Delivered by

infotrieve®

THANK YOU FOR YOUR ORDER

Thank you for your recent purchase from Infotrieve. If you need further assistance, please contact Infotrieve Customer Service at customerservice@infotrieve.com. Please include the Infotrieve Order ID, so we can better assist you.

This is not an invoice.

CUSTOMER INFORMATION

Ordered For:

Company:

Client ID:

Address:

Country:

Phone:

Fax:

Email:

ORDER INFORMATION

Infotrieve Order ID:

Ordered For:

Ordered For Email:

Ordered:

Deliver Via:

Delivery Address:

Tracking Info.:

DOCUMENT INFORMATION

Std. Num.:

Publication:

Publisher:

Vol(Iss) Pg:

Date

Title:

Author(s):

Usage:

Type:

Copies:

Urgency:

Genre:

Total Fee:

The contents of the attached document are copyrighted works. You have secured permission to use this document for the following purpose:

You have not secured permission through Infotrieve, Inc. for any other purpose but may have other rights pursuant to other arrangements you may have with the copyright owner or an authorized licensing body. To the extent that a publisher or other appropriate rights-holder has placed additional terms and conditions on your use of this document, such terms and conditions are specified herein under “Copyright Terms”. **If you need to secure additional permission with respect to this content, please purchase the appropriate permission via the Mobile Library.**

Copyright Terms:

Int. J. Biometeor. 1977, vol. 21, number 2, pp. 93-122.

Effects of High Altitude Stay on the Incidence of Common Diseases in Man

by

I. Singh, I. S. Chohan, M. Lal, P. K. Khanna, M. C. Srivastava, R. B. Nanda, J. S. Lamba and M. S. Malhotra

ABSTRACT. — Prolonged stay at high altitude significantly lowers the incidence of some of the diseases commonly encountered at sea level. This conclusion is based on a study involving 130,700 men stationed on plains between 760 m and sea level and 20,000 men stationed at altitudes between 3692 and 5538 m during the period 1965 to 1972. When yearwise differences in morbidity rates were determined for this period it was found that apart from amoebic hepatitis, goitre and lobar pneumonia, which show a higher incidence, the incidence of infections of bacterial, viral and protozoal origin, diabetes mellitus, hypertension and ischaemic heart disease, asthma and rheumatoid arthritis, gastric disorders, skin diseases, psychiatric ailments and anaemia was significantly lower at high altitude than at sea level. When the trend in morbidity rates was compared over the two subperiods of 1965 to 1968 and 1969 to 1972 it was found that generally increasing or decreasing trends on plains were reflected at high altitude. The overall incidence at high altitude however remained low. Part I of our communication deals with epidemiological data and these findings. Part II surveys the available literature and attempts to explain how improved hormonal state, enhanced fibrinolytic activity, accelerated humoral and cellular immune responses, favourable haemodynamics, better cardiac and cerebral functions, improved metabolic functions, and a relatively stable, dry and cold climate favourably influence the incidence of diseases at high altitude.

INTRODUCTION

Our Indian troops were stationed for the first time at altitudes between 3692 and 5538 m after the Chinese aggression in 1962. The initial experience of a large number of cases of high altitude pulmonary oedema, some of whom died, and of acute mountain sickness was baffling and left us anxious and guessing what our future would be at these altitudes. Some of us predicted poor brain, poor health and poor performance during prolonged stay at high altitude based on the experience of mountaineering expeditions and our own of certain diseases such as lobar pneumonia, amoebic hepatitis, and goitre of which the incidence was increased. Contrary to some of these expectations, however, during 1962 and 1965, it became increasingly clear that 2 to 3 years stay at high altitude was in fact associated with a tendency for a lower incidence of many of the diseases commonly met with on the plains. We have now data covering the period 1965 to 1972 which confirm these initial impressions. Since these observa-

Directorate General, Armed Forces Medical Services, New Delhi, India.
Received 29 November 1975.

tions are unique we have felt it was worthwhile publishing them. Part I of this communication deals with epidemiological aspects including climatic differences, personal habits, clothing, and physical activities and with the statistical evaluation of the year-wise differences in morbidity rates of certain diseases and their trend over this eight years period from 1965 to 1972 both in the plains and at high altitude. Part II surveys the available literature and our attempt to explain the favourable effects of high altitude on the morbidity rates of the diseases under study.

These findings, which are as yet unique may be helpful in the elucidation of pathogenesis of these diseases and their prevention and treatment. We therefore wish to report and explain them as far as we can on the basis of existing knowledge.

PART I

EPIDEMIOLOGICAL STUDY

MATERIALS: The material for this study consisted of 20,000 men stationed at altitudes between 3,692 m and 5,538 m and 130,700 men stationed on the plains between sea level and 760 m. The age of those stationed at high altitude as well as those stationed on the plains ranged between 18-54 years. The basic health was also the same for both groups. Men at high altitude were temporary residents for 2 to 3 years, sometimes more, during which they came to the plains for 2 months once a year.

CLIMATIC CONDITIONS. — At high altitude in winter, which lasted for more than 8 months in the year, the maximum temperature ranged between 13 and —9° C and the minimum temperature between —5 and —19° C. The average vapour pressure remained below 2.5 mb. It hardly ever rained.

In contrast, on the plains the maximum temperature ranged between 30 and 41°C and the minimum temperature between 7 and 21°C. The average vapour pressure during monsoons, which lasted for 3-4 months in a year, was 40 mb while during the dry season it was 20 mb.

CLOTHING. — Suitable clothing was provided for protection against severe cold and windy conditions in winter at high altitude. It consisted of a four layered garment, from inner to outer of a cotton vest, a woolen shirt, a woollen jersy pullover and a purkha coat stitched in two layers with an inner lining of woollen material and an outer wind proof covering with fillings of dawns of Eider duck in between as an insulating layer. A purkha pants was worn to cover the legs. Shoes were snowproof. During sleep living quarters were partially warmed by improvised heaters. Summer clothing depended on the temperature.

In contrast, the clothing in plains consisted of a cotton vest, a cotton shirt and a pair of cotton trousers and ordinary shoes and socks through out the year.

PHYSICAL ACTIVITIES. — All men both at high altitude and in plains underwent regular physical training. At high altitude, in addition, they were trained to negotiate the hills.

DIET. — The daily diet on the plains consisted of proteins 120 g, fats 100 g, and carbohydrates 600 g with a coloric value of 3,780 K cal. At high altitude the caloric value was +600 K cal over and above the caloric value at sea level.

PERSONAL HYGIENE. — The personal hygiene of men at high altitude compared with men at sea level was relatively poor as regards opportunities of routine daily baths and change of underclothing.

TABLE 1. Year-wise differences in morbidity rates per thousand from 1965 to 1972 of diseases at sea level and high altitude.

No.	Diseases	1965		1966		1967		1968		1969		1970		1971		1972	
		SL	HA	SL	HA	SL	HA	SL	HA	SL	HA	SL	HA	SL	HA	SL	HA
1.	Chickenpox	7.97	1.12**	4.47	1.63**	5.09	2.28**	3.66	1.98**	4.37	1.34**	4.19	2.28**	6.21	1.18**	3.96	2.84*
2.	Dysentery and diarrhoea	11.20	6.18**	8.64	5.10**	9.21	2.68**	7.36	3.61**	7.25	3.54**	9.53	6.99**	10.10	5.78**	3.39	3.64
3.	Infectious hepatitis	9.47	2.55**	14.24	3.75**	7.23	2.68**	7.10	2.32**	7.81	1.71**	6.82	2.33**	7.72	2.84**	13.87	3.49**
4.	Malaria	0.84	0.00**	0.74	0.05**	1.00	0.00**	1.04	0.23**	1.65	0.05**	2.36	0.11**	3.20	0.86**	3.77	1.82**
5.	Meningitis	0.02	0.00	0.03	0.00	0.07	0.00**	0.09	0.00**	0.09	0.05	0.09	0.00**	0.13	0.00**	0.00	0.07**a
6.	Mumps	2.30	1.68*	4.72	0.49**	2.51	1.08**	0.97	4.58**a	2.84	1.07**	2.13	1.72	2.85	4.07	2.95	2.18
7.	Pneumonia	1.40	2.54	1.48	3.04**a	1.17	1.42	1.33	2.09**a	1.77	1.61	1.44	1.83	1.92	1.98	2.00	3.64**a
8.	Respiratory infections	40.97	33.60**	34.41	26.22**	30.75	24.90**	41.70	41.09	38.10	30.41**	33.87	19.99**	32.37	23.18*	34.95	37.05
9.	Pulmonary tuberculosis	1.49	0.38**	1.80	0.27**	1.64	0.11**	2.73	0.17**	2.05	0.43**	1.75	0.44**	1.81	0.70**	2.15	0.51**
10.	Diabetes mellitus	1.44	0.31**	1.07	0.11**	1.03	0.06**	1.17	0.17**	1.35	0.32**	1.08	0.22**	1.23	0.05**	1.60	0.07**
11.	Hypertension	1.42	2.71	1.53	1.19	1.36	0.51**	1.58	0.79**	1.29	0.64**	1.09	0.44**	1.02	0.75	1.17	0.95
12.	Ischaemix heart disease	0.41	0.61	0.47	0.05**	0.87	0.00**	1.29	0.06**	1.55	0.64**	1.05	0.05**	1.00	0.21**	1.00	0.19**
13.	Peptic ulcer	1.71	1.28	1.52	0.81**	1.60	0.46**	0.67	0.73	2.43	1.82	2.05	1.72	2.02	0.75**	2.14	2.33
14.	Anaemias	2.90	2.84	2.72	1.41**	2.03	1.08**	1.69	0.79**	1.77	0.32**	1.97	0.34**	1.69	0.70**	1.74	0.80**
15.	Asthma	—	—	—	—	—	—			2.18	0.05**	1.98	0.33**	2.03	0.32**	2.24	0.36**
16.	Skin diseases	23.86	9.49**	23.14	9.88**	21.36	14.07**	20.48	13.39**	20.93	12.53**	22.18	10.88**	21.53	8.51**	11.40	13.47
17.	Psychiatric diseases	4.05	0.92**	3.60	1.41**	3.63	1.48**	3.34	1.30**	3.81	1.34**	4.42	2.55**	4.46	3.00**	5.34	2.91**
	(a) Neuroses	3.16	0.41**	2.67	0.76**	2.72	1.08**	2.54	1.02**	1.72	0.27**	2.81	0.61**	3.16	2.25**	3.80	2.18**
	(b) Psychoses	0.67	0.20**	0.60	0.16**	0.63	0.17**	0.62	0.28**	0.77	0.32**	0.63	0.56	0.66	0.27*	0.75	0.36
18.	All Causes	253.55	172.83**	244.29	169.32**	224.88	176.92**	243.16	208.31**	233.63	161.66**	217.22	157.47**	228.48	159.93**	248.67	193.97**

SL = Sea level; HA = High altitude

* $P < 0.05$ (High altitude rates are lower than sea level rates)

** $P < 0.01$ (High altitude rates are lower than sea level rates)

a = High altitudes rates are higher than sea level rates.

TABLE 2. Differences in the morbidity rates for the period 1965-1972 of diseases at sea level and high altitude.

No.	Diseases	Morbidity Rates Mean SL group	Morbidity Rates HA group	P t-test
1	Chickenpox	4.9900	1.8313	<0.01
2	Dysentery and diarrohoea	8.3350	4.6900	<0.01
3	Infectious hepatitis	9.2825	2.7088	<0.01
4	Malaria	1.8263	0.3900	<0.01
5	Meningitis	0.0650	0.0150	>0.05
6	Mumps	2.6588	2.1086	>0.05
7	Pneumonia	1.5638	2.2688	<0.05
8	Respiratory infections	35.8900	29.5550	<0.01
9	Pulmonary tuberculosis	1.9263	0.3763	<0.01
10	Diabetes mellitus	1.2463	0.1638	<0.01
11	Hypertension	1.3075	0.9963	>0.05
12	Ischaemic heart diseases	0.9550	0.2213	<0.01
13	Peptic ulcer	1.7675	1.2375	>0.05
14	Anaemias	2.0638	1.0413	<0.01
15	Asthma	2.1495	0.3703	<0.01
16	Skin diseases	20.6100	11.5188	<0.01
17	Psychiatric diseases	4.0813	1.8638	<0.01
	(a) Neuroses	2.8225	1.0725	<0.01
	(b) Psychoses	0.6663	0.2900	>0.05
	(c) Others	0.5925	0.5013	>0.05
18	All causes	236.7350	175.0513	<0.01

SL = Sea level; HA = High altitude

TABLE 3. Trends in morbidity rates for the periods 1965-1968 and 1969-1972 of diseases at sea level and high altitude.

