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ACTA ANDINA

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EDITORIAL

More than 30 million people throughout the world live at altitudes about 3000 meters. Above these elevations, human health, productivity and survival are at their limits because the fall of oxygen pressure. The reduced partial pressure of oxygen characteristic of high terrestrial elevations produces a state of hypoxia which influences almost all systems of the body. Human adaptation to such environment stresses depends not only on physiological responses but also on socioecultural, demographic,a nd biological factors.

Despite the unfavorable conditions that exist at high altitude, humans have inhabitated the Andean zone of South America for millenia. In addition, the Central Andes was the site of the highest pre-hyspanic civilization in America, which supported a population numbering in the millions. After the tragic population decline following the spanish conquest, the Andes has now recovered to its pre-hyspanic population level; whereas native americans have become extint in many places of the hemysphere, in the Andes today the native Quechua and Aymara are a distinct numerical majority.

There has been more than 70 years since the first peruvian expedition to high altitude under the guidance of Prof. Carlos Monge Medrano. After that, numerous scientists particularly peruvian scientists provided invaluable knowledge and evidence that andean populations have achieved an important degree of adaptation to high altitude.

During the last 50 years many meetings related to high altitude physiology has been carried out around the world. However, it is the first time that a world congress is organized related to physiology and Medicine of high altitude which includes the different kinds of exposure to high altitude: acute, subacute, chronic, intermitent, and that related to natives at high altitude.

On September 11-16, 1994 was carried out the First World Congress on High Altitude Medicine and Physiology, in La Paz, Bolivia, presided by Dr John Triplett with the coordination of Dr Gustavo Zubieta, a Bolivian Researcher. This meeting was attended by researchers devoted to high altitude around the world.

The meeting was fruitful and the discussion enriched the studies. At the end of the meeting, it was suggested that conferences presented in the meeting should be published in Acta Andina after revision by peer reviewers.

At this time, Acta Andina has received most of the contributions of the speakers at the meeting, and we are in condition to publish all material sent to the journal in two issues.

The first part includes 14 papers, most of them are original and others are reviews.

The second part will be published in January 1996, and it will include the rest of the material we received, which is still in revision.

We would like to express our gratitude to all scientists who send their research papers and also for their cooperation and friendship.

The Editors

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¿LA HEMOGLOBINA, ES UN MARCADOR GENETICO INVARIABLE? HALLAZGOS EN LA GALLINA CRIOLLA ANDINA.[1]

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RESUMEN. La gallina doméstica (Gallus gallus) fue introducida en Sud-América con la conquista española. Esta (Gal-NM), presenta una baja afinidad de la hemoglobina por el O_2 (Hb-O_2) e hipereritremia. Sin embargo, hemos encontrado en Taraco (Puno, 4,000 m), y reproducido a nivel del mar, un grupo de gallinas con una alta afinidad de la Hb-O_2 y ausencia de hipereritremia (Gal-ALT). La afinidad de la Hb-O_2 (P_{50}) fue determinada por el método de las mezclas en sangre total y en Hb libre de fosfatos (Hb-lavada) antes y despúes de la adición de inositol hexafosfato (IHP). La adición del IHP se comportó de manera diferente en las dos hemoglobinas lavadas. La diferencia (Hb-lavada-Hb+IHP) fue 42.2 torr para Gal-NM y 26.3 torr para Gal-ALT, lo que es una indicación de que Hb de la Gal-ALT es fosfato-dependiente. Una mutación, Thr-->Ser, encontrada en la posición 69 de la cadena ß podría haber inducido la fosfato-dependencia. Nuestro hallazgo muestra un cambio genético en la función de la Hb, adquirido en un periodo evolutivo extremadamente corto, de aproximadamente 500 años; muestra también, que individuos de una misma especie, que viven a NM y en la altura, pueden diferenciarse genéticamente mediante un cambio en la función de la Hb como reflejo de un cambio en su estructura.

Palabras claves: altura, afinidad de la hemoglobina, gallina, inositol hexafosfato, mutación.

ABSTRACT. Chicken (Gallus gallus) were introduced in South America during the Spanish conquest and therefore their adaptation time to high altitude is approximately 500 years. A group of chicken from the Peruvian Andes (4,000m) carrying a high hemoglobin-oxygen affinity has been identified and reproduced at sea level. The hemoglobin-oxygen affinity (P_{50}) has been determined, by a mixing technique, in whole blood and in phosphate-free hemoglobin solutions before and after the addition of inositol hexaphosphate (IHP). The Andean chicken alpha and beta globin genes were sequenced. A mutation Thr->Ser in position 69 of the ß-chains of Hb A has been found. The addition of IHP to the phosphate-free hemoglobin solutions increased the affinity significantly less in the sea-level chicken (42.2 torr) suggesting that the high-affinity hemoglobin is probably dependent on a molecular change affecting the allosteric regulation. These findings show the unprecedent observation in nature of a hemoglobin genetic change in an exceptionally short evolutionary time in a sea-level terrestrial bird. This observation also shows that the same species can be differentiated from its sea-level counterpart by a genetic change in the Hb function as a reflect of its structure.

Key words: high altitude, hemoglobin-oxygen affinity, hen, inositol hexaphosphate, mutation.

INTRODUCCION

La necesidad de oxígeno en el ambiente hipóxico de las grandes alturas puede satisfacerse de diversas maneras. Entre éstas podemos mencionar: la variación de la afinidad de la hemoglobina por el O_2 (Hb-O_2) y/o la modificación de las propiedades de oxigenación de la sangre, el aumento de la capilaridad y la redistribución del flujo sanguíneo, el cambio del dintel de respuesta a la hipoxia y la producción de un mayor número de glóbulos rojos, entre otros; de estos, la oxigenación de la sangre, a cargo de la Hb, tiene un papel sustancial. Esta es una función intrínseca de las propiedades de la Hb en su unión con el O_2, así como de la interacción de ésta con efectores heterotrópicos como fosfatos polianiónicos, O_2, protones e iones cloro los cuales disminuyen la afinidad de la Hb por el O_2. El inositol 1,2,3,4,5,6 penta o hexa-fosfato (IPP o

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IHP), se une tanto a la Hb aviar como humana, reduciendo su afinidad, y es el más efectivo modulador de la Hb en el glóbulo rojo, con una predominancia de concentración en los glóbulos rojos de las aves.

Los mamíferos y aves andinos, entre otras características, presentan como propiedad adaptiva de gran importancia, una alta afinidad de la Hb-O_2 y no responden a la hipoxia con hipereritremia (Monge-M. y Monge-C, 1968; Monge y Whittembury, 1976; Black y Tenney, 1980). Los animales de nivel del mar poseen por el contrario, una baja afinidad de la Hb-O_2 y hacen importantes hipereritremias cuando son expuestos a bajas presiones parciales ambientales de O_2 (PO_2). Con respecto a las aves se ha postulado (Braunitzer y Hiebl, 1988; Espinoza, 1988) que es en base a estas características que las aves nativas de la altura: gallaretas (*Fulica americana peruviana*) y gaviotas andinas (*Larus serranus*), yanavicos (ibis, *Plegadis ridgway*), huallatas (ganso andino, *Chloepaga melanoptera*), ganso de los Himalayas (*Anser indicus*), etc. son capaces de anidar y reproducirse con gran eficiencia en su ambiente hipóxico, sin presentar evidencias de mal de altura. La gallina doméstica, oriunda del Viejo Mundo (Murra, 1981; Dunin-Borkowski, 1986), tiene, por el contrario, no sólo una limitada capacidad para reproducirse en la altura como resultado de su baja incubabilidad, sino que además es susceptible de adquirir el mal de altura en la etapa adulta (Burton y Smith, 1969; Ploog, 1973). Esta enfermedad se caracteriza por la presencia de hipereritremia con baja afinidad de la Hb-O_2; el corazón derecho se hipertrofia, se eleva grandemente la presión de la arteria pulmonar y en casos severos sobreviene la muerte por insuficiencia cardiaca. Aún cuando la gallina doméstica comercial es la más extendida a todo lo largo del país, en las grandes alturas del Perú (por encima de 3,500 m.), se pueden ver gallinas "criollas" que presentan un adecuado éxito reproductivo, alta resistencia a las enfermedades comunes, y en particular al mal de altura (testimonios y testificación directa).

Con el fin de determinar las características de la Hb de estas gallinas criollas de altura, se llevó a cabo un estudio bajo la siguiente hipótesis: la intensa mortalidad de gallinas en el ambiente hipóxico de las grandes alturas, y la fuerte presión ambiental que constituye la disminución de la PO_2 habrían actuado favorablemente de manera de provocar el desarrollo de una línea de gallinas adaptadas a la altura. Esta adaptación estaría expresada como una mayor afinidad de la Hb por el oxígeno (León-Velarde y col., 1991), ocasionada ya sea, por la aparición de cierta cantidad de una variante de Hb, o por la variación en la concentración de los moduladores de la afinidad. De tratarse de una variante de la molécula de Hb original, ésta se expresaría como una Hb con una cadena adicional o como una Hb con una modificación en la secuencia de aminoácidos (León-Velarde y col., sometido para publicación) que altere, ya sea la unión de la Hb con el O_2, o la unión de la Hb con sus efectores alostéricos (Mejía y col., 1994).

MATERIAL Y METODOS

a) Afinidad de la Hb por el oxígeno.

Se trabajó con gallinas criollas de Taraco, Puno (Gal-ALT; 4,000 m); en ellas se determinó la afinidad de la Hb por el oxígeno con el método de las mezclas por medio de la medición de la PO_2 en la sangre a 50% de saturación de la Hb con oxígeno (P_{50}). El proceso analítico se basa en la determinación del PO_2 de una mezcla, a 41° C, de 2 alícuotas iguales de la misma sangre, una totalmente oxigenada y la otra totalmente reducida (Edwards y Martin, 1966; Sheid y Meyer, 1978). El factor Bohr utilizado para corrección del pH fue de -0.38 para la sangre de NM y de -0.51 para la sangre de la Gal-ALT. Para la determinación de la concentración de Hb, se utilizó el método colorimétrico por reacción con la azidometahemoglobina. Las lecturas se realizaron con un fotocolorímetro Hemocue.

b) Secuenciamiento de la Hb.

Las muestras de sangre de todos los animales nativos de la altura (n=9) y de 5 de sus descendientes a nivel del mar se enviaron al Instituto Palo Alto de Medicina Molecular (California) para la determinación de las secuencia de aminoácidos de la Hb mediante la técnica de la "Polimerase Chain Reaction", PCR, (cDNA a mRNA).

c) Obtención de la Hb "lavada".

Las muestras de sangre de todos los animales fueron "lavadas" de los fosfatos, y se midió

posteriormente, la magnitud del efecto del fosfato comercial más usado para estos fines, el inositol hexafosfato (IHP). Todas las determinaciones fueron comparadas con muestras de sangre provenientes de gallinas criollas de nivel del mar (Gal-NM). Para "lavar" la Hb, las muestras de sangre total fueron centrifugadas en una centrífuga refrigerada por 5 min a 3,000 rpm y el plasma removido por aspiración. Los glóbulos rojos se lavaron por 3 veces en una solución de NaCl 0.154M. Luego de la lisis de los eritrocitos con agua destilada, el hemolizado se centrifugó a 9,500 rpm por 30 min para remover el estroma. Esta Hb quedó libre de fosfatos orgánicos e inorgánicos al pasarla por una columna de celulosa de intercambio aniónico (DEAE Cellulose, Sigma Chemical Co. San Luis, Mo) que previamente fue equilibrada con Tris-HCl 0.05M, pH 7.4 y eluída con el mismo buffer. La solución de Hb obtenida se concentró por aproximadamente 15 horas hasta obtener una concentración de Hb = 5-6 g/dl. Esta Hb fue la designada como "lavada" (Isaacks y col., 1976). Se determinó el P_{50} a pH 7.5, PCO_2, 40 torr y 41° C en muestras de sangre total, en soluciones de Hb "lavada" y en presencia de 2 mM de IHP. Las muestras de sangre se mantuvieron en hielo, y se trabajó rápidamente teniendo en cuenta la alta tasa metabólica de los glóbulos rojos nucleados, cambio de pH y contenido de fosfatos orgánicos.

RESULTADOS

a) Afinidad de la Hb por el oxígeno.

La Tabla 1 contiene los parámetros sanguíneos obtenidos a partir de la determinación in-vitro del P_{50}. Puede verse que tanto los valores corregidos (P_{50}) como no corregidos de P_{50} (P_{50} std) son significativamente diferentes entre las Gal-ALT y Gal-NM ($p<0.001$). La alta afinidad de la Hb-O_2 de las gallinas de altura ha sido transmitida a los descendientes incubados y nacidos a nivel del mar (Lima) lo que asegura el caracter genotípico de este hallazgo. La presión parcial de CO_2 (PCO_2) de las muestras de sangre equilibradas no mostró diferencias, sin embargo el pH fue menor en la sangre de Gal-ALT ($p<0.012$), lo que probablemente indica una menor capacidad amortiguadora de la sangre de las Gal-ALT. Dado que todas las aves fueron estudiadas a nivel del mar, la concentración de Hb resultó la misma en los dos grupos (León-Velarde y col., 1991).

b) Secuenciamiento de la Hb.

El análisis estructural de la cadena ß de la Hb de la Gal-ALT mostró una sustitución thr---> Ser en la posición 69. No se encontró ningún cambio en el secuenciamiento de la cadena α. El secuenciamiento completo de la Hb de la Gal-ALT, se encuentra en el Banco Mundial de Genes (N° de Acceso: M73995) (León-Velarde y col., envíado a publicación).

Tabla 1. Parámetros de la curva de disociación de la Hb en animales de nivel del mar (Gal-NM; n=8) y de la altura (Gal-ALT; n=9)

	Hb	pH (g/dl)	PCO_2 (torr)	n	P_{50} (torr)	Bohr	P_{50}std (torr)
Gal-NM	9.80	7.48	39.40	3.45	51.90	-0.36	50.90
ES	0.40	0.04	2.56	0.23	2.89	0.03	2.82
Gal-ALT	9.00	7.33	38.30	3.48	35.60	-0.51	28.90
ES	0.82	0.04	3.69	0.17	2.01	0.05	0.87
P	0.58	0.01	0.80	0.92	0.00	0.09	0.00

B= pendiente de la relación log PO_2 = f(delta pH).
n= valor de Hill, pendiente de la relación log (Sat. O_2/100 - Sat O_2)= f(log PO_2).

c) Efecto del IHP en la Hb "lavada".

La Tabla 2 contiene los datos que permiten comparar el P_{50} std entre la sangre total, la Hb "lavada", y la Hb "lavada" + IHP en ambos grupos. El P_{50} std de la sangre total en las Gal-NM fue de 51.1 torr. significativamente mayor que el de las Gal-ALT que fue de 31.4 torr. Estos valores confirman los resultados de la Tabla 1. Los valores de la HB "lavada" fueron 6.3 y 6.0 torr, para las Gal-NM y Gal-ALT respectivamente. Luego de la adición de la misma concentración de IHP a la sangre con Hb "lavada", los P_{50} std fueron de 48.5 torr para Gal-NM y 32.3 torr para Gal-ALT. La adición de IHP se comporta de manera diferente en las dos Hb "lavadas". La diferencia (Hb lavada-Hb+IHP) es de 42.2 torr para Gal-NM y de 26.3 torr para Gal-ALT ($p<0.001$). Esto es, expuestas las dos hemoglobinas a idénticas concentraciones de IHP, la afinidad de la Hb de la Gal-ALT es casi la mitad de la afinidad de la Hb de la Gal-NM. esta diferencia es una indicación de que la Hb de la Gal-ALT es fosfato-dependiente (Mejía y col., 1994).

Tabla 2.- Afinidad de la Hb-O_2 (P_{50}), pH y hemoglobina en sangre total, Hb-lavada y Hb-lavada+inositol hexafosfato en gallinas de nivel del mar y en gallinas de altura

	Sangre total			Hb-Lavada			Hb-Lavada+IHP (2 mM)		
	Hb	pH	$P_{50}St$	Hb	pH	$P_{50}st$	Hb	pH	$P_{50}St$
Nivel del mar (Gal-NM)									
1	10.7	7.2	43.2	4.9	6.8	6.1	5.8	7.0	48.5
2	9.9	7.2	50.6	5.1	6.8	5.0	5.1	6.8	42.0
3	10.5	7.2	47.6	4.6	6.5	6.7	4.6	6.8	41.5
4	9.9	7.1	50.9	6.8	6.6	7.5	6.8	6.9	54.4
5	12.1	7.2	59.2	4.0	6.8	8.6	4.0	6.8	53.8
6	8.3	7.2	55.1	4.0	6.0	4.0	4.2	6.7	50.6
X	10.2	7.2	51.1	4.9	6.6	6.3	5.1	6.8	48.5
ES	0.5	0.0	2.3	0.4	0.1	0.7	0.4	0.04	2.3
Altura (Gal-ALT)									
1	10.9	7.4	31.3	4.0	6.8	6.2	6.6	6.9	25.3
2	14.2	7.4	36.7	5.3	6.9	6.5	5.3	7.1	35.6
3	12.5	7.2	25.8	5.6	6.9	6.1	6.3	7.0	30.6
4	20.3	7.4	33.6	6.4	6.8	4.7	8.9	7.1	35.9
5	16.9	7.4	29.6	6.8	7.0	6.4	5.4	6.9	34.3
X	15.0	7.4	31.4	5.6	6.9	6.0	6.5	7.0	32.3
ES	1.6	0.05	1.85	0.5	0.1	0.35	0.7	0.05	2.0
p	0.008	0.001	0.00	NS	NS	NS	NS	0.00	0.0

DISCUSION

Se ha reportado una alta afinidad de la Hb por el oxígeno en una gran variedad de aves y mamíferos genéticamente adaptados a la vida en la altura (Hall, 1936; Lutz, 1980; Holle y col., 1977; Black y Tenney, 1980; Espinoza, 1988). Entre estos, en los últimos años, las aves han recibido particular atención. Hiebl y col (1986) proponen un mecanismo tipo cascada para el transporte de O_2 en la Hb del ganso de los Himalayas; el mecanismo implicaría un cambio Pro---> Ala en la posición 119 de la Hb A. Asimismo, una sóla mutación en la cadena ß, posición 55 de la Hb del ganso andino ha sido considerada beneficiosa para la vida en la altura (Hiebl y col., 1987). En el caso del Gyps rueppellii, un ave a la que se le ha visto volando hasta los 11,300 m, se ha descrito también un mecanismo tipo cascada para el transporte de O_2 de la Hb, pero con la presencia de hasta 4 tipos diferentes de Hb (en vez de dos) con tres niveles de afinidad: baja (A y A'), alta (D/D), y afinidad intermedia (Hiebl y col., 1988). Resumiendo todos estos hallazgos, Braunitzer y Hiebl (1988) han postulado que la adaptación a la altura es el resultado de una mutación específica que distingue a estos animales de sus más cercanos parientes de nivel del mar. Estos cambios parecerían tener como rol fisiológico el responder al ambiente hipóxico manteniendo un adecuado suministro de oxígeno al organismo. La gallina de altura no parecería ser la excepción. En este caso, es probable que el reemplazo de los aminoácidos en la cadena ß, haya inducido a un cambio en la conformación del sitio de unión del IHP, del sitio mismo de la unión con el IHP, o en general, del ambiente local en el que se da la unión de la Hb con el mismo, generando como resultado una menor afinidad de la Hb de la Gal-ALT por el IHP.

En los mamíferos andinos, particularmente los Lamini, la alta afinidad se ha logrado por control genético al reducir el efecto alostérico del 2,3 difosfoglicerato con las cadenas ß. Este efecto disminuído ha sido interpretado como debido a una mutación en ß2 (His---> Asn) que interrumpiría el contacto en α-2 (Asp), dando como resultado un aumento en la afinidad de la Hb-O_2. La Asn en ß-2 se encuentra presente también en la alpaca y la vicuña, lo que estaría indicando que esta mutación apareció en el ancestro común del guanaco y la vicuña (posiblemente el género Hemiauchenia) que dió origen a las formas domésticas llama y alpaca. Este control genético como mecanismo de adaptación a la altura, difiere de los Camélidos, los cuales también tienen una alta afinidad de la Hb por el O_2, pero fosfato-independiente (Braunitzer, 1980; Kleinschmidt y col., 1986). Ambos mecanismos son fundamentalmente diferentes, por lo que sugieren que la alta afinidad de la Hb de los actuales Camelus y Lamini, se adquirió de manera independiente, que no sería un caracter heredado de un ancestro común, sino más bien una convergencia evolutiva en lo que a la función se refiere.

Nuestro hallazgo, de un cambio genético en la función de la Hb (que habría dado como resultado una mayor afinidad de la Hb por el O_2 fosfato-dependiente) que puede ser adquirido en un corto período evolutivo, sustenta la posibilidad de la presentación de cambios en la función de la Hb (afinidad de la Hb-O_2) sin tener que recurrir a explicaciones filogenéticas sobre la adquisición de este caracter. La alta mortalidad de gallinas con Hb de baja afinidad y elevada concentración de hemoglobina, y la fuerte presión ambiental que constituye la baja PO_2 de las grandes alturas, contribuiría a la selección del genotipo de alta afinidad que hemos identificado.

La adquisición de esta Hb de alta afinidad se habría llevado a cabo en un período evolutivo que corresponde aproximádamente a los 500 años del descubrimiento de América, periodo practicamente despreciable en términos evolutivos. Desde un punto de vista académico, el hallazgo del caracter flexible de la alta afinidad de la Hb-O_2 (cambio de baja afinidad a alta afinidad de la Hb-O_2 en una misma especie) en un periodo evolutivo extremadamente corto, constituye la primera descripción de este tipo en la clase vertebrados. Desde un punto de vista práctico, este hallazgo establece la posibilidad de regenerar una línea de gallinas de "altura" genéticamente adaptadas, allí donde la reproducción y producción masiva de aves de corral es una tarea casi imposible. Los pobladores de las altiplanicies andinas ya no se verían obligados a obtener gallinas de la costa o de la selva elevando los costos de dicho producto. El presente estudio supone la posibilidad de reproducir gallinas aún en las grandes alturas y de generar un mejor acceso de esta fuente de proteína animal al habitante de los Andes peruanos.

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BIOMEDICAL FACTORS ASSOCIATED TO HIGH FERTILITY AT HIGH ALTITUDE[1]

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SUMMARY. The present study has been designed to analyze information from the National Peruvian Census, 1993, and the Demographic Survey, 1991-1992 carried out in Peru (Peru, 1994; Endes, 1992) to determine population size at high altitude and Global Fertility Rate. The study has been also designed to investigate in populations living at sea level and at high altitude, age at menarche and age at menopause, the prevalence of pregnancies in adolescents, the percentage of pregnancies during breast feeding in women who never use modern contraceptives, and the serum prolactin levels during first three post partum months in women during breast feeding. Lenght of reproductive life (years) was significantly higher at sea level than at high altitude. The highest the altitude of residence, the lowest the reproductive life span. The administrative regions located at high altitude, except Arequipa, have high Global Fertility Rates than populations living at the coast of Peru (La Libertad, Grau and Lima). The three regions located at the jungle of Peru have also high GFR. The GFR according natural geographical regions were 2.1 children per woman in Metropolitan Lima, 3.3 in the rest of the coast, 4.9 in altitude, and 5.1 in the jungle. In 224 mothers who never used modern contraceptivemethods, interval between births was significantly lower at Cerro de Pasco (2.7 $\pm$ 0.15 years) than at Cusco (3.1 $\pm$ 0.29 years) or Lima (3.8 $\pm$ 0.36 years).

