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Adaptation, Aging and Disease Epidemiology in High Altitude Population of Ladakh

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While altitude acclimatization refers to the physiological responses that takes place on ascending to hypobaric hypoxic high altitude environment; adaptation is both genetic and non-genetic, consisting of physiological, biochemical or behavioral adjustments. Average hemoglobin of 17.46 (± 2.18) g/dl and SpO_2 84 % (± 9.5 %) found in natives of korzok (4550 m) is a well known response to low oxygen saturation. However a substantially higher value of FEVI/FVC and MMEF in these highlanders was a surprise finding. About 2% of korzok men develop chronic mountain sickness at about 48 years, a condition of accelerated ageing due to decreasing hypoventilatory drive following prolonged stay at altitude. CAVI shows extreme increase with age in some high altitude natives. Changing disease ecology comparing contemporary scenario with historical perspective indicates a marked rural- urban distinction. Nutritional factor, poor food and water hygiene, poor health care facilities, high risk diet, environmental dust and domestic fire pollution are responsible for high prevalence of upper GI and hepatobiliary cancers and poor respiratory health in rural population. Obesity, diabetes, coronary heart disease and vehicular accidents are the main disease burden in the urban population. High prevalence of HBV carriers (8 %) in rural population and *H. pylori* acquisition in (95 % of population) resulting in high prevalence of chronic liver disease, liver cancers and cancer of the stomach are cause of concern in the contemporary disease epidemiology.

Introduction

Adaptation to life at high altitude is a matter of optimization of oxygen delivery to the metabolizing cells. It has physiological and genetic component. The study of fitness for survival in this wild population is best carried out in the field and in matching environment. We therefore studied population of Korzok, a village on the bank of the lake Tsomoriri at an altitude of 4450m in Ladakh in the Indian Himalaya[1,2)] .

Materials and Methods

We initially studied a total of 574 subjects, men and women, ranging in age from 17-82 residing at differing altitude[3)] . We examined their pulmonary function as a function of age, gender and altitude. Hemoglobin concentration, blood pressure, heart rate, arterial saturation and end-tidal PCO_2 were measured in them as physiological functions related to high altitude life.

Results

Hemoglobin was determined on blood obtained from venipuncture using a portable, battery powered photometer (Hemocue AB, Sweden) calibrated to an accuracy of ± 0.3g/dl. End-tidal PCO_2, pulse oximetry, (SpO_2); respiratory rate, and pulse rate were measured using a portable battery powered capnograph (Nelicor Puritan Bennett NPB-75). Blood pressure was measured using a sphygmomanometer. Pulmonary function test was performed using a portable battery powered spirometer (Microloop; micromedical UK). This is a fixed orifice Spirometer that utilizes turbine technology. Accuracy is ± 3%. In addition to measured values of lung volume and flows, the spirometer provided data on predicted values based on age, height, race (Caucasian or non- Caucasian) and gender referenced to normal values published by the European coal and steel community (ECCS)[4)] . Individuals from other races tend to have smaller lung volume for the same height and age, a factor adjusted

Table 1　Study subjects and site in the preliminary study

Village	Height	Women (age range)	Men (age range)
Tibetan refugee camp near Leh	3300m	70 (23-83)	46 (24-79)
Phey village	3300m	55 (20-85)	17 (20-81)
Chumathang village	4193m	47 (20-81)	29 (20-82)
Lake Tatsangkaru	4540m	57 (17-83)	38 (23-80)
Korzok village	4550m	70 (16-77)	84 (18-78)

for the microloop spirometer by multiplying final values by an adjustment factor of 0.9. Pulmonary function tests were remarkable in all parameters except for peak expiratory flow. Finding PEF values not higher than predicted was surprising, given that reduced air density at high altitude should result in higher than predicted peak flows. In contrast the, the forced expiratory volume in 1second (FEV1) and the mid-maximal expiratory flow (MMEF) were significantly elevated in both Ladakhis and Tibetans compared to % predicted for any race or to sojourners. As it is measured when the lung is about half empty, MMEF describes the function of the mid size airways and , because it is presumed to be independent of effort, a reliable indicator of lung mechanics per se. such improved lung mechanics could be an important adaptation to the sustained high levels of ventilation of these populations at high altitude by reducing the work of breathing. Both FEV1 and forced vital capacity (FVC) were significantly higher than predicted in both Tibetans and Ladakhis at each altitude except for Tibetan women at 3300 m. (Table 2)

