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A Description of Some Effects Produced by Residence at Moderate Altitude

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The increase in the oxygen-carrying-capacity of the blood produced by residence at altitude is well known and a change in the white blood cell picture of people living above sea-level has also been described (Ruppannar, 1920 ; Stammers, 1933 ; Hartman, 1933 ; Peterson and Peterson, 1935 ; Roberts, 1948). The results of the routine examination of workers on the tea-estates of Ceylon and observations made on medical students, who were taken on a short expedition up the mountains of Ceylon, have confirmed the reality of these blood changes and have indicated that alterations in other physiological characteristics of the body may be produced by residence at moderate altitude.

METHODS

Subjects :—In the beginning, the blood pictures of workers on tea-estates situated at various altitudes were determined during routine nutrition surveys. These workers were chosen at random, came from both sexes and their ages ranged from 18 to 45 years.

The determinations of plasma volume, tissue fluid volume, etc., were made at 2 elevations using 25 male subjects at each elevation. These subjects came within the age group 21 to 25 years and all had a good medical history. They were admitted to the estate hospitals at 7 p.m. on the evening prior to the day of the experiment. No food was allowed them after admission and no fluids were given after midnight until the experiments were completed. The subjects rested in bed from the time of admission to the end of the experiments. The basal metabolism was determined between 6 and 8 a.m. on the morning following admission. Immediately following this the volumes of the plasma and the tissue fluid space were determined by means of Evans-Blue (T 1824) dye and sodium thiocyanate. Then blood was obtained for the determination of oxygen saturation and carbon dioxide content, capillary blood was obtained from the finger for the blood cell determinations and, finally, observations on the blood pressure (brachial artery), radial pulse rate by palpation, respiratory rate and the vital capacity were made.

The preliminary bleeding for blood volume and blood gas determinations are a stress in themselves and may, therefore, produce *per se* blood cell changes. As similar manoeuvres were applied to each group of subjects at each altitude a comparison of the group results for each altitude would seem to be justified.

Determinations of plasma volume, tissue fluid volume, blood cell picture, and also adrenal cortical function were similarly made on 6 male students (aged 20-22 years) at sea-level (Colombo) and while living at an elevation of 6,200 feet for 10 days.

Techniques :—Haemoglobin was determined in a Sahli haemoglobinometer, previously calibrated by the oxygen capacity method.

Red blood cell counts were made in a Thoma haematocytometer using Hayem's diluting solution.

White blood cell counts were made in a Thoma counting chamber with a gentian violet in acetic acid diluting fluid. Four counts were made and averaged.

Differential white cell counts were made from films stained with Leishman's stain and by counting 400 cells.

Red cell size was estimated with an Eve's Halometer, which had been calibrated previously against direct cell measurements by the Price-Jones technique.

Packed cell volume was determined in a Wintrobe tube after centrifuging for 30 minutes at 3,500 r.p.m. and using heparinized blood.

The basal metabolic rate was estimated by the Douglas-bag technique using a mouth-piece and nose-clip. The expired air was collected for 10 minutes ; the inspired air was out-door air. The volume of the expired air was measured in a compensated and controlled spirometer and duplicate samples of the expired air were analysed with a Haldene apparatus. The accuracy of the gas analyses were controlled by analyses of out-door air at frequent intervals ; the maximum differences between the combined $C0_2$ and 0_2 percentages and the theoretical values did not exceed 0·03 per cent. The rate of metabolism in calories was calculated from the estimated R.Q. using the tables of Zuntz and Schumberg (1948) and the surface area of each subject was determined by the Du Bois' chart.

The plasma volume and the tissue fluid volume were determined by the use of the blue dye, T 1824, and sodium thiocyanate respectively. A sample of venous blood was withdrawn and then about 10 ml. (the actual volume was noted in each case) of a solution containing 50 mg. T 1824 and 500 mg. sodium thiocyanate per 10 ml. was injected intravenously. Further venous blood samples were withdrawn 10, 30, 60, 120 and 180 minutes later. These samples were collected with paraffined syringes and needles and delivered into paraffin-coated centrifuge tubes containing 500 units Heparin (0·5 ml.). Haematocrit readings were taken on all samples and the concentrations of the dye and the sodium thiocyanate in the plasma were determined on all the post-injection samples. The plasma dye concentration at zero time was obtained by extrapolation from the post-injection concentrations, assuming that the mixing was complete in 10 minutes and that the disappearance of dye from the circulation was occurring at the same rate throughout the first 30 minutes after injection. The plasma volume was calculated from the dye dilution ; the total blood volume was estimated from the plasma volume and the observed haematocrit, the latter being multiplied by the factor 0·96 to allow for plasma trapped between the red cells (Gregersen and Schiro, 1938). The 'available fluid' volume was calculated by dividing the mg. thiocyanate injected by the estimated mg. thiocyanate per litre of plasma when diffusion was complete. The tissue fluid volume was derived by subtracting the plasma volume and 70 per cent. of the red cell volume from the available fluid volume (Gregersen and Stewart, 1939). The T 1824 was estimated after extraction by the method of Cooke and Morris (1924) and the sodium thiocyanate by the method of Bowler (1944). Readings were made in a photoelectric colorimeter.

More accurate methods of measuring the plasma and tissue fluid volumes could not be used owing to the limited facilities of our mobile laboratory.

The adrenal cortical function was assessed as follows. No food was taken after 6 p.m. the previous day but water was allowed. 200 ml. water was drunk at 6 a.m., 8 a.m. and 10 a.m. Urine was collected for the 6 to 8 a.m. and 8 a.m. to 12 noon periods. Adrenaline, 0·3 mg., was administrated subcutaneously at 8 a.m. Eosinophil counts were made at 8 a.m. and 12 noon (Thorn *et al*, 1948). These direct eosinophil counts were made on oxalated venous blood, by Dunger's method (Forsham *et al*, 1948). Four pipettes and 8 double-cell Neubauer counting chambers were used for each determination, the eosinophils in 8 large squares of each cell being counted.