The percentage of women who got pregnant during breastfeeding increased as it increased the altitude of residence. Serum prolactin levels were significantly higher in women natives at sea level than at high altitude ($P<0.01$).

In conclusion our data suggest that women at high altitude have more reproductive efficiency.

Key words: Altitude, Global Fecundity Rate, Prolactin, Breastfeeding, Reproductive life, Fertilization.

RESUMEN El presente estudio ha sido diseñado para analizar la información del Censo Nacional del Perú, 1993 y la Encuesta Demográfica de Población, 1991-1992 realizada en el Perú (Perú, 1994; Endes, 1992) para determinar la población que habita en las alturas del Perú y la Tasa Global de Fecundidad (TGF). El estudio ha sido diseñado para investigar en poblaciones que viven a nivel del mar y en la altura, la edad de menarquia, la edad de menopausia, la prevalencia de embarazos en la adolescencia, el porcentaje de embarazos durante la lactancia materna en mujeres que nunca utilizaron contraceptivos, y los niveles de prolactina sérica durante los tres primeros meses posteriores al parto en mujeres que dan lactancia materna exclusiva. La duración de la vida reproductiva fue mayor a nivel del mar que en la altura, donde a mayor altitud de residencia menor es la duración de la vida reproductiva. Exceptuando a Arequipa, las poblaciones de las regiones administrativas ubicadas en la altura tienen una mayor TGF que las localizadas en la costa del Perú (La Libertad, Grau y Lima). Las tres regiones localizadas en la selva tienen también una alta TGF. La TGF según regiones naturales fue de 2.1 niños por mujer en Lima Metropolitana, 3.3 en el resto de la costa, 4.9 en la altura, y 5.1 en la selva. En 224 madres que nunca usaron métodos contraceptivos, el intervalo entre hijos fue menor en Cerro de Pasco (2.7 $\pm$ 0.15 años) que en Cusco (3.1 $\pm$ 0.29 años) o Lima (3.8 $\pm$ 0.36 años).

El porcentaje de mujeres que se embarazaron durante la lactancia aumentó conforme aumentó la altitud de residencia. Los niveles de prolactina sérica fueron significativamente mayores en las lactantes de nivel del mar que en la altura ($P<0.01$).

En conclusión nuestros datos sugieren que en la altura hay más eficiencia reproductiva.

Palabras claves: Altura, Tasa Global de Fecundidad, Prolactina, Lactancia, Vida reproductiva, Fertilización.

INTRODUCTION

In different populations in the world, number of children is determined by social and religious factors. Demographic analysis have demonstrated that in populations without access to modern forms of contraception, birth intervals are determined principally by the duration of breastfeeding (Bongaarts and Potter, 1983). Breastfeeding controls fertility not only during amenorrhea period but also beyond the resumption of menses (Singh et al, 1993).

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Studies on populations living at high altitude of Hymalayas have revealed that fertility is reduced. This has been confronted by recent studies carried out in Peruvian Andean populations (Gonzales, 1993).

Prevalence of use of modern contraceptives in populations living at high altitude is still lower (Alarcón and Gonzales, 1993). However, when social factors and use of modern contraceptives is controlled, a high fertility is still observed at high altitude (Gonzales et al, 1993) suggesting that fertility in populations living at high altitude may be also determined by biomedical factors as a mechanism of adaptation to high altitude. For instance, diseases like hyperprolactinemia, which is a common cause of infertility in women living at sea level, has low prevalence at high altitude (Gonzales and Carrillo, 1993).

High fertility in any population is determined by long lenght of reproductive life based on the onset of menses (age at menarche) and the end of menses (age at menopause), high prevalence of pregnancies in adolescent ages, shorter intergenesic interval, which depends from length of post-partum sexual abstinence, and lenght of breast-feeding.

The present study has been designed to analyze information from the National Peruvian Census, 1993 and the Demographic Survey, 1991-1992 carried out in Peru (Peru, 1994; ENDES, 1992) to determine population size at high altitude and Global Fecundity Rate. The study has been also designed to investigate in populations living at sea level and at high altitude, age at menarche and age at menopause, the prevalence of pregnancies in adolescents, the percentage of pregnancies during breastfeeding in women who never use modern contraceptives, and the serum prolactin levels before three months after parturition in women during breastfeeding.

MATERIAL AND METHODS.

The basic data used here come from the Demographic survey carried out in Peru during 1991-1992 and the National Peruvian Census carried out in July 1993 under the auspices of the National Institute of Statistics and Informatic, Peru. The main objective of the study was to determine the effects of biomedical factors present in women at high altitude on fertility. Data from the National Peruvian Census were analyzed on departments basis (24 in 1993), whereas data from the Demographic survey was recorded by Administrative Regions. In Perú, during 1991-1992, it was defined 13 administrative regions. The following regions have populations living mainly at altitude: Andres Cáceres (70.6%), Arequipa (83.9%), Inka (85.9%), Mariátegui (75.5%).

Age at menarche was assessed in 296 women residing at Lima (150 m), Cusco (3400 m) and Cerro de Pasco (4340 m). Age of menarche was recorded by the Recall Method in women from 20-30 years old. Data were calculated as mean ± SEM.

Age at menopause was assessed in 128 women residing at Lima (150 m), Cusco (3400 m) and Cerro de Pasco (4340 m). Data were obtained from women aged over 50 years. Age at menopause was recorded by the Recall Method, and data were calculated as mean ± SEM.

Prevalence of women who got pregnancies during breast feeding was obtained after a survey carried out in Lima at two public hospitals, Cayetano Heredia Hospital and Arzobispo Loayza Hospital, and in Cerro de Pasco at one public hospital, Daniel A Carrión Hospital. The study was done in women who never used modern contraceptives methods. This study was carried out in Lima (150 m), Tarma (3000 m), Cusco (3400 m) and Cerro de Pasco (4340 m). Data were referred as percentage of women who got pregnancies before the last parturition despite of breast-feeding. In these women intergenesic interval was calculated indirectly by calculating interval between two births.

Serum prolactin levels were determined in 33 women from Lima (150 m) and 12 from Cerro de Pasco (4340 m) with exclusive lactation between 1-3 months of post-partum. Between 08.00-10.00 h a venous blood sample was obtained from each

women after fastnight and during 30-60 minutes after last suckling. Blood sample was centrifuged at 3000 RPM and serum was removed and kept frozen at -20°C until assayed for prolactin.

Serum prolactin concentration was measured by radioimmunoassay (RIA) using reagents provided by the World Health Organization. ^{125}Iodine-prolactin was used as reactive marker for the RIA. Data are referred as mIU/ml.

Data were analyzed using parametric and non parametric statistics. Differences among mean age at menarche or mean age at menopause were analyzed by analysis of variance and the multiple range test. Differences among prevalence of pregnancies during breast feeding were analyzed by chi square test. Differences between serum prolactin levels in Lima and Cerro de Pasco were assessed by Student t test. A difference was considered as significant when p was below 0.05.

RESULTS.

Populations with $>1x10^6$ inhabitants in Peru

The population in Peru during 1993 was 22'128,466 inhabitants. These were distributed in the 24 departments, seven of them having >1 million inhabitants (Table 1). From these, four of them were located at altitudes over 2000 meter.

Distributed as natural geographic regions, 11'558,204 inhabitants were at the coast, 7'904,-711 at altitude, and 2'665,551 inhabitants at the jungle of Peru.

Table 1.- Departments with higher 1 million inhabitants during 1993 and place of location

Departments	Inhabitants	Location
Cajamarca	1'273,596	Altitude
Cusco	1'016,954	Altitude
Junín	1'026,946	Altitude
La Libertad	1'279,472	Sea level
Lima	6'483,901	Sea level
Piura	1'437,675	Sea level
Puno	1'057,606	Altitude

Source: National Population Survey. Peru, 1993.

Table 2 shows that, excepting Arequipa, all the administrative regions located at high altitude have high Global Fecundity Rates than populations living at the coast of Peru (La Libertad, Grau and Lima).

The three regions located at the jungle of Peru (Loreto, Ucayali and San Martín) have also high GFR ranging from 4.6 to 5.5 children per woman.

The GFR according natural geographical regions were 2.1 children per woman in Metropolitan Lima, 3.3 in the rest of the coast, 4.9 in altitude, and 5.1 in the jungle.

Rate of fertilization

Interval between births (months) were lowest at highland places than at the coast or jungle. This low interval (29.2 months) compared with that observed at jungle (29.4 months) was lower despite of higher use of contraceptives (49.5% vs 48.3%) and low sexual activity (70.5% at altitude vs 76.4% at jungle) (Table 3).

Analysis of 224 mothers who never use modern contraceptive methods having the second child demonstrated that interval between children was significantly lower at Cerro de Pasco (2.7 $\pm$ 0.15 years) than at Cusco (3.1 $\pm$ 0.29 years) and Lima (3.8 $\pm$ 0.36 years).

Table 2. Global Fecundity Rate (per thousand of women) in women according administrative regions in Peru

Administrative region	GFR (Children per woman)	Percent of population living at altitude	Number of live children
Inka	5.2	85.9	6.2
Arequipa	3.0	83.9	4.0
Mariátegui	4.4	75.5	5.6
A. Cáceres	4.6	70.6	6.1
Chavín	4.2	52.5	5.9
Libertadores	5.2	51.6	6.7
Nor-Oriental	4.1	43.4	5.7
La Libertad	3.9	21.4	5.9
Grau	3.9	10.8	6.5
Lima	2.3	1.1	3.8
Loreto	5.5*	0.0	6.5
Ucayali	5.0*	0.0	7.0
San Martín	4.6*	0.0	6.5

*Located at the jungle of Peru. GFR: Global Fertility Rate.

Table 3. Interval between births according natural geographical regions in Peru and prevalence of use of contraceptives

Natural Region	Median of interval between births (months)	Use of any contraceptive methods (%)	Sexually active during the last 4 weeks of the survey (%)
Metropolitan Lima	39.9	72.7	73.0
Rest of coast	31.6	63.9	74.6
Altitude	29.2	49.5	70.5
Jungle	29.4	48.3	76.4

Source: Endes, 1992

Table 4. Lenght of reproductive life at Lima (150 m), Cusco (3400 m) and Cerro de Pasco (4340 m).

Place	Altitude (m)	Age at menarche (yrs)	Age at menopause (yrs)	Length of reproductive life (yrs)
Lima	150	12.94±0.21	48.4±0.75	35.5
Cusco	3400	14.12±0.25*	45.5±0.67**	31.4
Cerro de Pasco	4340	14.65±0.20*	42.6±0.39*	28.0

Data are mean ± SEM. *P<0.01; **P<0.05 with respect to values at Lima.

Reproductive life span

Lenght of reproductive life (years) was significantly higher at sea level than at high altitude (Table 4). The highest the altitude of residence, the lowest the reproductive life span.

Age of mother at first child.

Age of mother at first child at coast region was 21.5 years for women actually ranging 25-49 years of age; age at first child at highland region was 21 years, and at jungle, it was 19.7 years (ENDES, 1992).

Percentage of Women who got pregnancies during exclusive breastfeeding

The percentage of women who got pregnancies during breastfeeding increased as it increased the altitude of residence (Table 5).

Serum Prolactin levels in women during first three months of exclusive breastfeeding

As it was shown in Table 6, serum prolactin levels were significantly higher in native women at sea level than at high altitude ($P<0.01$).

Table 5.- Percentage of women who got pregnancies during exclusive breastfeeding at sea level and at high altitude.

Place	Altitude (m)	Number	% of pregnant women
Lima	150	92	6.4
Tarma	3000	24	25.0*
Cusco	3400	62	24.2*
Cerro de Pasco	4340	82	37.8*

*$P<0.05$ with respect to Lima (150 m).

Table 6.- Serum prolactin levels (mIU/ml) during first three months of exclusive breastfeeding.

Place, altitude	Prolactin (mIU/ml)
Lima, 150 m (33)	2473.56 ± 211.97
Cerro de Pasco, 4340 m (12)	1353.33 ± 331.61*

Data are mean ± SEM. Between parentheses are number of data. *$P<0.01$ with respect with values in Lima.

DISCUSSION

Data from the present study revealed that reproductive life span as defined as by age at menarche and age at menopause is shorter at high altitude populations than at sea level, as a consequence of later age at menarche and earlier onset of menopause at high altitude, as reported previously (Gonzales, 1994; Gonzales and Ortíz, 1994). However, despite of this shorter reproductive life span, Global Fecundity Rate (GFR) was higher in Peruvian high altitude populations than those living at the coast. A high GFR was also observed at populations living at jungle of Peru. The high GFR at jungle was explained due to a high prevalence of pregnancies at adolescent ages (Wilhelm et al, 1991). However, this is not the case for women living at high altitude. In fact, at the coast, age of mother at first child was 21.5 years for women actually ranging 25-49 years of age; at highland places age at first child was 21 years, and at jungle was 19.7 years (ENDES, 1992).

This high GFR at high altitude results in high population growth. As, it is observed in the data of the present study, from seven departments with

higher 1 million inhabitants, four are located at high altitude. If we except Lima, with about 6 millions inhabitants, which is the capital of the country where industry, commerce, and see of government is concentrated, and the number of migrant people is extremely high, we have that from six departments with high population, 66% of them are at highlands.

Use of contraceptives is an important mechanism to explain differences in population size. For instance, in Peru use of contraceptives is still lower in populations from high altitude and jungle, being lowest in the last group. However, interval between births (months) were lowest at highland places than at the coast or jungle. This low interval (29.2 months) compared with that observed at jungle (29.4 months) was lower despite of higher use of contraceptives (49.5% vs 48.3%) and low sexual activity (70.5% at altitude vs 76.4% at jungle) as it is shown in Table 3. If we select women who never use contraceptive methods, and we analyze the birth interval between first and second child, we found that this interval is lower at high altitude than at sea level suggesting a more reproductive efficiency at high altitude (Gonzales, 1993).

Birth interval and intergenesic interval depends of several factors, as use of contraceptives after parturition, post-partum sexual abstinence, maternal breastfeeding.

Controlling use of modern contraceptive methods, we have observed that interval between first and second child was significantly lower at Cerro de Pasco (4340 m) than at Cusco (3400 m) and Lima (150 m). As sexual abstinence duration after parturition was similar at sea level and at high altitude, it was suggested that differences in rate of fertilization between sea level and high altitude population must be in maternal breastfeeding habits.

Previously we have demonstrated that exclusive maternal lactancy is more frequent at high altitude than at sea level populations, and that frequency of suckling was similar between both population groups (Gonzales, 1994a). This situation should produce a high protection to women living at high altitude against a pregnancy during lactation, since exclusive breastfeeding is an effective contraceptive method (Diaz et al, 1989), however, our data demonstrate that maternal breastfeeding is not protecting against a new pregnancy at high altitude as well as at sea level.

Amenorrhea produced by lactancy prolongs the interval between births (Rosner and Schulman, 1990), but variation in the duration of post-partum infertility by lactancy between populations has been reported (Díaz et al, 1982; 1991; Shaaban et al, 1990; van Look 1988). No studies has been carried out about prevalence of returned menses after parturition during exclusive breastfeeding at high altitude.

Prolactin, a glycoprotein hormone, which when it is anormally increased is associated with infertility (Gonzales and Carrillo, 1993), may be the hormone associated to lactational amenorrhea (McNeilly, 1988). Our study demonstrated that serum prolactin levels were lower during first three months of breastfeeding at high altitude than at low altitude.

In conclusion our data suggest that women at high altitude have more reproductive efficiency.

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PNEUMATIC MEASUREMENT OF INTRAOCULAR PRESSURE: INTERPRETATION OF HYPOBARIC AND HYPOXIC EFFECTS[1]

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Abstract. Using a non-contact tonometer, we previously demonstrated that intraocular pressure (IOP) was reduced after exposure to 446 mm Hg for two hours, as well as during 15 days of residence at Pikes Peak (4300 m, ~446 mm Hg). Although a definite acclimatization effect was shown during the latter exposure, the nature of the abrupt 20% reduction in IOP (15.8 ± 0.6 vs 12.9 ± 0.9 mm Hg, mean ± S.E., n=11) during the 2-h altitude simulation was of concern. We hypothesized that the reduction could be due either to the reduction in barometric pressure (P_B) and/or to the physiological effects of hypoxia. In two, 2-h series of experiments separated by one week, seven subjects were exposed to either normobaric hypoxia (P_B=760 mm Hg; 12.8% O_2) (NH) or hypobaric normoxia (P_B= 446 mmHg; 37.3% O_2)(HN). During NH, IOP gradually decreased, reaching statistical significance after two hours ($P<0.009$). During HN, IOPs were reduced at 0.5 hours ($P<0.0001$) and remained decreased for the entire two hours. Within two minutes of return to normobaria after HN, IOP returned to 17.1±1.0 mm Hg, demostrating an immediate pressure effect on the measurement of IOP. These results indicate that the reduction in IOP observed during altitude exposure is the result of the combination of hypobaria and a physiological hypoxic effect. The hypobaric effect is relatively immediate, and the hypoxic effect manifests itself after a minimum of two hours of exposure. The previously-observed IOP changes with altitude exposure remain valid.

Keywords: intraocular pressure, hypobaria, hypoxia, altitude

Resumen. Anteriormente, usando un tonómetro de no contacto, demostramos que la presión intra-ocular (PIO) estaba reducida después de una exposición a 446 mm de Hg durante dos horas, como también durante una estadía de 15 días en Pikes Peak (4300 m ~446 mm Hg). A pesar de que se observó una aclimatación durante los 15 días, el origen de la súbita reducción del 20% en la PIO (15.8±0.6 vs 12.9-±0.9 mm Hg, promedio±SE, n=11) durante la exposición de 2 horas es de preocupación. Hemos formulado la hipótesis que la reducción podría ser debida ya sea a la presión barométrica (PB) y/o a los efectos fisiológicos de la hipoxia. En 2 series de experimentos de 2 horas, separados por una semana, siete sujetos fueron expuestos a una hipoxia normobárica (PB=760 mm Hg; 12.8% O_2) (HN) o normoxia hipobárica (PB=446 mm Hg; 37.3% O_2)(NH). Durante la HN, la PIO gradualmente disminuyó, alcanzando significación estadística después de dos horas ($p<0.009$). Durante NH, las PIOs se redujeron a la 0.5 horas ($p<0.0001$) y permanecieron disminuídas por las 2 horas restantes. Dos minutos después de retornar a la mormobaria después de la NH, la PIO retornó a 17.1±1.0 mm Hg, demostrando un efecto inmediato de la presión en la medición de la PIO. Estos resultados indican que la reducción en la PIO observada durante la exposición a la altura es el resultado de la combinación de la hipobaria y un efecto fisiológico hipóxico. La influencia hipobárica es relativamente inmediata y los efectos hipóxicos se evidencian después de un mínimo de 2 horas de exposición. Los cambios de la PIO con la exposición a la altura previamente observados permanecen válidos.

Palabras Claves: Presión intraocular, hipobaria, hipoxia, altitud.

INTRODUCTION

Altitude effects on intraocular pressure have been examined on mountain expeditions and in mountain field laboratories with results that appear contradictory. No changes in IOP were found in four subjects who were members of a team of British and Sherpa climbers (Clarke and Duff, 1976). Using a Perkins contact tonometer which was very uncomfortable and unpopular, Clarke and Duff obtained measurements between 1800 and 2100 hours, a time when IOP is at a nadir in its diurnal cycle. Measurements performed in the morning when the IOPs can be 3-4 mm Hg higher are more likely to show observable changes. Reductions in IOP and retinal venous dilatation in Himalayan climbers two weeks after descent have also been obser-

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ved, but these decreases were associated with the climbers' increased physical activity (Brinchmann-Hansen and Myhre, 1989). However, the physical exertion effect on IOP usually lasts only minutes after exertion (McDaniel et al., 1983). It is difficult to believe that significant reductions of 1-5 mm Hg in 21 subjects would still be evident two weeks after altitude exposure.

Because of confounding problems that can affect IOP such as hyperventilation (hypocapnia) and increases in blood osmolality and blood pressure associated with climbing expeditions, we measured IOPs under more controlled, resting conditions. A series of field and chamber studies were conducted to determine whether IOP changes occurred under both normobaric hypoxic (hypoxia) and hypobaric normoxic (hypobaria) conditions and to correlate noncontact tonometer measurements with a contact tonometer under altitude conditions.

METHODS

Studies were conducted at the Pikes Peak Altitude Laboratory (4,300 m, Colorado Springs, CO) or the hypobaric chamber at U.S. Army Research Institute of Environmental Medicine, Natick, MA. Subjects remained quietly seated for at least 10 minutes before any measurements were taken. Only right eye IOPs were measured. Pneumatic tonometer measurements were always performed first to avoid any potential errors due to application of a short-acting local anesthetic used in conjunction with the Tono-Pen (See study 6).

Study 1: intraocular pressure measurements, using a non-contac pneumatic tonometer (CT-20 Tonometer, Topcon Corporation, Paramus, NJ), were obtained on 11 resting male volunteers (29$\pm$1 yr) on days 2, 12, and 15 of a 19-day residence at the summit of Pikes Peak, CO (4,300m) IOP at Pikes Peak.

Study 2: To determine whether hypobaria affects the measurement of IOP using a pneumatic tonometer, a calibrated "test eye" was obtained from the Topcon Corporation and attached to the CT-20 tonometer. IOPs were measured within 30 minutes at each 1,000 ft interval of simulated altitudes from sea level (760 torr) to 4,587 m (428 torr).

Study 3: To determine the acute effect of hypobaria per se on IOP, seven volunteers were exposed to a hypobaric, normoxic environment by reducing hypobaric chamber ambient pressure to 446 torr (4,300 m). To maintain sea-level inspiratory PO_2 values volunteers breathed a 37.3% oxygen-balance nitrogen gas mixture. A mean of three measurements was obtained every 0.5 hours for two hours with control measurements made at 760 torr before and immediately after exposure.

Study 4: To determine the effect of hypoxia per se on IOP, seven volunteers were exposed to a normobaric hypoxic environment by breathing a gas of 12.3% oxygen-balance nitrogen at sea- level barometric preassure (760 torr). A mean of three measurements was obtained every 0.5 hour for two hours with control measurements made at 760 torr breathing room air before and immediately after exposure. Blood oxygen saturation was monitored using a finger pulse oximeter (Oxyshuttle, Sensormetics Corp, Anaheim, CA).