Hemoglobin was highly variable in our subjects but generally elevated as seen in other high altitude natives. We found that 21/141 men studied (15%) had excessive polycythemia (Hb over 20 gm/dl). A 60 degree head up tilt (HUT) was carried out on eight men from korzok with or without CMS as a test of baroreceptor function mainly to study autonomic nervous system function at high altitude. All but one of the eight subjects showed remarkable orthostatic tolerance test. During HUT, cardiac output temporarily falls because of pooling of blood below the heart. To maintain adequate blood flow in the coronaries, there is an immediate vasodilatation initiated by endothelial mechanism. Additionally a variety of baroreceptor induced vasoconstrictor mechanism comes into play in different vascular beds, to maintain blood pressure and support blood flow to vital tissues such as the heart and the brain.

Genetic Adaptation: we studied Himalayan highlanders living at 4450 m of Korzok village in Ladakh, among the male subjects who were studied for adaptation. We excluded subjects with significant acute or chronic clinical condition or those that had visited altitude below 2000m in the three months preceding the study. Venous blood samples were obtained for hemoglobin and hematocrit determination and for RNA assays. 8 male subjects with chronic mountain sickness and 5 male controls from the same village were taken up for the study. They were studied first in the ambient air and the after exposure for one hour to hyperoxia at the same altitude (Fig 1). Blood samples were obtained before and after 1 hour of hyperoxia and immediately transferred to appropriate tubes for RNA Analysis. (Details of the hyperoxia procedure and RNA analysis mentioned elsewhere[8] .

This study was a part of a collaborative study carried out in Andeans, African highlanders (Ethiopia) and Himalayas (Korzok Ladakh). Molecular signatures (distinct patterns of gene expression) of hypoxia related genes, in white blood cells from Andeans with (n=10) and without CMS (n=10) and sea-level controls from Lima (n=20) were compared with those obtained from CMS (n=8) and control (n=5) from Indian Himalyan

Table 2 Mean values of Hemoglobin, SaO2 and P.F.T in Ladakhi men at different altitudes.

Place	Altitude (in mts)	Age	SaO_2	Hb	FEV_1	FVC	FEV_1/FVC Ratio
Leh	3357	52 (46)	91.89 (46)	15.48 (46)	2.88 (39)	3.17 (40)	91.26 (39)
Chumathang	4193	51 (29)	87.21 (29)	16.87 (29)	3.00 (26)	3.14 (26)	95.62 (26)
Sumdo-Chumur	4540	45 (38)	83.37 (38)	17.82 (38)	3.14 (34)	3.61 (34)	94.82 (34)
Korzok	4647	39 (84)	85.50 (84)	17.97 (84)	3.31 (53)	3.61 (53)	92.94 (51)


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If You Can't Take the Height, Get Off the Mountain

By Andrea Lu
ScienceNOW Daily News
17 June 2008

Life at high altitudes isn't easy. The thin mountain air can cause a slew of health problems, even for people who have lived at elevation for centuries. Some groups fare better than others, however, and researchers now think they've found one reason: varying expression levels of a gene called *PDP2*, which codes for a protein that helps transform food to fuel.

Taking a breather. Himalayan subjects suck in oxygen as part of the study.

CREDIT: OTTO APPENZELLER

Many groups have adapted to low oxygen levels at high altitudes by boosting their production of red blood cells, which carry oxygen to the body's tissues. The strategy comes at a cost: All of those cells can thicken the blood and impede its flow, leading to headaches, fatigue, insomnia, and memory impairment. Susceptibility to the condition, known as chronic mountain sickness (CMS), varies among populations. A team of researchers led by neuroscientist Otto Appenzeller of the New Mexico Health Enhancement and Marathon Clinics Research Foundation wanted to find out why.

