# Influence of Exposure to Moderate Altitude on the Plasma Concentration of Cortisol, Aldosterone, Renin, Testosterone, and Gonadotropins*

E. Humpeler, F. Skrabal, and G. Bartsch

Institute of Physiology, Clinic of Internal Medicine and of Urology of the University of Innsbruck, Fritz-Pregl-Str. 3, A-6010 Innsbruck, Austria

**Summary.** The influence of 11 days at moderate altitude (2,000 m) combined with exercise on plasma concentration of testosterone, FSH (follicle-stimulating hormone), LH (luteinizing hormone), cortisol, aldosterone, and renin activity was studied in ten healthy subjects. Within 48 h of arrival at moderate altitude a significant increase in testosterone was found whereas FSH had decreased significantly and LH showed a tendency to decrease. Cortisol increased significantly at the beginning and reached a maximum at the end of altitude exposure. The plasma aldosterone level rose continuously and on the last day of altitude was significantly elevated. Plasma renin activity showed a tendency to decrease. On return to low land all measured parameters returned to base line values within 2 days.

The findings of increases in plasma levels of aldosterone and testosterone (and serum $T_3$ and $T_4$, as reported by others) are in contrast to the previously found decrease of urinary excretion of all these hormones. This appears to be a distinct dissociation of serum levels of adrenal (and thyroid) hormones from their urinary excretion.

The observed increase in plasma aldosterone is probably mediated through ACTH and the rise in plasma potassium, since plasma renin activity showed an opposite trend. The rise in plasma testosterone is probably of adrenal origin since plasma gonadotropins declined simultaneously.

The increase of plasma levels of glucocorticoids, mineralocorticoids, and androgens after an ascent from 600 m to 2,000 m above sea level is compatible with an ACTH-mediated stimulation of the entire adrenal cortex and/or a diminished elimination of adrenal steroids: The concomitant fall of FSH, LH, and plasma renin would then be a consequence of a direct negative feedback inhibition of these hormones.

* This study was supported partly by a "Forschungsförderungsbeitrag des Landes Vorarlberg", by the Fonds zur Förderung der wissenschaftlichen Forschung, Austria, and by the Jubiläumsfonds der Nationalbank

*Offprint requests to:* Dr. E. Humpeler (address see above)

0301-5548/80/0045/0167/$ 02.00

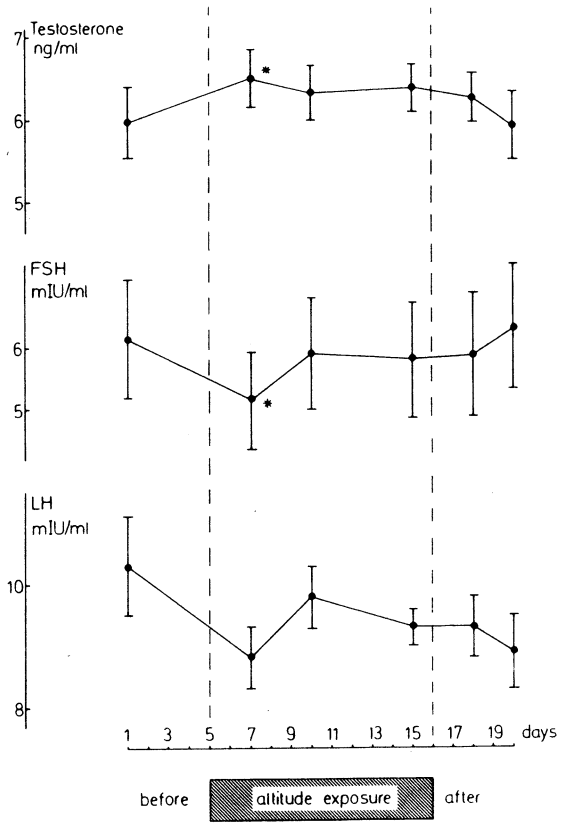


**Fig. 1.** Mean values (± S.E.M.) of the plasma concentration of testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) before, during, and after exposure to medium altitude