Study 5: In order to determine whether hypobaria affected long term pneumatic IOP measurements, the Topcon CT-20 tonometer was maintained at 446 torr in the hypobaric chamber for four continuous days. Every morning IOPs were obtained from two volunteers immediately upon descompression to 446 torr.

Study 6: To determine whether pneumatic tonometry correlated with a more direct measurement of IOP, we compared measurements taken from a contact and pneumatic tonometer on the summit of Pikes Peak (4,300 m). Morning IOPs were obtained from 19 volunteers for the first three days using both the Topcon CT-20 pneumatic tonometer and a contact tonometer (Tono-Pen XL Tonometer, Mentor O&O, Norwell, MA). The Tono-Pen uses a micro strain gauge which is gently tapped four times over a 1.5 mm area of anesthetized cornea to obtain a mean and coefficient of variation.

RESULTS AND DISCUSSION

Figure 1A shows the IOP results from the 1992 Pikes Peak Field Study. The acute hypobaric chamber exposure resulted in a significant reduction in IOP after 2 hours of simulated

altitude exposure. After transport to Pikes Peak, CO (4300 m), a slightly greater reduction was observed after 2 days with a gradual increase toward pre-exposure values after 2 weeks residence. The reduction in IOP could be related to the reduction in barometric pressure and/or the partial pressure of oxygen and subsequent physiological consequences. In order to obtain further information of the cause of the reduction, a calibrated "test" eye was exposed to simulated altitude in a barometric chamber.

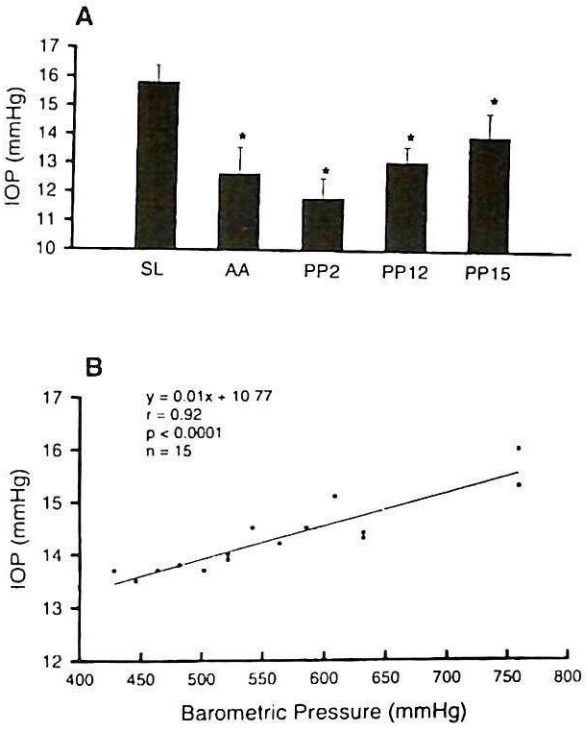

Figure 1. (A) Pneumatic intraocular pressure measurements from 11 resting male volunteers (29 ± 1 yr) at sea level (SL), 2 hours of exposure to simulated altitude in a hypobaric chamber (4,300 m, AA), and on days 2 (PP2), 12 (PP12), and 15 (PP15) of a 19-day exposure at the summit of Pikes Peak, CO (4,300m). *P<0.005. (B) Linear regression of a calibrated test eye exposed to ambient barometric pressure ranges from 425 to 760 torr. Measurements were made within 0.5 h at each barometric pressure.

Results indicated that there is a reduction in the pressure measured by the pneumatic tonometer that linearly correlated with the ambient pressure (Figure 1B). Therefore, some of the reduction observed acutely in the chamber and at Pikes Peak could be due to the direct effects of hypobaria on the tonometer, i.e., a lower barometric pressure would result in a less dense puff of air and a lower reading. However, direct barometric effects (which would be constant) could not explain the changes observed during acclimatization, i.e., the gradual increase with time at altitude.

The next two studies were designed to assess the independent effects of hypobaria and hypoxia in the two hour time frame that resulted in a reduction in IOP in the original study. Figure 2A shows the results of seven volunteers exposed to two hours of hypobaric normoxia. There was an immediate reduction in IOP with exposure of subjects and tonometer to hypobaria. The reduction lasted the entire two hours and then returned to normal with exposure to normobaria. While these results showed IOP decreases with HN, it could not be discerned whether the reduction was due to effects on the subject or the instrument. Therefore, one week later, the same seven subjects were exposed to normobaric conditions, but this time they breathed a mixed gas containing 12.8% O_2. Figure 2B shows no change in IOP until two hours of hypoxic breathing, indicating that the hypoxic effect on IOP takes at least two hours to manifest itself. Finger pulsed oximeter readings for the 2-hour period were 84.8±11.1% O_2 saturation. Therefore, there is an immediate, physical effect on IOP dependent solely on barometric effect after two hours.

The next question was whether continuous exposure of the tonometer to hypobaria caused any change in the instrument's ability to measure IOP. If changes with time under hypobaric conditions were found, then conclusions concernig IOP acclimatization effects could be in question. Figure 3A indicates no change in the IOP of subjects acutely exposed to hypobaric hypoxia using a machine that was kept under hypobaric conditions for four days.

A study recently conducted at Pikes Peak afforded the opportunity to compare IOP measurements taken with the same pneumatic tonometer as previously used with those obtained using a contact Tono-Pen. Measurements made with the Topcon pneumatic, non-contact tonome-

ter were found to signicantly correlate with the Tono-pen validating the changes observed in our initial study, at least for the first three days of altitude exposure (Figure 3B).

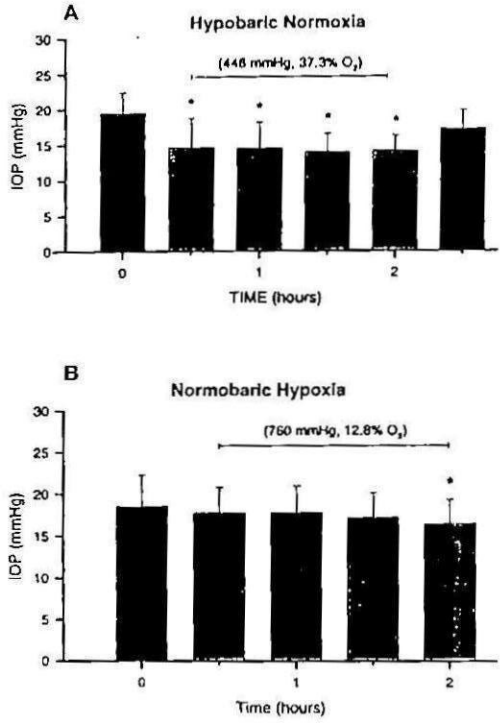

Figure 2. (A) The effects of exposure to a hypobaric (446 torr), normoxic (37.3% O_2) environment. A mean of three measurements were obtained from seven volunteers with measurements made every 0.5 hour for two hours. Control measurements were made at 760 torr before and immediately after exposure (black bars). (B) The effects of exposure to normobaric (760 torr), hypoxia (12.3% O_2). A mean of three measurements from seven volunteers was obtained every 0.5 hour for two hours with control measurements made at 760 torr breathing room air before exposure (black bar). *P-<0.05.

In summary, hypobaria causes a systematic reduction in the measurement of IOP using a pneumatic tonometer. However, a physiologic reduction in IOP is also caused by hypoxia *per se* that is evident after two hours. The reduction in IOP and the possible acclimatization effect that was observed at Pikes Peak receives further validity based on the direct correlation of pneumatic and direct contact tonometer measurements. Direct contact tonometer measurements were found to be in support of the pneumatic tonometer data which indicated a reduction in IOP with short term high altitude exposure and an acclimatization effect after two weeks.

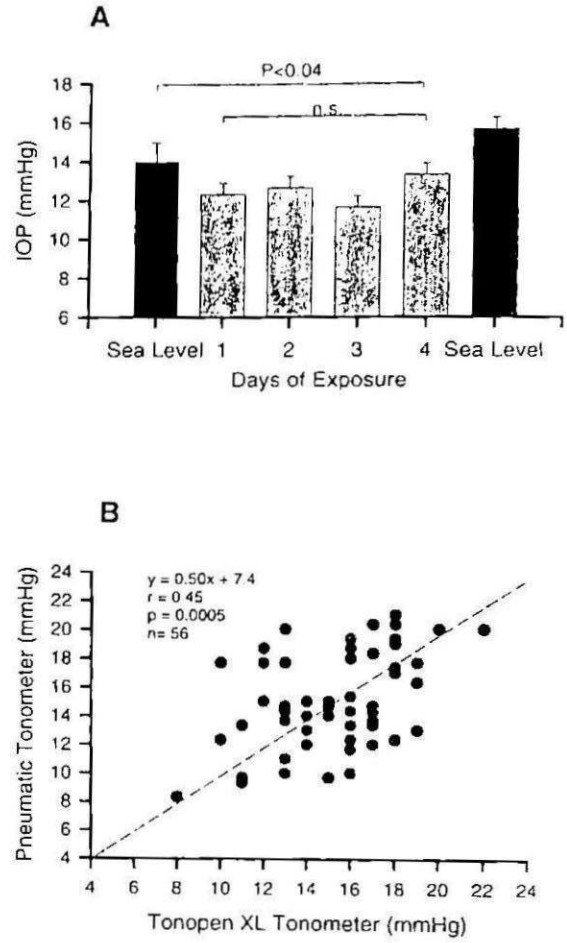

Figure 3. (A) The Topcon CT-20 tonometer was maintained at 446 torr in the hypobaric chamber for four continuos days. Every morning IOPs were obtained from two volunteers immediately upon decompression to 446 torr. (B) 19 volunteers were acutely exposed to hypobaric hypoxia on the summit of Pikes Peak. Measurements were obtained using both the pneumatic tonometer and the Tono-Pen each of three successive mornings.

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The assistance and contributions of Drs. T. Mader, B. Gilbert, and J. Ng of the Madigan Army Medical Center, Tacoma, WA and Dr. C. Blanton of the Naval Medical Center, San Diego, CA is greatly appreciated. They enthusiastically included the comparison study of the pneumatic tonometer and the Tono-Pen in their broader study of the effects of radial and laser keratotomy on vision at high altitude.

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AUGMENTED CHEMOSENSITIVITY AT ALTITUDE AND AFTER RETURN TO SEA LEVEL: IMPACT ON SUBSEQUENT RETURN TO ALTITUDE[1]

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SUMMARY. Augmentation of hypoxic (HVR) and hypercapnic (HVCR) ventilatory chemosensitivity is a component of acclimatization in lowlanders sojourning at high altitude. Previous studies suggest that the augmented ventilatory chemosensitivity declines upon return to sea level (SL) over one or more weeks. We hypothesized that some degree of ventilatory acclimatization would be retained upon reintroduction to altitude (RA) 8 days following return to SL due to retention of enhanced chemosensitivity. Ventilation (VE/VCO_2), arterial oxygenation (SaO_2), HVR ($\triangle VE/\triangle Sa-O_2$) and HCVR ($VE/PCO_2$) of 11 male lowlanders were measured during rest at SL, after 1, 2 and 14 days residence at 4300 m, and at 1, 3 and 7 days after return to SL and in 6 subjects during a 24 hr RA after 8 days at SL. Ventilatory acclimatization produced an increase ($P < 0.005$) in VE/VCO_2 (-12%), SaO_2 (-10%), HVR(-170%) and HCVR (-43%). After returning to SL, HVR and HCVR remained elevated ($P<0.05$) for at least 3 days. During RA, subjects demonstrated a retention of -90 and -67% of their acclimatization responses for VE/VCO_2 and SaO_2 respectively, even though HVR and HCVR were no longer statistically elevated. These measurements of ventilation and arterial oxygenation during re-exposure to high altitude clearly indicate the retention of ventilatory acclimatization, thus lessening the hypoxic stress during subsequent sojourns to altitude within that time period. However, the absence of augmented chemosensitivity to either hypoxia or hypercapnia in these subjects leaves the mechanism for this enhanced ventilatory response in question.

Keywords: acclimatization, deacclimatization, altitude, ventilation, control of breathing.

RESUMEN. El aumento de la sensibilidad de los quimioreceptores a la hipoxia (HVR) e hipercapnia (HCVR), es componente de la aclimatación en residentes del nivel del mar que ascienden a la altura. Estudios previos sugieren que esta mayor sensibilidad de los quimioreceptores declina al retornar a nivel del mar (NM) por el lapso de una a más semanas. Hemos formulado la hipótesis que algún grado de aclimatación ventilatoria se mantendría al re-ascender a la altura (RA) 8 días después del retorno a NM, debido a una retención de la hipersensibilidad de los quimioreceptores. La ventilación (VE/VCO_2), oxigenación arterial (SaO_2), HVR (VE/SaO_2) y HCVR (VE/PCO_2) de 11 hombres del nivel del mar se midieron en reposo a nivel del mar, después de 1, 2 y 14 días de residencia a 4300 m, a los 1, 3 y 7 días después de retornar a NM y en 6 sujetos que estuvieron durante 24 horas en RA, 8 días después a nivel del mar. La aclimatación ventilatoria produjo un incremento ($p<0.05$) en VE/VCO_2 (-12%), SaO_2 (-10%), HVR (-170%) y HCVR (-43%). Después de retornar a NM, HVR y HCVR permanecieron elevadas ($P<0.05$) por lo menos durante 3 días. Durante el re-ascenso, los sujetos demostraron una retención de -90 y -67% de sus respuestas de aclimatización para la VE/VCO_2 y SaO_2 respectivamente, a pesar que el HVR y HCVR ya no estaban estadísticamente elevadas. Estas mediciones de la ventilación y oxigenación arterial durante la re-exposición a la altura claramente apuntan a la retención de la aclimatación ventilatoria, y consecuentemente disminuyen el stress hipóxico durante subsecuentes reascensos a la altura en ese período. Sin embargo, la ausencia del aumento de la sensibilidad de los quimioreceptores a la hipoxia o a la hipercapnia en estos sujetos, deja en interrogante cual es el mecanismo para esta respuesta ventilatoria incrementada.

Palabras Claves: aclimatization, deaclimatization, altitud, ventilación, control of respiración.

INTRODUCTION

The time course and expression of a wide variety of physiological adaptations to altitude acclimatization have been well studied. However, the same cannot be said for the process of deacclimatization to high altitude (HA), or the physiological responses accompanying reintroduction to high altitude following recent residence at altitude. It is logical to assume that the physiological responses which accompany altitude acclimatization undergo a deacclimatization

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process of similar duration upon return to low altitude.

Ventilatory acclimatization to high altitude occurs over a period of several days to weeks. Upon return to sea level (SL), resting ventilation decreases toward sea level values but initially remains slightly elevated. Several studies have reported resting ventilation and ventilatory chemosensitivity to hypoxia (HVR) and hypercapnia (HCVR) to be elevated above pre-altitude exposure controls from a few days to as long as 45 days after return to SL (Forster et al., 1971; Lahiri et al., 1972; Sato et al.1992). For example, Sato et al. found that HVR, decreased approximately 40% over the first 7 days following return to SL from six days residence at 3,800 m. However, we are not aware of any studies which have longitudinally examined the ventilatory responses of lowlanders before, during and after high-altitude residence and upon subsequent reintroduction to high altitude following return to sea level. Therefore, the purpose of this study was to test the hypothesis that some degree of ventilatory acclimatization to altitude would be retained upon re-exposure to HA eight days following return to SL. Specifically, we hypothesized that enhanced hypoxic and/or hypercapnic ventilatory responsiveness would be retained for this period following return to SL and upon re-exposure to HA.

METHODS

Eleven healthy male lowland residents participated in this investigation. All were young (mean$\pm$SD) (29$\pm$1 y), very fit (peak oxygen uptake 56$\pm$2 ml/kg/min) members of the U.S. Army Special Forces. All studies were conducted with the subjects resting semisupine and fasted at least 2 hr. Resting ventilation and metabolic rate were acquired using a metabolic chart while subjects breathed room air thru a low deadspace facemask. Arterial oxygen saturation (SaO_2) was measured by finger pulse oximetry. Progressive isocapnic HVR was measured using a rebreathing system containing an initial concentration of 21% O_2 for sea-level studies and 36% O_2 for high-altitude studies. HCVR was measured by the rebreathing technique. Subjects rebreathed from a bag initially containing 7% CO_2 in oxygen. During both the HVR and HCVR tests, all variables were digitally sampled at 50 HZ by a computer and averaged over four breath intervals. HVR($\triangle VE/\triangle SaO_2$) and HCVR($\triangle VE/\triangle PCO_2$) were calculated using least squares regression.

Studies were conduced over a period of 30 days. Sea-level control studies were conducted during the first week. Subjects then ascended by plane and car to the 4,300 m summit of Pikes Peak, CO. They resided on the summit a total of 18 days while a variety of test were performed. Ventilatory measurements were made on HA days 1, 2 and 14. Following the HA residence, the subjects were rapidly transported back to Natick, MA where upon arrival they entered and spent the night in a hypobaric chamber at a barometric pressure of 446 torr. The next morning, subjects were released from the chamber and entered into the post altitude (PA) test period. Ventilatory measurements were made on PA days 1, 3 and 7 at sea level after return from HA. Finally, on PA day 8, six of the eleven subjects were re-exposed (RA) to a barometric presssure of 446 torr for approximately 36 hr in a hypobaric chamber.

RESULTS

The SaO_2 decreased ($P<0.05$) to 79$\pm$8% on HA1 but increased ($P<0.05$) to 89$\pm$2% by the 14th day of residence at HA. After seven days post HA residence at SL, in the 6 subjects re-exposed to high altitude, SaO_2 was similar (85$\pm$3%) to those measured on HA14 but higher ($P<0.05$) than those measured on HA1. This sustained elevation of SaO_2 suggested that ventilation was likewise enhanced during RA.

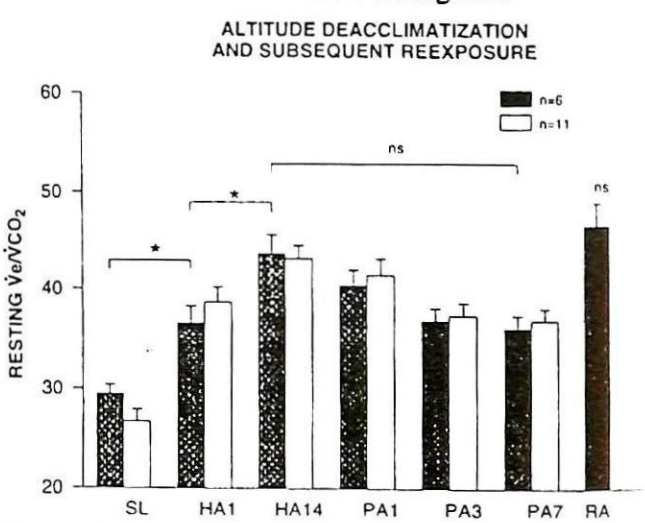

Figure 1: Resting minute ventilation, plotted as VE/VCO_2. Results are presented for the entire group of 11 subjects and also for the subgroup of 6 subjects who were subsequently re-exposed to altitude.

Resting minute ventilation, plotted as VE/-VCO_2 in Fig 1, demonstrated the expected acclimatization response, increasing by ~12% over 14 days residence at 4,300 m. Moreover, upon return to sea level, resting ventilation remained elevated throughout the seven day PA period and in the 6 subjects during RA. These results suggested that the ventilatory acclimatization response was retained over this period. Given that the mechanism of ventilatory acclimatization to altitude includes augmentation of ventilatory chemosensitivity to hypoxia and hypercapnia, we evaluated the HVR and HCVR across this same period.

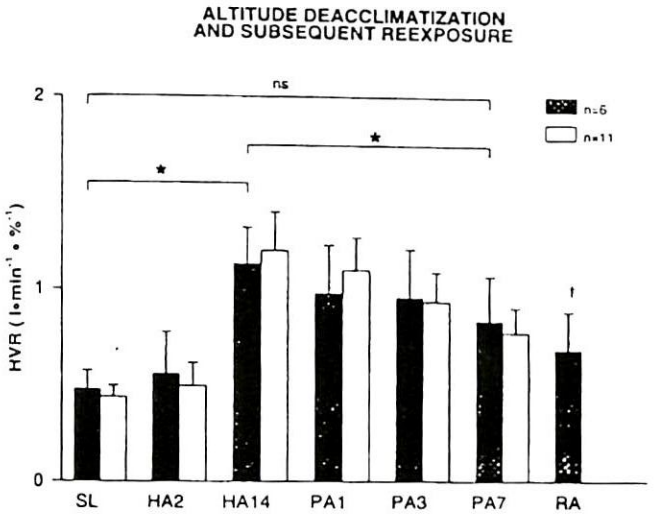

Figure 2: Hypoxic ventilatory response ($\Delta VE/\Delta SaO_2$) as a function of residence at altitude.

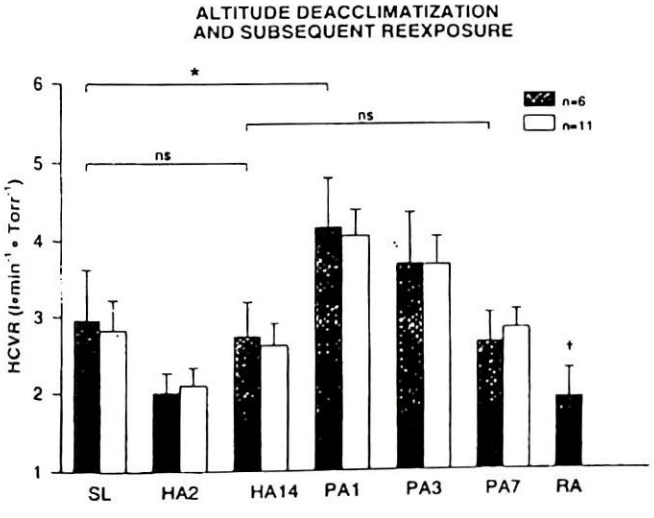

Figure 3: Hypercapnic ventilatory response ($\Delta VE/\Delta PCO_2$) as a function of residence at altitude.

HVR increased ($P<0.05$) ~170% by the 14th day at 4,300 m (Fig 2). Compared to the SL control period, HVR was elevated ($P<0.05$) during the first three days after return to SL from HA. In the six subjects during RA, HVR was not significantly different from their pre-acclimatization SL control. As ilustrated in Fig 3, somewhat similar results were observed with the subjects' HCVR. Although HCVR did not demonstrate any change from SL control (2.83 ± 1.33 l/min/torr) during the period of HA residence, upon return to sea level HCVR was elevated ($P<0.05$) on PA1 (4.06 ± 1.14 l/min/-torr) and PA3 (3.68 ± 1.22 l/min/torr), but returned to SL control values by PA7. During RA, HCVR was actually decreased ($P<0.05$) compared to the preacclimatization SL control value.