The urine was collected under toluene or, for the ketosteriods, concentrated HCl, and the 17-ketosteroids (using the method of Callow *et al* 1938) as modified by Talbot *et al*, 1942 and Robbie and Gibson (1943), creatinine and creatine (by the alkaline sodium picrate method), uric acid (using Benedict's phosphotungstic acid reagent in a sodium cyanide-urea solution) and potassium (by an adaptation of the method of Jacob and Hoffman, 1931) contents determined. The excretions were expressed in relation to the creatinine excretion so as to avoid difficulties of interpretation due to possible alterations in the rates of urine formation. Forsham *et al* (1946) have demonstrated that the creatinine excretion is unaffected by the injection of adrenaline, A.C.T.H. or the Compound E.

The arterial oxygen saturation and carbon dioxide content of arterial blood were determined by using the modification of the Haldane method suggested by Courtice and Douglas (1947).

RESULTS

(*a*) *The Relative and Absolute Lymphocytosis Produced by Residence at Altitude* :—

Many other investigators have observed a change in the white blood cell picture of people living above sea-level. Some examples from the literature are—

Reference	*Place*	*Altitude in Feet*	*Per cent. Lymphocytes*
Stammers (1933)	Johannesburg	5,750	39·72
Ruppanner (1920)	Switzerland	7,382	38·25
Hartman (1933)	Himalayas	9,184	45·0
Peterson and Peterson (1935)	Butte, U.S.A.	5,755	36·26
Roberts (1948)	Nairobi, Kenya	5,500	41·6

Similarly in Ceylon, blood examinations on tea-estate workers showed a gradual increase in average total lymphocytes in the blood with increasing altitude (Table 1). For comparative purposes these tea-estate workers constitute fairly well standardised communities ; not only do they have the same occupation and belong to the same ethnic group (Indian Tamil) but their conditions of housing, sanitation, pay and medical care are all standardised by law.

TABLE 1

The Variation of White Blood Cells with Elevation above Sea-Level.

(*a*) Male Subjects.

Elevation in feet	Number of Subjects	WHITE BLOOD CELLS IN THOUSANDS/c.mm							
		Total		Polymorphonuclears		Lymphocytes		Eosinophils	
		Mean	S.e.±	Mean	S.e.±	Mean	S.e.±	Mean	S.e.±
(1) Zero	52	7·47	0·300	3·98	0·120	2·52	0·107	0·820	0·087
(2) 200	49	6·32	0·293	3·54	0·128	2·21	0·080	0·449	0·065
(3) 1300	51	7·29	0·102	3·67	0·101	2·78	0·103	0·752	0·057
(4) 2500	132	8·06	0·246	3·58	0·076	3·35	0·072	1·070	0·056
(5) 4000	52	8·67	0·277	4·53	0·133	3·17	0·102	0·865	0·069
(6) 6000	50	7·75	0·247	3·91	0·103	3·26	0·114	0·530	0·059

(*b*) Female Subjects.

(1) Zero	53	8·16	0·342	4·33	0·123	2·82	0· 05	0·971	0·088
(2) 200	50	7·70	0·404	4·21	0·130	2·73	0·114	0·700	0·055
(3) 1300	51	7·81	0·297	4·61	0·167	2·87	0·136	0·875	0·075
(4) 2500	155	7·87	0·205	3·36	0·075	3·39	0·076	1·031	0·051
(5) 4000	53	8·47	0·333	3·97	0·136	3·58	0·169	0·838	0·072
(6) 6000	54	8·53	0·326	4·18	0·141	3·62	0·130	0·648	0·041

S.e. = Standard Error of Mean.

Significant differences between the means:—

(*a*) Male Subjects :—

Total W.B.C.	*Polymorphonuclears*	*Lymphocytes*
$1>2$ $P=0{\cdot}01$	$1>2$ $P=0{\cdot}01$	$1>2$ $P=0{\cdot}02$
$3>2$ $P=0{\cdot}01$	$1>3$ $P=0{\cdot}05$	$3>2$ $P<0{\cdot}001$
$4>3$ $P=0{\cdot}01$	$1>4$ $P=0{\cdot}01$	$4>3$ $P<0{\cdot}001$
$5>6$ $P=0{\cdot}02$	$5>4$ $P<0{\cdot}001$	
	$5>6$ $P=0{\cdot}001$	

(*b*) Female Subjects :—

Total W.B.C.	*Polymorphonuclears*	*Lymphocytes*
	$4<1, 2, 3, 5, 6$ $P=0{\cdot}001$	$4>1, 2, 3$ $P=0{\cdot}001$
	$3>5$ $P=0{\cdot}01$	$5>1, 2$ $P=0{\cdot}001$
	$3>6$ $P=0{\cdot}05$	$5>3$ $P<0{\cdot}01$
		$6>1, 2, 3$ $P=0{\cdot}001$

There is, in addition, a tendency for the total white blood cell count, and the polymorphonuclear cell content to increase with altitude in both sexes but the most consistent variation (in both the absolute and the relative numbers) is shown by the lymphocyte count (see comparison of means by Student's T Test). This latter tends to reach a maximum at between 2,500 and 4,000 feet. This recalls the fact that Hartman (1933) found that the relative lymphocyte count did not increase as the members of the German expedition to the Himalayas in 1931 assended from 9,000 feet to 25,000 feet (if anything his figures show a decrease).

TABLE 2

The Variations in the Relative Proportions of the Varieties of White Blood Cells with Elevation above Sea-Level.

(*a*) Male Subjects.

Elevation in feet	Number of Subjects	PER CENT. OF TOTAL WHITE BLOOD CELLS AS			
		Polymorphonuclears Cells		Lymphocytes	
		Mean	S.e. ±	Mean	S.e. ±
(1) Zero	52	53·3	1·62	35·1	1·43
(2) 200	49	56·1	2·02	35·0	1·27
(3) 1300	51	50·3	1·38	38·1	1·42
(4) 2500	132	44·3	0·94	41·5	0·90
(5) 4000	52	52·2	1·53	36·6	1·17
(6) 6000	50	50·5	1·33	42·0	1·46

(*b*) Female Subjects.