**Key words:** Moderate altitude – Hormones of adrenal cortex – Plasma renin activity – Pituitary gonadotropins

Few reports exist concerning the influence of altitude exposure on the activity of plasma renin (Gould and Goodman 1970) and of hormones, such as cortisol (McKinnon et al. 1963; Moncloa et al. 1965, 1968; Singh et al. 1974; Timiras et al. 1957), aldosterone (Ayres et al. 1961; Jung et al. 1971; Maher et al. 1975; Slater et al. 1969; Williams 1966), testosterone and gonadotropic hormones (Bangham and Hackett 1978; Guerra-Gracia 1971; Sobrevilla and Midgley 1971; Vander et al. 1978), and most data were obtained at altitudes higher than 3,500 m. However, a moderate altitude (2,000 m) to which millions of tourists are acutely exposed is of particular interest. Halhuber and Gabl (1964), Sailer and Verzár (1950) and Koller et al. (1954) reported an increased urinary excretion of 17-OHCS on ascent to moderate altitude. As far as we are aware, the effect of exposure to moderate altitude on plasma concentration of cortisol, aldosterone, renin activity, testosterone, LH, and FSH has not been studied. The present study was aimed at obtaining information about how adrenal steroids and gonadotropins are affected by the combination of moderate altitude and the exercise usually performed by tourists at this altitude.

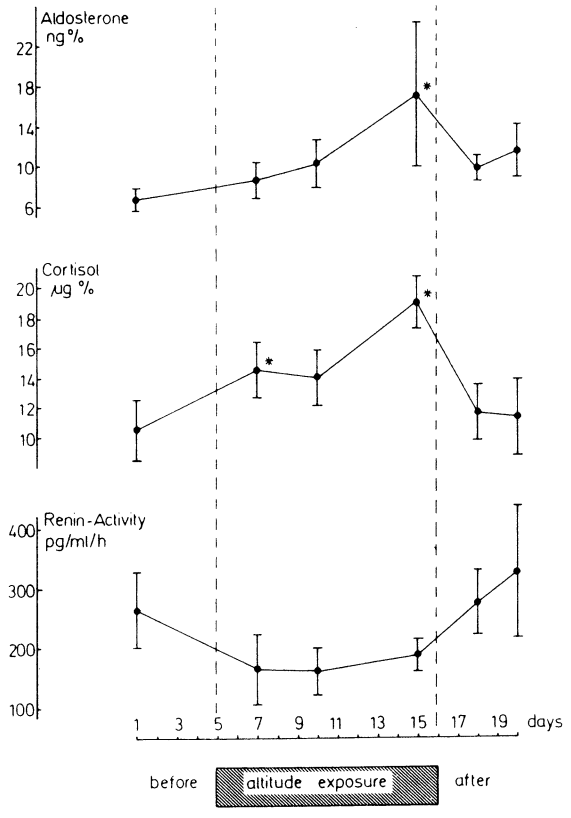


**Fig. 2.** Mean values (± S.E.M.) of plasma concentration of aldosterone and cortisol and of the plasma renin activity before, during, and after exposure to medium altitude

## Material and Methods

Subjects of this study were ten healthy men (medical students) aged 19–31 years (22.9 ± 2) with a mean body weight of 72.6 kg ± 2.1 and a mean height of 183 cm ± 1.6, all fully informed of the nature of the experiments. Samples were taken in Innsbruck (576 m) ("low land") before, 2 and 4 days after altitude exposure. During the 11 days at moderate altitude in the alpine research center of Innsbruck University at Obergurgl (2,040 m) in Tyrol, Austria, measurements were made on the 2nd (within 48 h after arrival), 5th, and 10th days. The subjects were allowed the activity usually performed by tourists which was exactly registered. This involved a daily average of 4.4 h walking over a mean distance of 12.7 km, up to an average altitude of 2.847 m. The mean barometric pressure measured in the alpine research laboratory was 607.4 mmHg, varying from 603–610 mmHg. The maximum temperature was between 17.8° C and 22.2° C (19.5 ± 0.34), the minimum temperature being between 2.6° C and 9.1° C (8.0 ± 0.5). The mean relative humidity was 58% (± 2.5), at 8 a.m., 30.4% (± 2.5) at midday, and 49.1% (± 4.2) at 8 p.m.

On the test days, after an overnight fast and 2 h supine bed rest 30 ml blood was taken from the forearm for the hormone measurements.