Figure 1 Hyperoxia in a tent at 4450 m, on the Tibetan plateau, at Korzok village in Ladakh, India

Korzok Ladakh. We further analyzed the expression of a subset of these genes in Ethopian highlanders (n=8). In all subjects, we performed the studies at their native altitude and after they were rendered normoxic. We identified a gene that predicted CMS is Andeans and Himalayans (PDP2). To assess the impact of specific genes on the CMS scores, using a sliding scale of CMS-scores derived from both controls and CMS patients, an "impact table " was constructed for the cerrro de pasco groups at altitude and at Lima. A linear regression model shows that the best predictor of CMS in this population is the expression of PPD2, a gene encoding a protein phosphatase that de-phosphorylates the EI-alpha subunit of pyruvate dehydrogenase and thus promotes pyruvate entry into the Krebs cycle. A similar table was constructed for our Himalayan subjects while at their resident altitude breathing ambient air. The best predictor of CMS in a linear regression model in the Himalayas is also PDP2. This supports the importance of PDP2 in predicting CMS. After achieving normoxia, WBC gene expression still distinguished Andean and Himalayan CMS subjects. Remarkably, analysis of the small subset of genes (n=8) studied in all 3 highland populations showed normoxia induced gene expression changes in Andeans, but not in Ethiopians nor Himalayan controls. This is consistent with physiologic studies in which Ethiopians and Himalayans show a lack of responsiveness to hypoxia of the cerebral circulation and of the hypoxic ventilatory drive, and with the absence of CMS on the East African altitude plateau.

Chronic mountain sickness: After completing the pattern of cardio-pulmonary function at different altitude in the Indian Himalayan population of Ladakh, we studied the male population of Korzok exclusively, (alt. 4450 m; n=91) with a view to look for the prevalence of chronic mountain sickness in the Indian Himalayas and to study physiological and genetic factors responsible for adaptation and maladaptation.

Criteria for inclusion were all men aged 18 and above who were borne at that altitude and who had not lived at low altitude for more than three months during the previous year. Chronic mountain sickness (CMS) is a clinical syndrome that occurs in native or life long residents above 2500m. it is characterized by excessive erythrocytosis (female, Hb ≥ 19 g/dl; male ≥ 21g/dl), severe hypoxemia, and in some cases moderate or severe pulmonary hypertension, which may evolve to cor pulmonale, leading to congestive heart failure. The clinical picture of CMS gradually disappears after descending to low altitude and reappears after returning to high altitude.

Questionnaire of sign and symptoms designed by CMS scoring of international consensus group was administered. Dilatation of veins in hands and feet (61%), cyanosis of lips, face and fingers (59%) dizziness (53%) injected conjunctivae (40%) and headache (34%) were the common features. The prevalence of the various signs and symptoms making up the CMS score in the Himalayas was significantly different from that found earlier in the Andes. (Fig 2) This suggests the need for a better scoring system specifically for the Himalayas.

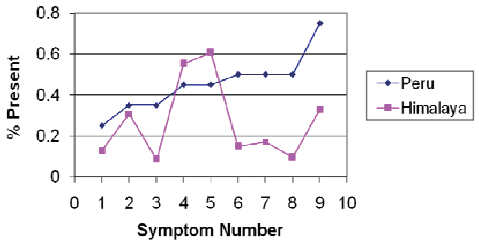
The 2% of our subjects had severe; 7% moderate; and 16% had mild CMS scoring. Altitude hypoxia and hypoventilation result in low PaO_2. This hypoventilatory response may be due to low hypoxic ventilatory response. Aging results in both reduced lung function and reduced hypoxic ventilatory response, especially in a life spent at high altitude, thus further lowering the PaO_2. The low PaO_2 results in low SaO_2. It also stimulates secretion of erythropoietin and hence an increase in packed cell volume.

