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## High Altitude Hyperuricemia (33451)

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Since the original observations of Viault, it is known that permanent residents at high altitude develop an adaptive polycythemia, and later the studies of Hurtado *et al.* (1) have shown an absolute increase in the circulating red cell mass and a slightly diminished total plasma volume. The occurrence of hyperuricemia in association with polycythemic states is well known (2) and the relationship between hyperuricemia and renal function has been extensively examined in primary hyperuricemia (3).

Since a potentially harmful role for excessive levels of serum urate has been suggested (4), we decided to study a group of subjects living permanently at 4200 m in Cerro de Pasco, Peru, to determine the occurrence and extent of hyperuricemia in this polycythem-

TABLE I. Hematocrit, Serum Urate, and Creatinine in 15 Male Subjects Living at Cerro de Pasco (14,000 ft).

| Subject | Age | Hematocrit (%) | Urate (mg/100 ml) | Creatinine (mg/100 ml) |
|---|---|---|---|---|
| J.S.S. | 22 | 50.5 | 6.94 | 1.6 |
| E.C.C. | 21 | 54 | 5.19 | 0.8 |
| R.F.M. | 30 | 60 | 10.30 | 1.7 |
| R.A.D. | 29 | 68.6 | 6.13 | 1.4 |
| M.J.M. | 36 | 60 | 6.04 | 1.4 |
| A.C.F. | 46 | 58.7 | 6.66 | 1.1 |
| L.M.R. | 29 | 55.5 | 6.70 | 1.3 |
| D.C.Z. | 31 | 76 | 9.14 | 1.7 |
| P.C.S. | 33 | 65.2 | 6.48 | 1.6 |
| P.L.N. | 25 | 60.5 | 6.88 | 1.5 |
| J.P.C. | 32 | 67 | 8.26 | 1.1 |
| R.D.R. | 26 | 55 | 6.92 | 1.4 |
| C.I.P. | 35 | 52.5 | 7.19 | 1.4 |
| V.T.P. | 37 | 62.5 | 6.65 | 1.0 |
| E.A.C. | 41 | 53 | 7.24 | 1.2 |
| Mean | 31.5 | 59.90 | 7.11 | 1.34 |
| SEM | | 1.75 | 0.34 | 0.07 |

TABLE II. Hematocrit, Serum Urate, and Creatinine in 15 Male Subjects Living at Lima (Sea Level).

| Subject | Age | Hematocrit (%) | Urate (mg/100 ml) | Creatinine (mg/100 ml) |
|---|---|---|---|---|
| J.M.M. | 35 | 50.5 | 5.64 | 1.2 |
| A.V.M. | 32 | 50 | 5.90 | 1.5 |
| O.K.U. | 27 | 48.5 | 6.62 | 1.0 |
| F.S.C. | 24 | 50 | 4.71 | 1.3 |
| C.V.S. | 24 | 46 | 4.69 | 1.2 |
| J.C.G. | 24 | 53 | 5.79 | 1.2 |
| M.P.S. | 27 | 51.5 | 6.64 | 1.2 |
| L.B.C. | 28 | 51.5 | 6.19 | 1.1 |
| A.P.M. | 26 | 46 | 6.27 | 0.6 |
| R.R.T. | 30 | 53 | 4.60 | 0.5 |
| E.C.T. | 25 | 47.5 | 5.45 | 1.8 |
| M.K. | 27 | 47 | 6.26 | 1.2 |
| M.M. | 28 | 45 | 4.73 | 1.4 |
| C.Z.D. | 23 | 46 | 4.97 | 1.0 |
| H.S.R. | 27 | 44 | 7.67 | 1.2 |
| Mean | 27.13 | 48.63 | 5.74 | 1.16 |
| SEM | | 0.79 | 0.24 | 0.08 |

ic population, and the relationship of uric acid levels to sex, hematocrit, and serum creatinine.