(1) Zero	53	53·0	1·50	34·6	1·29
(2) 200	50	54·7	1·69	35·5	1·49
(3) 1300	51	50·9	1·84	36·8	1·49
(4) 2500	155	42·7	0·95	43·1	0·96
(5) 4000	53	46·9	1·61	42·3	1·99
(6) 6000	54	49·0	1·65	42·4	1·53

S.e. = Standard Error of Mean.

Significant differences between the means of the relative proportions of lymphocytes:—

(*a*) Male Subjects :—

$4>1, 2$ $P<0·001$
$4>3$ $P=0·05$
$4>5$ $P<0·01$
$6>5$ $P=0·01$
$6>1, 2$ $P=0·001$

(*b*) Female Subjects :—

$4>1, 2, 3$ $P=0·001$
$5>1, 2$ $P=0·01$
$5>3$ $P=0·05$
$6>1$ $P=0·001$
$6>2$ $P<0·01$
$6>3$ $P=0·02$

The types of polymorphonuclear cell were studied, by Cooke's modification of the Arneth method, in certain subjects at three elevations (Table 3). It is evident that there is a statistically significant 'shift to the left' in the type of polymorphonuclear cell as the altitude increases.

TABLE 3

The Variation of the Cooke Count with Elevation above Sea-Level.

Elevation above sea-level in feet	Number of Subjects	PER CENT. OF POLYMORPHS. BELONGING TO TYPE									
		I		II		III		IV		V	
		Mean	S.e.	Mean	S.e.	Mean	S.e.	Mean	S.e.	Mean	S.e.
(1) Zero	50	10·9	0·68	32·4	1·30	47·7	1·10	8·5	0·60	0·5	0·14
(2) 2500	50	14·2	0·74	38·8	0·83	38·8	1·31	7·8	0·50	0·4	0·08
(4) 4000	50	15·8	0·82	54·4	1·07	26·9	1·10	2·8	0·35	0·1	0·07

S.e. = Standard Error of Mean.

All the subjects were Males.

Significant differences between the means:—

Cell Type

I	*II*	*III*	*IV*	*V*
2>1 $P<0{\cdot}01$	2>1 $P<0{\cdot}001$	1>2 $P<0{\cdot}001$	1>3 $P<0{\cdot}001$	1>3 $P=0{\cdot}02$
3>1 $P<0{\cdot}001$	3>2 $P<0{\cdot}001$	2>3 $P<0{\cdot}001$	2>3 $P<0{\cdot}001$	

The red blood cell picture of these Ceylonese workers indicates, as was to be expected, increasingly high red blood cell counts and blood haemoglobin concentrations with increasing height above sea-level, although the mean red cell size, colour index and mean corpuscular haemoglobin content do not vary so consistently (Table 4). Presumably variations in the available iron content of the diet and in the incidence of such diseases as Ankylostomiasis may affect the red blood cell picture and so tend to mask the effects of altitude. (Examination of a single specimen of the stools from each subject showed about 95 per cent. of the subjects from eaeh community had a helminth-infestation of the bowel. This probably accounts, also, for the high eosinophil cell count shown by these subjects).

In addition to the cellular content of the blood, other physiological characteristics have been studied in tea-estate labourers living at two different altitudes. The resting, fasting basal metabolic rate, the plasma volume, the tissue fluid volume (' thiocyanate volume '), the percentage oxygen saturation and the carbon dioxide content of arterial blood, the blood pressure, the vital capacity and the respiratory rate have all been measured (Table 5) at the elevations 2,500 and 4,500 feet above sea-level. At each altitude 25 male subjects (Indian Tamils) aged 21-25 years, and with good health records were examined.

TABLE 4

The Variation of Red Blood Cell Count and Blood Haemoglobin Level with Elevation above Sea-Level.

(*a*) Male Subjects.

	Elevation in feet	Number of Subjects	R.B.C. Count		Blood Haemoglobin		Red Cell Size		Colour Index		Corpuscular Haemoglobin	
			Mean in millions/c.m.	S.e. of Mean ±	Mean in millions/c.m.	S.e. of Mean ±	Mean in μ.	S.e. of Mean ±	Mean	S.e. of Mean ±	Mean	S.e. of Mean ±
(1)	Zero	52	4·16	0·093	12·6	0·39	7·49	0·024	1·010	0·077	29·9	0·705
(2)	200	49	4·19	0·082	14·1	0·46	7·65	0·075	1·127	0·063	33·3	0·488
(3)	1300	51	4·60	0·050	13·5	0·32	7·36	0·241	0·986	0·055	29·2	0·474
(4)	2500	132	4·68	0·081	16·8	0·28	7·70	0·024	1·232	0·021	35·8	0·632
(5)	4000	52	4·59	0·048	13·7	0·20	7·62	0·020	1·007	0·045	29·8	0·383
(6)	6000	50	4·56	0·068	15·0	0·18	7·58	0·030	1·117	0·014	33·05	0·417

(*b*) Female Subjects.

	Elevation in feet	Number of Subjects	R.B.C. Count		Blood Haemoglobin		Red Cell Size		Colour Index		Corpuscular Haemoglobin	
			Mean in millions/c.m.	S.e. of Mean ±	Mean in millions/c.m.	S.e. of Mean ±	Mean in μ.	S.e. of Mean ±	Mean	S.e. of Mean ±	Mean	S.e. of Mean ±
(1)	Zero	53	3·64	0·087	9·95	0·415	7·65	0·040	0·903	0·030	26·7	1·050
(2)	200	50	3·66	0·097	11·1	0·34	8·01	0·044	1·048	0·031	31·0	0·938
(3)	1300	51	3·90	0·069	10·8	0·33	7·72	0·040	0·939	0·022	27·7	0·496
(4)	2500	155	4·05	0·049	13·8	0·25	7·84	0·024	1·185	0·023	34·5	0·713
(5)	4000	53	4·26	0·058	12·6	0·11	7·53	0·028	0·997	0·014	29·5	0·429
(6)	6000	54	4·05	0·066	13·0	0·33	7·61	0·040	1·080	0·024	32·1	0·594

S.e. = Standard Error.

TABLE 4 (*Contd.*)

The Variation of Red Blood Cell Count and Blood Haemoglobin Level with Elevation above Sea-Level.