DISCUSSION

During 18 days residence at 4300 m, acclimatization produced an increase in resting ventilation, arterial oxygen saturation and ventilatory chemo-responsiveness. Upon return to sea level, elevated ventilation and enhanced HVR and HCVR persisted for approximately 1 week, such that on the seventh day the HVR retained about 45% of its acclimatization response. These results are similar those previously reported by Lahiri et al. (1972) and Sato et al. (1992). After eight days at SL, during re-exposure to altitude, subjects demonstrated a retention of approximately 90 and 67% of their acclimatization responses for ventilation and arterial oxygenation respectively. However, HVR and HCVR were no longer statistically elevated. These measurements of resting ventilation and arterial saturation during re-exposure to high altitude clearly indicate the retention of ventilatory acclimatization. However, the absence of augmented chemosensitivity to either hypoxia or hypercapnia in these subjects leaves the mechanism for this enhanced ventilatory response somewhat in doubt. With the exception of possible methodological errors in our measures of HVR and HCVR during reexposure, it is possible that other factors such as attenuation of hypoxic ventilatory depression may have contributed to the enhanced ventilatory response upon altitude rexposure. Nevertheless, we conclude that ventilatory acclimatization to altitude is retained for at least eight days following return to sea level, thus

lessening the hypoxic stress during subsequent reexposure to altitude within this time period.

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PATHOGENESIS OF HIGH-ALTITUDE PULMONARY EDEMA[1]

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ABSTRACT. Madison strain Sprague-Dawley rats were exposed to low barometric pressures of 294 and 236 torr, or 8.5% oxygen at normal pressure for 8-10 hours. This resulted in an increase of pulmonary artery or right ventricular systolic pressure from 30.5 to 49 torr. Ultrastructural studies of the lung showed evidence of stress failure of pulmonary capillaries including disruption of the capillary endothelial layer, alveolar epithelial layer, or all layer of the wall, red blood cells (RBCs) and edema fluid in the alveolar wall interstitium, proteinaceous fluid and RBCs in the alveolar spaces, and fluid-filled protrusions of the endothelium into the capillary lumen. These appearances are consistent with the ultrastructural changes we have previously described in rabbit lung when the capillaries are exposed to high transmural pressures, strongly suggesting that the pathogenesis of HAPE is stress failure of pulmonary capillaries.

Key Words: stress failure of pulmonary capillaries, pulmonary hypertension, high-permeability edema.

RESUMEN. Ratas Sprague-Dawley de la especie Madison fueron expuestas a baja presión barométrica de 294 y 236 torr, o 8.5% de oxígeno a presión normal por 8-10 horas. Esto resultó en un aumento de la presión de la arteria pulmonar y de la presión sistólica ventricular derecha de 30.5 a 49 torr. Los estudios ultraestructurales del pulmón mostraron evidencia de una insuficiencia por stress de los capilares pulmonares que incluyen una interrupción de la capa endotelial capilar, la capa epitelial alveolar, o todas las capas de la pared, eritrocitos y edema en el intersticio de la pared alveolar, fluido proteináceo y eritrocitos en los espacios alveolares, y protrusiones llenas de líquido del endotelio en la luz de los capilares. Estas características son consistentes con los cambios estructurales que previamente hemos descrito en pulmones de conejos cuando los capilares son expuestos a altas presiones transmurales, lo que fuertemente sugiere que la patogénesis de HAPE es una insuficiencia por stress de los capilares pulmonares.

Palabras Claves: Insuficiencia por stress, Capilares pulmonares, Hipertensión pulmonar, Edema.

INTRODUCTION

The pathogenesis of high-altitude pulmonary edema (HAPE) remains obscure. We have recently proposed that HAPE is due to damage to the walls of pulmonary capillaries as a result of very high wall stresses caused by increased capillary transmural pressures (West et al., 1991; West and Mathieu-Costello, 1992). These high capillary pressures are the result of uneven hypoxic pulmonary vasoconstriction as originally proposed by Hultgren (1969). Extensive studies in our laboratory have shown that raising the capillary transmural pressure in rabbit lung causes ultrastructural damage to the capillary walls including disruptions of the capillary endothelial layer, alveolar epithelial layer, and sometimes all layers of the wall (West et al., 1991; Tsukimoto et al., 1991; Costello et al., 1992; Fu et al., 1992; Elliot et al., 1992). The result is a high-permeability of form of edema (Tsukimoto et al., 1994).

In this paper we report studies on Madison strain Sprague-Dawley rats exposed to simulated high altitude. These animals have previously been shown to develop high pulmonary artery pressures and pulmonary edema under these conditions. Ultrastructural studies of the lung showed the typical changes of stress failure of

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pulmonary capillaries, and we proposed that this is the mechanism of HAPE.

METHODS

Twenty-nine Madison strain Sprague-Dawley rats, body weigth 290-327 g, were used. Thirteen animals were exposed to a pressure of 294 torr in a low pressure chamber for 3 to 12.5 hours. Four rats were exposed to a pressure of 236 torr for up to 8 hours. Four animals breathed 8.5% oxygen for up to 8 hours, and eight animals were studied as controls. The protocols were approved by the Animal Subjects Committees of UCSD and Dartmouth Medical School.

Measurements of pulmonary artery and right ventricular pressures were carried out via implanted catheters inserted 48 hours prior to the experiment (Sardella and Ou, 1993). Pressure measurements were done immediately after taking the rats out the low pressure chamber and transferring them to a Plexiglass box where they breathed 8.5% oxygen if they had been exposed to a pressure of 294 torr, 6.6% oxygen if they had been exposed to 236 torr, or ambient room air if they were controls.

The lungs were prepared for electron microscopy by perfusion fixation with buffered glutaraldehyde as described previously (Tsukimoto et al., 1991).

RESULTS

Pulmonary artery or rigth ventricular pressures.

In all rats exposed to a low Po_2, increases in pulmonary artery or rigth ventricular pressure were seen. The mean pulmonary arterial systolic pressure in the control animals breathing air was 30.5± 0.5 (SE) torr (n=4). The animals exposed to a pressure of 294 torr, 236 torr or 8.5% oxygen had a mean pulmonary arterial or rigth ventricular systolic pressure of 49 ± 2 torr (n=15).

Macroscopic appearance of lung and light microscopy.

Blood-stained frothy fluid was seen in the trachea of 2 animals exposed to a pressure of 294 torr, and in 1 animal exposed to a pressure of 236 torr. In over half the animals exposed to hypoxia, the lungs showed various degrees of macroscopic abnormalities ranging from irregular sparse dark areas to large hemorrhagic regions.

Ultrastructural appearances of lung parenchyma.

Red blood cells were seen in the alveolar spaces as well as electron-dense granular material which represents edema fluid with a high protein concentration. There was also edema of the interstitium of the alveolar wall, fluid-filled protrusions of the endothelium into the capillary lumen, and swelling of alveolar epithelial cells. There was also clear evidence of disruptions of the capillary endothelial and alveolar epithelial layers consistent with stress failure of pulmonary capillaries (Tsukimoto et al., 1991). Red cells were seen in the interstitium of the alveolar wall indicating disruption of the capillary endothelial layer in the proximity. Figure 1 shows complete rupture of the blood-gas barrier with a red cell passing from the capillary lumen into the alveolar space.

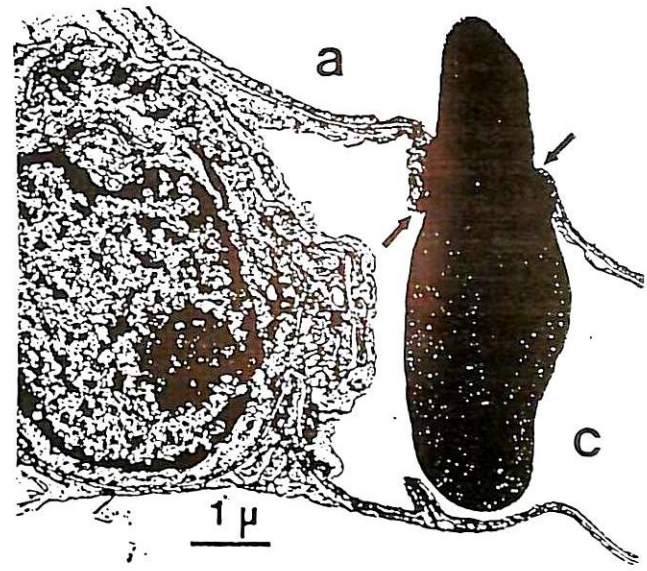

Figure 1. Electron micrograph of lung parenchyma in Madison rat exposed to 294 torr barometric pressure for 4 hours. Note complete rupture of the blood-gas barrier (arrows) with a red blood cell passing into the alveolar space (a); c, capillary. From West et al., 1995)

DISCUSSION

The hypothesis that HAPE is caused by stress failure of pulmonary capillaries fits with many features of the disease. One is the marked correlation between HAPE and pulmonary hypertension. For example, direct pressure measurements in patients with HAPE show high values (Hultgren et al., 1964). Also, patients who develop HAPE tend to have an unusually high degree of hypoxic pulmonary vasoconstriction (Hultgre et al., 1971). Finally, reducing the pulmonary arterial pressure, for example by giving the calcium channel blocker nifedipine usually causes rapid dissappearance of the edema (Oelz et al., 1989), and nifedipine is also effective in preventing HAPE in a high risk group (Bärtsch et al., 1991).

It is also known that the edema of HAPE is of the high-permeability type. Schoene et al. (1988) and Hackett et al. (1986) obtained samples of alveolar fluid by bronchoalveolar lavage in patients with HAPE and reported that fluid was of the high-permeability type with a large concentration of high molecular weight proteins and many cells. Increased concentrations of leukotriene B_4 and complement fragment C5a were also found (see below).

The combination of a hydrostatic pressure basis for HAPE and abnormalities of the capillary walls which are required for the high-permeability edema, can be explained on the basis of stress failure of pulmonary capillaries. Studies from our laboratories have shown that raising the pressure in capillaries of rabbit lung causes ultrastructural changes in the capillary disruption of the capillary endothelial layer, alveolar epithelial layer and sometimes all layer of the wall (West et al., 1991; Tsukimoto et al., 1991). We suggested that this might be the pathogenic basis of HAPE (West et al., 1991) but there were no electron micrograph studies of the lung in that disease, and it is difficult to find animal models. Evidence of ultrastructural changes similar to those reported here was found in lung of rats exposed to acute decompression in a hypobaric chamber (Mooi et al., 1978), but the mechanism was not recognized. In this study, we used Madison strain Sprague-Dawley rats because they do show a strong pulmonary pressor response to hypoxia, and some animals develop pulmonary edema (Colice et al., 1992).

The mechanism of pulmonary hypertension during acute exposure to high altitude is known to be hypoxic pulmonary vasoconstriction. Since this chiefly occurs in small pulmonary arteries (Kato and Staub, 1966), it is not immediately clear why some pulmonary capillaries would be exposed to the high pressure. The explanation is presumably that given by Hultgren (1969) who suggested that the vasoconstriction is uneven with the result that some capillaries are not protected from the increased pressure in the pulmonary arteries. This hypothesis is supported by the very patchy nature of the edema in HAPE (Hultgren et al., 1964; Vock et al., 1991) and the increased dispersion of transit times in hypoxic animal lungs (Dawson et al., 1983).

It has been suggested that HAPE may have an inflammatory basis because of the presence of inflammatory markers including leukotriene B_4, other lipoxygenase products of arachidonic metabolism, and C5a complement fragment in the lavage fluid (Schoene et al., 1988). At first sight these findings seem to argue for some other mechanism than stress failure of pulmonary capillaries. However an important feature of the ultrastructural changes in stress failure is that the basement membrane of capillary endothelial cells are frequently exposed (Tsukimoto et al., 1991). The exposed basement membrane is electrically charged and highly reactive, and can be expected to activate leukocytes and platelets. Indeed in bronchoalveolar lavage studies of our rabbit preparations, leukotriene B_4 is seen in the lavage fluid (Tsukimoto et al., 1994). Platelet activation will result in the formation of small thrombi which are a feature of the pathology of HAPE (Arias-Stella and Kruger, 1963).

If HAPE is caused by stress failure of pulmonary capillaries, the main therapeutic objective is to reduce the pulmonary artery pressure. Since the pressure is high because of hypoxic pulmonary vasoconstriction, the best way to reduce it is by rapid descent or by giving oxygen if this is available. Calcium channel blockers such as nifedipine are also effective because they rapidly reduce the pulmonary arterial pressure (Oelz et al., 1989).

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ENERGY BALANCE AT HIGH ALTITUDE: 6542 m.[1]

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SUMMARY. Weight loss, due to malnutrition and possibly intestinal malabsortion, is a well known phenomenon in high altitude climbers. Up to ~5000 m energy balance may be attained and intestinal energy digestibility remains normal. In order to see whether 1) energy digestibility would play a significant role in the energy deficit, energy intake, energy expenditure, body composition and energy digestibility of 10 subjects (four women and six men, 27-44 yr) were assessed during a 21 day sojourn on the summit of Mt. Sajama, Bolivia (6542 m). Energy intake was measured during two 3 day intervals: 7-9 (EI_1) and 17-19 (EI_2). Total fecal energy loss during EI_1 was calculated from fecal energy measured by bomb calorimetry. Average daily metabolic rate (ADMR) at altitude was measured in six subjects, two women and four men, with doubly labeled water over a 10-day interval: 9-19. Basal metabolic rate (BMR) was measured before and after the expedition by respiratory gas analysis. Body composition was estimated from skinfolds and body mass before and during the altitude sojourn. Subjects were in negative energy balance throughout the observation period (EI_1 - ADMR = -2.9±1.8 MJ/d and EI_2 - ADMR = -2.3±1.8 MJ/d, based on a gross energy digestibility of 95%). The loss of fat mass (3.7±1.5 Kg) represented 74±15% of the loss of body mass. Energy content of the feces was 21 kJ/d dry weight and gross energy digestibility amounted to 85%. The energy deficit increased to 3.5 MJ/d after correction for the decreased energy digestibility. In conclusion, energy balance was not attained at 6542 m. The resulting energy deficit appeared to result mostly from malnutrition and only a limited part could be attributed to malabsorption.

Key words: Energy intake, Digestibility, Malabsorption, Energy expenditure, Body Composition, Doubly labeled water.

RESUMEN. La pérdida de peso debido a malnutrición y posiblemente a malabsorción intestinal es un fenómeno conocido en escaladores de montaña. Hasta 5000 metros el balance de energía es mantenido debido a que la energía por la digestión intestinal permanece normal. Se han estudiado 10 sujetos (cuatro mujeres y seis varones, 27-44 años) durante una permanencia de 21 días en el pico del Monte Sajama, Bolivia (6542 m), para observar si la energía de la digestión juega un rol importante en el déficit de energía, ingesta de energía, gasto de energía, composición corporal, y energía de la digestión. La ingesta de energía se midió durante dos intervalos de 3 días: 7-9 (EI_1) y 17-19 (EI_2). La pérdida de energía fecal total durante EI_1 fue calculada de la energía fecal medida por un calorímetro de bomba. La tasa metabólica diaria promedio (ADMR) en la altura fue medida en seis sujetos, dos mujeres y cuatro varones, con agua marcada con deuterio sobre un intervalo de 10 días: 9-19. La tasa metabólica basal (BMR) fue medida antes y después de la expedición por análisis de gas respirado. La composición corporal fue estimada de los panículos adiposos y de la masa corporal antes y durante la estadía en la altura. Los sujetos estuvieron en balance energético negativo durante todo el período de observación (EI_1 - ADMR = -2.9±1.8 MJ/d y EI_2 - ADMR = -2.3±1.8 MJ/d, basado en una gruesa energía de digestión de 95%). La pérdida de masa grasa (3.7±1.5 Kg) representó 74±15% de la pérdida de la masa corporal. El contenido de energía de las heces fue de 21 kJ/d de peso seco y la energía gruesa de la digestión llegó a 85%. El déficit de energía aumentó a 3.5 MJ/d después de corregir la disminuída energía de la digestión. En conclusión el balance energético no fue alcanzado a 6542 m. El deficit energético resultante parece ser el resultado de malnutrición y tan sólo una limitada parte puede ser atribuído a malabsorción.

Palabras Claves: Ingesta de energía, Digestibilidad, Malabsorción, Gasto de Energía, Composición Corporal, Agua con doble marca.

INTRODUCTION

Weight loss at high altitude is a well known phenomenon. Several hypotheses have been forwarded to explain this phenomenon like e.g. simple malnutrition, loss of body water and intestinal malabsortion (for a review see Imray et al 1992). With regard to malnutrition there is evidence that subjects can maintain energy balance during exposure at altitudes up to ~5000 m. During a one month stay at 5050 m it was recently shown that, in the presence of

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sufficient comfort and palatable food, weight loss can be largely prevented (Kayser 1992). With regard to malabsortion it appears that up to 5000-5500 m intestinal absorptive function for macro nutrients remains normal (Butterfield et al 1992, Kayser et al 1992). It remains unclear whether malnutrition and malabsortion would play a significant role for energy balance at altitudes greater than 5500 m.

The present study was therefore designed to complement the foregoing studies on energy metabolism at very high altitude. The primary aim of the study was to test the hypothesis that energy balance can also be maintained at an altitude of 6542 m. The secondary aim of the study was to test the hypothesis that, in case energy balance could not be maintained, a decrease in energy digestibility would explain, at least in part, the energy deficit observed. To these aims energy intake, energy expenditure, body composition and energy digestibility of 10 subjects were assessed during a 21-day sojourn on the summit of Mt Sajama (6542 m).

METHODS

Subjects were four women and six men, age 35±6 (SD) yr, body mass index 22.0±1.5 kg/m^2. All residing at sea-level for at least 5 years before participating in the present study and all with previous high altitude experience (maximum altitude reached ranging from 4350-8760 m). The observations started with baseline measurements at sea level (Paris, France and Maastricht, The Netherlands). Subjects subsequently travelled to La Paz, Bolivia (3600 m) where they stayed for 5 days to acclimatize and to further organize the expedition. Subsequently, the remaining altitude change from 3600 to 6542 m was covered in 13 days. The stay in tents on the large flat summit of Mt. Sajama (6542 m) lasted 21 days. During the stay on the summit the subjects' activity level was low, mean ambient temperature was - 13° C. Finally, sea level observations were again performed upon return to Paris and Maastricht 10 days after leaving the summit. Energy balance was determined after the initial acclimatization, by measuring energy intake and energy expenditure.

Energy intake (EI) at altitude was measured with a dietary record over two 3-day intervals: day 7-9 (EI_1) and day 17-19 (EI_2). Food items were weighed with a table scale in most cases and volumes were measured with a graduated container. The energy content (metabolizable energy (ME) = gross energy (GE) - fecal energy - urinary energy) of the food intake was derived from food tables and the percentage for the intake of carbohydrate, fat and protein were calculated (Randoin 1982). From these data, the GE content of the diet (which includes undigestible material such as cellulose) was calculated using Atwater's factors for the heat of combustion (Widdowson 1955). In order to determine nutrient absorption and nitrogen balance, subjects collected 24 h urine for one day and total feces for all days of the first 3-day dietary record interval as described before (Kayser et al 1992). Energy content of the feces was measured with an adiabatic bomb calorimeter (Janke & Kunkel, IKA Kalometer C-400, Staufen). Nitrogen content of the feces and urine was measured with a Heraeus analyser (type CHN-O-rapid, Heraeus, Hanau).

Energy expenditure was measured under field conditions (average daily metabolic rate, ADMR) at altitude. Basal metabolic rate was measured with a ventilated hood system. At altitude, ADMR was measured in 2 women and 4 men randomly selected among the 10 subjects with doubly labeled water as described before (Westerterp et al 1994). The observation interval lasted 10 days from day 9-19 of the stay at the summit. Body fat and lean body mass were estimated according to Durnin and Womersley (1974).

Results are presented as mean±SD unless stated differently. Values obtained before, during, and after the stay on Mt. Sajama were compared with the Wilcoxon signed-rank test.

RESULTS

Mean EI showed a non significant increase from 7.8±3.1 MJ/d in interval one to 8.2±3.5 MJ/d in interval two, at the start and at the end of the observation interval of ADMR with doubly labeled water, respectively. The overall mean EI, calculated as the average of both values, was 8.0±3.2 MJ/day based on standard figures for nutrient absorption. Mean fluid intake over the two 3-day observation intervals, inclu-

ding water in drinks as well as water in the food, was 1.9±0.5 l/d, respectively. The energy content of the feces was 20.6±1.7 kJ/g dry weight (range 18.0-23.0 kJ/g). The total energy loss in the feces from the food consumed in the 3 day observation period was 3.6±1.3 MJ. The GE content of the food consumed over the interval was 25.2±9.8 MJ. Combining these two figures, the average energy digestibility amounted to 85.2±4.7%. The combination of the dietary record with the nitrogen output in feces and urine allowed calculation of protein balance. Protein digestion was 88.6±3.8%. Protein balance was -28.6±24.2 g/d, based on the measured protein digestion. The figure for protein balance based on the dietary record and urine nitrogen output using the standard figure for protein digestion from the food tables was similar (-26.3±24.5 g/d).

Water loss and energy expenditure as calculated from isotope elimination are presented in Table 1. Comparing water loss with water input needs correction of water intake for metabolic water (see discussion). ADMR was higher than EI in all subjects; the mean difference was 24±14% of ADMR. Comparing BMR values before and after the expedition, differences were insignificant (mean difference -3±7%, n.s.).

Table 1. Body mass, body composition and basal metabolic rate before and after high altitude exposure, and fluid intake, fluid output, energy intake, and average daily metabolic rate during high altitude exposure.

	before			during				after		
Subj No.	BM kg	BF %	BMR MJ/day	$Fluid_{in}$ l/day	$Fluid_{out}$ l/day	EI MJ/d	ADMR MJ/d	BM* kg	BF* %	BMR** MJ/d
1	49.5	27.1	5.23	1.4	2.9	6.4	9.2	48.0	23.4	-
2	54.8	26.2	5.04	-	-	-	-	49.0	20.5	5.43
3	71.0	13.3	7.32	2.6	3.7	12.7	13.1	66.5	12.3	7.46
4	64.6	14.9	6.25	-	-	-	-	60.0	11.0	6.08
5	76.4	14.6	6.51	2.4	3.4	14.0	15.3	69.0	11.3	6.31
6	70.0	17.0	6.42	1.7	2.2	8.5	12.1	61.5	12.6	6.74
7	67.6	26.2	6.16	-	-	-	-	63.5	18.0	-
8	58.4	27.6	6.09	1.6	2.7	5.7	8.8	55.0	25.5	5.23
9	63.8	21.6	5.99	-	-	-	-	60.5	14.0	5.52
10	80.5	18.8	7.32	2.1	3.2	7.7	12.1	75.0	15.0	6.62
Mean	65.7	20.7	6.23	2.0	3.0	9.2	11.8	60.8	16.4	6.17
SD	9.6	5.7	0.74	0.5	0.5	3.4	2.4	5.5	5.2	0.76

*after 20 days at 6542 m; ** 10 days after descent from 6542 m (2 days after descent from 3600 m)
BM, body mass; BF, body fat as calculated from skinfold thickness; BMR, basal metabolic rate as measured in the early morning with a ventilated hood; $Fluid_{in}$, fluid intake; $Fluid_{out}$, Fluid output; ADMR, average daily metabolic rate.
The two missing values of BMR after the expedition were due to non availability of the subjects for practical reasons.