Before each experimental day 24 h urine samples were collected for the determination of sodium and potassium excretion. Since there were no facilities for a proper balance study, 24 h urine sodium and potassium were measured as an index of sodium intake. We have shown that supine

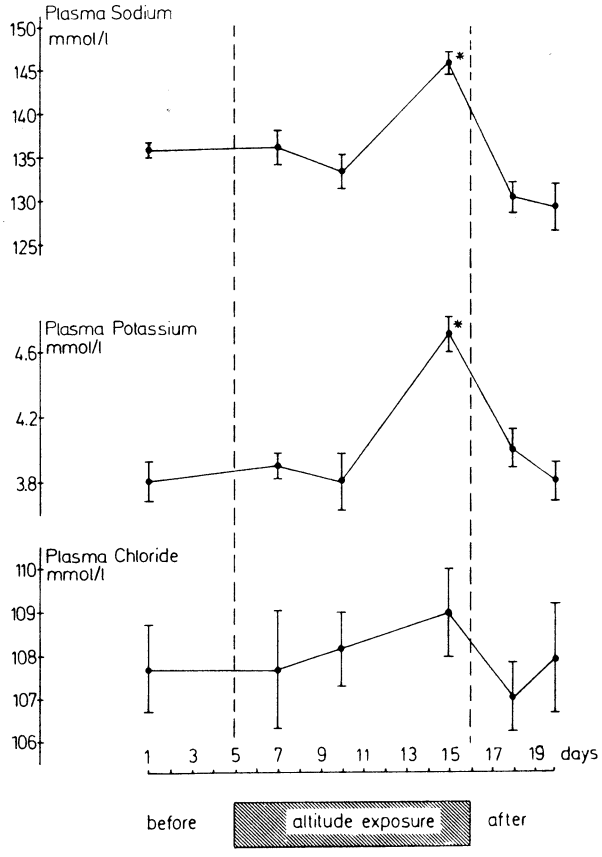


**Fig. 3.** Mean values (± S.E.M.) of the plasma concentration of sodium, potassium and chloride before, during, and after exposure to medium altitude

plasma renin activity and plasma aldosterone are relatively independent of sodium intake above ad libidum intakes higher than 3 g sodium chloride per day (Skrabal 1975, 1979).

Serum and urine electrolyte were analyzed by flame photometry. Plasma aldosterone was measured by a modification of the method of Ito et al. (1972), plasma cortisol by competetive protein-binding assay (Murphy 1967). The method of Boyd et al. (1966) was employed for the plasma renin activity determination. Other radioimmunoassays used were as follows: testosterone by the method of Bartke et al. (1973), FSH and LH by the method of Crosignani et al. (1970).

Hemoglobin concentration was measured by the cyanmethemoglobin method and the hematocrit by centrifugation of the blood in capillary tubes with a microhematocrit centrifuge at 16,000 rpm for 4 min.

Alterations in hormonal concentrations were tested for statistical significance with the non-parametric Wilcoxson test for paired values (Sachs 1968). Data are reported as $\bar{x} \pm$ S. E. M. Comparison reported as statistically significance have $p$-values of at least 0.05.

## Results

The change of each parameter measured is shown as a function of time in Figs. 1–4. Changes of plasma concentration of testosterone, FSH, and LH are indicated in Fig. 1. The first measurement, which was made within 48 h of arrival

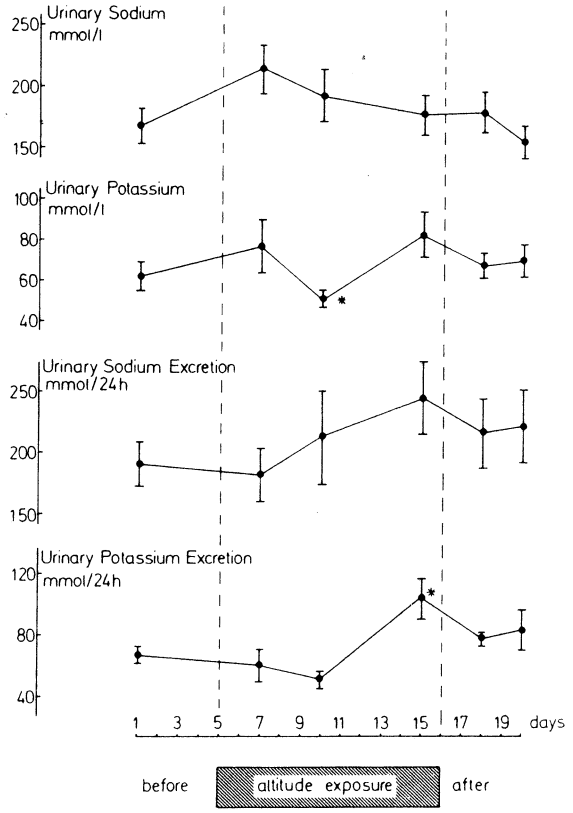


**Fig. 4.** Mean values (± S.E.M.) of urinary sodium and potassium concentration and of the urine sodium and potassium excretion per day