Significant Differences between the Mean:—

	R.B.C.	*Haemoglobin*	*Red Cell Size*	*Colour Index*	*Mean Corpuscular Haemoglobin*
(*a*) Male Subjects	$3>2, 1$ $P<0\cdot001$	$2>1$ $P=0\cdot02$	$4>1$ $P<0\cdot001$	$4>1$ $P=0\cdot01$	$2>1$ $P<0\cdot001$
	$4>2, 1$ $P<0\cdot001$	$4>1, 2, 3, 5, 6$ $P\leq0\cdot001$	$4>5$ $P=0\cdot02$	$4>3, 5, 6$ $P<0\cdot001$	$2>3$ $P<0\cdot001$
	$5>2, 1$ $P=0\cdot001$	$5>1$ $P=0\cdot02$	$4>6$ $P=0\cdot01$	$6>3$ $P<0\cdot001$	$2>5$ $P<0\cdot001$
	$6>2, 1$ $P=0\cdot001$	$6>1, 3, 5$ $P=0\cdot001$	$5>1$ $P<0\cdot001$	$6>5$ $P=0\cdot02$	$4>2$ $P=0\cdot01$
			$6>1$ $P=0\cdot02$		$4>5$ $P<0\cdot001$
					$4>6$ $P=0\cdot001$
					$6>5$ $P<0\cdot001$
(*b*) Female Subjects	$3>1$ $P=0\cdot02$	$2>1$ $P=0\cdot05$	$4>1, 5, 6$ $P<0\cdot001$	$2>1$ $P=0\cdot001$	$2>1$ $P=0\cdot01$
	$3>2$ $P=0\cdot05$	$4>2$ $P<0\cdot001$		$2>3$ $P=0\cdot01$	$2>3$ $P=0\cdot01$
	$4>1, 2$ $P<0\cdot001$	$4>3$ $P<0\cdot001$		$4>2$ $P=0\cdot001$	$4>2$ $P=0\cdot01$
	$5>3$ $P=0\cdot001$	$4>5$ $P<0\cdot001$		$4>5$ $P<0\cdot001$	$4>5$ $P<0\cdot001$
	$5>4$ $P=0\cdot01$	$5>3$ $P<0\cdot001$		$4>6$ $P=0\cdot01$	$4>6$ $P=0\cdot02$
	$5>6$ $P=0\cdot02$	$6>3$ $P<0\cdot001$		$5>3$ $P=0\cdot05$	$6>5$ $P=0\cdot001$
				$6>5$ $P=0\cdot01$	

TABLE 5

The variation of certain Physiological Factors with Elevation above Sea-Level (Subjects—Estate Labourers).

Physiological Factor	ELEVATION ABOVE SEA-LEVEL (FEET)			
	2,500		4,500	
	Mean	S.e. ±	Mean	S.e. ±
Systolic Blood Pressure	109·7	1·30	101·8	1·23
Diastolic Blood Pressure	64·6	1·98	57·8	1·74
Respiratory Rate	17·8	0·62	19·1	1·87
Plasma Volume	2·711	0·076	2·330	0·092
Blood Volume	5·756	0·228	5·249	0·279
Tissue Fluid Volume	13·997	0·509	11·315	0·535
Basal Metabolic Rate	50·36	2·291	53·42	3·180
Vital Capacity	2·027	0·026	2·275	0·066
Haematocrit (per cent.)	55·0	2·85	57·9	1·73
Blood Oxygen Capacity	22·8	1·32	24·0	1·53
Blood Oxygen Saturation (per cent.)	93·4	1·76	89·8	1·66
Blood Carbon Dioxide	46·3	1·95	42·1	1·20

At each elevation 25 subjects were examined.
B.P., is measured in mm.Hg.
Pulse and Respiratory Rates are given per minute.
Volumes are measured in litres.
B.M.R., is expressed in Calories/hour.

Comparing the means of the various physiological factors obtained from the two groups of men, it is evident that the residents at 4,500 feet have significantly lower means for systolic blood pressure ($P = 0{\cdot}001$), diastolic blood pressure ($P = 0{\cdot}02$), plasma volume ($P = 0{\cdot}01$) and tissue fluid volume ($P = 0{\cdot}001$) and a significantly greater mean vital capacity ($P = 0{\cdot}01$) than of those possessed by residents at 2,500 feet. The mean respiratory rate, basal metabolic rate, haematocrit and arterial blood oxygen capacity are also higher while the mean blood volume, arterial blood oxygen saturation and blood carbon dioxide content are lower for the group living at 4,500 feet but the differences are not significant.

The differences in the rates of respiration, in the blood gas contents and in the haematocrit values can all be readily explained on the basis of the lowered atmospheric oxygen tension at the higher altitude. The slightly greater basal metabolic rate may possibly be attributed to the slightly lower temperature (22·2°C, cf. 24·4°C) at 4,500 feet during the experiments.

The differences in the blood pressures and the body-fluid volumes are more difficult to explain. The decreasing plasma volumes with increasing altitude may be merely compensatory to the increased red blood cell volume which occurs simultaneously, but the differences in the tissue fluid volume would require another explanation.

These volumes are often expressed per unit weight or per unit body surface area since they are known to vary with the size of the person. The two groups of subjects had similar physical characteristics and the volumes per unit weight or per unit surface area still show the same variations as the absolute volumes themselves (Table 6).

TABLE 6

Mean Weights, Surface Areas and Body-Fluid Volumes at Different Elevations.

Factor	ELEVATION ABOVE SEA-LEVEL (FEET)			
	2,500		4,500	
	Mean	S.e. ±	Mean	S.e. ±
Weight—Kg.	46·9	1·12	46·3	0·88
Surface Area—m^2	1·464	0·045	1·466	0·022
Plasma Volume/Weight (c.c./kg.)	57·9	1·11	50·3	1·36
Plasma Volume/Surface (l./m^2) Area	1·86	0·063	1·59	0·076
Blood Volume/Weight (c.c./kg.)	131·3	3·44	113·1	4·09
Blood Volume/Surface (l./m^2) Area	4·22	0·195	3·56	0·230
Tissue Fluid Volume/Weight (c.c./kg.)	293·6	7·36	244·2	7·85
Tissue Fluid Volume/Surface Area (l./m^2)	9·10	0·411	7·73	0·408

Therefore, the differences noted cannot be due to variations in physique between the two groups of subjects.