Table 3 Detail demographic features of the Korzok population (n=91)

	Mean	Std Dev (±)
Age	42.2	14
BMI	23.4	3.1
SaO_2 (%)	84.2	4.5
CMS score	8.3	6.4
SPB (mmHg)	124.3	19.4
DBP (mmHg)	82.1	11.9
Heart Rate /min	75.9	12.3
pH	7.4	0.02
$PaCO_2$	29.8	2.9
PaO_2	42.1	4.7
Lactate (mmol/L)	0.8	0.3
HCO_3	19.4	1.8
TCO_2	20.4	1.9
BE	- 5.1	2
Na	139.8	1.8
K	4.2	0.4
Cl	107.2	1.8
BUN	14.1	4.1
Glucose	97.6	20.5
Hct	53	6.8
Hb	18.1	2

Ageing: A typical case description of one of our CMS patient represents the classical features of CMS as well as depicts the syndrome as an accelerated aging process in certain percentage of highlander male population. The 53 year old man born & lived all his life in Korzok (4554 m), a non smoker, non obese (BMI 23), with no thoracic cage deformities, no H/o COPD or congenital heart disease. Until 45 years, he was amongst fittest highlander, managed horse, cattle & live stocks efficiently. At 48 years he develops symptoms of CMS and his parameters were as Table 4.

Doppler on Common Carotid and Brachial Artery revealed, normal intima media thickness in this subject Echo showed mild AR trivial TR and concentric RVH/ LVH. We assessed the neurocardiovascular function of 40 residents older than 70 years (19 men and 21 women; mean age 74.7 ± 3.3 years) and compared the findings with 324 elderly citizens (97men; and 227 women, mean age: 80.7 ± 4.7years) living in Tosa town , kochi, Japan (altitude: 250m) [5] Although high-altitude residents had a lower SpO_2, a higher respiratory rate, an increased diastolic Blood pressure and a larger increase in heart rate with postural change from the supine to the standing position, there was no difference in PWV. A correlation of CAVI with age, however shows that several subjects have very high CAVI



Symptoms (Signs) Number for CMS scores in the Peruvian Andes (4338 m. Peru) and Himalayan (4450 m.)

1-SaO2 (±2SD) below normal for altitude;
2-Breathlesness, palpitations;
3-Sleep disturbances;
4-Cyanosis of lips, face or fingers;
5-dilated veins;
6-Paresthesias in fingers and/or toes;
7-Tinnitus;
8-Hb (±2SD) above normal for altitude;
9-Headache.
*Denotes significant differences.

Figure 2 % Present by symptom by Location

Table 4 Parameters of a typical case of CMS

CMS	BP	Hb	SpO2	SaO2	Hct	pH	pCO2	pO2
score 26	140/100 mm Hg	24.6 gm/dl	73 %	68 %	>75 %	7.39	32.8	35
Lactate	HCO3	TCO2	BE	Na	K	Glucose		
1.02	20	21	(-5)	144	3.8	(fasting) 87/90		

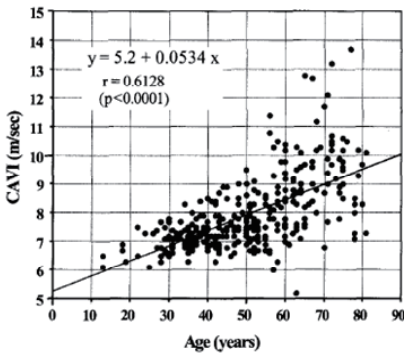


Figure 3 Correlation between PWV, gauged by CAVI, and age in high-altitude residents of Leh, Ladakh. CAVI increases linearly with age. Several citizens show very high values of CAVI, however. For the prevention of adverse cardiovascular outcomes, including myocardial infarction, stroke and dementia, this measure of PWV could be very useful, especially in high-altitude populations.

values.(Figure 2). There are several cases who show an extreme increase in CAVI.