No.	Diseases	Sea level group			High altitude group		
		Mean 1965-68	Rates 1969-72	P* t-test	Mean 1965-68	Rates 1969-72	P* t-test
1	Chickenpox	5.2975	4.6825	<0.05[a]	1.7525	1.9100	>0.05
2	Dysentery and diarrhoea	9.1025	7.5675	<0.01[a]	4.3925	4.9875	>0.05
3	Infectious hepatitis	9.5100	9.0550	>0.05	2.8250	2.5925	>0.05
4	Malaria	0.9050	2.7475	<0.01	0.0700	0.7100	<0.01
5	Meningitis	0.0525	0.0775	>0.05	0.0000	0.0300	>0.05
6	Mumps	2.6250	2.6925	>0.05	1.9575	2.2600	>0.05
7	Pneumonia	1.3450	1.7825	<0.01	2.2725	2.2650	>0.05
8	Respiratory infections	36.9575	34.8225	<0.01[a]	31.4525	27.6575	<0.05[a]
9	Pulmonary tuberculosis	1.9150	1.9375	>0.05	0.2325	0.5200	>0.05
10	Diabetes mellitus	1.1775	1.3150	>0.05	0.1625	0.1650	>0.05
11	Hypertension	1.4725	1.1425	<0.01[a]	1.2975	0.6950	<0.05[a]
12	Ischaemic heart disease	0.7600	1.1500	<0.01	0.1800	0.2625	>0.05
13	Peptic ulcer	1.3750	2.1600	<0.01	0.8200	1.6550	<0.05
14	Anaemias	2.3350	1.7925	<0.01[a]	1.5300	0.5525	<0.01[a]
15	Skin diseases	22.2100	19.0100	<0.01[a]	11.7075	11.3475	>0.05
16	Psychiatric diseases	3.6550	4.5075	<0.01	1.2775	2.4500	<0.01
	(a) Neuroses	2.7725	2.8725	>0.05	0.8175	1.3275	>0.05
	(b) Psychoses	0.6300	0.7025	>0.05	0.2025	0.3775	>0.05
	(c) Others	0.2525	0.9325	>0.05	0.2575	0.7450	>0.05
17	All causes	241.470	232.000	<0.01[a]	181.845	168.2575	<0.01[a]

* P (1969-72 rates are higher than 1965-68 rates)
[a] = 1969-72 rates are lower than 1965-68 rates.

einde band 6 - Kanters, Biometeorology 21/2 (art. Singh e.a.)

METHOD. — The study was carried out to examine the differences in the morbidity rates between the two groups, one stationed at high altitude and the other on the plains. For this yearwise morbidity rates for 1965-72 were computed for a number of specific diseases in each group (Table 1). Differences in the average morbidity rates for plains and for high altitude for the period 1965-72 as a whole were also tested for statistical significance (Table 2). To examine whether there was any systematic trend in disease specific morbidity rates, the period 1965-72 was split into two sub-periods 1965-68 and 1969-72. The differences in the average morbidity rates during these two sub-periods were tested for statistical significance for both plains and high altitude separately (Table 3).

YEAR-WISE DIFFERENCES IN MORBIDITY RATES

In Table 1 it will be seen that the morbidity rates for chickenpox, infectious hepatitis, malaria, pulmonary tuberculosis, diabetes mellitus, asthma and psychiatric diseases (combined neuroses, psychoses and others) in the plains were significantly higher than those for high altitude for every year. So also was the case with morbidity rates for all diseases combined.

For dysentery and diarrhoea, respiratory infections, hypertension, ischaemic heart disease, peptic ulcer, anaemias and skin diseases the morbidity rates were higher for the plains than for high altitude. But the differences were significant for some years and not for others.

Diseases for which the morbidity rates in some years for high altitude were higher than for plains were meningitis, mumps and pneumonia.

DIFFERENCES IN MORBIDITY RATES FOR THE PERIOD 1965-72

Significantly higher rates were recorded for plains than for high altitude for chickenpox, dysentery and diarrhoea, infectious hepatitis, malaria, respiratory infections, pulmonary tuberculosis, diabetes mellitus, ischaemic heart disease, anaemias, asthma, skin diseases and some of the psychiatric diseases (neuroses).

The average morbidity rates for meningitis, mumps, hypertension, peptic ulcer and some of the psychiatric diseases (psychoses) were higher for plains than for high altitude but the differences were not statistically significant.

Pneumonia was the only disease for which the morbidity rate was significantly higher for high altitude than for plains. Significantly lower rates were observed for all diseases combined at high altitude than those for plains.

TRENDS IN MORBIDITY RATES. — Significantly lower rates were recorded during the period 1969-72 as compared to 1965-68 for both plains and high altitude in respect of respiratory infections, hypertension and anaemias.

A declining but statistically not significant trend was also recorded in respect of infectious hepatitis.

Statistically significant increasing trend was observed for malaria, peptic ulcer, and psychiatric diseases (combined neuroses, psychoses and others) for both plains and high altitude.

Statistically, though not significant, an increasing trend was also observed for both the groups in case of meningitis, mumps, pulmonary tuberculosis, diabetes mellitus and psychiatric diseases (neuroses and psychoses individually).

A significant decline in trend for chickenpox and dysentery and diarrhoea was observed for plains whereas an insignificant increasing trend for these diseases was recorded for high altitude. A significant and an insignificant decline was also observed for skin diseases for plains and high altitudes respectively. All causes showed a significant decline for both plains and high altitude.

DISCUSSION

At altitudes above 1500 m the changes in meteorological characteristics to which an individual will be subjected are: (1) reduced partial oxygen pressure; (2) differences in the quality and quantity of solar radiation particularly for the invisible ultraviolet part of the solar spectrum with wave lengths of 290-380 nm; (3) generally lower mean daily temperatures; (4) usually less atmospheric turbulence and water vapour; (5) often higher ozone content; (6) reduced number of large ions and an increased number of small ions; and (7) smaller pollutant content of the atmosphere, such as of duct, allergens and chemical pollutants (Tromp and Bouma, 1974).

As a result of such exposure a number of clinically important physiological changes occur. Within an hour lung ventilation, vital capacity, peripheral blood flow, and cerebral blood flow, particularly in the hypothalamus, are increased. After repeated exposure to 1,500 m for one hour a day for a long period the respiratory function improves considerably, the sensitivity of the autonomic nervous system is increased, the adrenal hormonal function and the blood-producing mechanisms are stimulated, the overall thermoregulation efficiency improves, after an initial increase fibrinogen levels of the blood and erythrocyte sedimentation rate are reduced, acid production in the stomach is reduced, and changes may occur in the composition of the blood (Tromp and Bouma, 1974).

The above physiological changes resulting from intermittent exposures to high altitude have been put to good therapeutic effect, and certain forms of anaemia, peripheral blood circulation disorders, disturbed functions of the autonomic nervous system, asthma, hypertension, schizophrenia, arthritic diseases, nonallergic eczemas, hypothyroidism, and various thermoregulatory disorders have been successfully treated with natural or simulated high altitude. General recovery after long lasting infections and other conditions has also been promoted (Tromp and Bouma, 1974). In the USSR the natural high altitude climates of the Caucasus and Pamir regions are used for therapeutic purposes. During therapy natural acclimatisation is not allowed to occur and the beneficial processes which come into play during short exposures to high altitude are thereby kept sustained. Our studies indicate that even prolonged exposure to high altitude has a beneficial effect on the incidence of certain diseases. Apart from amoebic hepatitis, goitre, and lobar pneumonia, the incidence of other diseases commonly met with in the plains is significantly reduced at high altitude.

PART II

FACTORS WHICH INFLUENCE INCIDENCE OF DISEASES

INFECTIONS. — (Fig. 1-3): It has been shown that the subjects reaction to their environment is not altered by their microbial flora nor is the microbial flora influenced by the individuals environment. Thus no quantitative or qualitative changes in throat flora (normal throat flora, mycoplasma species, B-haemolytic streptococci, staphylococci, and coliform bacilli), in the skin flora from the forehead and back (coliform bacilli, diphtheroids, A-streptococci, B-haemolytic streptococci, staphylococci, candida species, and aspergillus species), or in the faecal flora were found in subjects sampled at Fort Sam Houston and Pikes Peak (Weiser, Peoples and Hull, 1969).

In the absence of changes in the bacterial flora at high altitude both host resistance and local factors appear to lower the incidence of infections at high altitude.

There is convincing evidence that small negative air ions have lethal action on bacteria and fungi (Phillips, Harris and Jones, 1964), and alter the rate of migration of amoebae (Andriese, 1969).

When mice exposed to altitudes of 5500-8800 m are challenged to bacterial and viral pathogens which attack lungs, skin, central nervous system or produce a generalised

systemic infection, the results are reproducible but there is a lack of consistency in terms of the host response in that specific environment may increase host resistance to certain agents but not to others. Likewise a specific micro-organism may or may not show altered virulence when the animal is exposed to different environments. How-

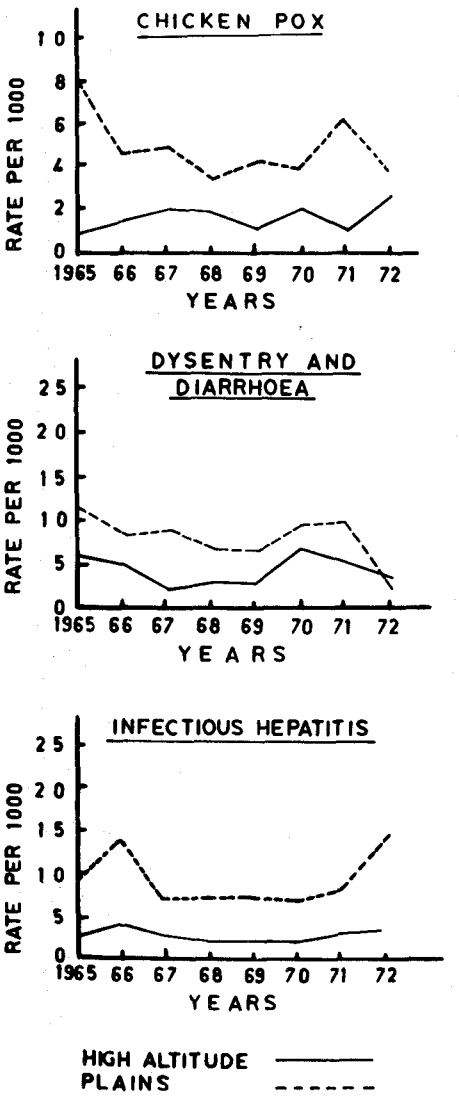

Fig. 1. Year-wise morbidity rates per 1000 for 1965 to 1972 in plains and high altitude for chicken pox, dysentery and diarrhoea, and infectious hepatitis.

ever acute exposure to hypoxic conditions after infection seems to offer some protection as seen by the increase in survival time. The survival time of animals continuously exposed or exposed only before infection is not affected (Schmidt, 1969).