If the decrease in plasma—and tissue fluid-volumes with increasing altitude of residence is a true physiological response on the part of the organism, then it should be possible to demonstrate similar decreases in subjects who travel from sea-level to higher altitudes. Therefore, six male medical students were taken by rail from Colombo to a station 6,200 feet above sea level. The blood picture, the plasma volume and the tissue fluid volume of each subject were determined on two occasions in Colombo and again on two occasions at altitude. As it is known that desoxycorticosterone produces changes in the plasma and tissue fluid volumes (Thorn *et al*, 1939) and that administration of the 11, 17-oxysteroid causes changes in the lymphocyte and eosinophil content of the blood (Thorn and Forsham, 1949), simple tests of adrenal cortical function were also applied to these students (see Methods). The routine at altitude was as follows :—

Day 1 :—(24 hours after arrival) :—White blood cell count, differential count, eosinophil count and urine analysis before and after administration of adrenaline.

Day 2 :—Haemoglobin, red blood cell, haematocrit, plasma volume and tissue fluid volume determinations.

Day 7 :—Repeat of Day 2.

Day 8 :—Repeat of Day 1.

For convenience in discussion, the results of the body fluid estimations and the blood count determinations will be given separately.

Body Fluid Volumes (Table 7) :—

TABLE 7

Variation in Plasma, Blood and Tissue Fluid Volumes with Altitude.

Subject Number	PLASMA VOLUME			HAEMATOCRIT			BLOOD VOLUME			TISSUE FLUID VOLUME		
	Sea-Level	Altitude 2 days	Altitude 7 days	Sea-Level	Altitude 2 days	Altitude 7 days	Sea-Level	Altitude 2 days	Altitude 7 days	Sea-Level	Altitude 2 days	Altitude 7 days
1	2·33	1·71	1·59	42·0	53·0	55·8	3·73	3·48	3·43	14·07	13·61	13·54
2	2·31	2·34	2·02	41·1	46·2	50·0	3·63	4·20	3·88	13·04	12·01	12·28
3	3·17	3·06	2·87	44·1	45·7	48·9	5·48	5·44	5·40	10·91	11·42	11·04
4	2·56	2·97	2·09	44·1	44·0	52·7	4·46	5·13	4·23	14·50	14·97	13·41
5	2·29	2·44	2·25	48·0	47·3	47·6	4·25	4·46	4·13	14·46	15·40	14·43
6	2·34	1·73	1·58	41·4	50·8	53·1	3·77	3·38	3·23	14·81	14·91	13·06
Average	2·50	2·38	2·07	43·5	47·8	51·4	4·22	4·35	4·05	13·63	13·72	12·96

The plasma-,blood—and tissue fluid-volumes were all reduced after 7 days residence at 6,200 feet, although the group average changes were not statistically significant. The variation of these fluid-volumes with residence at altitude was in the same direction as that shown by the Indian Tamil labourers and may be a true physiological response. The results are suggestive but certainly not conclusive ; a much larger group of subjects would be required to obtain statistical significance.

(The changes in these volumes after 2 days residence at altitudes were not consistent, in some cases increasing and in others decreasing).

This apparent tendency towards decreased body-fluid volumes was accompanied by decreased excretion of potassium in the urine voided at altitude (Table 8). In two subjects there was an initial rise in the potassium excretion and these were 2 of the 3 subjects who demonstrated an initial increase in their plasma volumes. (It was not possible with the facilities available in the emergency laboratory to estimate sodium).

TABLE 8

The Response of Potassium Excretion to Adrenaline at Sea-Level and at Altitude.

Subject Number	POTASSIUM/CREATININE RATIO					
	BEFORE ADRENALINE			PER CENT. VARIATION AFTER ADRENALINE		
	Sea-Level	Altitude 1 day	Altitude 8 days	Sea-Level	Altitude 1 day	Altitude 8 days
1	3·97	3·36	3·16	+ 26·8	+ 10·0	+ 87·7
2	4·16	2·88	2·84	+ 64·6	+ 42·8	+ 63·1
3	2·80	2·90	2·26	+ 65·9	+ 57·6	+ 68·6
4	2·43	2·84	2·12	+ 7·9	– 8·6	+ 36·5
5	1·45	1·97	1·04	+ 83·3	+ 49·7	+ 201·8
6	3·02	2·08	1·97	+ 94·3	+ 46·1	+ 141·2
Average	2·97	2·67	2·23	+ 57·1	+ 32·9	+ 98·2

The injection of adrenaline causes an increased excretion of potassium at sea-level and this response is less at first at altitude, only to be accentuated later.

The Blood Picture :—As was to be expected the haemoglobin concentration and the red blood cell count were both increased by residence at altitude, most of the increase occurring during the first 2 days (Table 9).

TABLE 9

The Variation in Haemoglobin Concentration and Red Blood Cell Count with Residence at Altitude.

Subject Number	HAEMOGLOBIN CONCENTRATION (g./100 c.c.)			RED BLOOD CELLS PER c.mm.		
	Sea-Level	Altitude 2 days	Altitude 7 days	Sea-Level	Altitude 2 days	Altitude 7 days
1	13·9	17·1	17·3	5,040,000	6,160,000	6,255,000
2	13·2	16·4	16·5	4,400,000	4,920,000	4,960,000
3	13·9	14·3	17·0	4,900,000	5,030,000	5,985,000
4	15·1	17·4	16·5	4,770,000	5,500,000	5,220,000
5	16·0	16·2	15·5	5,300,000	5,370,000	5,130,000
6	14·2	16·5	16·5	5,320,000	6,060,000	6,180,000

The total lymphocyte count was definitely raised in 3 subjects after only one day, the other students showing a slight fall in the number of these cells. After 8 days residence the count was raised in all cases when compared with the count at sea-level. Adrenaline caused a decrease lymphocyte count in 4 subjects at sea-level. All six students showed a lymphocytosis after an adrenaline injection on the first day at 6,200 feet, but, after 8 days this response was reduced, there being actually a decrease again in 4 subjects. (Table 10).