Changing Disease Epidemiology

Leh, the capital town of district Ladakh is located on an alluvial fan. To the east of Leh on either bank of Indus river is an alluvial plain stretching over an area

of 30 square kilometers. (Indus Valley) This is the most fertile level land where several rural settlements of Ladakh are located. During the last thirty years the vast stretch between Leh and these rural villages have been colonized by rural people representing most of the villages of district Ladakh. These new settlements, an urbanization process, having come in search of better job opportunities and civic amenities are now rapidly adopting a western model of life style threatening an impending disease of the new millennium.

Contemporary scenario & historical perspective:

In a comparative disease scenario between 1867 and 2001; Dr. Rais Aktar has researched into incidence of disease in Leh in the month of July and August in 1867 & 2001 (Table 5, 6). This data and his paper[6,7] raises some interesting question besides highlighting the importance of socio-economic and cultural practices in occurrence of disease in the middle of the nineteenth century and those which occur at present. While the sources of the data are reliable being made by responsible professionals of that time, we can make some inferences.

Until middle of the twentieth century, maintaining cleanliness of the water in streams, springs, canals and rivers was practiced with cultural and religion devotion; it is not surprising therefore that occurrence of dysentery occupies almost the last position in 1867 disease pattern. Opening of the Leh - Srinagar; Leh - Manali road, in 1970's, speeding up of development work and influx of labourers, tourists and traders in late part of 20th century brought in deterioration in environmental cleanliness and an unaware society realized its impact in July - August of 1991, when Leh and its surrounding villages experienced the first ever epidemic of cholera affecting 112 patients with one mortality. (Norboo, personal observation)

Trend in incidence of cancer in Ladakh: Caley's data in 1867 reports 6 cases of carcinoma in Leh seen

Table 5 Leh District: Incidence of diseases (Up to July, 2000 - 01)

Disease	No of Cases
Respiratory Tract Infection (RTI)	11957
Dental	9123
Acute Diarrhea	6828
Hyperacidity	3397
Ophthalmic cases (other than cataract)	2670
Skin problem	1861
ENT	1369
Hypertension	1042
Mumps	0333
T.B.	0073
Chicken pox	0076
Leprosy	0003
STD	0001

Source: Chief medical officer, Leh

Table 6 Leh: Incidence of disease (July - August, 1867)

Diseases	No. of cases	Disease	No. of cases
Fever	66	Constipation	2
Dyspepsia	61	Lepra	2
Ophthalmic	45	Anemia	1
Rheumatism	38	Scabies	1
Caries of teeth	32	Hepatitis	1
Syphilis	25	Frostbite	1
Neuralgia	17	Sinus	1
Ulcer	16	Eczema	1
Bronchitis	16	Dysentery	3
Gonorrhea	8	Laryngitis	3
Cataract	7	Fatty tumours	2
Carcinoma	6	Tonsillitis	2
Entropion	4	Paralysis	4

Source: Cayley, H, 1868

in the month of July-August. Though no mention is made of the organ affected, stomach and liver could very well be the probable site as dyspepsia is on the list of the first two of common disease that time. During the last three decades doctors in Ladakh have been increasingly diagnosing cancers of various organs of which cancer of upper and lower Gastrointestinal tract and hepatobiliary system forms 61% of the cancer.