The beneficial effect of exposure to hypoxia after infection seems to depend on the quality and quantity of immunoglobulin synthesis. Marked changes occur in the quantity of antiprotein antibody produced by guinea pigs exposed to low temperature or high altitude, and resistance to viral infection is greater and resistance to bacterial

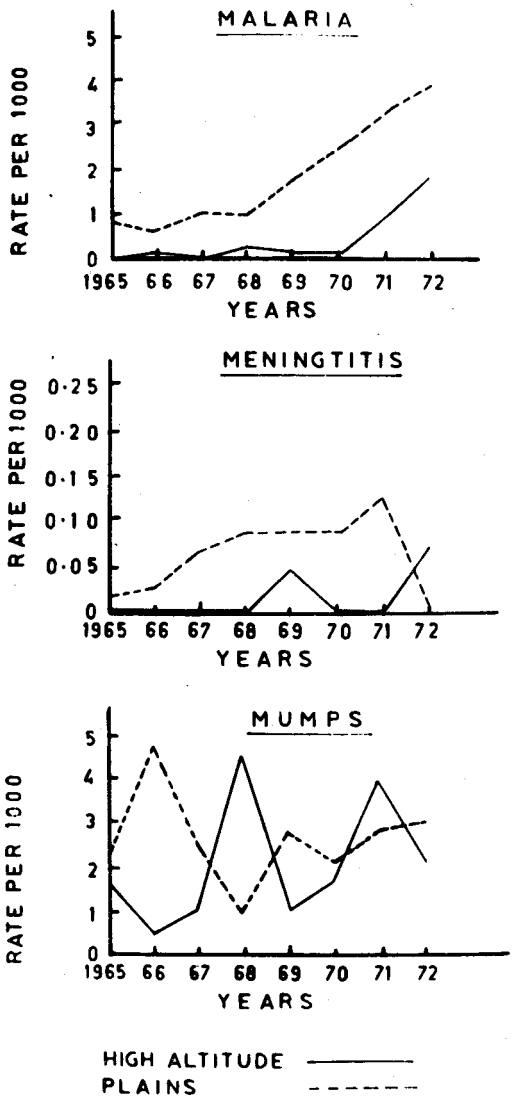

Fig. 2. Year-wise morbidity rates per 1000 for 1965 to 1972 in plains and high altitude for malaria, meningitis, and mumps.

infection is lower in high-altitude-adapted animals than in low-altitude controls (Trapani, 1966). Since immunoglobulin IgM is more efficient than immunoglobulin IgG in regard to bacterial inactivation (Pike, 1967) it has been postulated that the

decrease in resistance to bacterial infection is a result of inadequacy of IgM immunoglobulin synthesis and increased resistance to viral infections is related to an increase in IgG immunoglobulin synthesis (Trapani, 1969).

The IgA immunoglobulin, the levels of which are raised at high altitude (Chohan

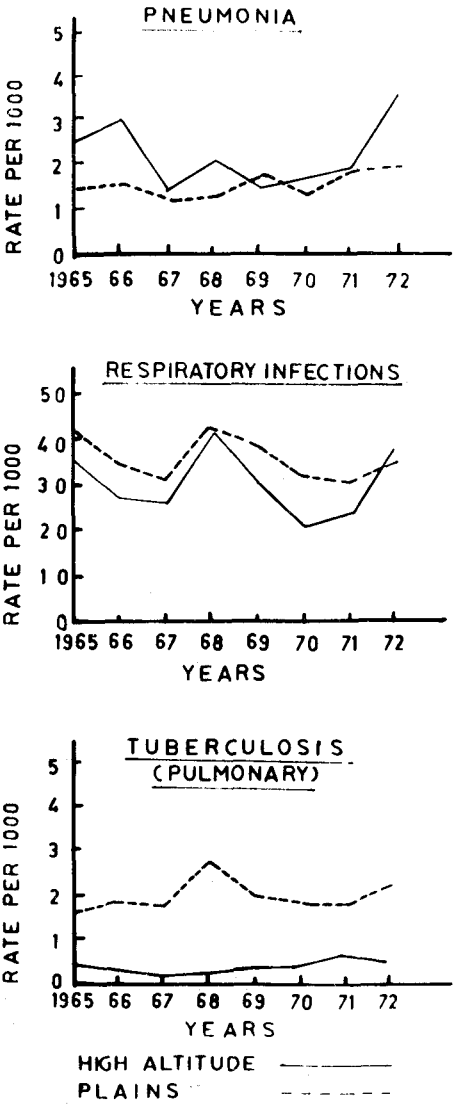

Fig. 3. Year-wise morbidity rates per 1000 for 1965 to 1972 in plains and high altitude for pneumonia, respiratory infections, and pulmonary tuberculosis.

et al., 1975), is dominantly present in a variety of secretions such as colostrum, saliva, tears, nasal mucus, tracheobronchial secretions, the lumen of small intestines and may play a protective role at the respective mucous surfaces (Humphrey and White, 1970).

As the secretory form of IgA is resistant to digestion by proteolytic enzymes and reducing agents it may be a contributory factor in the lower incidence of intestinal infections and upper respiratory tract infections at high altitude. The immunoglobulin response obtained in our cases are summarised in Fig. 4.

Although the incidence of infectious hepatitis at high altitude is lower than at sea level (Fig. 1), the incidence of hepatitis associated surface antigen (HBsAg) carriers among high altitude natives is higher than in sea level residents (Chohan et al., 1975).

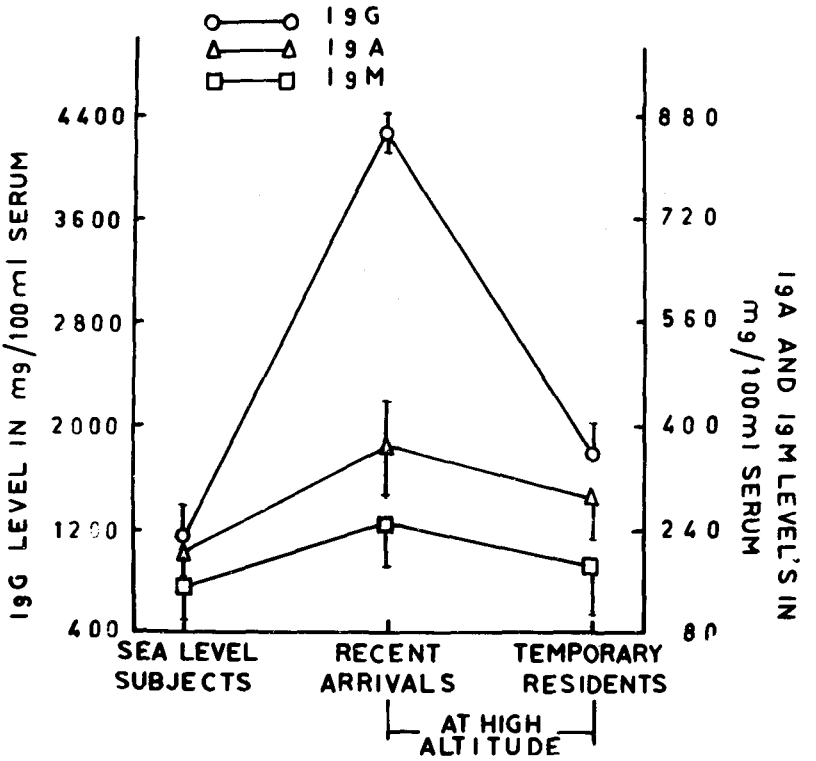

Fig. 4. Immunoglobulin IgG, IgA, and IgM levels in sea level subjects, in recent arrivals, and temporary residents (2-3 years) at high altitude. Brackets represent the mean ± SE.

It is known that HBsAg is likely to persist after subclinical hepatitis and is possibly associated with an impaired T-cell response as is indicated by a poor response to dinitrochlorobenzene (Dudley, Fox and Sherlock, 1972). Work is in hand to show whether a diachotomy between humoral and cell-mediated immunity (CMI) occurs at high altitude or not. It is of interest to note that the lowered incidence of infectious hepatitis and increased incidence of HBsAg carriers at high altitude occurs inspite of various factors which operate at high altitude and lower hepatic resistance (Singh et al., 1974).

Injection of an endotoxin into animals and certain infections in humans have been likened to the Sanarelli-Shwartzman reaction which is characterised by thrombosis as well as haemorrhage. It has been speculated that the generalised Shwartzman reaction represents one extreme of spectrum of response in relation to the haemostatic mech-

anisms with reference to infectious diseases. Intravascular coagulation may occur in less dramatic presentation in viral, rickettesial and bacterial infections and differing degrees of intravascular activation of coagulation mechanisms may be responsible for a significant part of the pathophysiology of many infectious diseases (Dennis et al., 1968). Counteracting the coagulation mechanism, fibrinolytic system may afford uncovering and elimination of the infectious organisms, making them more vulnerable to the defence mechanisms like phagocytosis by the macrophages and the reticuloendothelial system, providing an effective immune clearance. High altitude provides both the fundamental protective measures of enhanced fibrinolytic activity and accelerated immune response. Increased fibrinolysis and immune responses may act synergistically at high altitude in eliminating the infectious organisms (Chohan et al., 1975).

Owing to low environmental temperature there is no active transmission of malaria at high altitude. Cases of malaria which occur at high altitude are either relapse cases or those who have incubatory disease at the time of induction to high altitude. The incidence of relapses however is very much lower at high altitude than at sea level. Intravascular coagulation which occurs during the malarial infection (Jaroonvesama, 1972) probably protects the parasites in various organs and is responsible for severity of disease, resistance to therapy, and relapses. As fibrinolytic activity increases on arrival at high altitude it is likely that malarial parasites are made more vulnerable to the increased immune response at high altitude. In this connection it is relevant to state that IgG immunoglobulin and to a lesser degree IgM immunoglobulin, which are increased at high altitude, are closely related to the malarial antibodies (Tobie, Wolff and Jeffery, 1966).

Disseminated intravascular coagulation which occurs in patients with meningococcaemia (Dennis et al., 1968) and affords protection to the invading organism has been held responsible for a fulminant picture. Enhanced fibrinolytic activity at high altitude may deprive this protection to the infecting microbes and this may be further facilitated by an accelerated immune response at high altitude.

At sea level the predilection of the disease for the upper and posterior parts of the lungs in post-primary tuberculosis has been attributed to the biochemical advantages in the tissue environment in those parts of the lungs. At high altitude hyperventilation seems to rob the *Myco.tuberculosis* of these advantages. Ultraviolet radiation at high altitude may prevent the dissemination of the organisms.

Although the personal hygiene of men at high altitude is comparatively poor due to lesser opportunities for routine daily baths as well as for changing underclothing, it is remarkable that the incidence of skin infections at high altitude is much lower than at sea level (Fig. 12). The lowered incidence of skin diseases at high altitude could be attributed to the high degree of atmospheric dryness and rapid evaporation of perspiration. Dampness and heat which are conducive to multiplication of skin organisms and spread of disease do not exist.

Although the total incidence of acute respiratory infections at high altitude is lower than at sea level, the incidence of lobar pneumonia is higher at high altitude than at sea level (Fig. 3). In lobar pneumonia the infecting pneumococci are aerobes and/or facultative anaerobes, generally types (1, 2, 3, 5, 7, 14) normally inhabiting the upper respiratory tract. High altitude hypoxia may promote the selective growth of pneumococci which are facultative anaerobes. Once an infection develops the accumulation of carbondioxide in the alveolar spaces resulting from respiratory distress and poor ventilation may provide an ideal environment for rapid growth of these pneumococci. A relative inadequacy of IgM at high altitude would result in a fulminant infection with a prolonged course or a high mortality.

Akin to a higher incidence of lobar pneumonia at high altitude than at sea level is our finding that latent amoebiasis (a protozoal infection) is aggravated at high altitude (Singh et al., 1974).

