excess; P_{50}, half-saturation O_2 concn of hemoglobin; *N*, Hill's parameter; Pm, median ligand concn.

altitude of residence for extended periods of time. Their work does not require travel, because it is mainly mining, herding, and farming. When travel is required, transportation by bus and rail is readily available. There is little climatic variation in this region. These geographic and cultural differences might have serious implications for the interpretation of comparative results. Our populations were specifically selected to be controlled in as many ways as possible. Thus, no individuals were selected for the comparative study in Chile who had ever worked in the mines. Moreover, age matching is extremely important, because chronic mountain sickness in the Andes has been associated with increasing age (19).

Our results generally support the previous findings of Beall (3–5) that hematocrits tend to be lower in Sherpas than in Quechua Indians in spite of the slightly lower barometric pressure in Khunde compared with Ollagüe. It is interesting, however, that the difference in hemoglobin concentration is less significant, and that no difference in erythrocyte counts could be demonstrated. Although we believe the hematocrit measurements in our studies are more accurate than either hemoglobin concentration or erythrocyte counts, this result implies that the erythrocytes of Quechua Indians are slightly larger than those of Sherpas.

Beall has interpreted the lower hematocrits in Nepal as showing a greater degree of adaptation in Sherpas. Our finding of lower erythropoietin concentrations at equivalent hematocrits in Sherpas suggests that their erythropoietic response to hypoxia is more adequate than the Quechua Indians'. Thus, although the Indians' hematocrits are higher than the Sherpas', they may still be functionally anemic.

In the absence of a clear demonstration of an advantage of a 4% lower hematocrit value in the Sherpas, their superior adaptation will be difficult to prove. We have argued, on the basis of hemodilution studies, that even mild erythrocytosis may serve no useful physiological purpose (19). We also have the clinical impression that

Sherpas suffer less from the stress of altitude than do Quechua Indians. A clear explanation for the lower hematocrit and hemoglobin values in Nepal compared with Chile cannot be determined from our data. Simple nutritional differences might be expected to be apparent in the mean cell hemoglobin concentration, mean cell hemoglobin, or mean cell volume, in the case of iron deficiency. Our data provide only a suggestion (without statistical significance) that the erythrocytes in Sherpas contain slightly less hemoglobin than those in the Quechuas we studied.

Two possible causes for reduced erythrocyte hemoglobin are iron deficiency and α-thalassemia. We have no evidence for either, but previous surveys in the Khumbu region of Nepal (1, 2, 5) and in the Peruvian Andes (19) have failed to reveal iron deficiency. α-Thalassemia is a particularly attractive hypothesis, because it has a genetic basis. Deletion of a single α-globin gene could lead to the results we observed in Nepal: smaller erythrocytes with slightly reduced hemoglobin content. These small cells could have a low viscosity for a given hematocrit (J. P. Crowley, J. B. Metzger, E. W. Merrill, and C. R. Valeri, personal communication) and, therefore, they would be expected to have favorable flow properties and enhanced O_2 delivery (higher hemoglobin/unit volume at the same viscosity). In any case, deficient hemoglobin synthesis resulting from either iron deficiency or α-thalassemia is unlikely because erythropoietin would be expected to be higher, not lower, than in Quechua Indians.

If the hematopoietic response to hypoxia is different in Sherpas and Quechua Indians, there are several possible control points, which suggest specific studies to demonstrate them. First, the stimulus to erythropoiesis could be less in the population with lower hematocrit (Sherpas). This could occur because of a higher alveolar P_{O_2} as the result of differences in ventilation, higher arterial P_{O_2} because of differences in pulmonary diffusion, or differences in the ventilatory response to exercise, hypoxia, or during sleep. Second, the response of erythropoietin production to a given level of O_2 stimulation could be different. Finally, the effect of erythropoietin on the stimulation of erythrocyte production could be different, either because of differences in erythropoietin itself, its biological effects, or to differences in erythrocyte production.

In sea-level subjects, secondary polycythemia is associated with elevated erythropoietin (1, 17), indicating that erythrocytosis does not completely compensate for hypoxia. Our results, both in Nepal and Chile, generally suggest that in most of our high-altitude subjects erythropoiesis is appropriate to the degree of hypoxia. When hematocrits are extremely high (see Fig. 2), however, erythropoietin tends to rise, consistent with our earlier hypothesis (19) that erythrocytosis in high-altitude natives may lead to further hypoxia. Our single case of chronic mountain sickness in Chile may represent the pathological end point in this "vicious cycle" (19).

Hematocrits <50%, whether in Chile or Nepal, are associated with elevated erythropoietin levels. Our data cannot establish a "normal" erythropoietin concentration in either of these populations, but they do suggest that above a hematocrit of ~52% the erythropoietin concentration is stable, around a mean of about 4–5 mU/ml. For most subjects, therefore, a hematocrit of between 50 and 55% seems to be normal for the altitude (3,700 m). This agrees quite well with our previous observations at Cerro de Pasco (4,200 m) where the median hematocrit is about 52% (19).

The data also show that many subjects in Nepal who have hematocrits <47% have elevated erythropoietin and are therefore still hypoxic. What limits the erythrocyte production in these subjects? Our studies do not answer this question, but attention should be directed at the ability of the bone marrow to produce erythrocytes at high altitude, including nutritional factors necessary for hemoglobin and erythrocyte production.

Finally, the rate of turnover of erythropoietin could play a role in the different mean levels found in the two populations we studied. Whether or not such differences exist must await development of methods to measure turnover.

Our studies do not provide information on the possibility that Sherpas are better adapted to moderate altitude than Quechua Indians. Of interest would be measurements of erythropoietin and O_2 transport in the two populations residing at sea level. Studies of the control of ventilation at rest, during exercise, and sleep would also be valuable in evaluating the possibility of genetic adaptation.

The authors are grateful to CODELCO for help in transportation of equipment in Chile and to Corning Instruments for the use of the blood gas analyzer. In Chile, Drs. Arraya and Stoppel were indispensable in planning and organizing our subjects, as were Bobby Chetri and Pasang Kami in Nepal.

This work was supported in part by Grant PCM-84-16125 from the National Science Foundation and by a grant from the National Geographic Society.

The views presented herein are the private opinions of the authors and not of the US Army or Department of Defense.

This work was presented in abstract form at the American Physiological Society Meeting, May 1988.

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Received 27 June 1988; accepted in final form 19 October 1988.

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