TABLE 10

The Response of the Total Lymphocyte Count (cells per c.mm.) to Adrenaline at Sea-Level and at Altitude.

Subject Number	LYMPHOCYTES BEFORE ADRENALINE			PER CENT. VARIATION AFTER ADRENALINE		
	Sea-Level	Altitude 1 day	Altitude 8 days	Sea-Level	Altitude 1 day	Altitude 8 days
1	3030	3740	4160	− 6·1	+ 5·1	− 15·1
2	2815	4090	3520	− 1·2	+ 72·2	+ 10·2
3	3195	2970	5110	− 9·8	+ 80·1	− 15·8
4	3268	3040	3980	+ 16·8	+ 69·8	− 16·3
5	4183	4050	5130	+ 12·0	+ 12·8	+ 6·0
6	2769	3340	7350	− 8·6	+ 121·0	− 55·4
Average	3210	3538	4875	+ 0·5	+ 60·2	− 16·4

The total eosinophil count showed no consistent or significant variation with residence at altitude (Table 11), but the number of neutrophil cells was increased in the first day, this being followed by a decrease in all but one subject at 8 days (Table 12).

TABLE 11

The Response of Eosinophil Cell Count (cells per c.mm.) to Adrenaline at Sea-Level and at Altitude.

Subject Number	EOSINOPHILS BEFORE ADRENALINE			PER CENT. VARIATION AFTER ADRENALINE		
	Sea-Level	Altitude 1 day	Altitude 8 days	Sea-Level	Altitude 1 day	Altitude 8 days
1	214	202	186	− 40·1	− 24·2	− 56·5
2	527	480	380	− 32·2	− 36·5	− 51·9
3	127	160	186	− 35·4	− 30·6	− 38·7
4	172	153	194	− 32·6	+ 13·7	− 50·5
5	294	287	445	− 42·2	− 8·4	− 50·1
6	312	336	309	− 40·0	− 30·3	− 36·3
Average	274	270	283	− 37·1	− 19·4	− 47·3

TABLE 12

The Response of the Total Neutrophil Cell Count (cells per c.mm.) to Adrenaline at Sea-Level and at Altitude.

Subject Number	NEUTROPHILS BEFORE ADRENALINE			VARIATION AFTER ADRENALINE					
				ABSOLUTE			PER CENT.		
	Sea-Level	Altitude 1 day	Altitude 8 days	Sea-Level	Altitude 1 day	Altitude 8 days	Sea-Level	Altitude 1 day	Altitude 8 days
1	5730	5610	4360	+ 600	+ 4400	+ 3880	+ 10·5	+ 78·5	+ 89·0
2	3840	4980	3740	+ 1335	+ 4830	+ 4650	+ 34·8	+ 92·0	+ 124·0
3	2698	3620	3940	+ 2362	+ 3840	+ 2390	+ 82·4	+ 106·0	+ 60·7
4	2858	4350	3880	+ 2022	+ 1800	+ 2420	+ 71·0	+ 41·4	+ 62·4
5	5825	7320	6580	+ 3285	− 380	+ 720	+ 56·4	− 5·2	+ 10·9
6	3190	6240	5960	+ 1240	+ 4200	− 350	+ 38·9	+ 67·3	− 5·9
Average	4024	5353	4743	+ 1807	+ 3115	+ 2285	+ 49·0	+ 63·3	+ 56·9

The reduction in the number of eosinophil cells produced by the injection of adrenaline at sea-level is lessened after one day's residence at altitude but increased after 8 days. Conversely, adrenaline injection causes an enhanced, compared to the sea-level response, neutrophil leucocytosis in 4 subjects on the first day and this response is reduced in 4 subjects after 8 days. The distribution of the types of neutrophil cells present also varies with residence at altitude, there being in general a ' shift to the left ' on the first day with a tendency to return to a normal distribution after 8 days (Table 13).

TABLE 13

The Response of the Distribution of Types of Neutrophil Cells to Adrenaline at Sea-Level and at Altitude.

Subject Number	PER CENT. OF TOTAL NEUTROPHILS PRESENT AS TYPES I AND II					
	BEFORE ADRENALINE			VARIATION AFTER ADRENALINE		
	Sea-Level	Altitude 1 day	Altitude 8 days	Sea-Level	Altitude 1 day	Altitude 8 days
1	79	80	80	+ 3	+ 11	+ 11
2	72	73	76	+ 20	+ 11	+ 4
3	65	69	63	+ 16	+ 16	+ 13
4	71	87	67	+ 13	0	+ 18
5	63	67	65	+ 14	+ 9	+ 11
6	79	75	71	+ 22	+ 8	+ 9
Average	71·5	75·2	70·3	+ 14·7	+ 9·2	+ 11

The total white blood cell count merely reflects the combined lymphocyte and neutrophil changes. In all subjects there was a raised count at day one and a further increase on the eighth day in four subjects (Table 14).

TABLE 14

The Response of the Total White Blood Cells Count (cells per c.mm.) to Adrenaline at Sea-Level and at Altitude.

Subject Number	W.B.C. BEFORE ADRENALINE			VARIATION AFTER ADRENALINE					
				ABSOLUTE			PER CENT.		
	Sea-Level	Altitude 1 day	Altitude 8 days	Sea-Level	Altitude 1 day	Altitude 8 days	Sea-Level	Altitude 1 day	Altitude 8 days
1	9,200	10,000	9,025	+ 50	+ 4,160	+ 3,141	+ 0·5	+ 41·6	+ 34·8
2	6,860	10,450	8,450	+ 1,790	+ 6,910	+ 4,080	+ 26·2	+ 66·3	+ 48·3
3	6,040	7,400	9,750	+ 1,650	+ 6,320	+ 1,380	+ 27·4	+ 85·5	+ 13·8
4	6,460	8,100	8,650	+ 2,410	+ 3,500	+ 3,516	+ 37·3	+ 43·2	+ 40·7
5	10,680	12,460	13,200	+ 3,190	+ 40	− 780	+ 29·9	+ 0·3	− 5·9
6	6,530	10,250	14,475	+ 570	+ 10,270	− 4,800	+ 8·7	+ 100·1	− 33·2
Average	7,628	9,777	10,592	+ 1,610	+ 5,200	+ 1,090	+ 21·7	+ 56·2	+ 16·4

The white blood cell picture, therefore, altered during residence at altitude so that initially the neutrophil and the lymphocyte cells increased and then, in few days, while the neutrophil count returned to more normal values the lymphocytes continued to increase. The number of eosinophil cells did not vary consistently.