Helicobacter Pylori colonization in Ladakhi Population: Being one of the isolated populations with poor socio-economic status and food hygiene, we presumed that H. Pylori colonisation will be high in this population. We therefore examined 189 patients (117 women and 72 men with a mean age of 38 ± 12 years, age range 12-75 years) reporting with gastrointestinal symptoms. Sera was obtained from all 189 patients and endoscopy with biopsy was performed on 102 patients[8)] . For comparative purposes, sera from 50 US patients from Nashville were taken who' s *H. pylori* status was known. Of these 20 persons were not carrying *H. pylori*, 30 were *H. pylori* positive with 15 persons in the latter group carrying cagA positive strains and 15 carrying cagA negative strains. Gastric biopsy specimens from Ladakh collected in sterile microcentrifuge tubes maintained and transported on dry ice to laboratory in Nashville was submitted for culture on selective media. The antigens present in the *H. pylori* strains from Ladakhi patients were assessed by western blotting details described elsewhere[8)] . The antigens present in Ladakhi *H. pylori* antigen were assessed by immunoblotting with sera from both Ladakhi (n=11) and US (n=2) patients. The sera from the Ladakhi and US patients recognized the same band in both preparations. Since these findings confirmed our general expectations, we next examined the utility of Ladakhi antigen in an ELISA format for the screening of human serological responses to *H. pylori*. As shown in table 8 and 9, the value of serology with the *H. pylori* whole cell antigen and cagA antigen is additive. When the results of the assays with the whole cell and cagA antigen are combined, use of essay with the cagA antigen complemented use of essay with the US antigen as well as use of the essay with the Ladakhi antigen. There were clearly persons who were *H. pylori* culture positive who responded only to the cagA antigen and not to either the US (26%) or the Ladakh (7%) whole cell antigen thus these data indicate that the use of both the whole cell and cagA antigens is more accurate way to diagnose *H. pylori* infection than use of either antigen alone. That nearly all (95.8%) patients were *H. pylori* positive (and carried cagA positive strains) is not only typical for a preindustrial society but also explains the high prevalence of Adenocarcinoma of the stomach at a relatively much younger age.

Table 7 Evaluation of *H. pylori* antigen from Ladakh or U.S. strains in 50 U.S. patients of known *H. pylori* status.

H. *Pylori* status of Patient[a]	No. of patients Studied	No. of patients positive		
		U.S. antigen		Ladakh
		CagA[b]	*H. pylori*[c]	*H. pylori* antigen[c]
H. *pylori* -	20	0	0	1
H. *Pylori* +, Cag +	15	15	15	15
H. Pylori +, Cag -	15	0	15	14

[a] As determined by culture of gastric biopsy specimens and cag*A* PCR (9,11,13).

[b] The CagA antigen is pORV220, a recombinant 66-kDa CagA fragment expressed by E. coli cells (3).

[c] The U.S. antigen is from a pool of five isolates from U.S. patients (14,19), and the Ladakh antigen is from a pool of four isolates from Ladakhi patients.

Table 8 *H. pylori* serological status of 189 persons from Ladakh in relation to antigens used for serological testing.

Serological status		U.S. *H. pylori* antigen[b]		Ladakh *H. pylori* antigen[b]	
H. *pylori* antigen	CagA[a]	No. of Patients	% of patients	No. of patients	% of Patients
+	+	119	63	150	79
+	-	11	6	14	7
-	+	48	26	17	9
-	-	11	5	8	4

[a] The CagA antigen is a recombinant 66-kDa fragment expressed in E. coli (3).

[b] The U.S. antige is from a pool of five isolates from U.S. patients (25,26), and the Ladakh antigen is from a pool of four isolates from Ladakhi patients.

Table 9 Serology of 102 Ladakhi patients of known *H. pylori* cultural status.

Serological status			No. of patients by *H. pylori* Cultural status	
H. pylori antigen		CagA Antigen	Culture Positive	Cultural Negative
Ladakh	U.S.		(n = 68)	(n = 34)
+	+	+	45	17
+	+	-	2	3
+	-	+	13	5
+	-	-	1	2
-	+	+	0	1
-	+	-	0	0
-	-	+	5	3
-	-	-	2	3

[a] May be falsely negative due to specimen contamination.

A recent survey carried out by LIP during 2006-2009 revealed that 5.7% of the Ladakhi rural adult subjects are HBsAg positive (Table 10) and vertical transmission is the commonest mode of transmission. Occurrence of high prevalence of hepatocellular carcinoma in Ladakhi population is therefore not surprising.