Body mass and body composition were different before and after 20 days at 6542 m (Table 1). Body mass decreased 4.9±2.0 kg ($P<0.01$) and fat mass (FM) decreased 3.5±1.5 kg ($P<0.01$). The decrease in fat-free mass (FFM) with 1.3±2.3 kg was not significant. However, changes in body composition as estimated during the stay at altitude with skinfold

thickness measurements have to be interpreted with some care (Fulco et al 1992). One subject (N°8) showed indications of altitude edema. This fact probably influenced the accuracy of the skinfold thickness as a measure for body fat and this measurement for N°8 was therefore excluded from further analysis.

DISCUSSION

Water balance over the observation interval can be calculated from fluid input and fluid output correcting the former for metabolic water production. Metabolic water production was calculated from dietary intake and catabolism of body stores according to Consolazio et al (1972). Thus, there was no significant difference between water input and water output, i.e. subjects were in water balance. However, water balance was reached at a low level of water turnover. Water turnover was probably limited by a reduced water availability and comparable to the value of 3.3 ± 0.6 l/day measured during climbing between 5000 and 8872 m on Mt. Everest (Westerterp et al 1992).

Energy balance can be calculated from energy intakes as measured with the dietary record and energy expenditure as measured with doubly labeled water. Mean energy intake, the average over three days at the start and at the end of the ten-day observation period with doubly labeled water, was 2.6 ± 1.5 MJ/d lower than energy expenditure. There was a tendency for an increase in energy intake, probably as a result of a reduction in symptoms of acute mountain sikness (AMS). Thus, there was only a trend to a balance between energy intake and energy expenditure over the three week stay at 6542 m, leaving on average a gap of at least 2.3 MJ/day or 20% of ADMR.

The observed digestibility of 85% was lower than that usually measured at sea level (94%) (Widdowson 1955, Consolazio et al 1992), at 4300 m (95%) (Consolazio et al 1992) or at 5050 m (96%) (Kayser et al 1992). At first glance it therefore appears that the present subjects indeed experienced a certain degree of intestinal malabsortion. However, the energy content of the feces of the subjects (21 kJ/g dry weight) was actually lower than that reported for a mixed diet at sea level (22 kJ/g dry weight (Diem et al 1971)) and the same as that measured at 5050 m (Kayser et al 1992) for a diet of similar macronutrient and fiber composition, suggesting on the contrary a normal intestinal absorptive capacity. Thus, the present energy content of the feces seems to exclude significant malabsortion of fat or other macronutrients. The above evidence of malabsorption should therefore be interpreted with care and additional experiments seem necessary before the hypothesis of malabsortion at high altitude can be accepted. If one accepts the observed figure for digestibility it can be calculated that the mean difference between intake and expenditure increased from -2.6 ± 1.5 MJ/d to -3.5 ± 2.4 MJ/d. It thus appears that even if some degree of malabsortion would indeed develop at high altitude it would be relatively small when compared to the energy deficit resulting from simple malnutrition.

Body weight decreased 4.9 ± 2.1 kg from before until after 20 days at 6542 m, representing on average 74% body fat. Fulco et al (1992) recently stated that the skinfold method was not acceptable for the measurement of body water measurement, one of the subjects in the present study showed peripheral subcutaneous edema and had to be excluded from the analysis.

The activity level of the subjects can be calculated by expresing ADMR as a multiple of BMR, the physical activity index (PAI). Assuming BMR over day 9-19 at 6542 m was the same as at sea level and averaging BMR values before and after the expeditions, the mean PAI was 1.84 ± 0.28 (range 1.56-2.39). This value falls just outside the range of 1.5-1.8 for light to moderately active subjects (WHO 1985), but is lower than the mean PAI of 2.2 measured during climbing at high altitude (Westerterp et al 1992). Of course the PAI value has to be interpreted with some care as at high altitude BMR has been shown to be increased. Butterfield et al (1992) measured an increase of BMR during a 21-days stay at 4300 m of 0-15% compared to sea-level values. Whatever happened with BMR at 6542 m, ADMR was relatively high for subjects with a sedentary life style, living in tents and occasionally getting out in the close surroundings.

In conclusion the result from this study indicates that subjects with ad libitum access to food do not attain energy balance during a 3-

week sojourn at 6542 m. Energy intake is low while energy expenditure reaches values comparable to those for moderate activity at sea-level. The resulting energy deficit appears to be due mostly to malnutrition and only a limited part can be attributed to malabsorption.

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INADEQUATE TREATMENT OF EXCESSIVE ERYTHROCYTOSIS[1]

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SUMMARY. Patients with Chronic Mountain Sickness or Excessive Erythrocytosis (EE) are permanent residents of high altitude 3600 m, and have red blood cell counts (RBC) above 6.5 x 10^6 and appear cyanotic. This causes aesthetic and psychological problems in their life. Occasionally, observers may believe they are alcoholics. When RBC are increased, they search for a miraculous cure. According to several previously evolved concepts of EE, treatments have included: leeches, marrow radiotherapy by administration of radioactive substances like phosphorous, and more recently, phlebotomies, tea infusions, garlic tablets and most dangerously, administration of a previously prohibited cytotoxic agent, phenylhydrazine. One concept of providing treatment for EE patients is to permanently destroy their RBCs. However, the effect of phenylhydrazine usage is toxic for the bone marrow, the liver and other tissues, changing the color of the skin from cyanotic to yellow, with jaundice. The conjunctivae of the eyes become icteric and the urine becomes dark brown. Once started on treatment, patients are tested periodically and their RBC count indeed diminishes, and they may feel satisfied. However this toxic medication may have a fatal outcome. By reducing the number of RBCs, the arterial oxygen content (CaO_2) of the blood is diminished. We have found the majority of patients with EE to have abnormal chest x-rays. Ergometric testing of these patients may produce severe oxygen debt. In one of the patients, on the 4th stage of the Bruce Protocol, intense pain in both legs gradually became intolerable and he required post-exercise oxygen. Following interruption of the phenylhydrazine, CaO_2 returned to normal in approximately 60 days, with a rise of RBCs slightly above previous levels. The patient experienced no symptoms of illness. This case and multiple other cases have lead us to believe that EE is a compensating mechanism for lung disease at high altitude and that the RBC mass should not be decreased.

Key words: Excessive erythrocytosis, Phenylhydrazine, treatment.

RESUMEN. Los pacientes con el mal de montaña crónico o eritrocitosis excesiva (EE) son residentes de la altura (3600 m) con ≥ 6.5 x 10^6 glóbulos rojos (GR) que presentan cianosis. Esto ocasiona problemas estéticos y psicológicos en su vida ya que las demás personas creen que son alcohólicos. Cuando hay aumento de los GR, ellos buscan una cura milagrosa. De acuerdo a los conceptos evolutivos de la EE, los tratamientos han incluído: sanguijuelas, radioterapia de la médula ósea mediante administración de substancias radioactivas como el fósforo, y más recientemente, flebotomías, infusiones de té, tabletas de ajo y la más peligrosa la administración de la fenilhidrazina, agente citotóxico prohibido. Encontramos que la mayoría de los pacientes con EE tienen placas radiográficas de tórax anormales. El concepto de los tratamientos es el de disminuir los GR. Sin embargo, la fenilhidrazina es tóxica para la médula ósea, el hígado y otros tejidos, cambiando el color de la piel de cianótica a ictérica. Las conjuntivas se tornan ictéricas y la orina café oscura. Una vez iniciado el tratamiento, la sangre de los pacientes es analizada periódicamente y el recuento de GR disminuye, con lo que quedan satisfechos. Sin embargo, este medicamento tóxico puede producir la muerte. Al reducir los GR, el contenido arterial de oxígeno (CaO_2) en la sangre disminuye. Las pruebas ergométricas en estos pacientes durante el tratamiento producen gran débito de oxígeno. En el paciente descrito, en el 4to nivel del protocolo de Bruce, el dolor intenso de ambas pantorrillas se hizo intolerable y requirió oxígeno post ejercicio. Al interrumpirse la fenilhidrazina, el CaO_2 retorna a niveles normales en aproximadamente 60 días, con una elevación de los GR por encima de los valores iniciales, y mejoría de la capacidad de ejercicio. Este y muchos otros casos nos llevan a creer que la EE es un mecanismo de compensación de la enfermedad pulmonar en la altura y que la cantidad de GR no debe ser disminuída.

Palabras claves: Eritrocitosis excesiva, tratamiento, fenilhidrazina.

INTRODUCTION

Since Monge (Monge, 1928; 1929; 1943) described chronic mountain sickness (CMS), the treatment of these patients has been controversial. These high altitude inhabitants suffer from an increased number of red blood cells and are cyanotic. They usually are diagnosed with Excessive Erythrocytosis because they consult a physician due to their cyanosis or headaches, or simply because a routine blood test reveals an increased hematocrit. Frequently they are told that their high hematocrit is very dangerous and so their understood objective is to find a doctor to be treated to reduce the number of red blood cells. Unfortunately, they may fall

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easily into the hands of unscrupulous physicians. Hence they receive multiple panaceas or see physicians who propose phlebotomies. However some physicians have given these patients, phenylhydrazine, a hemolytic agent long abandoned because of its toxicity (Litter M. 1984). In the past, we have seen several cases treated with this medication.

We present a case report in order to illustrate the toxic effects of this drug in a patient with EE. He was initially seen by us, before being given the treatment and later while he took the drug.

METHODS

Patient FG was first seen in consultation because of cyanosis, headaches and fatigue. He was a non-smoker, drank alcoholic beverages occasionally, had minor digestion problems. His father died of lung cancer and his mother had a cardiac pacemaker. Five brothers were healthy. A complete physical examination was performed on this 44 year old subject. Weight was 74.3 Kg, height 163 cm, blood pressure 120/90 mm Hg and his pulse was 90 per minute. The electrocardiogram revealed elevation of S-T segments in V-2 and V-3. On laboratory examination, the hematocrit was 67%, hemoglobin 22.3 gm%, 7.5 million red blood cells per mm^3, and 8700 white blood cells per mm^3 and a 70 % neutrophil differential count. The urine analysis was normal.

Pulmonary function studies found a diminished forced vital capacity (FVC), 79% of predicted, FEV.1, 77% predicted and FEF 25-75, 59% of predicted. A flow-volume curve was compatible with chronic bronchial obstruction. The Nitrogen Washout test revealed a diminished Total Lung Capacity (87% predicted), and residual volume (72% of predicted), with no signs of uneven ventilation. Radial artery blood gases at rest found a $PaCO_2$ of 39 mm Hg, PaO_2 39 mm Hg and pH of 7.38, a compensated respiratory acidosis. His chest x-rays, showed enlarged hila, nodular images distributed in both lungs, a 2 cm in diameter calcified nodule, and an enlarged heart.

A hyperoxic test breathing 100 % oxygen showed significant pulmonary shunt reaching a PaO_2 of only 104 mm Hg (normal above 200 mm Hg). He was diagnosed as having chronic obstructive pulmonary disease, cor pulmonale, myocardial ischaemia and pulmonary shunting with compensatory excessive erythrocytosis. He was given antibiotics, mucolitics, bronchodilators, and a weight loss diet. On the second visit, two months later, he felt much better, his hematocrit increased to 73 % and blood gases improved (Fig. 1). He naturally thought he was getting worse. He was lost to follow-up, but reappeared confidently 6 months later with a hematocrit of 53% and leukocytosis of 10300. In the interim he had received phenylhydrazine, two tablets a day prescribed by a hematologist. He was pale yellow with jaundice readily evident in his sclerae.

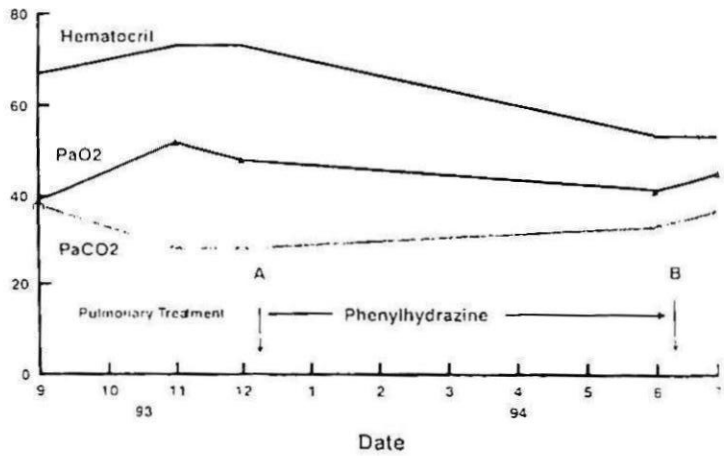

Fig. 1. Effect of Phenylhydrazine in a patient with Excessive Erythrocytosis who was in pulmonary treatment until line A, when he consulted elsewhere and was started on phenylhydrazine, to be later rechecked by us in line B.

The urine analysis showed a dark brown color, ketones +, nitrites +, bilirrubin +++, Urobilinogen +++, protein ++ and hemoglobin ++++. The blood smear showed target cells along with poikilocytes and anisocytosis (Fig. 2).

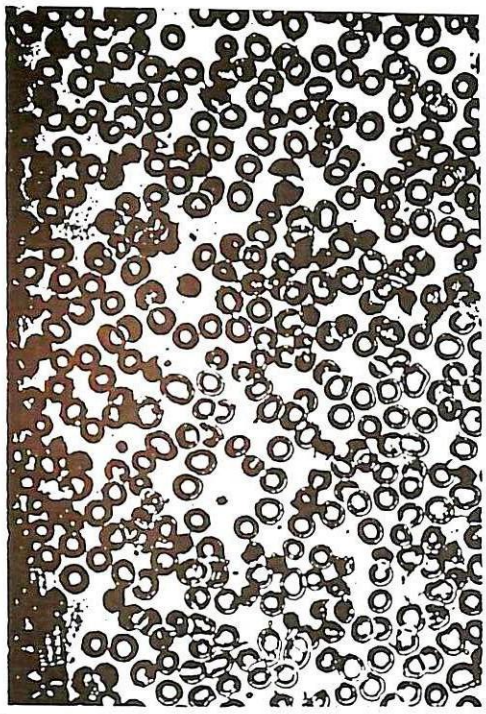

Fig. 2. Red cell smear with Wright stain in the same patient while receiving Phenylhydrazine at line B of fig 1.

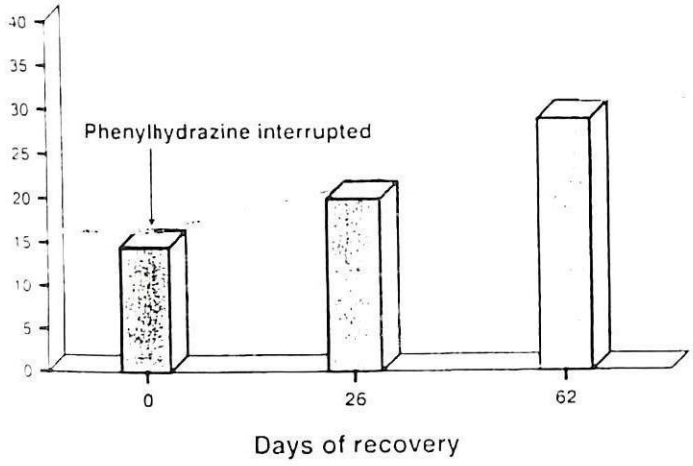

Fig. 3. Once Phenylhydrazine is interrupted the oxygen content rises in 3 months as observed in another patient.

On a treadmill exercise test with the Bruce Protocol, he made an effort to reach 5 levels. Upon stopping, he was extremely cyanotic, could hardly talk, was very dyspneic and complained of intense pain in both calves. He was given oxygen because we had never seen so severe oxygen debt post exercise.

DISCUSSION

This is another case of the previously reported iatrogeny (Zubieta-Calleja and Zubieta-Castillo, 1989). This patient was diagnosed as having EE secondary to long term cardio-pulmonary disease at high altitude (3600 m). When he was originally treated by us, we focused the treatment on improving the pulmonary function and his hematocrit increased, but so did his PaO_2 (52 mm Hg). While receiving Phenylhydrazine his oxygen content was reduced dramatically and due to the large shunt, his PaO_2 was 41 mm Hg although he looked less cyanotic (actually yellow). The exercise test found him capable of achieving the 5th level (normal, for a sedentary healthy person at 3600 m) but at great oxygen debt. This was a patient with a large intra-pulmonary shunt whose compensating EE was significantly reduced. Therefore the oxygen content of his blood was reduced along with his work capacity. In another patient, the arterial oxygen content gradually increased in 62 days, upon interruption of Phenylhydrazine and it was observed that there was a significant improvement on uphill walking the steep streets of La Paz, something he had been unable to do while on the drug (Fig. 3).

In the first patient, blood and urine analysis showed intense hemolysis, characteristic of the use of phenylhydrazine. This can be extremely dangerous leading to renal insufficiency, hepatotoxicity and bone marrow toxicity. The pulmonary shunt could not be improved by decreasing the red blood cell mass. Unfortunately we did not perform an exercise test before receipt of the drug.

Our previous experience in patients with EE found no one with the intense post-exercise cyanosis and oxygen debt that this patient experienced. Although unable to reach level 5, their recovery is usually uneventful. We strongly recommend that patients with EE and pulmonary disease, not be treated with this drug, nor should they have their RBC mass reduced. To our knowledge there is no safe drug treatment for reduction of EE. Treatments should be directed at the etiology of the pulmonary lesions that cause EE at high altitude, not at the secondary increased red cell mass.

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BIOLOGICAL BASIS OF CHRONIC MOUNTAIN SICKNESS[1]

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SUMMARY. The Andes completed its present elevation about 18 million years ago when mammals had already expanded at sea level about 65 million years ago. Therefore, mammals are recent invaders of the Andean high altitude. Andeans are newcomers to high altitude with only thousands of years of hypoxic exposition. High altitude is a great biological challenge for animal life and chronic mountain sickness is the result of this disease at sea level, where mammals evolved their respiratory function in the hyperoxic atmosphere. Chronic mountain sickness constitutes an excessive response of physiological mechanisms which appear in the course of acclimatization of newcomers to high altitude or in high altitude natives, which eventually lead to symptoms of intolerance to the hypoxic environment. There is total loss of hyperventilation with PaO_2 of 40 Torr in high altitude natives with excessive polycythemia and symptoms of chronic mountain sickness compared with 32 Torr in the younger asymptomatic ones (excessive hypoventilation). About 33 % of the population living in Cerro de Pasco (4340 m) older than 50 years have concentrations of hemoglobin above 21.3 g/dl. In chronic mountain sickness is observed an exaggerated increase in arterial pulmonary hypertension, enlargement of the carotid bodies in high altitude natives and a high incidence of chemodectomas.

Key Words. Acclimatization, Andes, Evolution, Chronic Mountain Disease.

RESUMEN. Los Andes completaron su elevación actual hace 18 millones de años cuando los mamíferos ya se habían expandido por el nivel del mar 65 millones de años atrás. Por lo tanto, los mamíferos son invasores recientes de los Andes. Los andinos son recién llegados a la altura con sólo miles de años de exposición a la hipoxia. La altura es un gran reto biológico para la vida animal y el mal de montaña crónico es el resultado de esta enfermedad a nivel del mar, donde los mamíferos evolucionaron su función respiratoria en la atmósfera hiperóxica. El mal de montaña crónico constituye una respuesta exagerada de los mecanismos fisiológicos que aparecen en el curso de la aclimatización de los recién llegados a la altura o en los nativos de la altura, que eventualmente conduce a síntomas de intolerancia al medio hipóxico. Hay una total pérdida de la hiperventilación con PaO_2 de 40 Torr en nativos de la altura con excesiva policitemia y síntomas de mal de montaña crónico comparado con 32 Torr en los sujetos jóvenes asintomáticos (hipoventilación excesiva). Cerca del 33 % de la población de Cerro de Pasco (4340 m) mayores de 50 años tienen concentraciones de hemoglobina por encima de 21.3 g/dl. En el mal de montaña crónico se observa un aumento exagerado de la hipertensión arterial pulmonar, agrandamiento de los cuerpos carotídeos en nativos de la altura y una alta incidencia de quemodectomas.

Palabras Claves. Aclimatización, Andes, Evolución, Mal de Montaña Crónico.

The evolution of mammals is a late evolutionary event during which the concentration of oxygen in the atmosphere reached maximum values.

The lung function of mammals evolved in this highly oxygenated atmosphere. Blood of mammals saturates at the sea level PaO_2 pressure of about 100 Torr and any elevation above sea level will unsaturate the blood. From this point of view, altitude starts as soon as we leave sea level.

The Andes completed its present elevation about 18 million years ago when mammals had already expanded at sea level about 65 million years ago. Therefore, mammals are recent invaders of the Andean high altitude niche and carry with them a basic sea level design but with enough evolutionary time to develop genetic adaptations to the hypoxic environment.

Andeans are newcomers to high altitude with only thousands of years of hypoxic exposition and without enough geographic isolation to reach the genotypic capacities of the better

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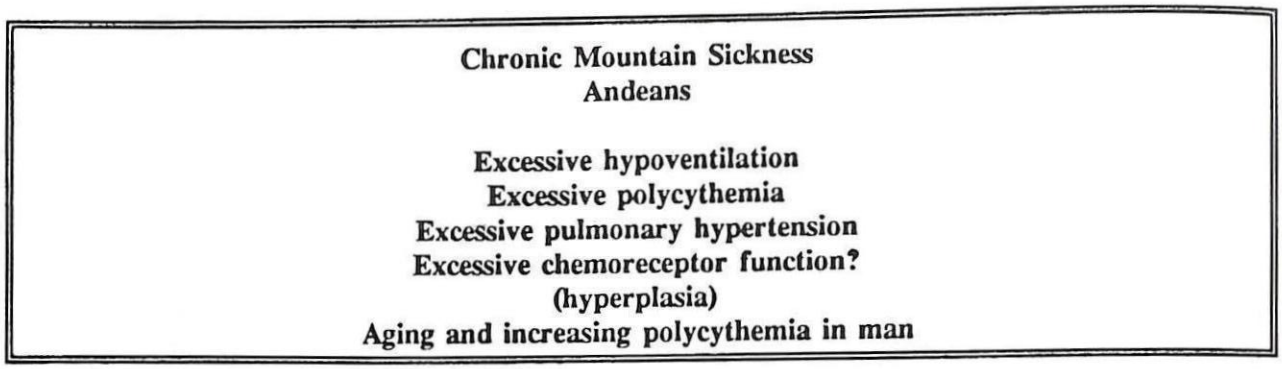

Figure 1.- Excessive physiological adaptive responses of Andeans to the hypoxic environment.

adapted animal species. High altitude is a great biological challenge for animal life and chronic mountain sickness is the result of this disease at sea level, where mammals evolved their respiratory function in the hyperoxic atmosphere.