*Material and Methods.* Thirty healthy subjects, 15 males and 15 females, living permanently at Cerro de Pasco, a mining town (30,000 inhabitants) in the Andean plateau at 4200 m. of altitude, form the high altitude group (HA). Thirty healthy subjects, 15 males and 15 females, living in Lima, at 150m of altitude form the sea level group (SL). All subjects work at the "Policlinico Obrero de Cerro de Pasco," one of the local Hospitals, or at the "Hospital Loayza," in Lima,

TABLE III. Hematocrit, Serum Urate, and Creatinine in 15 Females Living at Cerro de Pasco (14,000 ft).

| Subject | Age | Hematocrit (%) | Urate (mg/100 ml) | Creatinine (mg/100 ml) |
|---|---|---|---|---|
| B.LI.C. | 27 | 54 | 3.39 | 1.6 |
| A.A.M. | 24 | 46.7 | 3.88 | 1.8 |
| F.G.H. | 30 | 48 | 5.10 | 1.4 |
| I.F.J. | 26 | 43 | 4.85 | 1.0 |
| A.T.M. | 30 | 41.2 | 2.76 | 1.2 |
| E.B.B. | 40 | 54.7 | 3.72 | 1.4 |
| J.B.V. | 26 | 51 | 5.74 | 1.4 |
| M.Z.F. | 27 | 50 | 4.35 | 1.2 |
| D.M.C. | 27 | 51 | 6.24 | 1.2 |
| E.V.S. | 32 | 52 | 6.77 | 0.9 |
| Y.M.C. | 24 | 49.5 | 4.39 | 0.9 |
| D.L.P. | 28 | 44 | 5.37 | 1.3 |
| A.S. | 32 | 48 | 4.51 | 1.1 |
| F.A. | 27 | 55 | 6.78 | 0.7 |
| R.G.S. | 31 | 49 | 5.64 | 0.7 |
| Mean | 28.73 | 49.14 | 4.89 | 1.18 |
| SEM | | 1.11 | 0.32 | 0.08 |

TABLE IV. Hematocrit, Serum Urate, and Creatinine in 15 Female Subjects Living at Lima (Sea Level).

| Subject | Age | Hematocrit (%) | Urate (mg/100 ml) | Creatinine (mg/100 ml) |
|---|---|---|---|---|
| N.N. | 32 | 44 | 4.90 | 1.2 |
| R.G.M. | 28 | 40 | 3.91 | 0.8 |
| R.H.A. | 25 | 48 | 2.90 | 1.0 |
| P.C. | 21 | 40.5 | 4.52 | 0.8 |
| R.C.W. | 24 | 42 | 6.08 | 0.7 |
| R.C. | 26 | 43 | 3.05 | 0.5 |
| I.R. | 24 | 42 | 3.42 | 0.6 |
| A.V. | 26 | 43 | 4.86 | 0.8 |
| I.A. | 27 | 39 | 4.09 | 0.5 |
| S.C. | 21 | 43 | 4.07 | 0.5 |
| M.C. | 29 | 46 | 3.96 | 0.8 |
| B.V.A. | 21 | 40.5 | 3.83 | 0.9 |
| I.C.E. | 26 | 41 | 3.22 | 0.7 |
| G.S.T. | 24 | 44.5 | 3.32 | 1.3 |
| R.M.C. | 25 | 45 | 4.98 | 0.7 |
| Mean | 25.27 | 42.76 | 4.07 | 0.78 |
| SEM | | 0.67 | 0.23 | 0.06 |

Peru having similar hospital diets. Their age ranged from 21 to 46 years. The ethnic composition of both groups was similar.

Blood samples were taken from an antecubital vein, the hematocrit was determined immediately, and the serum was frozen for the biochemical determinations that were carried out in our Laboratories in Lima. Hematocrit was determined by the microhematocrit technique, using heparinized capillaries and the special microhematocrit centrifuge. Serum urate determinations were done by the enzymatic-spectrophotometric method described by Liddle *et al.* (5), using a commercial preparation of uricase, Lot 116-B-8040, purchased from Sigma, St. Louis, Mo. Serum creatinine was determined by the alkaline-picrate method as modified by Philips (6). Statistical analysis was carried out using conventional methods.