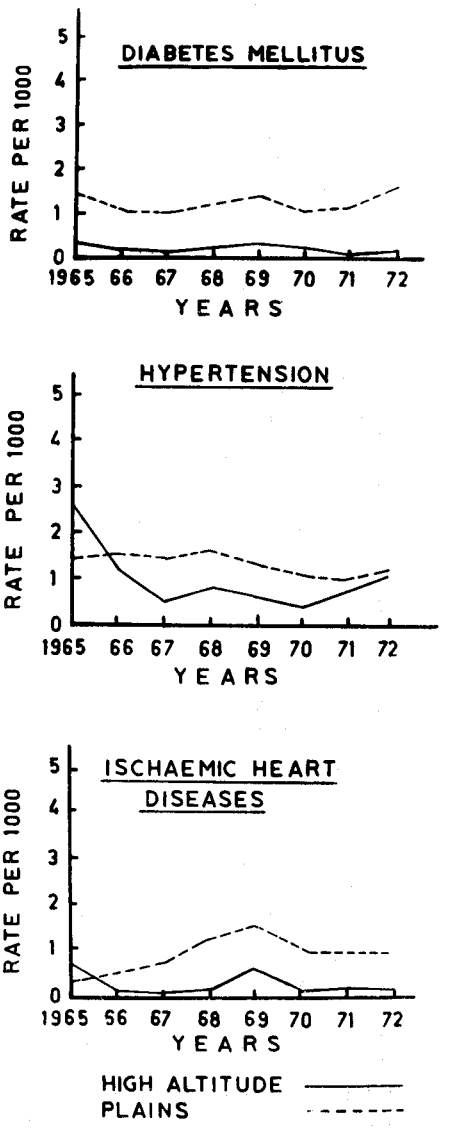

Fig. 5. Year-wise morbidity rates per 1000 for 1965 to 1972 in plains and high altitude for diabetes mellitus, hypertension, and ischaemic heart disease.

DIABETES MELLITUS (Fig. 5): Forbes (1936) reported that fasting blood sugars decreased as men went from sea level to 3,660 m and then increased at higher altitudes. These lower basal blood glucose levels do not depend entirely on the higher haematocrit values. Blood glucose values have been described as being normal or slightly hypoglycaemic after 3 weeks exposure at an altitude of 3,800 m (Blume and Pace, 1967). High laltitude natives have been reported to have reduced blood sugars (Picon-Reategui, Buskirk and Baker, 1970). In our subjects the blood sugar has been found to be raised at 2 weeks after arrival at high altitude. The rise persists even at 10 months.

But at 24 months it is significantly lower than the initial values at sea level before sojourn to high altitude. On return to sea level at one month the blood sugar is still low in comparison with the initial values at sea level (Fig. 6).

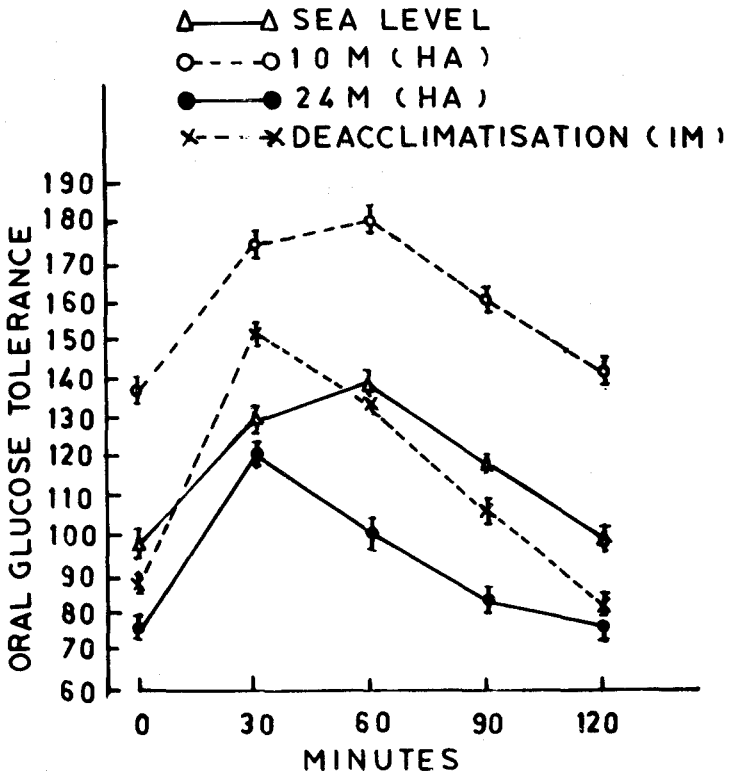

Fig. 6. Oral glucose tolerance at sea level, after 10 months, and after 24 months stay at high altitude and after deacclimatisation at sea level for 1 month. Brackets represent the mean ± SE.

Both oral and intravenous glucose tolerance tests have indicated that glucose utilisation is increased in high altitude natives. 14-C glucose infusion studies show that this is also the case in recent arrivals at high altitude (Johnson et al., 1974).

Concomitantly with the reduced blood sugar levels the liver has lower glycogen content (Blume and Pace, 1967; Johnson et al., 1974). Reduction of liver glycogen stores is probably one of the reasons why glucose tolerance tests do not produce as large an elevation in blood glucose levels at high altitude as at sea level. Glycogen synthesis would be stimulated by reduced stores and this would rapidly remove the excess glucose from the blood.

In laboratory animals chronically exposed to altitude there is a definite increase in the rate of glycogenesis, not only in the liver but in the heart and the muscles as well. While the liver and heart show a steadily diminishing amount of stored glycogen after one hour, the muscles which represent the largest pool tend to hold the glycogen over 2 hours (Blume and Pace, 1969). These changes are directly associated with the hexose portion of the glycolytic sequence (Blume and Pace, 1967). The glucagon-induced

plasma glucose response at high altitude is of a shorter duration than at sea level (Johnson et al., 1974).

Plasma cortisol, basal urinary 17-hydroxy and ketosteroids, cortisone secretion rates, responses to metapyrone, and the suppressive effects of dexamethasone are all similar in high-altitude natives to those found in sea level inhabitants. Adrenal stimulation with 1-5 units of ACTH, however, produces significantly lower responses in the high-altitude natives (Urdanivia et al., 1975).

Although free fatty acid levels are increased and the fasting blood sugar is decreased at high altitude, the immunoreactive insulin concentrations at high altitude and sea level are the same (Garmendia et al., 1973). It thus seems that the sensitivity to endogenous insulin is increased at high altitude. This increased sensitivity to endogenous insulin is, however, partly balanced by increased growth hormone levels (Sutton et al., 1970) and increased catecholamine responses to insulin-induced hypoglycaemia (Moncloa, Gomez and Hurtado, 1965). The cortisol responses to tolbutamide-induced hypoglycaemia are also increased (Urdanivia et al., 1975).

Further, hypoxia inhibits intestinal absorption of actively transported sugars in the rat (Liluch and Ponz, 1962) and in dogs exposed to simulated altitudes at 5,000 m. A report by Panin (1964) suggests a possible delay in absorption.

Therefore at least six mechanisms may be involved in keeping the incidence of diabetes mellitus low at high altitude: (1) delay in absorption of sugars, (2) increased glycogen synthesis, (3) decreased glycogenolysis, (4) increased sensitivity to endogenous insulin, (5) decreased sensitivity to endogenous ACTH, and (6) increased rate of utilisation of glucose.

HYPERTENSION (Fig. 5): The systemic blood pressure at high altitude is lower than at sea level. This clinical impression has been widely held for many years in the native Andean population and has been confirmed in epidemiological studies by Ruiz et al. (1968). This has been attributed to diminished peripheral resistance resulting from vasodilation and hypervascularisation in response to chronic hypoxia.

Diastolic blood pressure values in men, however, have not been found significantly different at high altitude from those at sea level. This has been attributed to the neutralising effect of increased blood viscosity and peripheral resistance resulting from polycythaemia (Ruiz et al., 1968). In women below 40 years both systolic and diastolic pressures are lower at high altitude than at sea level. This has been attributed by Ruiz et al. (1968) to a lesser degree of polycythaemia in younger females resulting from menstrual losses. In our subjects the systolic pressure during 2 years at high altitude has ranged between 110-120 mm Hg and the diastolic between 70-90 mm Hg (Fig. 7). As is the case in our subjects Marticorena et al. (1969) have demonstrated a lowering in blood pressure of sea level white males after a long residence at high altitude.

Brief periods of moderate hypoxia increase cardiac output in man. This is associated with an enhancement of total flow of blood and a major readjustment of the partitioning of this cardiac output to various tissues. In animal experiments the renal and the vascular beds have been shown to be the source of the flow fraction diverted to the heart, brain, and muscles. But this is carried out without the expense of reducing normal flow to the kidneys, liver and the intestine (Vogel, Pulver and Burton, 1969). Renal flow has also been found to be unaffected by hypoxia in man (Caldwell, Rolf and White, 1949).

The onset of exposure to high altitude is associated with a reduction in plasma volume (Consolazio et al., 1968; Hannon, Shields and Harris, 1969). The degree of plasma reduction is usually 500-900 ml, or between 20 and 30% of the initial plasma volume at the point of maximum change. Lowered values have also been reported over a period of several months (Hannon, Shields and Harris, 1969).

Hypoxia disturbs the stability of the balance between the sympathetic and the parasympathetic nervous system. Initially there is a tendency for the sympathetic system to dominate, giving way to a reversal response later (Keys, Stapp and Violante, 1943).

There is then significant lowering of the heart rate and the cold pressor response (Malhotra and Mathew, 1974).

Cardiac output has been reported normal in healthy Andean residents (Penaloza et al., 1963). In Caucasian people at 3100 m Hartley et al. (1967) reported subnormal values of cardiac output both at rest and during exercise.

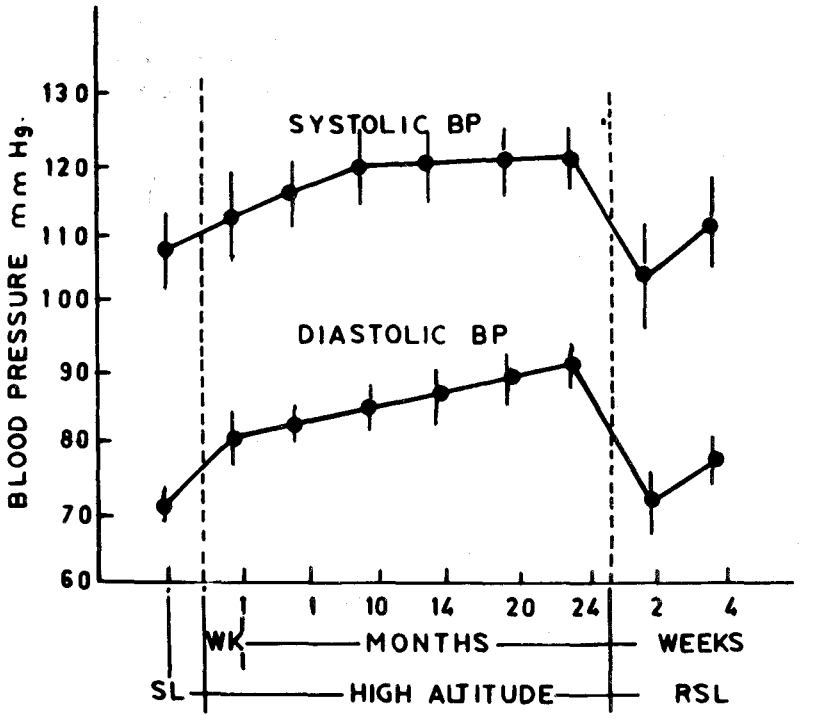

Fig. 7. Blood pressure at sea level, at the end of 1 week, 1, 10, 14, 20 and 24 months stay at high altitude, and on deacclimatisation at sea level for 2 and 4 weeks. Brackets represent the mean ± SE.

Apart from diminished peripheral resistance, therefore, four other factors may help to promote either normotension or hypotension at high altitude: (1) a normal renal blood flow, (2) lower blood volume, (3) parasympathetic dominance associated with lower heart rate and the cold pressor response, and (4) lower cardiac output.

ISCHAEMIC HEART DISEASE (Fig. 5): In the experience of the Andean doctors, people from high altitudes are in some way protected from developing ischaemic heart disease. Jeri (1947) out of 182 cases of myocardial infarction from different parts of the country found no case in pure native Indians. At Cerro de Pasco (4,375 m) Ramos et al. (1967) found no case of myocardial infarction or coronary artery disease in 300 autopsies performed in their laboratory. Epidemiological studies by Ruiz et al. (1969) in Milpo (4,100 m) showed that the incidence of angina of effort, ECG signs of myocardial ischaemia, and arterial hypertension were significantly lower than at sea level. Several factors seem to be contributory to this.