at altitude, revealed a small but significant increase of testosterone concentration, whereas LH tended to decrease. The first altitude value of FSH was significantly below the control level. Figure 2 shows the changes in plasma aldosterone, cortisol, and plasma renin activity. Aldosterone increased continuously and at the end of altitude exposure was significantly elevated (17.4 ng% ± 3.2) above the initial, normal lowland values (6.7 ng% ± 1.1). Cortisol already increased significantly at the beginning of altitude, rising from 10.6 μg% ± 2.0 to 14.5 μg% ± 1.9 on the 2nd altitude day, and reaching a further maximum on the 10th day (18.9 μg% ± 1.7). After the subjects' return to low land both aldosterone and cortisol decreased and did not differ significantly from the control values. At altitude, plasma renin activity showed a tendency to decrease, although the fall was not significant ($0.05 \pm p < 0.08$) and, after the descent, the activity returned to the prealtitude value. Figure 3 demonstrates the values for plasma sodium, potassium and chloride. Sodium as well as potassium were unchanged on the 2nd and 5th days, but on the 10th day both were significantly elevated above the Innsbruck values; no significant changes in plasma chloride were found. Figure 4 shows the urinary concentration and 24-h urinary excretion of potassium and sodium. The 24-h urinary excretion of

potassium showed a significant increase on the 10th day, whereas the increase in sodium excretion was not significant.

No significant change of hemoglobin concentration and of hematocrit was found.

## Discussion

This study demonstrates that an acute exposure of healthy men to moderate altitude combined with the exercise usually performed by tourists produces a small but significant increase in plasma testosterone, a simultaneous significant decrease in FSH and also a tendency to decrease of LH. The lack of similar studies at moderate altitude renders comparisons impossible, but our observations agree, at least in part, with studies carried out at higher altitudes (above 4,000 m): Vander et al. (1978) found at an altitude of 4,300 m a small but not significant fall in plasma FSH and LH and also a tendency to increasing testosterone values, which paralleled our own observations. Guerra-Garcia (1971) found a decreased urinary testosterone excretion on the 3rd day in men exposed to an altitude of 4,250 m, but on the 7th day the mean daily excretion rate of testosterone increased and rose above the inital values. Caution should be applied here in comparing our data with the findings of these authors because urinary testosterone is only a small and variable proportion of the total testosterone produced. Our findings agree to some extent with the results of Sobrevilla and Midgley (1971) who reported a significant decrease in LH on the second and third days at high altitude. In 36 Sherpas, Bangham and Hacket (1978) also found a significant small increase in LH after 3.1 days and a decrease after 10.4 days at an altitude of 4,240 m, with no significant variations in LH and testosterone.

The increase in plasma testosterone concomitantly with a fall in plasma gonadotropins in the present study suggest that the rise in plasma testosterone is of adrenal origin.

The results concerning the plasma cortisol are, at least indirectly, comparable to findings of other authors, who investigated medium altitudes. Halhuber and Gabl (1964) kept five male students for 4 weeks at 2,000 m and during the first weeks of exposure found an increase of adrenocortical activity, as demonstrated by 17-OHCS excretion in urine. The values then decreased and returned to sea level values at the end of altitude stay. Sailer and Verzár (1950) also found elevations in 17-OHCS excretion during moderate altitude acclimatization, but only if muscular exercise was performed. We, however, found the first significant increase in plasma cortisol within 48 h after arrival, when no muscular activity was permitted. Koller et al. (1954) measured adrenal cortisol activity by determining the excretion of 17-ketosteroids and of reducing corticoids and found an increased excretion of these hormones after ascent to the Jungfraujoch (3,450 m) and – less marked – after ascent to Davos (1,600 m). They concluded that ascent to altitude is accompanied by an increased secretion of adrenocortical hormones. Similar reactions were recorded in studies carried out at higher altitudes (about 4,300 m), as demonstrated by the excretion of

OHCS (Moncloa et al. 1965; Timiras et al. 1957) and by plasma cortisol concentration (Moncloa et al. 1968). Moncloa et al. (1968) measured an increase in the mean plasma cortisol concentration from 9.9–15.5 μg% in young males on the 2nd day of exposure to an altitude of 4,330 m. This rise is only slightly higher than that found in our study, where the mean plasma cortisol concentration increased from 10.6 μg%–14.6 μg% on the 2nd day of altitude exposure. Our finding that plasma cortisol decreases to prealtitude levels after descont is in agreement with all of the above studies.