Gall stones are frequent in Ladakh and the initial analysis on gall stones composition of ten subjects was found to be predominantly cholesterol. We studied women in the age range of 25-59 years in spituk village in central Ladakh (n=272) and a remote village Dha Hanu 80 km west of Leh (n=165) who' s language and diet are different[9] . The aim of the study were to find out the prevalence of gall stones in Ladakh using ultrasonography, to ascertain in Ladakh slow intestinal transit as judged by stool form is indeed prevalent and to find out if gall stone disease in Ladakh is associated with constipation or high pulse consumption. The data were then compared with those of Bristol. Gall stones were less prevalent in Dha Hanu-the more remote village than in spituk (11/165; women=6.7% v/s 37/272=13.6% respectively, P=0.025) This was despite the fact that in Dha Hanu, multiparity was commoner (59% of all women were para 4+, v/s 42% in spituk, P< 0.001). The distribution of stool type and defecation frequency was similar in two villages. The study demonstrated that Ladakhi women are prone to gall stone disease at an early age despite being uniformly slim. They have lumpier stools and therefore slower intestinal transit the women in England.

Geo-ecology of health in Ladakh: There is a strong linkage between geo-environmental condition and an epidemiological scenario in Ladakh. The Indus valley in Ladakh is subjected to periodic loess derived from dust carried mainly in the streams flowing down the

Table 10 Hepatitis B virus carrier status in rural and urban population of Ladakh, (Data from LIP study 2006 - 2009)

		Rural		Urban	
		Count	Column %	Count	Column %
HBs Ag	Negative	615	94.3%	434	98.4%
	Positive	37	**5.7%**	7	**1.6%**
	Total	**652**		**441**	

Table 11. Prevalence (%) of gallstone disease in four age groups of women in Bristol and in two villages in Ladakh. The figures in brackets represent the total number of women in each age group. Also shown is the median prevalence of gallstone disease in published series of European women [14]

Places	Age group (years)			
	25 – 29	30 – 39	40 – 49	50 - 59
Bristol	3.9 (305)	6.4 (328)	6.5 (199)	14.1 (142)
Ladakh – Spituk	7.0 (57)	**15.1 (93)**	**18.5 (81)**	9.8 (41)
Ladakh – Da Hanu	9.1 (33)	4.5 (67)	7.7 (52)	7.7 (13)
Significance	NS	*P*=0.013*	*P*=0.008*	NS
Europe – median	4%	6.5%	13%	21%

glacier water originating from trans-Himalayan range of mountains. Dust storms prevalent in this river valley belt bring in further load of dust from far and wide.

The inhabitants are further exposed to the domestic fire soot apart from inhaling the respirable particles of the environmental dust containing silicon dioxide and silicates particle of the range of 0.5-5µm in diameter. Simultaneous exposure of villagers to free silica and soot results in mixed dust Pneumoconiosis. There are no mines or industries in any part of Ladakh and therefore, exposure to dust from such source is ruled out.

Measurements and results: An epidemiological and clinico-radiological study carried out by NIOH Ahmedabad[10] on 449 randomly selected subjects (Aged over 30) from three villages of central Ladakh showed signs of Pneumoconiosis in 101 (22.5%). 90.1% of these showed small opacities (less than 1 cm) and 9.9 %of the opacities were greater than 1cm. Changes included progressive massive fibrosis and eggshell calcification of the hilar glands.

The prevalence of pneumoconiosis in these three villages was 2.1% (Sabu), 20.1% (Shey) and 45.3% (Chuchot Gongma) and it corresponded with the severity of the dust storms and the use of chimneys in the kitchen. The corresponding indoor respirable dust concentrations in these villages were 0.509, 0.861 and 7.495 mg/m^3, respectively. A similar study by Norboo et al [11] in another two central Ladakh villages on 40 randomly selected subjects (age group 50 -62 years) showed a prevalence of Pneumoconiosis of 60% with a higher incidence in women. The two studies proved that people in Ladakh do suffer from Non-occupational pneumoconiosis and that this may be so severe that progressive massive fibrosis can occur. In pursuing the matter further, dust samples deposited on the filters obtained with standard air sampling pumps positioned at different indoor and outdoor locations were analyzed in the department of Mining and Mineral engineering university college Cardiff for its single particle content, together with its chemical composition expressed as