Arias-Stella and Topilsky (1971) found that the hearts from natives in Cerro de

Pasco had more abundant coronary channels than those from sea level. Carmelino (1970) reported the predominance of a right type of coronary distribution, the existence of a greater number of branches of the first order, and a greater number of intercoronary anastomoses in specimens from natives resident at Puno (3,466-4,287 m). In guinea pigs maintained in decompression chambers Valdivia (1962) found that number of capillaries per myocardial fibre was increased compared to the number observed in sea level animals. In puppies born at 6,000 m a larger capillary area in the heart was noted by Becker, Cooper and Hataway (1955). As a result of increase in the number of capillaries and larger vessels, the coronary reserve is greatly increased at high altitude (Nurmatov, 1970).

Coronary flow measured by the Kety and Schmidt method using the desaturation techniques is lower at high altitude than at sea level. Moret (1971) found it to be 49 ml/(min. 100 g) of left ventricle at 4,375 m and 71.7 at sea level (150 m) — a difference of approximately 30%. Coronary vascular resistance was increased with altitude. The decrease in coronary flow was not compensated by the increased haematocrit and oxygen content of the arterial blood. Therefore, the oxygen supply was also decreased at high altitude. However, the oxygenation of the myocardium was adequate, the extraction coefficient of oxygen did not decrease, and the oxygen content of the coronary sinus blood was also the same; the saturation percentage was lower, but the PO_2 was not lowered. The myocardial oxygen consumption was lower at high altitude: 8.7 ml/(min.100 g) left ventricle at 150 m, 7.1 at 3,700 m, and 6.8 at 4,375 m.

The cardiac output and the mean aortic pressure was the same at sea level and at high altitude. The myocardial efficiency increased from 31% at 150 m to about 40% at 4,375 m — an increase of approximately 30%, in spite of decrease in percentage of the coronary flow. At 150 m glucose contributed 36.5% of the total energy used by the heart, lactate 9.2%, and pyruvate 0.5%; fatty acids supplied 68%. At high altitude the lactate provided about 25% of energy and fatty acids 52%. As a result of greater contribution of carbohydrate the myocardial respiratory quotient rose from 0.81 at 150 m to 0.91 at 4,375 m. There was no evidence of anaerobic-type metabolic disturbances in spite of the low arterial PO_2. There was no lactate production; on the contrary, because of its high arterial content, its consumption increased. Moreover, the heart at high altitude, by development of ATP from glycolysis, could develop sufficient energy to maintain about 80% of its normal working capacity (Kubler and Spieckermann, 1970). The number of mitochondria (Ou and Tenney, 1970) and their internal and external surface per unit volume of myocardium (Heath, 1971) are both increased to facilitate this. Myoglobin is also increased (Musin, 1968). The findings of Moret along with those of Barbashova (1964), Reynafarje (1966), and Poupa et al. (1966) are indications of a more highly developed capacity for aerobic metabolism at high altitude than at sea level, and may explain partly the rarity of myocardial infarction at high altitude.

The development of the mitochondrial system, higher concentrations of myoglobin, and increased ATP-ase activity at a high altitude may actually result in improved compensatory hyperfunction. Meerson, Gomazkov and Shimkovich (1973) have shown that adaptation to high altitude hypoxia reduces the mortality rate in rats with a ligated coronary artery by 5 or 6 times and the size of the ischaemic necrosis by 35%. However, no difference in the vulnerability to ligation of the right circumflex was found in dogs and lambs from high altitude and sea level by Woolsey et al. (1971). Disturbances of the hearts contractible function in ischaemic myocardial necrosis are minimised. The deficit in the contractable force during maximal load on the heart is 4.4 times smaller in rats adapted to hypoxia than in rats not so adapted. The tissues also acquire an increased capacity for oxygen extraction from the blood probably from an increased capacity of the mitochondrial system (Meerson, 1970). At a lower level of cardiac output therefore, oxygen requirement of the tissue is met with a more economical circulatory function, functional cardiac reserve is increased, and the chances of ATP deficit in the myocardium are minimised. Similar adaptative mechanisms may

prevent myocardial infarction in the human population at high altitude. We have shown that 28% of patients of ischaemic heart disease, who have recovered according to our criteria, become fightingfit soldiers upto altitudes of 6,000 m (Singh et al., 1970). At high altitude they do not breakdown during the period of their stay which is normally 2 to 3 years.

The functional potential of sympathetic regulation of the heart is increased (Pshennikova and Manukhin, 1971). Poupa et al. (1966) found that maintaining animals in a low-pressure chamber protected them against the myocardial necrosis which could be caused by injecting isoprenaline. At high altitude there is also a marked reduction of adipose tissue (Consolazio, Matoush and Nelson, 1966) and weakening of the "oxygen-wasting" effect of noradrenaline, the catecholamine-induced uncoupling of oxidation and phosphorylation (Meerson and Gomazkov, 1971), and ATP deficits.

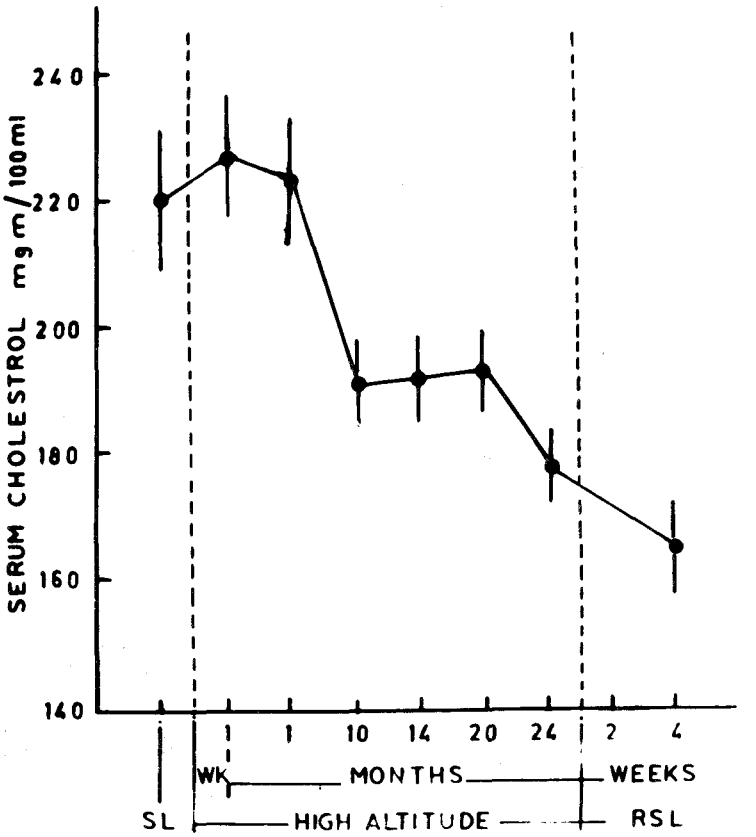

Fig. 8. Serum cholesterol at sea level, at the end of 1 week, 1, 10, 14, 20 and 24 months stay at high altitude, and on deacclimatisation at sea level for 2 and 4 weeks. Brackets represent the mean ⋆ SE.

Alterations in blood coagulation may also protect against ischaemic heart disease. To begin with, in recent arrivals at high altitude there is a tendency towards a hypercoagulation state which is indicated by increased level of factor X and thrombotest activity. These adverse changes are however countered by simultaneous increases in

fibrinolytic activity and factor XII. As a result of increased fibrinolytic activity there is an immediate fall in plasma fibrinogen level and factor VIII. Platelet adhesiveness and platelet factor 3 remain within normal range although an increase of them may occur towards the end of the second week. However, during continuous stay at high altitude compared with short term exposure, the hypercoagulation state regresses. Platelet adhesiveness, platelet factor 3, factor X, factor XII and thrombotest activity are decreased and the initial increase in fibrinolytic activity, which is partly balanced by increase in plasma fibrinogen and factor VIII, continues to persist (Singh and Chohan, 1974).

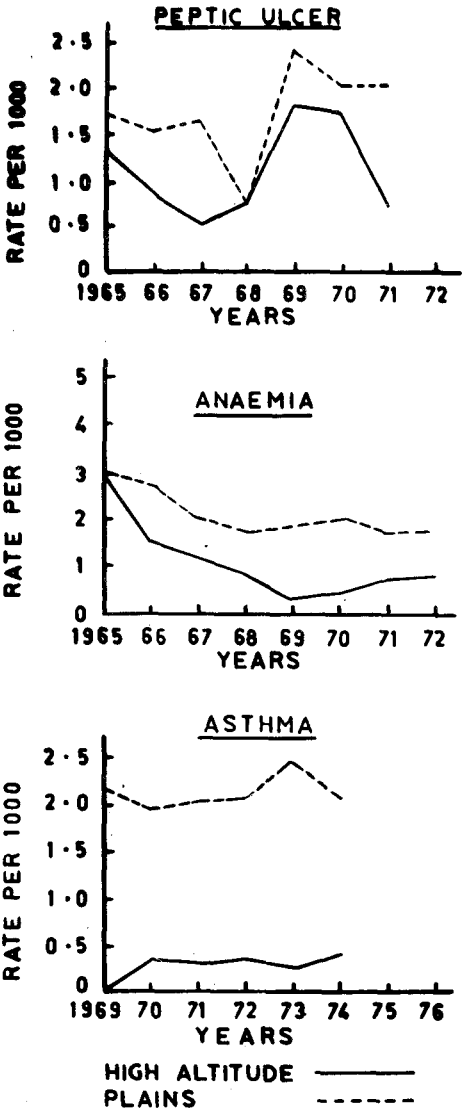

Fig. 9. Year-wise morbidity rates per 1000 for 1965 to 1972 in plains and high altitude for peptic ulcer, anaemia, and bronchial asthma.

Ruiz et al. (1969) found that the influence of the socalled coronary risk factors was almost eliminated at high altitude. The natives have low cholesterol, total lipids, triglycerides, and B-lipoproteins. They smoke occasionally. Arterial hypertension, obesity and diabetes mellitus are rare among them. Also, most of the natives belong to blood group O which is generally associated with lower values of cholesterol and less susceptibility to IHD at sea level. In our subjects there is a continuous fall in serum cholesterol during stay at high altitude and this tendency persists even at four weeks on return to sea level (Fig. 8).

The factors which may lower the incidence of ischaemic heart disease at high altitude therefore are: (1) increased coronary reserve, (2) adequate oxygenation of myocardium (3) low myocardial oxygen consumption, (4) highly developed capacity for aerobic metabolism, (5) higher potential of sympathetic regulation, (6) low incidence of coronary risk factors, and (7) increased fibrinolytic activity and hypocoagulation during continuous stay at high altitude.

PEPTIC ULCER (Fig. 9): Although the aetiology of chronic peptic ulceration is essentially obscure, gastric acid is intimately concerned with the chronicity of the ulcers. Chronic peptic ulcer does not occur in pernicious anaemia in which the gastric juice contains negligible quantities of acid and pepsin (Kahn, 1937). Acute superficial ulcers may develop in an atrophic mucosa apparently not secreting acid but they do not progress to chronic ulceration. Anacidity which develops spontaneously or after gastric irradiation always induces complete healing of peptic ulcer without recurrence for the duration of the achlorhydria (Kirsner, 1971). Viewed from the opposite angle, patients with simple peptic ulcer always possess an acid gastric juice and no case of histamine-fast achlorhydria has been found in proved cases of chronic gastric and duodenal ulcer (Palmer and Nutter, 1940).

Our findings at high altitude have shown (1) gastric motility is not altered, (2) gastric acidity diminished on arrival at high altitude and continues to remain low during the remainder of stay at high altitude, (3) pepsin activity is low during the first week of arrival at high altitude but reverts subsequently to sea level values, and (4) although the gastric acidity is low the response to pentagastrin stimulation is normal. In local residents the hydrochloric acid content of the gastric juice is low and the response to pentagastrin is also significantly impaired. Low gastric acidity on arrival at high altitude is probably a major factor in the low incidence of peptic ulcer in our cases at high altitude.