Administration of the 11, 17-oxysteroid produces an increase in neutrophil and a decrease in both lymphocyte and eosinophil cells. Both the A and the E oxysteroids cause a slight increase in uric acid excretion (Thorn and Forsham, 1949) and here it is noticed that moving from sea-level to altitude caused an increasing clearance of uric acid (Table 15).

TABLE 15

The Response of Uric Acid Excretion to Adrenaline at Sea-Level and at Altitude.

Subject Number	URINE URIC ACID/CREATININE RATIO					
	BEFORE ADRENALINE			PER CENT. VARIATION AFTER ADRENALINE		
	Sea-Level	Altitude 1 day	Altitude 8 days	Sea-Level	Altitude 1 day	Altitude 8 days
1	0·358	0·405	0·640	+ 33·0	+ 44·8	+ 23·2
2	0·316	0·385	0·520	− 39·5	− 10·3	+ 7·0
3	0·254	0·427	0·486	+ 46·8	− 19·2	+ 62·5
4	0·246	0·382	0·917	+ 84·5	+ 3·1	− 12·8
5	0·116	0·370	0·689	+ 249·5	− 39·4	+ 15·2
6	0·307	0·435	0·994	− 4·8	− 22·2	+ 11·2
Average	0·266	0·401	0·708	+ 61·7	− 7·2	+ 17·7

Stimulation of the pituitary—adrenal mechanism with adrenaline also raised the uric acid excretion at sea-level. This response was less (and in many was reversed in character), in 5 subjects after one day at altitude, but was returning to normal at 8 days.

TABLE 16

The Response of Keto-Steroid Excretion to Adrenaline at Sea-Level and at Altitude.

Subject Number	URINE KETO-STEROID/CREATININE RATIO × 10^3					
	BEFORE ADRENALINE			VARIATION AFTER ADRENALINE		
	Sea-Level	Altitude 1 day	Altitude 8 days	Sea-Level	Altitude 1 day	Altitude 8 days
1	7·8	7·1	6·5	+ 18·8	+ 30·8	+ 69·2
2	5·6	4·7	11·5	+ 10·4	− 3·5	+ 15·5
3	5·6	6·5	6·6	+ 55·5	+ 29·4	+ 42·0
4	4·5	2·7	18·5	+ 6·8	− 3·3	+ 39·6
5	13·2	5·2	23·3	+ 55·2	+ 6·0	+ 17·6
6	6·0	7·0	28·2	+ 39·2	+ 26·2	+ 62·8
Average	7·1	5·5	15·8	+ 31·0	+ 14·3	+ 41·1

The urinary excretion of keto-steroids was similarly increased, although in this instance there was reduced excretion by 4 subjects on the first day and one of these continued to show a decreased excretion on the eighth day (Table 16). The response to adrenaline was lessened after one day but enhanced at 8 days.

The creatine excretion was reduced during residence at altitude in all but one subject. (The students were not eating a creatine free diet nor, outside the experimental days, was their diet rigidly controlled).

TABLE 17

The Response of Creatine Excretion to Adrenaline at Sea-Level and at Altitude.

Subject Number	URINE CREATINE/CREATININE RATIO × 10^3					
	BEFORE ADRENALINE			PER CENT. VARIATION AFTER ADRENALINE		
	Sea-Level	Altitude 1 day	Altitude 8 days	Sea-Level	Altitude 1 day	Altitude 8 days
1	63	23	13	−17·6	+ 5·7	−37·8
2	216	141	131	−42·2	+ 6·0	−36·2
3	431	45	23	−47·7	− 8·2	−43·2
4	91	26	22	−53·2	− 13·4	−25·0
5	616	175	131	−45·0	− 32·4	−70·2
6	36	64	50	− 8·0	− 9·1	−22·2
Average	242	79	62	−35·6	− 8·6	−39·1

Like the response of the excretion of keto-steroids to adrenaline, the excretion of creatine showed reduced response to the injection of adrenaline in the first day but a greater response after 8 days at 6,200 feet.

For this small group of subjects most of the changes described were consistent with the observations of previous workers (e.g. rise in red blood cell and in lymphocyte counts) or with the variations noted in Tamil labourers resident at different altitudes (e.g. body fluid volumes) so that it is possible that the noted changes are real and would be statistically significant only if large groups of subjects were used.

DISCUSSION

The results of the determinations of various physiological characteristics, using Indian Tamil labourers living at different altitudes, suggested that the higher the site of residence then the less the volumes of the various extracellular body fluids, and the greater the lymphocyte (absolute and relative) and neutrophil (absolute) cell counts. Observations on 6 medical students, who travelled overnight by train from sea-level to a height of 6,200 feet, have tended to confirm the reality of these variations with residence at altitude. Within 7 to 8 days of commencement of residence at 6,200 feet, the plasma volume, total blood volume and tissue fluid volume were decreased while the concentrations of neutrophil and lymphocyte cells in the blood were increased. These increased white cell counts were not due merely to concentration of the blood by loss of plasma, since the relative fluid loss was much less than the relative increase in the cellular content.