During the 10 days at moderate altitude plasma aldosterone increased continuously and at the end of the stay it was significantly elevated above the initial levels. These findings are in contrast to measurements made at higher altitudes by Ayres et al. (1961) and Williams (1966), who found a marked fall in urinary aldosterone excretion during the first few days. Slater et al. (1969) transported six subjects by helicopter to the Plateau Rosa at 3,500 m for 6 days and also reported a 35% fall of aldosterone secretion rate and excretion during the altitude day. Jung et al. (1971) reported an age dependence of the behavior of plasma aldosterone levels during altitude exposure. On the 3rd and 5th days after arrival at an altitude of 3,500 m plasma aldosterone concentration in the younger male group (n = 4, mean age = 24 years) showed a tendency to increase, whereas in the older group (n = 4, mean age = 56 years) they are lowered. The findings of the younger group are in a good agreement with our results. The reason for the reported decrease in aldosterone excretion and the increase in plasma aldosterone found in the present study is not clear. Our results, however, were obtained at medium altitudes of 2,000 m whereas the reported decrease of acid-labile aldosterone excretion was found at altitudes of between 3,500 and 4,500 m. Another possible cause for these contradictory findings could be a dissociation of serum levels of adrenal hormones from their urinary excretion. This would be also in accordance with findings of Rastogi et al. (1977), who showed during a 16-day altitude exposure (3,700 m) an increase of serum $T_3$ and $T_4$ but a concomitant decrease of the urinary excretion of both $T_3$ and $T_4$. One possible explanation for these observations could be an impaired renal glucuronization of aldosterone by altitude exposure.

It is interesting in this respect that urinary testosterone, which is also excreted in the urine in the glucuronated form, has been reported to decrease at high altitudes, whereas we found an increase in plasma testosterone. A diminished renal excretion and/or reduced metabolism of adrenal steroids as a cause of the raised serum levels therefore will have to be a subject for further study.

An increase of plasma steroids as a consequence of hemoconcentration can also be excluded, since this would result in parallel increases of FSH, LH, and renin, which were not observed. In addition, the constancy of the hemoglobin concentration and of the hematocrit indicates that hemoconcentration did not occur. Furthermore, during an 8-day stay at moderate altitude (2,287 m) Greenleaf et al. (1978) found no change of total blood volume, plasma, and red cell volume.

Although it is a drawback that in the present study we were unable to monitor sodium intake, it is still obvious that the observed changes of renin and

aldosterone levels were not caused by changes of sodium intake. During the whole stay 24-h urinary sodium was unchanged. In addition to this, a reduced sodium intake would stimulate aldosterone secretion through the renin angiotensin system, which was suppressed in the present study.

Our results are physiologically more plausible than the previously reported fall in urinary aldosterone excretion. All known stimuli of aldosterone secretion increased either in the present or in previous studies, e.g., cortisol (and presumably ACTH) in the present and previous studies (Mackinnon et al. 1963; Moncloa et al. 1965, 1968; Singh et al. 1974; Timiras et al. 1957), serum potassium in the present and previous studies (Guerra-Garcia 1971), and plasma renin in the study performed by Slater et al. (1969). In the study performed by Slater et al. (1969) at the higher altitude of 3,500 m plasma cortisol rose, serum potassium and plasma renin activity increased, although aldosterone secretion and excretion fell. These authors were thus obliged to postulate an unknown control mechanism leading to suppression of aldosterone secretion. In contrast, we found an increase in both cortisol (and probably ACTH) and serum potassium, both of which would account for our observed increase of plasma aldosterone. Plasma renin activity would then, probably as a result of some degree of sodium retention, decrease.