However, in the Peruvian Andes the miners who live and work at altitudes above 3,030 m have been found to be very prone to develop gastric ulcer with marked disposition to haemorrhage (Garrido-Klinge and Pena, 1960). Due to lack of data we are unable to comment on this difference.

ANAEMIAS (Fig. 9): In our subjects we find that the tendency to polycythaemia persists only during the first 10 months stay at high altitude. Subsequently there is a progressive decline in the haemoglobin and the haematocrit between 10 months and 24 months stay at high altitude (Fig. 10).

The tendency to be polycythaemic at high altitude would reduce the incidence of anaemia. However during the period of decline anaemia could occur from any cause.

The cause of decline after 10 months stay at high altitude is not clear. Whether it is an adaptative change or due to the effect of cold on the fragility of the red blood cells resulting from a deficiency of vitamin E remains to be shown (Singh, 1964; Weiser and Weihe, 1967).

The elevation in the number of circulating red blood cells and haemoglobin which occurs at high altitude is due to an absolute polycythaemia associated with a greater cell volume and a normal or slightly reduced plasma volume. It has been shown that the polycythaemia is a consequence of increased erythropoietic activity as shown by bone marrow biopsies and of iron metabolism and utilisation (Reynafarje, 1959a). The

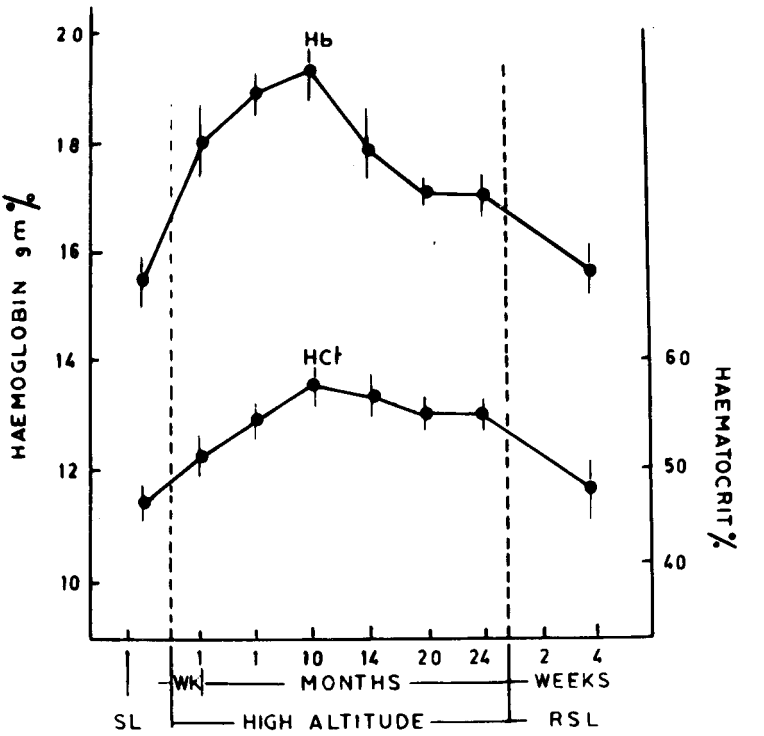

Fig. 10. Haemoglobin and haematocrit at sea level, at the end of 1 week, 1, 10, 14, 20 and 24 months stay at high altitude, and on deacclimatisation at sea level for 2 and 4 weeks. Brackets represent the mean ± SE.

effect of hypoxia on bone marrow occurs through an increase of erythropoietin in the circulating plasma (Carmena et al., 1967; Siri et al., 1966). The life-span of red cells at high altitude is normal (Reynafarje, 1959b).

BRONCHIAL ASTHMA (Fig. 9): Observations made in The Netherlands (Tromp and Bouma, 1974) have shown that asthmatics treated in low-pressure climatic chambers at simulated altitudes above 1,500 m, preferably 2,000-2,500 m, improve rapidly, and usually with 60-100 treatments are "cured". Before treatment these asthmatics have a poorly-functioning hypothalamic thermoregulatory centre as a result of which they react violently to abrupt changes in the thermal environment. Before treatment their adrenal function is often 1/3 to 1/5 below normal for their age and sex. The parasympathetic nervous system is dominant and they often have a relatively low blood pressure. Their threshold for the contraction of the bronchi, after atmospheric cooling, is much lower than in normal subjects. After treatment the efficiency of the thermoregulatory centre is improved, the corticosteroids output becomes normal, and the increased sensitivity of the bronchi to cold stimuli is reduced. That relief of asthma is obtained with altitude, in spite of exposure to the same allergens as before to which the individual was supposed to be sensitive, rules out the importance of allergens in the causation of asthmatic attacks.

The individual is not allowed to get acclimatised to altitude at any stage of the treat-

ment. There is a risk that favourable physiological effects may become less and less or may even get an inverse character in acclimatised individuals. Whereas usually 100% "cures" have been obtained in young asthmatic patients in low-pressure climatic chambers, the number of "cured" patients returning from high altitude clinics has been much smaller.

Our subjects have a tenure of 2 to 3 years or sometimes more at altitude between 3,692 m and 5,538 m during which they come to the plains on leave for 2 months once a year. It is likely that other factors, locally present, protect them in spite of the fact that during the long periods of their stay at high altitude acclimatisation cannot be avoided. These factors may be a much more reduced partial pressure of oxygen, marked differences in the summer and winter temperature, low humidity, difference in the quality and intensity of solar radiation, differences in the ozone content of the air, and greater reduction in the number of large ions. It will be seen from Fig. 11 that the 17-hydroxysteroid excretion in the urine remains 2-3 fold above the sea level values at 9 months after arrival at high altitude. Even at 15 months it is still higher than on the plains. Vegetation and therefore pollens are next to nil. Strong surface dust-raising winds are however common.

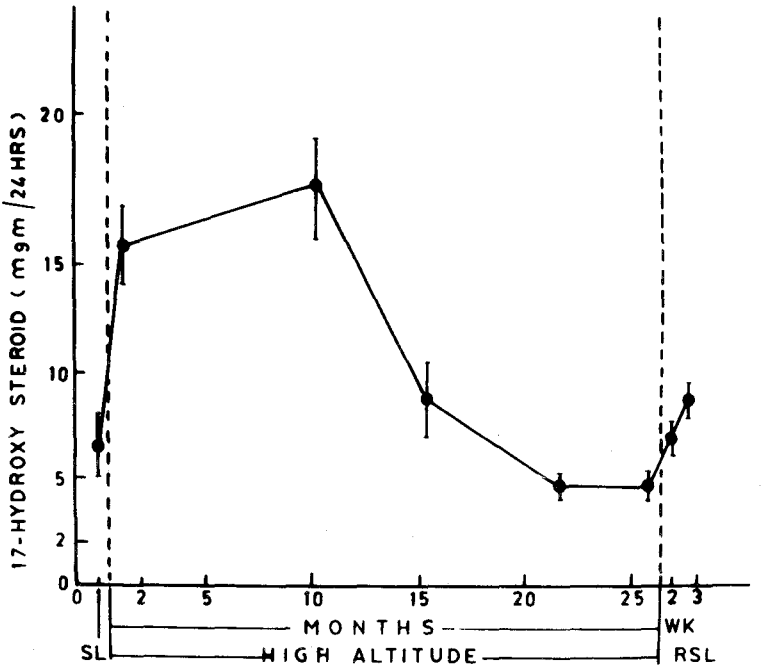

Fig. 11. 17-hydroxysteroids at sea level, at the end of 2, 10, 15, 20 and 25 months stay at high altitude, and on deacclimatisation at sea level for 2 and 3 weeks. Brackets represent the mean ± SE.

PSYCHIATRIC DISEASES (Fig. 12): General mental efficiency as indicated by scores for immediate visual memory, perceptual speed, sorting efficiency, and speed of routine mental work is slightly impaired on arrival at high altitude. As stay prolongs beyond one month these scores improve and become as good as at sea level. Mental concentration and psychomotor performance remain slightly impaired and depression is some-

what increased throughout the period of stay at high altitude. Anxiety manifests itself after about 18 months stay. In spite of slight anxiety and depression there is no trend towards neurotic or psychotic tendencies or emotional instability. The depression is born out of monotony of surroundings than anything else. Anxiety is related to domestic affairs. Although the outgoingness or zeal for active social participation may decline during the first month of stay at high altitude, acceptance of an individual by his group members is not adversely affected. The interpersonal relationships remain congenial (Fig. 13).

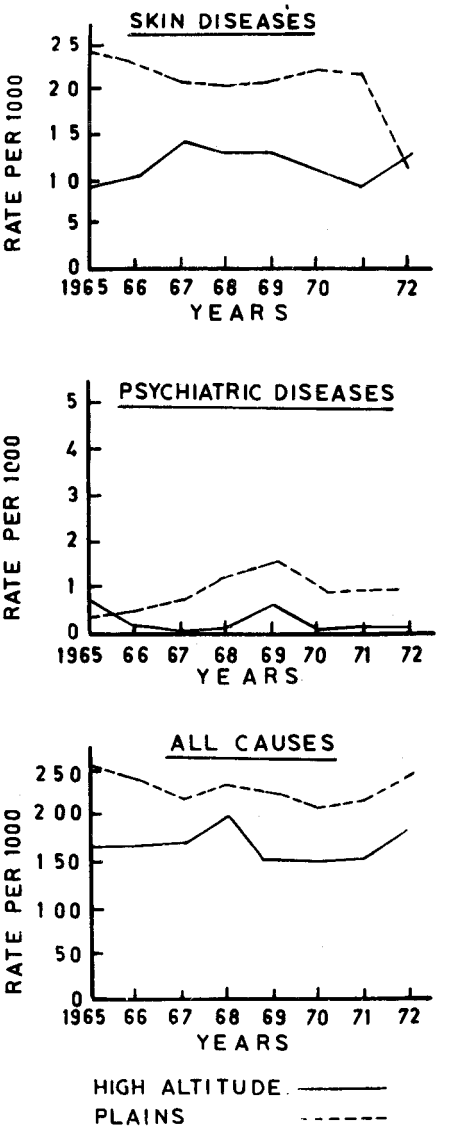

Fig. 12. Year-wise morbidity rates per 1000 for 1965 to 1972 in plains and high altitude for skin diseases, psychiatric diseases and all causes combined.

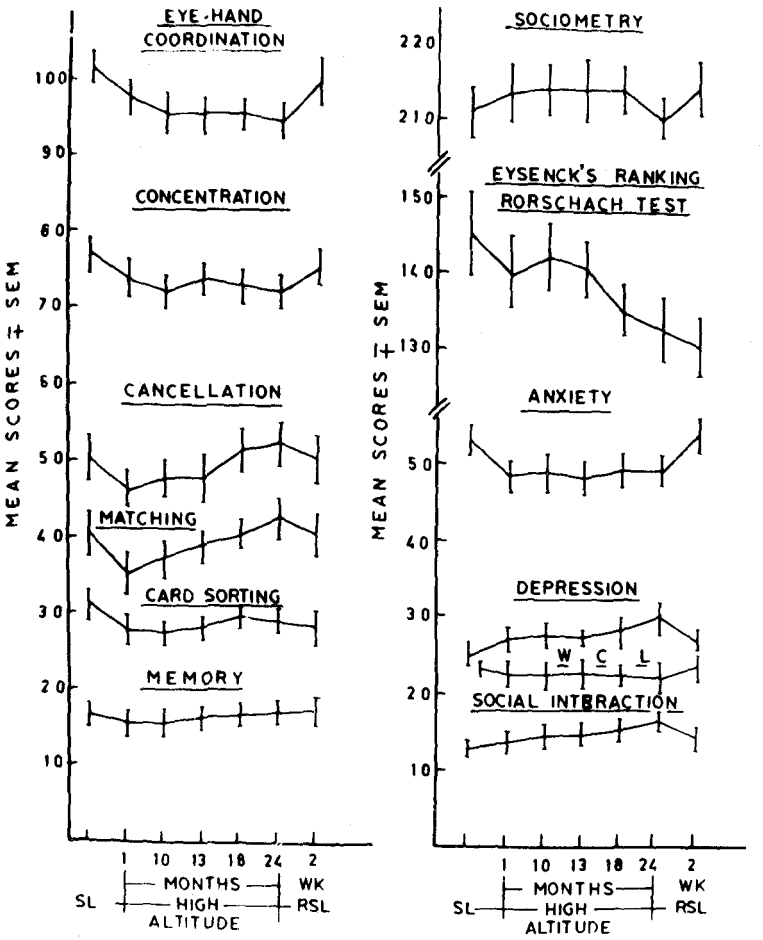

Fig. 13. Changes in various psychological factors at sea level, at the end of 1, 10, 13, 18 and 24 months stay at high altitude, and on deacclimatisation at sea level for 2 weeks. Brackets represent the mean ± SE of scores.
WCL = Crown's Word Connection list.