The basic design of the respiratory function of mammals and birds is a sea level design but the basic genetic capacity, which allows the fetus to live on top of "mount Everest" inside the uterus, can be expressed high altitudes.

Chronic mountain sickness is not a discrete clinical entity. It constitutes an excessive response of physiological mechanisms which appear in the course of acclimatization of newcomers to high altitude or in high altitude natives. Figure 1 summarizes some of these exaggerated responses which eventually lead to symptoms of intolerance to the hypoxic environment. Monge et al (1964) have reported the total loss of hyperventilation with PaO_2 of 40 Torr in high altitude natives with excessive polycythemia and symptoms of chronic mountain sickness compared with 32 Torr in the younger asymptomatic ones (excessive hypoventilation).

The epidemiological studies conducted in Cerro de Pasco at 4300 meters have set the maximum figure for hemoglobin concentration at 21.3 g/dl. About 33% of the population older than 50 years have concentrations above this figure (excessive polycythemia), (León-Velarde and Arregui, 1994); León-Velarde et al 1993; Monge CC et al, 1989).

Peñaloza et al (1971) have reported an exaggerated increase in arterial pulmonary hypertension in cases of chronic mountain sickness (excessive pulmonary hypertension). Arias-Stella (1963) described the enlargement of the carotid bodies in high altitude natives and Saldaña et al (1973) found an incidence of chemodectomas 10 times larger in high altitude natives than in sea level controls (excessive chemoreflex activity of the carotid bodies?).

The excessive responses described above seem to indicate that the continuous "struggle for oxygen" (Barbashova, 1964) in Andeans living at high altitude can lead to the loss of adaptation to their native high altitude environment. These results should not be extrapolated to other high altitude populations like Tibetans, who seem to have a better genetic selection for the hypoxic environment (Zamudio et al, .1993; Beall, 1993). However in future times when the genetic pool of Tibetans becomes diluted by admixture with sea level genes, when transportation facilities will impede geographic isolation and when industry will westernize life in the Hymalayas, it is very probable that the Andean model of weak high altitude adaptation will also be established in Tibetans.

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ASSESSMENT OF Q-HETEROCHROMATIN IN PATIENTS WITH ACUTE MOUNTAIN SICKNESS[1].

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SUMMARY. To determine genetic markers of the possible development of acute mountain sickness (AMS), we assessed the number and distribution of specific chromosomal regions, namely, Q-Heterochromatin regions (Q-HR) in 34 subjects who developed AMS after the ascent to 3600 m above sea level (Eastern Pamir). Controls were 36 subjects without signs of AMS. Q-HR analysis was performed using propil quinacrine mustard staining of the chromosomal preparations obtained from short-term lymphocyte culture. Unlike the controls, subjects with AMS were found to have certain differences in distribution of quantitative characteristics of chromosomal Q-HR variability; the total number of Q-HR in AMS subjects were 2.15 $\pm$ 0.19 in comparison to 1.06 $\pm$ 0.14 in the control group ($P<0,001$). Thus, these data suggested the role of the hereditary predisposition in the development of acute mountain sickness.

Key words: acute mountain sickness, Q-heterochromatin regions.

RESUMEN. El presente estudio se ha diseñado para determinar marcadores genéticos del posible desarrollo del mal de montaña agudo (MMA), para lo cual se ha evaluado el número y distribución de las regiones cromosomiales específicas, nominalmente, las regiones de heterocromatina-Q (Q-HR) en 34 sujetos que desarrollaron MMA después de ascender a 3600 metros sobre el nivel del mar (Eastern Pamir). Los controles fueron 36 sujetos sin signos de MMA. El análisis de Q-HR se realizó utilizando la tinción de mostaza de propil quinacrina de las preparaciones cromosomales obtenidas de los cultivos de linfocitos. A diferencia de los controles, los sujetos con MMA mostraron ciertas diferencias en la distribución de características cuantitativas de la variabilidad cromosomal Q-HR; el número total de Q-HR en sujetos con MMA fue de 2.15 $\pm$ 0.19 en tanto que en los controles fue de 1.06 $\pm$ 0.14 ($P<0,001$). Estos datos sugieren el rol de la predisposición hereditaria en el desarrollo del mal de montaña agudo.

Palabras claves: Mal de Montaña Agudo, Regiones de Heterocromatina-Q.

INTRODUCTION

Some biological and physiological characteristics of the high-altitude natives are known (Mirrakhimov, 1978). Our previous studies on aborigines in Eurasia and Africa have shown their significant heterogeneity in chromosomal Q polymorphism (Ibraimov and Mirrakhimov, 1982a,b,c; Ibraimov and Mirrakhimov, 1983). It was felt that the main reason for the observed interpopulation cytogenetic differentiation was the influence of climatic environmental factors rather than the racial, national or ethnic features of the population under study.

It was of interest the large decreases in chromosomal Q heterochromatin material in the gene stock of aborigines of high altitude and northern latitudes as compared to residents of moderate latitudes of Eurasia or subequatorial Africa (Ibraimov et al. 1986a,b). The same was found in mountaineers, who are well adapted to high altitude (Ibraimov et al., 1990).

We postulate that number of Q heterochromatin may play an important role in the development of acute mountain sickness (AMS) in subjects that living at sea level ascend to high altitude places.

The aim of the present investigation was

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the assessment of this hypotheses.

MATERIAL AND METHODS

During ascent from Gulcha (1650 m above sea level) to Murgab (Eastern Pamir, 3600 m above sea level) 70 volunteer men aged 18-20 years were studied. In 34 of these subjects signs of AMS were observed (headache, nausea, respiratory distress, exertional dyspnea, insomnia and loss of appetite, etc). In the other 36 subjects no signs or symptoms of AMS were observed.

In all subjects the number and distribution of Q-heterochromatin regions (Q-HR) were assessed. Q-HR analysis was performed using propil quinacrine mustard staining of the chromosomal preparations obtained from short-term cultures of peripheral blood lymphocytes (Ibraimov, 1983) . The calculation and registration of chromosomal Q-HR variants were performed using the criteria and methods described in detail elsewhere (Ibraimov and Mirrakhimov, 1985).

The differences between mean number of Q-HRS observed in subjects with and without AMS were analyzed by using Student's t-test .

RESULTS AND DISCUSSION

Unlike the controls, subjects with AMS were found to have certain differences in distribution of quantitative characteristics of chromosomal Q-HR variability (Table 1); the total number of Q-HR in AMS subjects were higher (2.15 ± 0.19) than in the control group (1.06 ± 0.14; $P<0.001$).

On the whole, the results obtained are in agreement with those of previous studies on chromosomal Q polymorphism in human population. According to the clinical results, the subjects with AMS were believed to be the less adapted to the high altitude climate as compared with the control group and these data suggest that measurement of chromosomal Q-heterochromatin material could be an important marker of selective adaptation of men to high-altitude climate (Ibraimov et al; 1990).

Table 1. Distribution of Q variants in AMS subjects and controls.

Number of Q variants	Subjects with AMS (N = 34)	Controls (N = 36)
0	0.09*(3)	0.31 (11)
1	0.32 (11)	0.33 (12)
2	0.15 (5)	0.36 (13)
3	0.29 (10)	-
4	0.09 (3)	-
5	0.06 (2)	-
Mean number of Q Variants	2.15±0.19**	1.06±0.14

* frequencies.
Between parentheses are the number of subjects
**P<0.01 with respect to controls (Student t test).

Thus, these data suggested the role of the hereditary predisposition in the development of the acute mountain sickness.

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IMMUNOLOGIC PROGNOSIS OF ACUTE MOUNTAIN SICKNESS[1].

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SUMMARY. In the persons predisposed to AMS, a reduction of EHC-rosette-forming cells (E-RFC), T-helper cells, a reduction of monocyte and neutrophil capacity for adhesion, an inhibition of C_3 - and Fc-receptors on the monocytic membrane, and an increase of O-cells level were observed.

Key words: Immunology, Acute Mountain Sickness, T-cells, monocytes, neutrophils, lymphocytes.

RESUMEN. En las personas predispuestas al mal de montaña agudo se observan, una reducción de EHC- células formadoras de rosetas (E-RFC), células T salvadoras, la reducción de monocitos y capacidad de los neutrófilos para la adhesión, la inhibición de C_3- y receptores Fc en la membrana, aumento de células O.

Palabras claves: Inmunología, Mal de Montaña Agudo, Células T, Monocitos, Neutrófilos, Linfocitos.

INTRODUCTION

The development of acute mountain sickness (AMS) is one of the common complications occurring after a short-term exposure to high altitude. In contrast to a favourable course of adaptation (FCA), AMS is characterized by a marked impairment of T- and B- related immunity (Mirrakhimov et al. 1986) and deep inhibition of mononuclear phagocyte system (Kitaev and Goncharov, 1987). In such patients immunodeficiency persists as long as 5 months after remission of clinical symptoms (Mirrakhimov et al. 1989).

The selection of persons for work under high altitude conditions is known to be based on the estimation of the functional state of the organism gas transporting systems (cardiovascular, respiratory system, red blood cells). However, the status of the immune system, which also contributes to the "adaptation cost", has not been taken into account.

The objective of the present work was to retrospectively study the dependence of AMS development on the initial immunologic background of persons adapting to high altitude.

METHODS

Immunologic observations were made at 1500 m above sea level (Gulcha settlement) before the ascent to high mountains.

The subjects were 421 practically healthy men, aged 18-20 years, divided into two groups according to their pattern of adaptation to high mountains of Easter Pamirs (3600 m above the sea level). The first group included 342 men with a favourable course of adaptation, the second comprised 79 men who developed mild to moderate AMS after 3 days exposure to high altitude. The diagnosis was made on the basis of the typical clinical picture (headache, dizziness, ear noise, marked breathlessness and cardiac palpitation on physical exertion or at rest, bleeding sickness, marked diffuse cyanosis, nausea, vomiting), and it was considered to be definite whenever the symptoms characteristic of this sickness persisted for at least 3-5 days.

Peripheral blood T- and B- lymphocyte testing included determination of E- and EHC-rosette-forming cells (RFC), T-helper cells and T-supressor cells (Jondal et al, 1972; Mendes et al. 1973; Pichler et al. 1978). The T-lymphocyte functional status was judged upon the blast

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transformation reaction (BTRL) with PHA (Samoilina, 1970). The functional evaluation of B-lymphocytes was made according to the level of serum immunoglobulins A, M, and G (Mancini et al, 1965). Furthermore, O-cells were counted (Froland and Natvig, 1973). In addition to this, phagocytic activity of monocytes and neutrophils with latex particles was studied by means of phagocytic index (IPI). EA and EAC-rosette-forming monocytes (RFM) were estimated for revealing receptors to complement C_3 fraction and immunoglobulin Fc-receptors on the monocyte membrane (Sokolov and Rendel, 1983).

RESULTS AND DISCUSSION

In this retrospective study of some peculiarities of adaptation to high altitude (3600 m) depending on the initial immunologic background in persons with AMS, a reduction of absolute and relative content of E-RFC and T-helper cells and the increase of O-cells in peripheral circulation were revealed at 1550 m above sea level (Table 1).

Table 1.- Background Profile of the immune status in patients with Acute Mountain Sickness (AMS) and subjects with FCA prior to ascent to Eastern Pamirs (3600 m).

	: Initial data (1550 m)		
Indices :	Patients AMS	Healthy FCA	P
E-RFC %	59,6 ± 2,4	63,3 ± 3,7	<0,05
BTRL with PHA%	73,6 ± 2,5	71,2 ± 1,3	>0,05
T-Helper cells%	40,4 ± 1,3	47,2 ± 0,9	<0,05
T-supressor cells %	7,9 ± 0,4	6,4 ± 0,2	>0,05
B-RFC%	16,8 ± 1,4	13,7 ± 1,5	>0,05
O-lymphocytes	23,2 ± 0,3	15,6 ± 0,2	<0,05

These data reveal that in persons predisposed to AMS, inhibition of thymus-dependent immunity link takes place. Besides, these persons show a reduction of monocyte and neutrophil with latex particles capacity for adhesion and inhibition of C_3 - and particularly Fc-receptors expression on the monocyte membrane (Table 2). Shifts of this kind lead to a negative effect on the adaptation process, they were revealed in 75% of the persons predisposed to AMS, and they may serve as a valuable diagnostic criterium in selecting people for work in the mountains.

Table 2.- Background Profile of monocytes and neutrophils functional activity in patients with Acute Mountain Sickness (AMS) and persons with FCA prior to ascent to high mountains of Eastern Pamirs (3600 m).

	Initial data (1550 m)		
Indices :	Patients AMS	Healthy FCA	P
monocyte PI %	27,2 ± 2,9	33,0 ± 2,4	<0,05
monocyte PN	1,7 ± 0,1	1,8 ± 0,1	>0,05
monocyte IPI	0,5 ± 0,09	0,6 ± 0,06	<0,05
neutrophil PI %	47,5 ± 1,1	52,2 ± 1,3	<0,05
neutrophil PN	4,7 ± 0,2	5,1 ± 0,1	>0,05
neutrophil IPI	2,3 ± 0,1	5,2 ± 0,1	<0,05
EA - RFM	31,6 ± 0,6	36,6 ± 0,9	<0,05
EAC - RFM	37,2 ± 0,8	46,2 ± 0,9	<0,05

Our previous studies demonstrated the development of a specific immunodeficiency status in AMS, that was marked by deeper disturbances in the immune system compared to the persons with FCA (Mirrakhimov et al. 1986; Kitaev and Goncharov, 1987; Mirrakhimov et al.). Patients with AMS showed T- and B-lymphopenia, the reduction of T-lymphocyte blast transformation under the influence of PHA, reduction of T-cells helpers content, and deep inhibition of phagocytic activity of monocytes and neutrophils. These changes in the immune system persisted from 1-1,5 to 5 months.

The mechanism of immunodeficiency development in AMS is likely to be related to

some latent defects in the immune system, which under the extreme high altitude hypoxia conditions express themselves in a marked and severe disbalance in the immune system.

Thus, the immune reactivity reduction in background predicts issues a negative influence on the adaptation process at high altitude and it should be taken into consideration when selecting people for work in the mountains and for prognosis of some possible disadaptation pathology.

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ANTIINFLAMMATORY EFFECT OF HIGH-ALTITUDE ADAPTATION IN PATIENTS WITH BRONCHIAL ASTHMA [1]

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SUMMARY: During some years we have already elaborated the method of high-altitude climatotherapy (HACT) in patients with bronchial asthma (BA) (on the Tuya-Ashu Pass, Northern Tien-Shan, 3,200m above the sea level). Complex bronchologic study including brochoalveolar lavage (BAL) was performed in 62 patients with BA before treatment (in Bishkek, 760 m above the sea level) and on the 25th day of HACT. BAL study included: cytologic composition, estimation of the viability and phagocytic activity of alveolar macrophages (AM) with latex particles, immunoglobulin Fc- and complement C_3-fraction receptors on AM membrane, assessment of secretory IgA (SIgA) and surface activity (SA) of surfactant. We found that the treatment of patients with BA at high-altitude to improve a number of parameters of BAL demonstrating the antiinflammatory effect of high-altitude climatotherapy.

Key words: Bronchial asthma, high-altitude climatotherapy, bronchoalveolar lavage, cytology, SigA, surface, activity.

RESUMEN: Durante muchos años hemos elaborado el método de climato-terapia de altura en pacientes con asma bronquial (en la Tuya-Ashu pass, Northen Tien-Shan, 3200 m). El estudio broncológico complejo que incluye el lavado bronquio-alveolar fue realizado en 62 pacientes con asma bronquial antes del tratamiento (en Bishkek, 760 m) y a los 25 días de climatoterapia en la altura. El estudio de lavado alveolar incluyó, la composición citológica, la estimación de la viabilidad y actividad fagocítica de los macrófagos alveolares con partículas de latex, receptores de membrana de los macrófagos alveolares de la fracción del complemento C_3, y F_c de la inmunoglobulina, determinación de la IgA secretoria, y la actividad de superficie del surfactante. Se encontró que la altura como tratamiento del asma bronquial mejora una serie de parámetros del lavado bronquial demostrando que la altura tiene un efecto anti-inflamatorio.

Palabras claves: asma bronquial, climatoterapia de altura, lavado bronquio-alveolar, citología, IgA, actividad de superficie.

INTRODUCTION

The climatic treatment of asthma by sojourns in the mountains has been prescribed since many years (M.M.Mirrakhimov, 1977; H. Razzouk, 1988), but the majority of mountain medical centres devoted to climatic treatment of asthma are situated at middle altitude ranging fron 1000 to 2000 meters. Presumably the highest one is the tuja-Ashu Sanatorium situated at 3200 meters above sea level in the Northen Tien-Shan mountains (Kyrgyzstan). For several years we have already elaborated the method of high-altitude climatotherapy (HACT), in patients with bronchial asthma (BA) on this scientific base. Our study was aimed at the investigation the local defense mechanisms of bronchial tree during HACT.

MATERIAL AND METHODS

Complex bronchologic study (with OLYMPUS bronchofiberscope) including bronchoalveolar lavage (BAL) was performend in 62 patients with BA before treatment (in Bishkek, 760 m above sea level) and on the 25th day of HACT. As a control group we investigated 8 healthy men at age 17-19 years. BAL study included: cytologic compositión, estimation of the viability and phagocytic activity of alveolar macrophages (AM) with latex particles, investigation of immunoglobulin Fc- and complement C_3-fraction receptors on AM membrane by EA-

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and EAC-rosette-forming tests, assessment of secretory Ig A (SIgA) and surface activity (SA) of surfactant.

METHOD OF HIGH-ALTITUDE CLIMATOTHERAPY: after the baseline examination in Bishkek (760 m above the sea level) the patients were transported by bus to the high-altitude sanatorium of the Kyrgyz Institute of Cardiology which is situated in the Tuya-Ashu Pass (Northern Tien-Shan, 3200 m above sea level). During the first 5-7 days of adaptation the patients were recommended to follow the limited exercise regimen in order to mitigate the course of acute mountain sickness. The patients were allowed to increase gradualy the exercise activity and they were administered exercise therapy and mountain tracking (N.Brimkulov,1991). Repeated examination was performend on the 25th day of high-altitude climatotherapy.

RESULTS

Our studies demonstrated (Table 1), that lowlanders with BA had decreased concentration of AM in BAL. Lavage liquid cellular content included a great number of neutrophiles typical of chronic bronchial inflammation, and eosinophilia that is the evidence of allergic genesis of the disease. High-altitude adaptation resulted in clinical improvement manifested in the increase of the concentration and viability of AM and significant decrease of neutrophile and eosinophile count, these changes were the evidence of local defensive mechanism activation and bronchial allergy inflammation reduction.

Phagocytic activity of AM in patients with BA at low altitude was decreased and integral phagocytic index was also reducing accordingly. During adaptation, the test parameters significantly increased. AM are known to include the receptors for immunoglobulins and complement that stimulate phagocytosis.

Immunoglobulin Fc- and C_3- complement receptors investigation on AM membrane revealed the decrease of these values at low altitude and their significant increase following high-altitude adaptation.

A number of papers demonstrated the presence of secretory Ig A in BAL which protects mucous membranes from bacteria and viruses. Secretory Ig A concentration in BAL in patients with BA at low altitude was decreased however, after high-altitude climatotherapy it was significantly increased. The Stability Index of BAL in response to high altitude climatotherapy increases also.

Table 1. Changes in cytology of BAL, alveolar macrophage functional activity, SIgA and stability index of BAL in patients with BA during HACT (M±SD).

Parameters	Control group	Patients With asthma Baseline	On 25th days of HACT
Neutrophils,%	5,2±1,1	25,4±2,46*	8,1±1,16**
Eosinophils,%	0,9±0,2	20,0±2,93*	5,3±1,62**
Lymphocytes,%	3,0±0,7	6,3±1,31*	2,3±0,46**
AM, %	90,5±1,3	48,3±4,31*	84,4±1,62**
AM viability,%	95,0±2,2	64,8±6,70*	90,3±2,16**
Phagocytic index, %	26,2±3,6	16,2±1,62*	47,4±2,77**
EA-rosette-forming AM,%	64,5±3,1	18,8±2,27*	32,4±2,27**
SIgA, g/L	-	0,2±0.02	0,6±0,03**
Stability index (SI)	1,61±0,1	0,8±0,06*	1,1±0,08**

AM: Alveolar macrophages
* $p < 0,05$ compared with control,
** $p < 0,05$ compared with baseline.

DISCUSSION

Our clinical data demonstrated the beneficial effect of high-altitude adaptation and its potential for the treatment of BA patients. In our previous investigations (N.Brimkulov, 1991) it was already demonstrated that during high-altitude climatotherapy in BA patients besides the decrease in dyspnea severity and number of asthmatic attacks, significantly improved bronchial permeability, decreased bronchial hyperreactivity and increased cortisol level in blood plasma. In this investigation we found, that severity of inflammatory changes in bronchial

tree decreased while the number of alveolar macrophages in lavage liquid increased and the number of neutrophiles and eosinophiles reduced. All these changes evidently allow to stabilize the conditions in the most BA patients.

Probably, it was due to the hypoxic stimulation of adrenal cortex and the improvement of the patients' condition was achieved. Also noteworthy are other sanogenic factors of high-altitude climate: purity of the air, the absence of the environmental allergens, high air ionization and insolation (M.M.Mirrakhimov, 1977; H.Razzouk, 1987; D.Charplin et al., 1988).

Thus, the treatment of patients with bronchial asthma at high-altitude results in the improvement of a number of parameters of BAL demonstrating high-altitude climatotherapy efficacy with evidence of local defense mechanism activation and bronchial allergy inflammation reduction. Using the bronchologic study including BAL can relieve to evaluate the efficacy of high-altitude climatotherapy. Applying the mutual bronchological investigation on altitudes from 3000 to 3500 m is safely and can be recommended for diagnosis and treatment.

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HIGH ALTITUDE DISEASE ON THE TIBETAN PLATEAU[1]

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ABSTRACT. In China, the Qinghai-Tibetan plateau is the highest and largest plateau in the world, in which lives both Tibetan natives and Chinese immigrants (Han). This paper deals with questions concerning high altitude disease (HAD) on the plateau. There are three main serious altitude health problems. First, high altitude pulmonary edema (HAPE). A high incidence is observed between newcomers to high altitude and lower incidence of HAPE after reascent of Tibetans are quite different with reports from North America and from the Andes. Second, high altitude heart disease (HAHD). The infants and children are especially at risk. Most infants affected by this disease are from Han origin, and presented severe congestive cardiac failure due to pulmonary hypertension few months after birth or after arrival to high altitude. Autopsies show right ventricular hypertrophy and muscular thickening of peripheral pulmonary arteries. The average mortality was 15%, so that infantile HAHD is a fatal disease. Third, Monge's disease or chronic mountain sickness (CMS). 15 patients with CMS in indigenous Tibetans were observed during 1991-1993. Pathophysiological studies were performed. Both epidemiological and clinical investigative data show that CMS exists on the Qinghai-Tibetan plateau.