Figure 4　Progressive massive fibrosis(PMF)

Figure 5　Egg Shell calcification

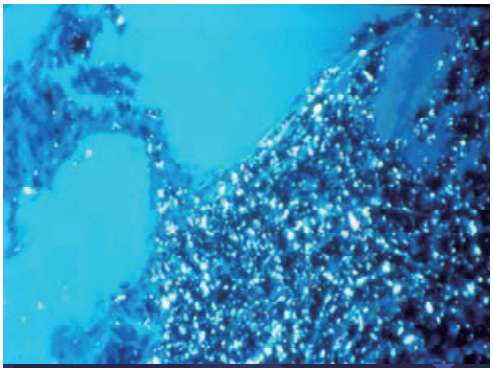


Figure 6　Microscopic examination of lungs with polarizing filters. Many birefringent particles seen among black dust.

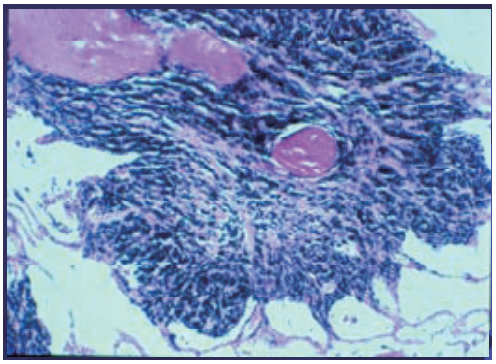


Figure 7　Microscopic examination of lymph node showing Whorled hyaline collagenous nodules.

oxide weight %. Weight of the dust on each filters and dust concentration exposure mg/m^3 analyzed and found to be significant in every location. The filters also showed significant difference in dust concentrations in kitchen with efficient chullas (stove) and smoky inefficient chullas and between dirt road and black topped roads thus giving a clear message for preventive measures.

Necropsy and histopathology of one subject from this area dying of violent death showed lung parenchyma studded with numerous black nodules measuring 1-2 mm across and a hilar lymph node measuring 1.5 mm across, black and hard. Microscopic examination of these materials showed that heavy deposition of black dust with polarizing filters showing many birefingent particles (Figure 6). The hilar lymphnodes were largely replaced by whorled hyaline collagenous nodules, the classic appearance of silicosis

(Figure 7).

Need for different public health approach in rural and urban population:

While a higher BMI, higher waist circumference, higher LDL level, lower HDL, relatively inactive population, indulging in tobacco smoking and rich unhealthy food in the urban population makes them susceptible to coronary heart diseases, type 2 diabetes mellitus, and metabolic syndrome. The study carried out by LIP on Neuro-cardiovascular epidemiology clearly indicates such trends with urban Muslims in particular and people with higher socio-economic status in general. A rural population of men and women indulging in regular locally brewed alcohol (chang), high prevalence (5.6%) of HBV carrier status, a higher colonization of *H. pylori* (95.0%) with deficient protective food (fresh vegetables and fruits) and higher altitude of stay makes the rural population more vulnerable to chronic liver disease, hepatocellular carcinoma, cancer of stomach, esophagus, and pancreas besides deficiency diseases, occupational and geo-ecological related diseases.

Conclusion

Natives of the Himalayas are borne and lives in a hypoxic environment The findings derived from studies of physiological adaptation and gene expression in hypoxic cells can have brought implication in clinical medicine at sea level like Alzheimer's disease, motore neurone disease, aging and cancers. *H. pylori* colonization of a pre-industrial population like Ladakh with familial transmission as predominant mode of spread in a crowded family condition with poor food hygiene demands a realistic preventive approach. High rate of HBV carrier status in a rural population with vertical transmission as predominant mode of spread demands universal immunization of hepatitis B in all age group. An impending disease of the new millennium in the urban Ladakh and occupational and neoplastic disease in a nutritionally deficient rural population demands separate preventive approaches.

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