In animal experiments, adaptation to high altitude hypoxia is accompanied by a number of changes in the brain which may play a role in the prevention of psychiatric diseases at high altitude in spite of environmental and other stresses. Thus adaptation to high altitude hypoxia is accompanied by gradually progressive activation of nucleic acids and protein synthesis in the neurons and glia of the brain, particularly in the cortex (Meerson, 1970). This process increases vascularisation of the brain (Domantovich, 1958) and augments the energy-generating capacility of the mitochondria per unit mass of brain tissue (Meerson, 1970; Smialek and Hamberger, 1970). The brain therefore acquires the capacity to utilise the available oxygen for ATP resynthesis. The increased capacity of the energy supply system in the brain promotes faster development of conditioned reflexes and greater resistance to excess stress in the adapted animals (Maizelis et al., 1970; Meerson et al., 1971). The lower incidence of psychiatric disease at high altitude suggests similar mechanisms may operate in human subjects.

GOITRE: Although the incidences of goitre for all ethnic groups was higher at high altitude than in the plains, certain ethnic groups were more affected than others. For example, in an ethnic group from North-Western India the incidence on the plains was 1.2/1000 and at high altitude 103.2/1000. In an ethnic group from South India it was 36.9/1000 on the plains and 223.0/1000 at high altitude.

The approximate caloric value of food intake on the plains was 3,780 cals and 4,380 cals at high altitude. There was no significant difference in the iodine content between the two scales.

We find that the mean TSH levels at sea level do not show any significant alteration at high altitude in recent arrivals nor does it show any change when they return to sea level within 10 days. The TSH levels in local residents and in subjects who have lived at high altitude for one year are also not significantly different. The TSH response to TRH is also not significantly altered at high altitude. However, a significant rise in mean total T^4 and T^3 concentration occurs soon after arrival at high altitude and this persists for two weeks. In the third week the T^4 levels tend to normalise where as wide fluctuations are still evident in serum T^3 levels. They, then tend to stabilise and local residents and subjects who have stayed for one year at high altitude have higher T^4 and T^3 levels than sea level residents. Both serum T^4 and T^3 levels revert to normal within a week when the recent arrivals return to sea level (Srivastava et al., 1976).

It thus seems that exposure to high altitude leads to enhanced thyroid activity. Continued stay at high altitude is associated with higher levels of circulating T^4 and T^3 levels. However, this thyroidal adaptation occurs without any significant alteration in serum TSH levels or pituitary responsiveness to TRH. Thyroidal enlargement which occurs seems to be compensatory. Unless nodular changes are present, it returns to normal on return to sea level.

RHEUMATOID ARTHRITIS: A large number of clinical studies appear to substantiate a worsening effect of climatic changes on arthritis (Holbrook, 1960). Period immediately preceding rainfall or storm are most painful for the arthritics (Nava and Seda, 1964). Controlled studies in the climatic chamber show that most of the rheumatoid arthritic patients are worsened by weather changes. There is a significant worsening of the arthritis within a few hours of exposure to a rise in humidity along with a fall in barometric pressure. The changing conditions, rather than the high humidity or low barometric pressure have been held responsible (Hollander and Yeostros, 1963).

Increasing humidity and falling barometric pressure is accompanied by diuresis and extrusion of intracellular fluid into the blood stream. Diseased tissue is not so permeable, holds fluid, and therefore maintains a relatively higher intracellular pressure than the surrounding normal tissue. This gradient in pressure leads to increased pain and swelling of the diseased part. There is some evidence that the patient's reaction may be proportionate to the magnitude of fluctuation in barometric pressure and humidity as well as the rate and frequency of change. Because of this the relatively dry, warm, and fairly stable climate of South-Western United States has been found to benefit many arthritics (Hill, 1972).

Naid, Sayen and Comroe (1945) reported that many patients receive symptomatic relief from a constant warm dry climate. Sooner or later, however, these patients relapse when they return to their usual climatic environment (Cecil, 1942). In the climatic chamber, exposures at 32°C and 35% humidity, have also helped patients to improve (Edstrom, 1944). Four out of 7 of Edstrom's patients became symptom free and returned to work, two improved at first but later relapsed, and one could not tolerate the environment.

However our men at high altitude were exposed to a dry and alternating cold and warm environment. The change in temperature does not seem to have adversely affected them. It is likely that increased fibrinolytic activity and the immune responses at high altitude rather than the meteorological variations protected them. An excess of deposition over removal of fibrin leading to its persistence underlies the chronic

inflammation of rheumatoid arthritis and is part of the vicious cycle whereby deposition of fibrin leads to an elevation of plasma fibrinogen and thus to more fibrinogen (Fearnley, Chakrabarti and Evans, 1966). A rapid and striking fall of plasma-fibrinogen of the order of 50% interrupts this vicious cycle and leads to improvement. When this effect is obtained with varying degree of success with phenformin, 25-75% of cases of chronic rheumatoid disease have responded to treatment (Fearnley, Chakrabarti and Hocking, 1965).

The increased excretion of 17-hydroxysteroids in the urine after arrival at high altitude for several months (vide supra) suggests that increased synthesis of corticosteroids may play a helpful role in the prevention of rheumatoid disease at high altitude.

Rotstein and Good (1961) in a review of 41 patients with congenital or acquired hypogammaglobulinaemia found one-third to be suffering from diseases of the connective tissue, including rheumatoid arthritis. As resistance to infection in these patients is notably low the authors believed that infection played an important role in the high incidence of connective tissue disease in these individuals. As we have mentioned above immunoglobulins IgA, IgG and IgM and immunoglobulins IgA and IgG in particular, are all increased at high altitude.

ACKNOWLEDGEMENTS

We are grateful to Mr. Arun Saxena and Mr. P. N. Kapoor of Army Statistical Organisation for statistical help, to Mr. N. K. Gupta for secretarial assistance, and to Air Marshal Ajit Nath, PVSM, PHS, FAMS, Director General Armed Forces Medical Services, for permission to publish this paper.

REFERENCES

ANDRIESE, P. C. (1969): Some Effects of Artificially Generated Air Ions on the Free-living Amoeba Hartmanella ryhsodes Sing. Ph.D. Thesis Department of Zoology, University of California, Berkeley, California.

ARIAS-STELLA, J. and TOPILSKY, M. (1971): Anatomy of the coronary circulation at high altitude. In: High Altitude Physiology: Cardiac and Respiratory Aspects. R. Porter and J. Knight (ed.), Churchill Livingstone, Edinburgh and London, 149-157.

BARBASHOVA, Z. I. (1964): Cellular level of adaptation. In: Adaptation to the Environment: D. B. Dill, E. F. Adolph and C. G. Wilber (ed.), Handbook of Physiology, Section 4, American Physiological Society, Washington, D.C., 37-54.

BECKER, E. L., COOPER, R. C. and HATAWAY, G. D. (1955): Capillary vascularization in puppies born at a simulated altitude of 20,000 feet. J. appl. Physiol., 8: 166-168.

BLUME, F. D. and PACE, N. (1967): Effect of translocation to 3,800 m altitude on glycolysis in mice. J. appl. Physiol., 23: 75-79.

BLUME, F. D. and PACE, N. (1969): Changes in the tissue distribution of glucose radiocarbon at altitude. Fed. Proc., 28: 933-936.

CALDWELL, F. T., ROLF, D. and WHITE, H. L. (1949): Effects of acute hypoxia on renal circulation in man. J. appl. Physiol., 1: 597-600.

CARMELINO, M. (1970): Tesis de Bachiller, Universidad Peruana Cayetano Heredia, Lima.

CARMENA, A. O., DE TESTA, N. G., SEGADE, A., and FRIAS, F. L. (1967): Erythropoiesis-stimulating activity in plasmas of young men living permanently at high altitude. Acta physiol. lat.-amer., 17: 145-148.

CECIL, R. L. (1942): Arthritis-curable disease? J. Mich. med. Soc., 41: 311-315.

CHOHAN, I. S., SINGH, I., BALAKRISHNAN, K. and TALWAR, G. P. (1975): Immune response in human subjects at high altitude. Int. J. Biometeor., 8: 137-143.

CONSOLAZIO, C. F., MATOUSH, L. O., JOHNSON, H. L. and DAWS, T. A. (1968): Protein and water balances of young adults during prolonged exposure to high altitude (4,300 meters). Amer. J. clin. Nutr., 21: 154-161.

CONSOLAZIO, C. F., MATOUSH, L. O., and NELSON, R. A. (1966): Energy metabolism in maximum and submaximum performance at high altitudes. Fed. Proc., 25: 1380-1385.

DENNIS, L. H., COHEN, R. J., SCHACHNER, S. H. and CONRAD, M. E. (1968): Consumptive coagulopathy in fulminant meningococcemia. J. Amer. med. Ass., 205: 183-185.

DOMANTOVICH, V. N. (1958): Some physiological mechanisms of the adaptation of the organism to oxygen insufficiency. In: Physiology and Pathology of Respiration, Hypoxia and Oxygen therapy, Kiev, 67-74.

DUDLEY, F. J., FOX, R. A. and SHERLOCK, S. (1972): Cellular immunity and hepatitis-associated, Australia antigen liver disease. Lancet, I: 723-726.

EDSTROM, G. (1944): Can rheumatic infection be influenced by an artificial tropical climate? Acta med. scand., 117: 376-414.

FEARNLEY, G. R., CHAKRABARTI, R. and EVANS, J. F. (1966): Fibrinolytic treatment of rheumatoid arthritis with phenformin plus ethyloestrenol. Lancet, II: 757-761.

FEARNLEY, G. R., CHAKRABARTI, R. and HOCKING, E. D. (1965): Phenformin in rheumatoid arthritis — a fibrinolytic approach. Lancet, I: 9-13.

FORBES, W. H. (1936): Blood sugar and glucose tolerance at high altitudes. Amer. J. Physiol., 116: 309-316.

GARMENDIA, F., TORRES, J., TAMAYO, R. and URDANIVIA, E. (1973): 8th International Diabetes Federation Congress, Brussels, Excerpta Medica Foundation, International Congress Series No. 280, Abst. No. 262.

GARRIDO-KLINGE, G. and PENA, L. (1960): Gastroduodenal ulcer in high mountains (Peruvian Andes). An. Fac. Med. (Lima), 43: 419-436.

HANNON, J. P., SHIELDS, J. L. and HARRIS, C. W. (1969): Effects of altitude acclimatization on blood composition of women. J. appl. Physiol., 26: 540-547.

HARTLEY, L. H., ALEXANDER, J. K., MODELSKI, M. and GROVER, R. F. (1967): Subnormal cardiac output at rest and during exercise in residents at 3,100 m altitude. J. appl. Physiol., 23: 839-848.

HEATH, D. A. (1971): In: High Altitude Physiology: Cardiac and Respiratory Aspects. R. Porter and J. Knight (ed.), Churchill Livingstone, Edinburgh and London, 145.

HILL, D. F. (1972): Climate and arthritis. In: Arthritis and Allied Conditions: J. L. Hollander and D. J. McCarty Jr. (ed.), Lea and Febiger, Philadelphia, 256-263.