Key Words: High altitude, Tibetan, Hen, Heart disease, edema, Monge's disease.

RESUMEN. En China, las altiplnicies de Qinghai en el Tibet son las más altas del mundo, y en ellas residen los Tibetianos nativos y los inmigrantes chinos (Han). Este artículo se ocupa de los problemas de las enfermedades producidas por la altura. Existen tres problemas serios producidos por la altura. Primero, el edema pulmonar de altura (HAPE); se observa una alta incidencia de HAPE en los recién llegados a la altura, y por el contrario una menor incidencia en los nativos de altura que reascienden a ella, lo que difiere con los reportes en Norte América y en los Andes. Segundo, la enfermedad cardiaca de altura (HAHD). Los niños y los infantes son los que se encuentran especialmente en riesgo. La mayoría de infantes afectados por esta enfermedad son de origin Han, y presentan insuficiencia cardiaca congestiva severa debido a hipertensión pulmonar dentro de los pocos meses de nacido o del arribo a la altura. Las autopsias muestran una hipertrofia ventricular derecha y un engrosamiento de la muscular de las arterias pulmonares periféricas. La mortalidad en promedio fue del 15%, tal que la HAHD infantil es una enfermedad fatal. Tercero, la enfermedad de Monge o Mal de Montaña Crónico (CMS). En los indígenas Tibetanos se han observado 15 casos de CMS entre 1991-1993. Los datos epidemiológicos y clínicos muestran que la CMS existe en la altiplanicie de Qinghai-Tibet.

Palabras claves: altura, Tibet, Hen, Enfermedad cardiaca, edema, Enfermedad de Monge.

INTRODUCTION

In China there are many high mountains and plateaus, and one of the most famous is Qinghai-Tibetan plateau, the so called "Roof of the world" because it is the world's highest and largest plateau, with an average elevation of more than 4,000 meters, it covers about 2'500,000 Km^2, which means one fourth the China's total area, and it plays a specific role in the national defense and in the economic development of China. The significance and importance of high altitude medical research in China are therefore selfevident.

The Qinghai-Tibetan plateau has a population of approximately ten millions inhabitants. Every year many hundred of thousands of people travel from low to highlands in this region, in fact, such large movement of populations from low plains to high altitudes has only occurred in Tibet. Therefore, how to provide medical advice to highlanders on how to maintain their health and strengthen their physical capacity is an important task for Chinese high-altitude medical researchers.

Based on the longer period of previous studies, it is clear that human and animals ascend-

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ing to, or those living permanently at high altitude are two groups with different biological status. We believed that a different biological models as well different physiological adaptive form exists in different populations. There is some evidence (Moore et al, 1992; Wu et al, 1994) that the Tibetan natives are better adapted to high altitude, and the Chinese Han immigrants are susceptible to the hypobaric hypoxia of high altitude. In fact, Han immigrants to the Tibetan plateau have to face the potential danger of high altitude disease. This paper deals with questions concerning HAD on the Qinghai-Tibetan plateau.

HIGH ALTITUDE DISEASE IN CHINA

The classification of HAD in China

The nomenclature of HAD in China differs some what from that used in the Western literature. For instance, in China mountain sickness is named "high altitude disease". Moreover, the classification of HAD based on the pathophysiology and clinical manifestation of illness seen at high altitude probably represents the current concept of altitude scientists in Qinghai-Tibet in general.

The terminology and classification of HAD in China is summarized as follows:

Acute High Altitude Disease (AHAD)
- Acute Mild Altitude Disease (AMAD)
- High Altitude Pulmonary Edema (HAPE)
- High Altitude Cerebral Edema (HACE)

Chronic High Altitude Disease (CHAD)
- High Altitude Deterioration HADT)
- High Altitude Heart Disease (HAHD)
- High Altitude Polycythemia (HAPC)
- Monge's disease or Chronic Mountain Sickness (CMS), also named "Mixed Form" of CHAD.

Among the various forms of HAD, there are three main serious altitude health problems, ie, HAPE, HAHD and CMS.

High Altitude Pulmonary Edema

The observations on the Qinghai-Tibetan plateau suggest the existence of two types of HAPE. The first type (Type 1, or ascent HAPE) afflicts lowland residents visiting high altitude above 3000 m (Wu and Li, 1989). The second type (Type 2, or reascent HAPE) affects persons living permanently at high altitude as well as high altitude natives after a sojourn at lower altitudes longer than seven days and subsequent reascent to areas above 3500 m (Wu et al, 1991).

In recent years, we have performed an epidemiological study of AHAD and HAPE on the tibetean plateau. Studies were carried out in three high altitude regions, a mountain area (Tanggula range, altitude 4,550 m), a pastural county (Madou, altitude 4,280 m) and a mining area (Muli, altitude 3,790-4,200 m).

The number of people visiting the Tibetan mountain areas resulting in an unique opportunity of contrasting the incidence of AMAD (AMS) and HAPE in newcomers to high altitude with that in Tibetan native who return to highland after visiting lowlands. For example, the Qinghai-Tibet Highway stretches from Xining (2261 m) to Lhasa (3658 m), covering a distance of 1937 km at an average altitude of 3500 m above sea level. Particularly, the section between Mt Kunlun and the Tanggula Range is situated permanently frozen earth above 4460-5200 m and is 500 km long. It has long been recognized as a dangerous road for tourists. Nevertheless, each year, about 120,000-150,000 of sojourners travel over this highway for visiting, pilgrimage or business purposes. Many adults with their children going back and forth between low and high altitude travel the road by buses. We recently performed a survey for AHAD at the rescue station of Tuo-Tuo river near the highway at 4,550 m, where most sojourners stay overnight. For this purpose, 5,355 adults and 464 children from both sexes were studied.

Madou county is a pasture-region situated near the source of Yellow's river at an elevation of 4,280 m above sea level. It has a resident population of 20,400 and approximately 92% of the

native Tibetan population is engaged in pasturing activities. Only four percent of Tibetan natives travel to low altitude each year, but is more than 5000 tourists visited annually. From these, 635 travellers who ascend the elevation for first time, and 1,720 Tibetan native residents who return to high altitude were included in the survey.

Muli is a mining community located on the Mt. Qulian at altitude between 3,790 and 4,300 m. A total of 602 newcomers of miners and their families from the plain areas to Muli during the 18 months of this study. The clinical observations were performed at the Madou county Hospital and the Muli mining Hospital.

In the present study, the diagnosis of AMS was based on history describing arrival at high altitude, and measured by an established symptom score derived from a questionnaire and physical examinations (Hackett et al, 1976; Maggiorini et al, 1990). The diagnosis of HAPE was based on radiographic criteria. The percentage incidence of HAPE is shown in Table 1.

Table 1.- Incidence of high altitude pulmonary edema in adults and children occurred on the Qinghai-Tibetan plateau.

Area	Altitude (m)	Subjects	Incidence (%)	Variety
Muli	3790-4200	602 newcomers	0.50	Type 1
Madou	4280	635 travellers	1.10	Type 1
		1720 Tibetans	0.17	Type 2
Tanggula	4550	5355 sojourners	1.27	Type 1
		464 children	1.51	Type 1
		1180 workers*	1.61	Type 1
		1638 Tibetans	0.24	Type 2

*Workers of constructing roads.

In Tuo-Tuo river of Tanggula ranges, the incidence of AMAD (AMS) and HAPE in adults was 38.2% and 1.27% as compared with 34.1% and 1.51% respectively in children. There was not statistically significant difference between adults and children ($P>0.05$). These data would suggest that lowland children are not more susceptible to AMS and HAPE than adults (Wu et al, 1987).

The incidence of 0.5-1.61% of HAPE in adults on the Tibet is in agreement with other reports in various altitudes and mountain areas of the world (Hackett et al, 1980; Hultgren, 1978; Menon, 1965).

The incidence of reascent HAPE on the Tibet was lower than those observed in South and North America. The incidence of reascent HAPE was reckoned to be as high as 6.1% by Hultgren and Marticorena (1978) in La Oroya (3750 m) in the Central Peru and 0.3-0.6% by Scoggin (1977) in Leadville, Colorado at 3100 m. The reasons for the differences are not clear, but it could reflect differences in the travel and the length of time to reascent from lowland to high altitude places. First, as La Oroya residents usually go to sea level, they travel to a lower altitude. In fact, many of the Tibetan residents did not go to sea level but usually they do to intermediate altitude such as Xining (2261 m), Lanchou (1800 m) or Xian (720 m). In addition, in Qinghai-Tibet, people who return to high altitude after a sojourn at a low altitude, travel only by railway or highway, from low altitude,they reach their altitude home in about 2 to 4 days. In contrast, in La Oroya, dwellers travel by modern highway only for a few hours. On the other hand, the severe HAPE was more common in children than in adults in Peru (Hultgren et al, 1961), but in Tibet, Tibetan children rarely travel to sea level because of the labour style and the economic condition.

In conclusion, HAPE is a serious health problem for high altitude dwellers in Tibet, but further epidemiological and pathogenesis studies are still needed.

High Altitude Heart Disease

Although Anand and Chandrawshekhar (1992) stated that the syndrome of sub-acute mountain sickness (SAMS) has only recently been described in man, in fact this illness was described in the Qinghai-Tibetan plateau by Chinese scientists earlier. It was first reported by Wu and Liu (1955). They described a Han (Chinese) infant girl aged 11 months born at Lhasa (3658 m) presenting dyspnoea, cyanosis and congestive cardiac failure.

At necropsy, marked right ventricular hypertrophy and muscular thickning of peripheral pulmonary arteries were found. The pathology ruled out the diagnosis of congenital and other organic heart disease, of these, the authors named the disease as: "High Altitude Heart Disease" (HAHD). Subsequently other similar cases were reported in Qinghai-Tibet. Now in China more is known about this syndrome (Wu and Lin, 1978; Wu et al, 1992).

Early clinical manifestations of HAHD were restlessness, nocturnal crying, sleeplessness, anorexia, coughing, polyhidrosis and hoarseness. During the attack of the illness,the patient presented with breathlessness, dyspnoea, cyanosis of the lips and fingers, and right-sided heart failure occurred (Lin and Wu, 1974). ECG and chest X-ray confirmed the presence of cardiac enlargement and dilatation of the pulmonary trunk. Echocardiography revealed significant right ventricular hypertrophy and dilatation in all studies. Right heart catheterization was performed in 7 cases during the onset of HAHD. The mean values for systolic, diastolic and mean pressure in the pulmonary artery were 68 ± 9.6 mm Hg (9.06 ± 1.28 KPa), 39 ± 7.8 mm Hg (5.2 ± 1.04 KPa) and 54 ± 8.2 mm Hg (7.2 ± 1.09 KPa), a degree of pulmonary hypertension two to three times greater than that corresponding to healthy children on the Tibet at the same altitudes. Necropsies were performed in 68 fatal cases (Lin and Wu, 1974; Li et al, 1966; Wu and Liu, 1955; Wu and Lin, 1978). The most significant pathological feature was the hypertrophy of the smooth muscle of the pulmonary arteries and arterioles. It thus seems clear that HAHD is the same illness as SAMS. In regard to the nature of HAHD, Wu et al (1965) were the first to propose that HAHD is a human model of Brisket disease in the cattle, which agrees with the recent view of Anand and Chandrawshekhar (1992). However, there are some special characteristics of HAHD observed in Qinghai-Tibet.

As a consequence of the rich accumulation of epidemiological and clinical data, we have strong evidence that HAHD has no age limit, and cases have been described in infants, children (Lin and Wu, 1974; Wu et al, 1965) as well as adults (Wu et al, 1965); the highest incidence ocurre in infants (89.5% of all the cases) (Lin and Wu, 1974). Most infants and children afflicted by this illness were of Han origin. There are three conditions in the occurrence of HAHD among children of Tibet (Lin and Wu, 1974; Wu and Liu, 1955; Wu and Lin, 1978). 1) Infants born at high altitude and remaining there since birth (account for 73.3%); 2) Infants born at low altitude and later brought up high altitude (16.1%); and 3) Children with their parents who migrated from an intermediate altitude to a higher altitude (10.2%). It is interesting to note that HAHD is rare in Tibetan native children and that a high degree of tolerance to hypoxia was shown in them, indicating that Tibetan children may be better adapted to high altitude, possibly due to a genetic adaptation.

On the contrary, some Han infants do not attain acclimatization even at moderate altitude. An epidemiological survey (Wu et al, 1983) showed that at altitudes between 2261-2808 m, the prevalence of HAHD was still 0.47% in Han children whereas there were no adult victims. At higher altitudes between 3050 and 5188 m, the prevalence of HAHD in children and adults appears to be 0.96% and 0.31% respectively, the former being significantly higher than the latter ($P<0.001$) (Wu, 1994). These data again suggest that susceptibility to HAHD is higher in children than in adults. Why are children more at risk than adults?. It is possible that at high altitude, children may have a more reactive pulmonary vascular reaction to hypoxia, the foetal structure of the pulmonary arterial tree resulting from increased pulmonary hypertension, may remain as a chronic condition after birth and may contribute to the development of HAHD in children.

In some of the pediatric patients the symptoms improved following treatment with oxygen, cardiotonics, diuretics and corticoids. HAHD can also be relieved by descent. However, sometimes the progress of the illness is so rapid than even descent cannot prevent a fatal outcome. In this malignant type, as well as the later stage of the illness, even when patients are brought down to hospitals at 2261 m, mortality is higher than 62%.

Since the average mortality for hospitalization was 15% (Wu et al, 1987), infantile HAHD seems to be a serious and potentially fatal disease. Finally, HAHD occurs on the Qinghai-Tibetan plateau offers a very important and timely problem to be investigated.

Chronic Mountain Sickness

Chronic mountain sickness (CMS) or Monge's disease is commonly described in Leadville, Colorado, and Cerro de Pasco, Peru (Winslow and Monge, 1987). On the Tibet, most of our patients with CMS are chinese Han immigrants, and the average length of stay at high altitude is over 10 years. Apparently, CMS occurrence among Tibetan natives residing on the Tibetan plateau has not been detailed; speculation is rife about this, the problem remains to be clarified.

Based on our previous investigations, we suggested that in some native Tibetans, after living for many years above altitude of about 4000 m, lose their acclimatization and develop CMS (Wu et al, 1992). During 1991-1993, we observed 15 cases of CMS occurred in indigenous Tibetans in Tibet. The mean age of the patients was 44.8 years with a range of 36-62 years. All patients were male, the resident elevation was between 3,719 m and 4,280 m above sea level. The diagnosis of CMS was confirmed by the clinical symptoms, physical examination and laboratory studies. The physiological parameters were compared with the healthy Tibetans, who were matched for age, sex, occupation and comparable elevation of residence.. The clinical and physiological characteristics of the cases of CMS in Tibetan natives were listed in Table 2.

As seen in Table 2, severe hypoxemia, excessive polycythemia, accentuated pulmonary hypertension, marked right ventricular hypertrophy and blunted peripheral chemoreceptors characterized the Tibetan patients who had CMS. The criteria for the diagnosis used by the physicians of our Institute are similar to those customarily described (Winslow and Monge, 1987). Thus, we were able to obtain a reliable diagnosis of CMS in the Tibetan natives.

Table 2.- Comparison of the physiological parameters between CMS in Tibetan natives and healthy Tibetans (M±SD).

	CMS (n=15)	Healthy Tibetans (n=20)	P value
Mean age (year)	44.8±8.2	40.4±5.7	NS
Hb (g/dl)	23.2±1.4	15.6±2.2	0.01
Hct (%)	75.3±9.4	58.6±4.8	0.01
PaO_2 (KPa)	5.6±0.6	6.7±0.6	0.01
HVR	Blunt	Normal	
2,3-DPG (umol/ml RBC)	5.1±0.8	4.5±0.6	0.05
PAM (KPa)	5.3±2.1	3.2±0.6	0.01
Right Ventricular hypertrophy	Marked*	None or Mild	
Congestive Hearth Failure	in 4 cases	None	

Hct: Hematocrit; HVR: Hypoxic Ventilation Response; 2,3-DPG: 2,3-Diphosphoglycerate;PAM: Mean Pulmonary Arterial Pressure. *Marked in all cases.

As indicated in the introduction, the Tibetans, who have lived at high altitude longer than other populations on the earth, have ample opportunities to adapt to hypoxia. Nevertheless, why are some persons of the Tibetan group suffering from CMS?. We attributed this to the following reasons. First, despite the fact that Tibetan population may be better adapted to high altitude, a few susceptible individuals may remain in the population. Second, the elevation of residence in some nomads Tibetan were as high as over 4,500-5,000 m above sea level, especially in the summer time, the pasture-grounds were always higher than 5,000 m. In addition, tibetan persons with heavy exertion for a long periods, or persons suffering from respiratory infections, or any other factors of increasing hypoxia, could be more liable to suffer from CMS. nswered questions yet to be investigated.

In any event both clinical and physiopathological data suggest that CMS (Monge's disease) exist in the Qinghai-Tibetan plateau. CMS occurrence among Tibetan natives residing in Tibet is of immense practical application, since it is clear that Monge's disease is a syndrome which represents a loss of acclimatization to high altitude.

In conclusion, the Qinghai-Tibetan plateau and its width, height, climate, topography and the various ethnic populations are not entirely similar to the other high altitude areas of the world. Therefore, in the field of high altitude medicine and physiology, comparative studies of populations who have lived at different altitude areas for varying lengths of time are needed. On the other hand, the Qinghai-Tibetan plateau is an optimal testing place for high altitude researchers. Tibet now, the mysterious land has a strong appeal to altitude scientists all over the world.

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MEDICAL PROBLEMS OF WORKING AT ALTITUDES OF 4000-5000 m[1]

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SUMMARY. Recently there have been increasing commercial activities at altitudes of 4000-5000 m, for example new mines in north Chile. Because the workers come from sea level, altitude intolerance is a major problem. This article addresses three areas: 1) Methods for selecting workers who can tolerate these high altitudes. 2) Optimal scheduling of time between the mine and the home at sea level. 3) Value of oxygen enrichment of room air in some parts of the mine. This last is remarkably effective. At these altitudes, each 1% increase in O_2 concentration (e.g. from 21 to 22%) reduces the equivalent the altitude by about 300 m. Control of the oxygen concentration can be regarded as a further logical step in man's control of his environment.

Key Words: altitude sickness, hypoxic ventilatory response, acclimatization, oxigen enrichment

RESUMEN. Recientemente se ha incrementado las actividades comerciales en altitudes de 4000-5000 m, como por ejemplo, las nuevas minas del norte de Chile. Debido a que los trabajadores vienen de nivel del mar, la intolerancia a la altura se constituye en una problema mayor. Este artículo enfoca tres aspectos: 1) Métodos para seleccionar trabajadores que puedan tolerar estas altas altitudes. 2) Fijación del tiempo óptimo entre la mina y la casa a nivel del mar. 3) El valor del enriquecimiento con oxígeno en algunos ambientes de la mina. Esto último es remarcablemente efectivo. En estas altitudes, cada 1% de aumento de la concentración de O_2 (ej. de 21 a 22%) se reduce el equivalente de 300 m de altura. El control de la concentración de oxígeno puede ser considerado como un siguiente paso lógico en el control del hombre sobre su medio ambiente.

Palabras claves: Enfermedad de altura, respuesta ventilatoria hipóxica, aclimatización, enriquecimiento de oxígeno.

INTRODUCTION

Recently there has been a substancial increase in commercial activities at altitudes of 3500-6000 m. Examples include new mines in north of Chile at altitudes of 4400 to 4700 m. Another example is the telescope facility at Mauna Kea, Hawaii at 4200 m.

Traditionally, high mines in the South American Andes have been worked by indigenous people who have been at high altitude for generations. Recently however, increasing use is being made of workers from sea level. One reason is that some mines require over a thousand workers and there are not enough people in these remote areas. Another reason is that as the mines become increasingly automated, indigenous people may not have the necessary skills to operate the complicated equipment.

Moving from sea level to altitudes of approximately 4500 m causes acute mountain sickness in many people. Tolerance of the altitude often improves after the first two or three days, but the hypoxia of these altitudes reduces work capacity, mental efficiency and sleep quality. There is considerable variability among individuals in their tolerance to high altitude. This paper deals with three challenging areas: 1) Selection of workers who are likely to tolerate the altitude. 2) Schedule of working between high altitude and family at sea level. 3) Oxygen enrichment of room air to relieve the

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hypoxia of high altitude.

SELECTION OF WORKERS TO TOLERATE HIGH ALTITUDE

Little is known about predictors of tolerance to high altitude. The best predictor is probably previous experience at high altitude. If someone has been shown to tolerate high altitude well on one occasion, he is likely to do so on another. Conversely, someone who is unable to tolerate high altitude on one occasion is likely to have the same experience on another. Therefore a history of being able to work well at high altitude would be a valuable clue. However, clearly this criterion cannot be used for all workers because otherwise no new people would enter the high altitude pool.

Another possible predictor is the strength of the ventilatory response to hypoxia. This is easily measured at sea level, and there is some correlation with tolerance for high altitude. Schoene (1982) showed that 14 high altitude climbers had significantly higher hypoxic ventilatory response (HVR) than 10 controls. This work was extended on the 1981 American Medical Research Expedition to Everest where it was shown that HVR measured before and on the expedition correlated well with performance high on the mountain (Schoene et al., 1984). Matsuyama et al. (1986) reported that 5 climbers who reached ·8000m on Kangchenjunga had a higher HVR than 5 climbers who did not.

However this correlation is by no means universal. In a prospective study of 128 climbers going to high altitudes, a measure of HVR did not correlate with the height reached whereas the sea level measured V_{02max} did (Richalet et al., 1988). This study also suggested that the heart rate response to acute hypoxia migtht be a useful predictor of performance at high altitude. There have been other studies showing a poor correlation between HVR and performance at extreme altitude (Milledge et al., 1983; Schoene et al., 1987; Oelz et al., 1986).

Another possible predictor is work capacity during acute hypoxia at sea level. The general argument here is that someone who is not able to tolerate acute hypoxia is more likely to be intolerant to chronic hypoxia. There is little evidence for or against this hypothesis. Soviet physiologists used tolerance to acute hypoxia as one of the criteria for selection of climbers for their 1982 Everest expedition (Gazenko, 1987). On the other hand, the changes that occur with acclimatization are so profound that it may be that performance during acute hypoxia is poorly correlated with ability to work during chronic hypoxia.

Another possible predictor is the increase in pulmonary artery pressure during acute hypoxia at sea level. This can be measured in some people non-invasively by Doppler ultrasound. The rationale for this test is that there is a correlation between the development of high-altitude pulmonary edema, and the degree of hypoxic pulmonary vasoconstriction at high altitude (Hultgren et al., 1971). However, since high-altitude pulmonary edema is uncommon in this population, the value of this test is questionable.