*Results.* Tables I through IV give the individual values for age, serum urate, serum creatinine, and hematocrit, and the mean ± SEM in males and females at HA and at SL. Table V summarizes the results. Mean serum urate values were higher in males and females in Cerro de Pasco, (Table V); the differences were more marked in the males. The differences are statistically significant for both groups. The four groups can be ar-

TABLE V. Mean Hematocrit, Serum Urate, and Creatinine in Males and Females at High Altitude and Sea Level.

| | Mean ± SEM | | |
|---|---|---|---|
| | Cerro de Pasco (14,000 ft) | Lima (SL) | $p$ |
| Males | | | |
| Urate (mg/100 ml) | 7.11 ± 0.34 | 5.74 ± 0.24 | <0.0025 |
| Hematocrit (vol. %) | 59.90 ± 1.75 | 48.63 ± 0.79 | <0.0005 |
| Creatinine (mg/100 ml) | 1.43 ± 0.07 | 1.16 ± 0.08 | <0.1 |
| Females | | | |
| Urate (mg/100 ml) | 4.89 ± 0.32 | 4.07 ± 0.23 | <0.05 |
| Hematocrit (vol. %) | 49.14 ± 1.11 | 42.76 ± 0.67 | <0.0005 |
| Creatinine (mg/100 ml) | 1.18 ± 0.08 | 0.78 ± 0.06 | <0.0005 |

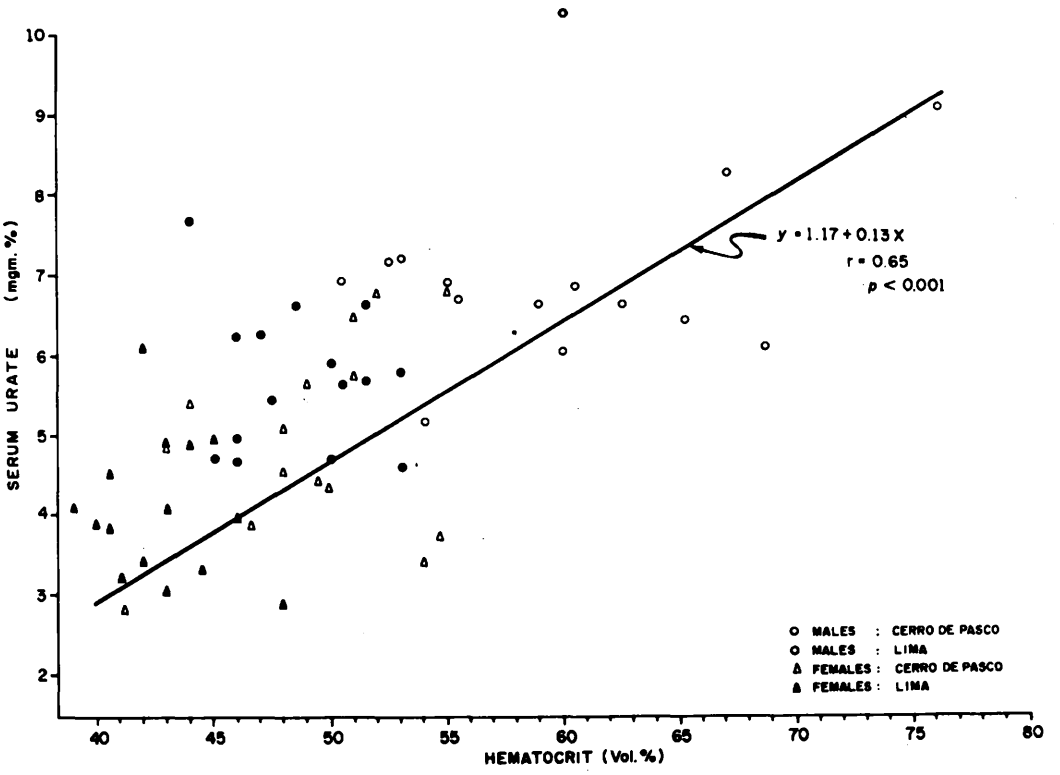


FIG. 1. Correlation of serum urate levels with hematocrit in all subjects.

ranged according to the degree of elevation, the HA males having the highest values, followed by the males from SL, and the females from HA; the subjects presenting the lowest values being the SL females. Mean values for serum creatinine were higher in males at HA, although the difference between them and their SL counterparts is not significant statistically. The HA females had values comparable to those of the SL males and significantly higher than those of the SL females (Table V). The mean hematocrit values were higher for males and females at HA. The mean hematocrit of the HA females is comparable to that of the SL males.

*Discussion.* The secondary polycythemia of high altitude has been known for a long time, the increased total circulating blood volume is due to a larger red cell volume with a slightly decreased total plasma volume as has been well documented by Hurtado *et al.* (1). Merino and Reynafarje showed a hyperplastic bone marrow (7), and Reynafarje *et al.* found an increased $^{59}Fe$ turnover rate (8). Our finding of elevated serum urate levels in the male and female groups at HA is not surprising since hyperuricemia is known to occur in association with secondary polycythemia of other etiologies. Similar findings were reported from Bolivia, using a colorimetric method (9).