To our knowledge no measurements of plasma ACTH at high altitude have been reported but all current evidence strongly suggest an increase of these hormones: in all studies (Mackinnon et al. 1963; Moncloa et al. 1965, 1968; Singh et al. 1974; Timiras et al. 1957) cortisol increased and also catecholamines are reported to increase at high altitude (Klain 1972) which would stimulate ACTH secretion.

Furthermore, the increase in concentration of plasma potassium, which we found, also stimulates the production of aldosterone. Subtile changes in $K^+$ concentration can alter aldosterone production in vivo and in vitro. An increase of 0.5 meq/l or less in the plasma $K^+$ perfusing the sheep adrenal gland stimulated aldosterone secretion (Funder 1969). An increase in plasma potassium from 3.8 mmol/l to 4.7 mmol/l as found in the present study is certainly an additional cause for the increased rate of aldosterone secretion. A possible explanation for the rise in plasma potassium might be muscular activity (Tibes et al. 1977).

Muscular exercise per se has also been reported to result in an increase of plasma aldosterone (Costill et al. 1976; Kosunen and Pakarinen 1976). After a running exercise of 3,300 m and after 60 min of exercise (60% $\dot{V}O_{2\ max}$), Kosunen et al. (1976) and Costill et al. (1976), respectively, found a significant elevation of plasma aldosterone. The pattern of this change in plasma aldosterone concentration paralleled that of plasma renin activity. Both increased during exercise, decreased rapidly during the first 2 h of recovery and returned to the pre-exercise level within 4–12 h. Therefore, we do not believe that the exercise performed on the previous day affected the hormone levels after an overnight rest and additional 2 h of supine bed rest, moreover, our measurements of an increase of plasma aldosterone concentration was accompanied by not an increase but a fall in renin activity.

The results reported here point to an ACTH mediated stimulation of the

entire adrenal cortex, glucocorticoids, mineralocorticoids, and adrenal androgens being likewise affected. By means of direct negative feedback renin and gonadotropins are suppressed. If this is confirmed the increase in plasma aldosterone has to been considered as a possible further factor in causing the fluid retention and redistribution characteristic for high altitude sickness. If hypersecretion of aldosterone indeed is involved in the pathogenesis of high altitude sickness, and if raised plasma aldosterone concentrations indeed occur only in young subjects, than this would explain the higher incidence of altitude sickness in young people.

*Acknowledgements.* The authors want to thank M. Ladner, M. Humpeler, G. Hölzl, and P. Dejaco for the proficient technical assistance.

## References

Ayres PJ, Hunter RC, Williams ES, Rundo J (1961) Aldosterone excretion and potassium retention in subjects living at high altitude. Nature 191: 78–80

Bangham CRM, Hackett PH (1978) Effect of high altitude on endocrine functions in the sherpas of Nepal. J Endocrinol 79: 147–148

Bartke A, Steele RE, Musto N, Caldwell EV (1973) Fluctuations in plasma testosterone levels in adult male rats and mice. Endocrinology 92: 1223–1228

Boyd GW, Adamson AR, Fitz AE, Peart WS (1966) Radioimmunoassay determination of plasma-renin activity. Lancet 1: 213

Costill DL, Branam G, Fink W, Nelson R (1976) Exercise induced sodium conservation: changes in plasma renin and aldosterone. Med Sci Sports 8: 209–213

Crosignani PG, Nakamura R, Hovland T, Mishell FR (1970) A method of solide phase radioimmunoassay utilizing polypropylene discs. J Clin Endocrinol Metab 30: 153–160

Funder JW (1969) Effect of plasma $K^+$ on the secretion of aldosterone. Endocrinology 85: 381–384

Gould AB, Goodman SA (1970) The effect of hypoxia on the renin-angiotensinogen system. Lab Invest 22: 443–447

Greenleaf JE, Bernauer EM, Adams WC, Juhos L (1978) Fluid-electrolyte shifts and $\dot{V}O_{2\,max}$ in man at simulated altitude (2,287 m). J Appl Physiol 44: 652–658

Guerra-Garcia R (1971) Testosterone metabolism in men exposed to high altitude. Acta Endocrinol Panam 2: 55

Halhuber MJ, Gabl F (1964) 17-OHCS excretion and blood eosinophils at an altitude of 2,000 m. In: Weihe WH (ed) Physiological effects of high altitude. Pergamon Press, Oxford, pp 131–138

Ito T, Woo J, Haning R, Horton R (1972) A radioimmunoassay for aldosterone in human peripheral plasma including a comparison of alternate techniques. J Clin Endocrinol 34: 106