The best to determine the possible value of these test of selection of workers is prospective study where the test are correlated with subsequent tolerance to high altitude. The usual way of measuring altitude intolerance is by questionnaries such as the Lake Louise (Hackett and Oelz, 1992). However it may be that in this population, questionnaries may be unreliable because of a worker's perception that if he admits to altitude intolerance, he might lose his job. There are objective measures of altitude intolerance such as quitting work, chest rales as an indication of subclinical pulmonary edema, and mild ataxia as an indication of subclinical high-altitude cerebral edema. However these features will only be seen in people with severe altitude intolerance, and a prospective study based solely on such measurements would be very insensitive.

SCHEDULING BETWEEN HIGH ALTITUDE AND SEA LEVEL

As indicated above, most of the workers in the new mines at high altitude will come from sea level where their families will reside. Designing the optimal schedule for moving between high altitude and sea level is a challenging problem.

The justification for spending several days at a time at high altitude is the advantage gained from acclimatization. Symptoms of acute mountain sickness usually go away after two to four days. The ventilatory response to hypoxia takes 7-10 days to reach a steady state (Lahiri, 1972; Dempsey and Foster, 1982), and therefore it is reasonable to recommend that the working period at high altitude be at least this long. However, other features of high-altitude acclimatization such as the development of polycythemia take several weeks to reach a steady state. On the other hand, the physiological value of polycythemia is unclear (Winslow and Monge, 1987).

Another important question is the rate of deacclimatization. Ideally the workers should not lose all the acclimatization that they have developed at high altitude during their period with their families at sea level. Relatively little information about the rate of deacclimatization is available although some measurements suggest that the rate of change of ventilatory response during deacclimatization is slower than during acclimatization (Lahiri, 1972).

Another factor which affects scheduling is the time required to move from sea level to high altitude and back. In the new mine at Collahuasi in north Chile, it only takes a few hours to reach the mine by bus from the coastal town of Iquique where most of the families are expected to live. However if a worker resides in Santiago, the trip will take over a day.

Although the physiological aspects of scheduling are important, it may be that social factors will be dominant. Experience has shown that miners are reluctant to leave their homes for more that 7 or 10 days, and it is probable that a schedule of 7 days at high altitude followed by 7 days at sea level, or 10 by 10 will be most acceptable.

OXYGEN ENRICHMENT OF ROOM AIR TO RELIEVE THE HYPOXIA OF HIGH ALTITUDE

This is a relatively new development that shows great promise (West, 1995). As pointed out earlier, even after period of acclimatization of several days at an altitude of 4500 m, the severe hypoxia reduces work capacity, mental efficiency and sleep quality. It would therefore be highly advantageous to reduce the degree of hypoxia in some parts of the mine if that were feasible.

The value of small amounts of oxygen enrichment to room air is remarkable. It has been shown that every 1% increase in oxygen concentration (e.g. 21 to 22%) reduces the equivalent altitude by 300 m. The equivalent altitude is that which has the same inspired Po_2 during air breathig as in the oxygen enriched room. Thus at an the altitude of 4500 m at the Collahuasi mine, raising the oxygen concentration of a room from 21 to 26% would reduce the equivalent altitude by 1500 m, and therefore take it down to 3000 m which is easily tolerated. The oxygen would be added to the normal room ventilation and would therefore be part of the air conditioning. We all expect that a room will provide a comfortable temperature and humidity. Control of the oxygen concentration can be considered a further logical step in man's control of his environment.

Oxygen enrichment has become feasible because of the introduction of oxygen concentrators that use molecular sieves. These devices preferentially adsorb nitrogen and thus produce an oxygen-enriched gas from air. They can work continuosly and only need electrical power which is in abundant supply at a modern mine. As a rough indication of the cost of oxygen enrichment, a small commercial device produces 300 L/hour of 90% oxygen with a power requirement of 350 watts and initial cost of about $ 1500. This would be sufficient to raise the oxygen concentration in a room by 3% for one person. It is also possible that liquid oxygen might be economical for a large facility.

There are several areas in a mine where oxygen enrichment might be considered. One would be the director's office or conference room where important decisions are being made. For example, if there is a crisis in the mine such as a serious accident, such a facility would probably result in clearer thinking than the normal hypoxic environment. Another place might be a laboratory where quality control measurements are being carried out. A further possibility is oxygen enrichment of dormitories

to improve sleeping quality.

It has been suggested that oxygen enrichment over a long period would reduce the degree of acclimatization to higher altitude. This is probably true but the real issue is working effiency. Everybody would sleep at a lower altitude if they could, and oxygen enrichment of the air in dormitories is simply equivalent to moving to a lower altitude to sleep. It is likely that the improved quality of sleep would improve working efficiency during the following day. Fire hazard is another issue that has been raised. However it can be shown that the fire hazard during this degree of oxygen enrichment at high altitude is less than at sea level because, of course, although the PO_2 is increased, it is still far below the sea level value.

The potencial value of oxygen enrichment can only be proved by careful studies, and it would be simple to do these in a double blind manner. Both psychometric performance and sleep quality should be studied. The result of such a study would be of great interest.

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THE ROMANCE BETWEEN MEDICINE AND MOUNTAINEERINGS[1]

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When I began researching this talk I expected to find the romance between medicine and mountaineering going back for thousands of years. Not so. Only recently has the relationship evolved. Mountain medicine is the child of a marriage which was consummated barely two hundred years ago.

I thought the religious respect for high places would mingle with the religion of healing. But healers did not live on mountains, and the art and science of medicine did not touch the art and science of mountains.

Look first at the beginning of the healing arts. Then see how early exploration necessarily moved onto mountains. As the mountain environment was found to affect health, this became a scientific challenge and mountain medicine was born.

In Egypt more than four thousand years ago illness was though due to imbalance between temporal and spiritual worlds. Physicians were respected tradesmen with a strict hierarchy, specializing in various diseases, coexisting with priests in complicated religious set based on natural forces.

Ancient chinese hearlers thought health was due to the balance between two forces: yin and yang and imbalance between them, together with metereological influences caused all illness. They recognized Qi to be a vital spirit like the Greek pneuma.

Four thousand years ago Ayurvedic medicine combined rituals, sorcery and omens with precise directions for handling trauma and many illnesses. Good health depended on a balance of five elementary substance: fire, earth, water, wind and space which appear in the body as breath, bile, and mucus.

Early Hebrew medicine was based on the belief that life is in the breath, blood is vehicle of the soul. Medicine had preventive and social aspects and was integrated into personal and public life.

In ancient times Hebrews shared medical practices with those of Egypt and Mesopotamia and in medieval days, with the Greco-Roman systems.

Most of that we know about Andean medicine dates only to the 16th century but the Incas understood what Monge has called "environmental aggression". Women who wanted children went to lower altitude; the Incas maintained one army for altitude, one for sea level. Strict laws controlled migration between high and low altitudes.

Greco-Roman medicine stems from Aesculapius and Hipocrates, based on four humors: blood, phlegm, choler (yellow bile) and melancholy (black bile). Galen taught that vital functions were based on fire, water, air, and earth; he also established the basis of anatomy and rudiments of physiology.

But physiology as we know it dates only to the 17th century when Harvey built on Colombo, Ibn al Nafis and others to solve the riddle of the circulation. Mayow did the same for respiration.

Descartes however believed in a "cardiac" fire (the heart) whose action heated the body; Van Heltont thought body heat due to fermentation.

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Man's feeling for mountains has varied greatly over time and place. Two thousand years

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ago Chinese Emperor Xuandi designated Five Sacred Mountains the abode of celestial beings to whom sacrifices were made by emperors, prayers said by the people, and poems written by scholars. Few climbed them.

In the Andes, mountains were worshipped for many reasons: mountain gods controlled the weather; fertility was an important reason for mountain worship. The souls of the dead were thought to reside on mountains. For closer communion with the gods, Andean peoples built hundreds of shrines and shelters as high as 21,000 feet. Many Himalayan peaks like Kailas and Kangchenjunga are considered holy. But shrines were not built on summits, and pilgrims did not climb them.

Ancient Greeks considered Mount Olympus sacred, the home of the gods. In 650 AD St Augustine described annual pilgrimages to the summit for religious sacrifices. The pagan revels of Dionysus and Bacchus were celebrated on mountains.

Travellers became aware of the hazards of high mountains. Two thousand years ago General Du Qin urged the Chinese Emperor that no envoys be sent to Kashmir over the high passes because the Stilk Road was too perilous:

"...travellers have to climb over Mount Greater Headache, Mount Lesser Headache, and the Fever Hills... they must support each other by ropes..."

Chinese pilgrim Too Kin wandered Asia for 15 years seeking enlightenment. He wrote:

"Fa-Hsien and the two others crossed the Little Snowy Mountains. On them the snow lies accumulated both winter and summer. On the north side... Hwuy-King could not go any farther. A white froth came from his mouth and he said to FaHsien, 'I cannot live any longer. Do you immediately go away, that we do not all die here'; and with these words he died".

Xenophon's Ten Thousand suffered greatly while crossing high passes, and Alexander the Great lost thousands of his men to altitude en route to India. Not surprisingly men avoided mountains when possible, but the recent discovery of a mummified body on a high alpine glacier makes us wonder if there were other mountain climbers like him.

We don't know. Chinese traders sought profit. Poets sought beauty. Pilgrims sought enlightenment. Kings grabbed empires. Scientists sought truth. Very few went onto the mountains for pleasure.

An early direct aid climb was by 300 picked soldiers of Alexander's famous army. To conquer the immense Soghdian Rock, they climbed a precipice which overlooked it using iron tent pgs driven into cracks in the rock and ropes to haul each other up. 30 fell to their deaths.

In 1492 Domp Julian climbed an extraordinary pinnacle called Mont Aiguille, using wooden pegs hammered into cracks; the climb was not repeated for 350 years. Shortly after this physician Conrad Gesner wrote:

"I have determined for the future, so long as the life divinely granted to me shall continue, each year to ascend a few mountains, or at least one...for...bodily exercise and delight of the spirit".

Neither General Du Qin nor Fa-Hsien or other early explorer mountaineers associated the illness that afflicted them on mountains with the quality of the air; many thougt it due to poisonous emanations from plants or minerals.

Marco Polo wrote about the:

"...lofty mountains (Yunan province) which no man may visit in summer at any price, because the air in summer is so unwholesome and pestilential that it is death to any foreigner".

In 1967 an anonymous traveller on the Peak of Teneriffe wrote:

"In this ascent some of our party grew very faint and sick, disordered by fluxes, vomiting and Anguish distempers... but called for some of our wine..."

The seventeeth century saw immense advances in science. Ancient descriptions of

circulation and respiration were proven wrong; speculations about the pulmonary circulation by Ibn al Nafis and Colombo were proven correct. Aristotle was shown in error about the nature of air and a vacuum, and the barometer was invented and used to demonstrate that air really was "thinne" - less dense and lighter as one climbed higher. The Guericke vacuum pump led to fascinating experiments with birds and animals - and once with Robert Hooke - exposed to decreased pressure. John Mayow showed that neither combustion nor life were sustaineed in a vacuum. Theories of a vital spirit, necessary for life and combustion were hatched. The foundations for altitude physiology were laid between 1600 and 1650 by these great scientists.

Although the high Andes have been inhabited for many thousand years, only the remains of religious shrines and mummified remains attest that Andean man climbed to, and perhaps lived for weeks, as high as 20-22,000 feet. In 1590 Jesuit missionary Acosta in the Andes and his contemporary Father Ovalde agreed:"When we come to ascend the highest point of the mountain, we feel an air so... subtile that it is with much difficulty we can breathe,... quick and strong and to open our mouths wider than ordinary so as not to be suffocated".

Others later recognized the benefits of acclimatization gained by long residence. However, only recently has medical research evolved in the Andes hand with mountain climbing.

****

Mountain Medicine really began in a small Alpine Village - Chamonix, on August 2nd 1787 when Horace-Benedict de Saussure made the second ascent of Mont Blanc and wrote:

"...Since the air had hardly more than half of its usual density, compensation had to be made for the lack of density by the frequency of inspirations..."

But he did not know that ten years earlier Priestley and Lavoisier had isolated oxygen and proven that it was necessary for life.

The first to clearly relate decreased atmospheric pressure, lack of oxygen and mountain sickness was Thomas Beddoes who explained de Saussure's symptoms in 1797: "Now in ascending these rugged heigths, the muscular exertion must expend a great deal of oxygen, which the rarefied atmosphere will supply but scantily... independent of its rarefaction, the atmosphere of very elevated mountains contains a far smaller proportion of oxygen than that of the lower regions..."

The Golden Age of alpine climbing ran from 1854 to 1875, and as many climbers described alarming symptoms, many theories evolved: "... a threefold source, viz, a gradually increasing congestion of the...circulatory apparatus, increased venosity of the blood, and loss of equilibrium between the pressure of the external air and that of the gasses existing within the intestines..."

"Mountain sickness is due to (a) decrease in the absolute quantity of oxygen, (b) rapidity of evaporation, (c) intensity of light,(d) expansion of intestinal gases and (e) weakening of the coxo-femoral articulation".

Others argued that diminished atmospheric pressure caused the fluids of the body to expand. An American surgeon blamed earth's magnetism. For several centuries emanations from plants (rhu-barb, marigolds, heather) or minerals (antimony, lead were blamed for what was called damgiri, puna, mareo, or soroche.

Many of these doctors were ardent mountaineers, but the man who put all the pieces together was not. Paul Bert was traineed as a plastic surgeon but caught the attention of the great physiologist Claude Bernard and succeeded him as profesor of Physiology.

Written in partnership with Denis Jourdanet, Bert's book Barometric Pressure remains the seminar work in altitude physiology. From accounts by hundreds of travellers, balloon ascents, and experiments in his decompression chamber Bert showed beyond reasonable doubt, that lack of oxygen was the cause of mountain sickness.

One of his comtemporaries, Angelo

Mosso, who was both doctor and climber, challenged Bert with his own studies. He was convinced that the decrease of carbon dioxide resulting from over-breathing was the cause of mountain sickness for which he coined the word 'acapnia'.

Physician Joseph Vallont examined the effects of altitude in his small laboratory near the summit or Mount Blanc. Astronomer Jules Janssen had himself pulled up the mountain on a sled and felt none of the unpleasant symptoms than affected the 42 men who dragged him. A young Chamonix doctor. Etienne Henri Jacottet hurried up to join Janssen, and died of high altitude pulmonary edema - the first martyr to high altitude science. Hugo Kronecker arranged for seven men and women to be carried up in chairs. Like Janssen, They did not have symptoms.

Meanwhile a mountain in Tibet had been found to be 29,028 feet high. Naturally mountaineers wondered if it would ever be climbed. Many believed that spending a nigh above 22,000 feet would be fatal. Balloonists had gone much higher with supplementary oxygen, but some had died.

Mountaineer-chemist Alexander Kellas calculated that a well acclimatized climber could reach the summit, but he died in route to Everest in 1924, at the start of the expedition when Mallory and Irvine disappeared near the summit and Norton reached over 28,000 feet.

In the first years of this century scientists and physicians climbed mountains all over the world. J.S. Haldane argued that the alveolar cells could secrete oxygen, making the oxygen pressure in the pulmonary vein higher than in the alveolus. Joseph Barcroft disagreed, and showed that his arterial blood always contained less oxygen than alveolar air.

None of these men had read the clinical descriptions of altitude illness written in 1913 by Tomas Ravenhill at high Andean mining community. Scientists were studying mountain sickness, but no higher than 15,000 feet and whithout attention to the needs of aviation.

In the First World War Victory in the air depended on altitude. Most effort went to developing oxygen equipment, and tests to select those aviators best suited for high altitude flight, and little attention was given to basic physiology.

By 1920 mountaineers were again going to the highest mountains but few were interested in science. In 1924, Hingston collected unique data about the heart and blood up 22,000 feet on Everest, and Norton came very close to the summit. Hurtado and Monge published important clinical work on mountain sickness and acclimatization. Andean research was born.

Cournad and Richards perfected a special cardiac catheter enabling direct measurement of cardiac dynamics, a major advance in basic studies of high altitude illnesses. Millikan developed the ear oximeter.

As Hitler developed his military machine, the air arm was emphasized and altitude physiology flourished for the next decade. Ulrich Luft published studies of acclimatization made on a Himalayan expedition, supported by the German air force. Then, while mountain expeditions were halted for several years the imperative of air combat stimulated many advances in hypoxia.

Soon after there was attention turned back to Everest. In 1946 a study called operation Everest showed that man could survive at a simulated altitude slightly than Everest, but the question remained: would the climber be able to do the strenuous work neccesary to reach that high cold point?

Today hundreds of men and women have climbed all the highest mountains without supplementary oxygen; hundreds of thousands climb mountains thought impossible a century ago. Millions sojourn among the lower mountains. What is left for the mountaineering scientist to accomplish?

More that ever! We are only beginning to grasp the interrelationships of neurotransmitters, hormones and enzymes. We understand only incompletely the factors that control ventilation, circulation, muscle energetics and the release of scores of hormones. The

effects of both short and long term hypoxia on the central nervous system remain uncharted and controversial. We do not understand why some individuals are peculiarly sensitive to even moderate altitude, while others are very tolerant. We do not know why one person may have mountains sickness on one day and not on another. We do not understand the problem of re-entry HAPE, first described thirty years ago. For the clinician parallels between normal man hypoxic at altitude, and impaired man at sea level cry out for attention.

In short, we have advanced from one small piece of territory to the boundaries of other, larger, almost limitless lands, and we have ever better instruments with which to explore these dazzling prospects.

****

I have emphasized the past which we often ignore. You are the present about which there is too much to tell here. The future is yours to explore. As we probe the mysteries of life we recognize that there are always further frontiers as the poet Flecker wrote:

> We are the pilgrims master We must go
> Ever a little further, it may be
> Beyond that last blue mountain
> Rimmed with snow

UNIVERSIDAD PERUANA CAYETANO HEREDIA

INSTITUTO DE INVESTIGACIONES DE LA ALTURA

CALL FOR ABSTRACTS

SECOND WORLD CONGRESS

on

HIGH ALTITUDE

MEDICINE AND PHYSIOLOGY

AUDITORIUM OF

INSTITUTO PERUANO DE SEGURIDAD SOCIAL

CUSCO, PERU

SEPTEMBER 24-27, 1996

Guests are invited and encouraged to submit abstracts for presentation at the Second World Congress on High Altitude Medicine and Physiology. Individual authors will have no more than five (5) abstracts accepted for presentation at this meeting.

There will be a ten-minute presentation of each chosen paper followed by five minutes of discussion. The work must not be previously published or presented prior to this meeting.

Mail to:

Dr Fabiola León-Velarde
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SECOND WORLD CONGRESS ON HIGH ALTITUDE MEDICINE AND PHYSIOLOGY

SEGUNDO CONGRESO MUNDIAL DE MEDICINA Y FISIOLOGIA DE ALTURA

The setting of the SECOND WORLD CONGRESS ON HIGH ALTITUDE MEDICINE AND PHYSIOLOGY was vindicated by several international participants attending the First World Congress on High Altitude Medicine and Physiology carried out during september, 1994 in La Paz, Bolivia.

This Second World Congress will be sponsored by the Universidad Peruana Cayetano Heredia and by the International Society for Mountain Medicine (ISMM). These meetings have been proposed to promote the progress of high altitude medicine and physiology by the interchange of ideas between the international community and the high altitude regions of the world.

This Second World Congress will be held in Cusco, Peru at 3500 m of altitude. Cusco was the Empire City of the Inkas. Cusco is an urban place located close to the famous Macchu Picchu.

The Congress will include 11 specialized sessions, invited lectures, oral presentations and posters.

Sessions:

1.- Hematological, cardiovascular and respiratory physiology and pathophysiology.
2.- The brain at high altitude: Clinical and Molecular physiology research.
3.- Intrauterine and Extrauterine development at high altitude.
4.- Physiology of acute and intermitent exposition to high altitude.
5.- Endocrine and Reproductive physiology.
6.- Molecular physiology and biochemistry of acute and chronic hypoxia.
7.- Excercise, sports and hypoxia training at high altitude.
8.- Oxygen-sensing and adjustments to acute and chronic hypoxia.
9.- Women exposed to acute and chronic hypoxia.
10.- Medical pathology.
11.- Public and occupational health at high altitude.

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SECOND WORLD CONGRESS ON HIGH ALTITUDE MEDICINE AND PHYSIOLOGY.
Cusco, Perú. September 24-27, 1996

ABSTRACT FORM (DO NOT FOLD)
Type Abstract within the lines below
Deadline: Postmarked by April 1, 1996.

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Abstract Number:_____
Session:_____
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Individual authors will have no more than five (5) abstracts accepted for presentation at this meeting.
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Guidelines For Abstracts.

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- **Objective:** An introductory sentence indicating the objective and purpose of the study.
- **Design:** A briefly worded description of the study design
- **Material and Methods:** A description of experimental procedures including applicable statistical evaluation.
- **Results:** A summary of the new previously unpublished and results.
- **Conclusion:** A statement of the study's conclusion.

b) Abbreviations used in abstracts must be defined. Abbreviations are permitted in titles if they immediately follow the term being abbreviated and are enclosed in parentheses. If used in the text, they should be defined at first mention if not already defined in the title.

2. FORMAT

The abstract must be typed, single-spaced, with the heading (title of the paper) in CAPITAL LETTERS, flush with the left margin of the abstract box. After the title, author's names should be listed consecutively, with initials first and surnames last, and the presenting author's name should appear first. Institutional affiliations (including the city and country) should follow the list of the authors. If multiple authors are credited, each department and institution must be identified with its respective author by a superscript (1,2,3, etc) preceding both the author's name and the institution name.

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The presenting author MUST include name, address, and telephone number and MUST sign the ABSTRACT FORM in the space provided.

5. DEADLINE AND REQUIREMENTS

a) Abstracts postmarked by an official service date stamp after April 1, 1996, will be returned unevaluated to the sender.

b) The official ABSTRACT FORM and two legible photocopies are required. The photocopies will be circulated to members of the Programme Committee.

c) Mailing instructions: The original ABSTRACT FORM with author's signature, and two photocopies of the abstract are to be sent as a single package to:

Dra Fabiola León-Velarde, Chairman
Second World Congress on
High Altitude Medicine and Physiology
Instituto de Investigaciones de la Altura
Box 4314, Lima 100, Peru
Fax (51-14)823435
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Before submitting your abstract, have you:

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Fe de erratas

En el artículo: "El cáncer en una población urbana de la altura" de los autores J. Ríos Dalenz, S. Casablanca, L. Medina y A. de Velasco publicado en Acta Andina (1995) 4:65-70, el autor ha enviado una corrección tipográfica, tal como sigue:

CIE-O	Lugar anatómico	Casos		Tasas Estandarizadas	
		Varones	Mujeres	Varones	Mujeres
181	Placenta	-	7	-	3.0 (no 30.3)
186	Testículos	60	-	2.7 (no 72.7)	-
187	Pene y otro sitio genital masculino	22	-	1.5 (no 51.5)	-

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