The mechanism responsible for the elevated urate levels found in association with the polycythemia secondary to cyanotic congenital heart disease was studied by Yü *et al* (10) who found an increase in nucleic acid synthesis using glycine-$^{15}N$ as a precursor, and it would appear likely that the hyperuricemia secondary to HA hypoxia has the same pathogenesis. In our study, the elevated urate levels have a high positive correlation with hematocrit levels ($r = 0.65$, $p<0.001$, (Fig. 1), reflecting the influence of the increased hematopoietic activity of the bone marrow. Acheson and O'Brien also noted the correlation between hemoglobin and urate levels in their study of a New Haven community (11).

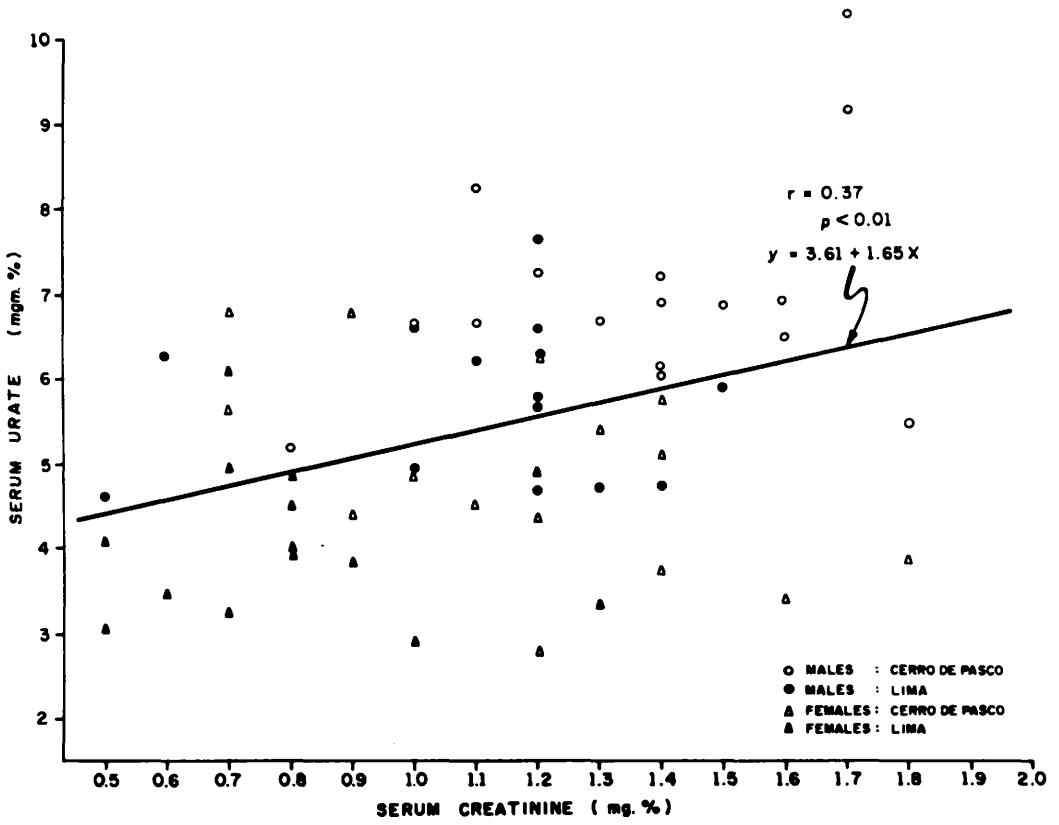


FIG. 2. Correlation of urate and creatinine levels in all subjects.

Severe renal functional impairment can cause hyperuricemia as a manifestation of failure of the kidney to excrete urate as well as other metabolic end products. The subjects we have studied were all healthy adults with levels of serum creatinine within the normal range and thus it is unlikely that the higher mean serum urate concentration could be due to retention because of renal insufficiency. Serum creatinine and hematocrit values are positively correlated in the series as a whole ($r = 0.48$ $p<0.001$, Fig. 3). The HA females having higher values than the SL males, indicating that the role of the rate of erythropoiesis reflected by the hematocrit is more important than that of sex. Urate and Creatinine are also correlated (Fig. 2).