Jung RC, Dill DB, Horton R, Horvath SM (1971) Effects of age on plasma aldosterone levels and hemoconcentration at altitude. J Appl Physiol 31: 593–597

Klain GJ (1972) Acute high altitude stress and enzyme activities in the rat adrenal medulla. Endocrinology 91: 1477–1449

Koller F, Schwarz E, Marti M (1954) Über die Reaktion der NNR beim Aufstieg im Hochgebirge. Acta Endocrinol 16: 118–140

Kosunen KJ, Pakarinen AJ (1976) Plasma renin, angiotensin II, and plasma and urinary aldosterone in running exercise. J Appl Physiol 41: 26–29

McKinnon PCB, Monk-Jones ME, Fotherby K (1963) A study of various indices of adrenocortical activity during 23 days at high altitude. J Endicrinol 26: 555–566

Maher JT, Jones LG, Hartley LH, Williams GH, Rose LI (1975) Aldosterone dynamics during graded exercises at sea level and high altitude. J Appl Physiol 39: 18–22

Moncloa F, Donayre J, Sobrevilla LA, Guerra-Garcia R (1965) Endocrine studies at high altitude. II. Adrenal cortical function in sea-level natives exposed to high altitudes (4,300 m) for two weeks. J Clin Endicrinol Metab 25: 1640–1642

Moncloa F, Velasco I, Beteta L (1968) Plasma cortisol concentration and disappearance rate of 4-$^{14}$C-cortisol in newcomers to high altitude. J Clin Endiocrinol Metab 28: 379

Murphy BEP (1967) Some studies of the protein binding of steroids and their routine micro- and ultra-micromeasurements of various steroids of body fluids by competitive protein binding radio-assay. J Clin Endocrinol Metab 27: 973

Rastogi GK, Malhotra MS, Srivastava MC, Sawhney RC, Dua GL, Sridharan K, Hoon RS, Singh I (1977) Study of the pituitarythyroid functions at high altitude in man. J Clin Endocrinol Metab 44: 447–452

Sachs L (1968) Statistische Auswertungsmethoden. Springer, Berlin Heidelberg New York, pp 293

Sailer E, Verzár F (1950) Die Ausscheidung von Corticosteroiden in Ruhe, bei Muskelarbeit und in der Höhe. Helv Phys Acta 8: C72–C74

Singh I, Malhotra MS, Khanna PK, Nanda RB, Purshottam T, Upadhyay TN, Radhakrishnan U, Brahmachari DH (1974) Changes in plasma cortisol, blood antidiuretic hormone, and urinary catecholamines in high altitude pulmonary oedema. Int J Biometeorol 18: 211–221

Skrabal F (1975) Nomogramm zur Schätzung der Plasmareninaktivität anhand des Natrium-Kreatinin-Quotienten im Spontanharn. Dtsch Med Wochenschr 100: 2649–2651

Skrabal F (1979) Aldosterone and in vivo mineralocorticoid activity in normotensive and hypertensive man. J R Soc Med 72: 252–259

Slater JDH, Tuffley RE, Edwards RHT, Ekins RP, Beresford CH, Sönksen PH, Williams ES, McLaughlin M (1969) Control of aldosterone secretion during acclimatization to hypoxia in man. Clin Sci 37: 327–341

Sobrevilla LA, Midgley AR (1971) The plasma gonadotropin response to high altitude exposure. Acta Endocrinol Panam 2: 47

Tibes U, Hemmer B, Böning D (1977) Heart rate and ventilation of relation to venous $K^+$, osmolality, pH, $P_{CO2}$, $P_{O2}$, exercise in athletes and non-athletes. Eur J Appl Physiol 36: 127

Timiras PS, Pace NG, Hwang CA (1957) Plasma and urine 17-hydroxycorticosteroid and urine 17-ketosteroid levels in man during acclimatization to high altitude. Federation Proceedings, Federation of American Societies for Experimental Biology 16: 340

Vander AJ, Moore LG, Brewer G, Menon KMJ, England BG (1978) Effects of high altitude on plasma concentrations of testosterone and pituitary gonadotropins in man. Aviat Space Environ Med 49: 356–357

Williams ES (1966) Electrolyte regulation during the adaptation of humans to life at high altitudes. Proc R Soc London Ser B 165: 266–280

Accepted September 17, 1980