Residence at altitude is also accompanied by changes in the renal clearance of certain constituents of the urine and the observations in general suggest that there are alterations in the activity of the adrenal cortex. The decreased plasma volume, tissue fluid volume, and urinary potassium excretion, for example, could be explained on the basis of lessened production of the mineral corticoids (e.g. DCA). The increased excretion of keto-steroids may be due to increased formation of adrenal androgens, although there are other sources for these excretory products. The increase in neutrophils, the decreased creatine excretion and the increased clearance of uric acid may all be caused by increased excretion of 11, 17-oxysteroid (Compound E). The eosinophil content of the blood, however, does not vary and this factor is said to be a sensitive index of the secretion of Compound E. Actually, if the observed eosinophil counts are corrected for change in the haematocint readings, then 4 of the 6 subjects did show a fall in the number of eosinophils in the blood, but more marked reductions might have been expected. Similarly, the administration of Compound E causes a fall in the lymphocyte cell count, but this is definitely increased when living above sea-level.

After the first day of residence at 6,200 feet, the majority of the students did show a rise in the number of neutrophil cell, and a fall in the number of lymphocyte and eosinophil cells in the blood, with increased uric acid and decreased creatine in the urine, and all these imply enhanced secretion of Compound E. Probably if the subjects had been examined a little earlier then more consistent evidence for increased adrenal cortical activity might have been obtained, especially when it is remembered that a more prolonged stay at this altitude, although accompanied by a further fall in the creatine excretion and a further rise in the uric acid excretions, produce a fall in the neutrophil count, and rises in the lymphocyte and the eosinophil counts. In other words, there is a suggestion of first an increase in the production of Compound E by the adrenal cortex and then a decrease ; but the results are not consistent.

Similarly there is evidence in some subjects for an increased plasma volume, tissue fluid volume and potassium excretion on the second day at 6,200 feet, this being followed by decreases in these factors on more prolonged residence. This again is suggestive of a preliminary increase and a later decrease in the activity of the adrenal cortex. It is unfortunate that earlier observations could not be made and that the expense of residence prevented a more prolonged stay.

There is another possible explanation of these results and that is based on the observations that prolonged administration of adrenotrophic hormone or of cortical hormone (White, 1949), causes a lymphocytosis (though still an eosinopenia). That is a lymphopenia is the immediate response to stimulation of the adrenal cortex and a lymphocytosis the effect of prolonged stimulation. Therefore the results reported here may be merely the difference between the responses of the adrenal cortex to acute or chronic stimulation. The uric acid and creatine excretion trends or the absence of an eosinopenia cannot be so explained. It must be remembered, too, that Compound A (11-dehydrocorticosterone) as well as Compound E can also produce increased uric acid excretion but it is difficult to see how this fact can help in the elucidation of the nature of the physiological variations here described. The keto-steroid excretion does not fit into the general pattern either, there being, first a decreased and later on an increased clearance. Till more is known about the metabolism of the keto-steroids further discussion of this phenomenon would be merely speculative. It should be stated, however, that Burrill and Ivy (1950) have reported a decreased excretion of 17-ketosteroids with a later return to normal levels during intermittent exposure to a simulated altitude of 18,000 feet.

The responsiveness of the pituitary-adrenal cortex mechanism to stimulation can be assessed by the injection of ACTH or adrenaline (Vogt, 1944, suggests that adrenaline stimulates the adrenal cortex direct but others, e.g. Long, 1947, believe that the anterior-pituitary is also involved). Such artificial stimulation produces an increase in the number of neutrophil cells and decreases in the numbers of lymphocyte and eosinophil cells (Thorn and Forsham, 1949).

After one day at 6,200 feet there is a decreased response in the part of the pituitary—adrenal mechanism to the injection of adrenaline. Thus, when compared with the changes produced at sea-level, there are produced smaller decreases in lymphocyte and eosinophil cell counts, smaller increases in potassium, uric acid, and keto-steroid excretions, and a smaller decrease in the creatine excretion. In some instances, the usual sea-level response is actually reversed; all six subjects show a lymphocytosis after adrenaline, one shows an increased eosinophil content, 2 show an increased creatine excretion, 4 show a decreased uric acid excretion, one shows a decreased potassium excretion and 2 show a decreased keto-steroid excretion. That is, after one day at altitude, the responses are abnormal both in degree and in type and the variations are not consistent from subject to subject. This corresponds with the period of increased functional activity on the part of the adrenal cortex. It is as though the potential activity of the adrenal cortex is so strained in dealing with the stress of adjustment to the new environment, that further stimulation finds a smaller reserve for response.

The above can only be considered to be general statements; individual behaviour and responses do vary. Thus two subjects showed an increased lymphocyte count after adrenaline at sea-level and so on. The balance of the experimental evidence does seem to favour the conclusion that, on travelling from sea-level to higher altitudes, there is first an increase in the activity of the adrenal cortex, with less reserve potential, followed by a decreased activity with an increased reserve.

The nature of the fundamental stimulus to the adrenal cortex cannot be stated from those experiments. Residence at altitude in Ceylon, when compared with living at sea-level, not only involves breathing inspired air with a lower oxygen tension but also the environmental temperature is lower, while there may be greater irradiation with ultra-violet (Stammers, 1933). It is known that hypoxia stimulates the adrenal cortex to increased activity (Evans, 1934; Armstrong and Heim, 1928; Langley and Clarke, 1942, etc.) but the majority of the experiments described in the literature have been concerned with much lower oxygen tensions in the atmosphere than existed at the moderate altitude studied in Ceylon.

The statistical inconclusiveness of the data obtained from the medical students, temporarily resident at 6,200 feet, emphasises the necessity of using large groups of subjects where minor variations in the physiological characters are being studied. Admittedly, these changes were consistent with those observed in Indian Tamil residents, but the latter subjects may give a biased picture because, for example, of such complications as massive infestation of most subjects with helminths. Because of these considerations animal experimentation has been resorted to in an effort to elucidate the response of the organism to residence at moderately low altitude (see Cullumbine, 1951).

Summary

Observations made on Ceylonese adults living at moderate altitudes (up to 6,200 feet) indicate that such residence is accompanied by an absolute and a relative lymphocytesis, a leucocytosis, and decreased plasma-, blood-, and tissue-fluid-volumes.

The experimental evidence indicates that, on travelling from sea-level to an altitude of 6,200 feet, there is first an increase in the activity of the adrenal cortex, with a lessened response to adrenaline, and then a decreased activity, with enhanced responses to adrenaline.

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