The influence of sex on the urate levels of subjects in the reproductive age group has been known since the earliest observations and longitudinal studies demonstrate that up to puberty the serum urate levels remain similar in both sexes, when males show an increase that reaches its maximum values at 20–25 years of age, the levels in the female increasing only after the menopause (12). In our study, the influence of sex can also be clearly observed, since although the mean hematocrit levels for the HA females and the SL males are comparable, the urate level of the SL males is higher (Table V).

Uric acid is poorly soluble, does not bind to macromolecules for transport, and is found in body fluids as the monovalent urate ion in concentrations approaching the solubility product of sodium urate (13). Urate deposition in tissues could occur whenever this limit is passed, but clinical observation indicates that urate deposits occur only at the higher level of 8 mg/100 ml by factors as yet not completely understood (13). Table I shows that 3 of the 15 male subjects at HA (20%) have urate concentrations above this limit and thus it is likely that urate deposition

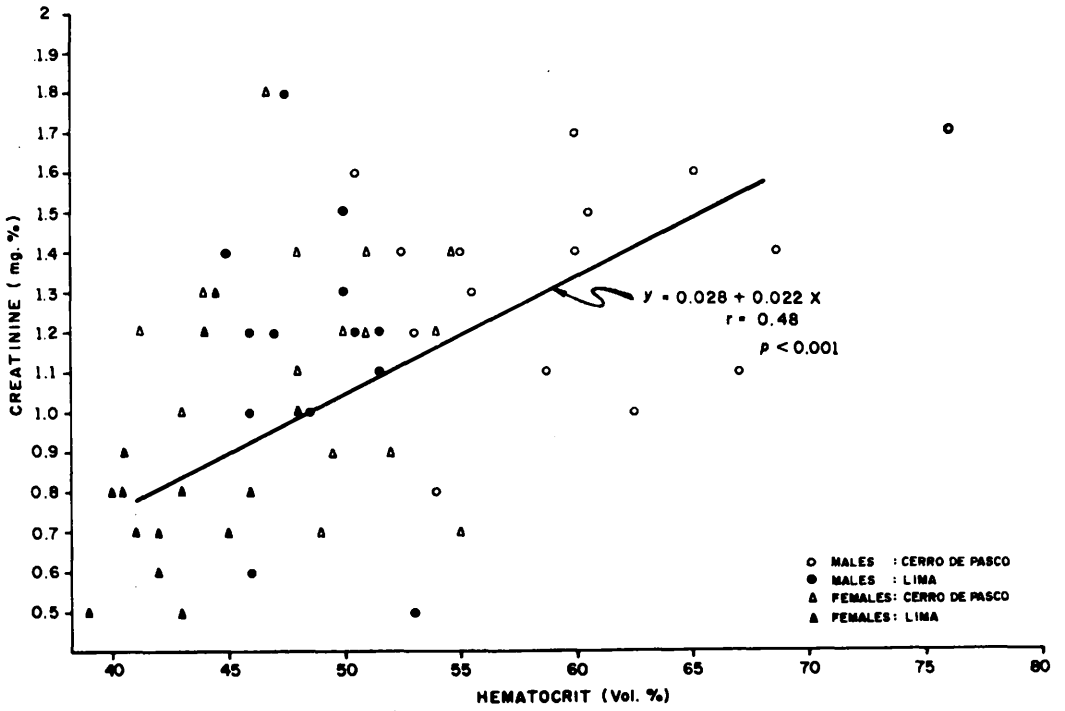


FIG. 3. Correlation of creatinine and hematocrit in all subjects.

might occur in their tissues. It has been postulated that hypoxia and an increase in glycolytic metabolism might enhance urate deposition. The role of these factors at HA remains to be elucidated.

*Summary.* Fifteen normal male and 15 normal female subjects living permanently at a mining town located at an altitude of 14,000 ft in the central Andean plateau demonstrated elevations of the values of serum urate, creatinine, and hematocrit when compared with equal numbers of normal subjects living at sea level. Of the HA male group, three subjects (20%) have urate values above 8 mg/100 ml, the level at which urate deposition in tissues might take place. There is a high degree of correlation between the serum urate levels and the hematocrit and between the serum creatinine and the hematocrit in the series as a whole. Although the mean hematocrit values of the HA females and the SL males are comparable, the latter have higher urate levels, reflecting the influence of sex on urate levels.

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