HOLBROOK, W. P. (1960): Climate and the rheumatic disease. In: Arthritis and Allied Conditions. J. L. Hollander (ed.), Henry Kimpton, London, 577-581.

HOLLANDER, J. L. and YEOSTROS, S. J. (1963): The effect of simultanous variations of humidity and barometric pressure on arthritis. Bull. Amer. meteor. Soc., 44: 489-494.

HUMPHREY, J. H. and WHITE, R. G. (1970): Immunology for Students of Medicine. Blackwell, Oxford, 148.

JAROONVESAMA, N. (1972): Intravascular coagulation in falciparum malaria. Lancet, I. 221: 223.

JERI, R. (1947): Quotation. In: High Altitude Physiology: Cardiac and Respiratory Aspects. R. Porter and J. Knight (ed.), Chuchill Livingstone, Edinburgh and London, 149.

JOHNSON, H. L., CONSOLAZIO, C. F., BURK, R. F. and DAWS, T. A. (1974):

Glucose-^{14}C-UL metabolism in man after abrupt altitude exposure (4,300 m). Aerospace Med., 45: 849-854.

KAHN, J. R. (1937): Absence of peptic ulcer in pernicious anaemia. Amer. J. med. Sci., 194: 463-466.

KEYS, A., STAPP, J. P. and VIOLANTE, A. (1943): Responses in size, output and efficiency of the human heart to acute alteration in the composition of inspired air. Amer. J. Physiol., 138: 763-771.

KIRSNER, J. B. (1971): Acid-peptic diseases. In: Cecil-Loeb Textbook of Medicine. P. B. Beeson and W. McDermott (ed.), Saunders, Philadelphia, 1259-1284.

KUBLER, W. and SPIECKERMANN, P. G. (1970): Quotation. In: High Altitude Physiology: Cardiac and Respiratory Aspects. R. Porter and J. Knight (ed.), Churchill Livingstone, Edinburgh and London, 180.

LILUCH, M. and PONZ, F. (1962): Influencia de la anoxia sobre la absorcion activa de azucares por el intestino. Rev. esp. Fisiol., 18: 157-162.

MAIZELIS, M. Ya., MEERSON, F. Z., LEIKINA, E. M., POPKO, N. A. and GVIRTSMAN, L. E. (1970): Effect of high-altitude training on intensity of protein synthesis in the brain and resistance of animals to convulsant factors. Bull. exp. Biol. Med., 69: 25-27.

MALHOTRA, M. S. and MATHEW, L. (1974): Effect of prolonged stay at altitude (4000 m) on autonomic balance. Aerospace Med., 45: 869-872.

MARTICORENA, E., RUIZ, L., SEVERINO, J., GALVEZ, J. and PENALOZA, D. (1969): Systemic blood pressure in white men born at sea level: changes after long residence at high altitudes. Amer. J. Cardiol., 23: 364-368.

MEERSON, F. Z. (1970): Pathophysiological principles of the prophylaxis of cardiac insufficiency. Kardiologiya, 10: 50-61.

MEERSON, F. Z. and GOMAZKOV, O. A. (1971): The role of the sympathetic factor in the pathogenesis of infarction and isoproterenol necrosis of myocardium. Kardiologiya, 11: 140-153.

MEERSON, F. Z., GOMAZKOV, O. A. and SHIMKOVICH, M. V. (1973): Adaptation to high altitude hypoxia as a factor preventing development of myocardial ischemic necrosis. Amer. J. Cardiol., 31: 30-34.

MEERSON, F. Z., ISABAYVA, V. A., IVANSCHINA, A. Z. et al. (1971): Conditioned reflexes in massive and distributed learning of animals of two different genetical lines in the process of adaptation to altitude hypoxia. J. wjsschei nervnoj dejatelnosti USSR, 21: 470-477.

MONCLOA, F., GOMEZ, M. and HURTADO, A. (1965): Plasma catecholamines at high altitudes. J. appl. Physiol., 20: 1329-1331.

MORET, P. R. (1971): Coronary blood flow and myocardial metabolism in man at high altitude. In: High Altitude Physiology: Cardiac and Respiratory Aspects. R. Porter and J. Knight (ed.), Churchill Livingstone, Edinburgh and London, 131-148.

MUSIN, B. S. (1968): Significance of cholinergic mechanisms in the transformations of the skeleto-muscular and respiratory systems and the heart under various conditions of ontogenic development. Dissertation. University of Moscow.

NAID, M., SAYEN, A. and COMROE, B. I. (1945): Characteristic vascular pattern in patients with rheumatoid arthritis. Arch. intern. Med., 76: 139-142.

NAVA, P. and SEDA, H. (1964): Quotation. In Climate and Arthritis. In: Arthritis and Allied Conditions: J. L. Hollander and D. J. McCarty Jr. (ed.), Lea and Febiger, Philadelphia, 257.

NURMATOV, A. A. (1970): Contractility and coronary flow of the isolated rat heart by hypertrophy. In: Proceedings of Institute of Normal and Pathological Physiology. AMN, USSR, Moscow, 127-128.

OU, L. C. and TENNEY, S. M. (1970): Properties of mitochondria from hearts of cattle acclimatized to high altitude. Resp. Physiol., 8: 151-159.

PALMER, W. L. and NUTTER, P. B. (1940): In: Diseases of the Digestive System.

S. C. Truelove and P. C. Reynall (ed.), Blackwell, Oxford, 185.
PANIN, A. F. (1964): Effect of protein administration on some aspects of gas exchange and nitrogen metabolism in dogs with acute hypoxia. Biol. Abstr., 45: 1873.
PENALOZA, D., SIME, F., BANCHERO, N., GAMBOA, R., CRUZ, J. and MARTICORENA, E. (1963): Pulmonary hypertension in healthy men born and living at high altitudes. Amer. J. Cardiol., 11: 150-157.
PHILLIPS, G. B., HARRIS, G. J. and JONES, M. W. (1964): Effect of air ions on bacterial aerosols. Int. J. Biometeor., 8: 27-37.
PICON-REATEGUI, E., BUSKIRK, E. R. and BAKER, P. T. (1970): Blood glucose in high altitude natives and during acclimatization to altitude. J. app. Physiol., 29: 560-563.
PIKE, R. M. (1967): Antibody heterogencity and serological reactions. Bact. Rev., 31: 157-174.
POUPA, O., KROFTA, K., PROCHAZKA, J. and TUREK, Z. (1966): Acclimation to simulated high altitude and acute cardiac necrosis. Fed. Proc., 25: 1243-1246.
PSHENNIKOVA, M. G. and MANUKHIN, B. N. (1971): Dynamic of norepinephrine concentration in rat myocardium at high-altitude hypoxia. Dokl. Akad. Nauk SSSR, 198: 1474-1478.
RAMOS, A., KRUGER, H., MURO, M. and ARIAS-STELLA, J. (1967): Quotation. In: High Altitude Physiology Cardiac and Respiratory Aspects. R. Porter and J. Knight (ed.), Churchill Livingstone, Edinburgh and London, 149.
REYNAFARJE, B. (1966): In: Proceedings of Fifth Meeting of the PAHO Advisory Committee on Medical Research. Scientific Publication No. 140, Pan American Health Organisation, Washington, D.C.
REYNAFARJE, C. (1959a): Bone marrow studies in the new born infant at high altitude. J. Pediat., 54: 154-161.
REYNAFARJE, C. (1959b): Red cell life span in new born at sea level and high altitudes. Proc. Soc. exp. Biol. (N.Y.), 100: 256-258.
ROTSTEIN, J. and GOOD, R. A. (1961): Atti Delx Congresso Della Lega Contro ii. Rheumatisms, 1: 277.
RUIZ, L., FIGUEROA, M., HORNA, C. and PENALOZA, D. (1968): Systemic blood pressure in high altitude residents. Progress Report to the World Health Organisation, Geneva.
RUIZ, L., FIGUEROA, M., HORNA, C. and PENALOZA, D. (1969): Prevalencia de la hipertension arterialy cardiopatia isquemica en las grandes alturas. Arch. Inst. Cardiol. Mex., 39: 474-489.
SCARO, J. L. (1960): Erythropoietic activity of urinary extracts of subjects living in high altitudes. Rev. Soc. argent. Biol., 36: 1-8.
SCHMIDT, J. P. (1969): Resistance to infectious disease versus exposure to hypobaric pressure and hypoxic, normoxic or hyperoxic atmospheres. Fed. Proc., 28: 1099-1103.
SINGH, I. (1964): Medical problems during acclimatization to high altitude. In: The Physiological Effects of High Altitude. W. H. Weihe (ed.), Pergamon Press, Oxford, 333-338.
SINGH, I. and CHOHAN, I. S. (1974): Adverse changes in fibrinolysis, blood coagulation and platelet function in high altitude pulmonary oedema and their role in its pathogenesis. Int. J. Biometeor., 18: 33-45.
SINGH, I., KHANNA, P. K., SRIVASTAVA, M. C. and HOON, R. S. (1970): Extent of possible rehabilitation of service personnel with ischaemic heart disease. Brit. Heart J., 32: 665-670.
SINGH, I., MADAN LAL, NANDA, R. B. and KUMAR, B. R. (1974): Hepatic amoebiasis at high altitude. Int. J. Biometeor., 18: 272-278.
SIRI, W. E., VANDYKE, D. C., WINCHELL, H. S., POLLYCOVE, M. PARKER, H. G. and CLEVELAND, A. S. (1966): Early erythropoetin, blood and phy-

siological responses to severe hypoxia in man. J. appl. Physiol., 21: 73-80.
SMIALEK, M. and HAMBERGER, A. (1970): The effect of moderate hypoxia and ischemia on cytochrome exidase activity and protein synthesis in brain mitochondria. Brain Res., 17: 369-371.
SRIVASTAVA, M. C., MALHOTRA, M. S., DUA, G. L., SAWHNEY, R. C., RASTOGI, S. K., SRIDHARAN, K. and I. SINGH (1976): Hypothalamo-pituitary-thyroid response at high altitude in man. J. Clin. Endocrinol. Metab., 43.
SUTTON, J., YOUNG, J. D., LAZARUS, L. and HICKIE, J. B., GARMENDIA, F. and VELASQUEZ, T. (1970): Harmonal response to altitude. Lancet, II: 1194.
TOBIE, J. E., WOLFF, S. M. and JEFFERY, G. M. (1966): Immune response of man to inoculation with plasmodium cynomolgi and challenge with P. vivax. Lancet, II: 300-302.
TRAPANI, I. L. (1966): Altitude, temperature and the immune response. Fed. Proc., 25: 1254-1259.
TRAPANI, I. L. (1969): Environment, infection, and immunoglobulin synthesis. Fed. Proc., 28: 1104-1106.
TROMP, S. W. and BOUMA, J. J. (1974): The Biological Effects of Natural and Simulated High Altitude Climate on Physiological functions of Healthy and Diseased subjects (in particular Asthmatics). Monograph Series Biometeor. Res. Centre, XIII, 5-16.
URDANIVIA, E., GARMENDIA, F., TORRES, J., ZUBIATE, M. and TAMAYO, R. (1975): Adrenal response to tolbutamide-induced hypoglycemia in high altitude dwellers. J. clin. Endocr., 40: 717-719.
VALDIVIA, E. (1962): Total capillary bed of the myocardium in chronic hypoxia. Fed. Proc., 21: 221.
VOGEL, J. A., PULVER, R. I. and BURTON, T. M. (1969): Regional blood flow distribution during simulated high-laltitude exposure. Fed. Proc., 28: 1155-1159.
WEISER, G. L., PEOPLES, N. J. and HULL, A. H. (1969): Effect of altitude on microbiota of man. Fed. Proc., 28: 1107-1109.
WEISER, H. and WEIHE, W. H. (1967): Effect of cold on the vitamin E requirement of rats. Nature (Lond.), 215: 1512-1513.
WOOLSEY, T., ROSS, R., TAPIA, F., FERNANDEZ, E. and MARTICORENA, E. (1971): Quotation. In: High Altitude Physiology: Cardiac and Respiratory Aspects. R. Porter and J. Knight (ed.), Churchill Livingstone, Edinburgh and London, 153.