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The Role of Adrenal Cortex in the Process of Acclimatization to High Altitudes

FINAL REPORT

By: Federico Moncloa

October 1967

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U. S. Army Element

Defense Research Office, Latin America

Rio de Janeiro, Brazil

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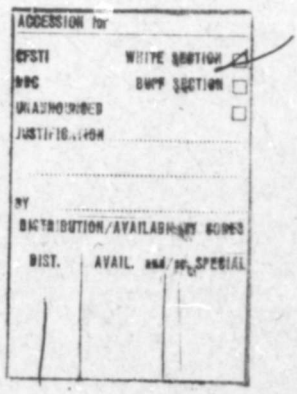

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REPORT NUMBER 3

THE ROLE OF ADRENAL CORTEX IN THE PROCESS OF ACCLIMATIZATION TO HIGH ALTITUDES

FINAL REPORT

BY

Federico Moncloa

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U. S. Army Element
Defense Research Office for Latin America
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ABSTRACT

The first part refers to some indexes of adrenal function and cortisol metabolism in acute exposure of sea level natives to 4,300 meters of altitude. The results show the following: a) Cortisol secretion rate is temporarily increased correlating with increases in its plasma concentration and in the urinary excretion of its metabolites; b) Hypoxia does not result in a maximal stimulus for the adrenal cortex since it can be further stimulated by exogenous corticotrophin; c) The adrenocortical response to high altitude can be blocked by the administration of dexamethasone; d) The second compartment in which cortisol is distributed is diminished. This may be related with the contraction of the radiosulfate space, observed under the same experimental conditions; and e) The metabolic clearance rate of cortisol is not significantly altered.

The second part refers to the study of corticotrophin half-life (t 1/2). Our results indicate that a 24 aminoacids ACTH has a t 1/2 slightly longer than a 39 aminoacids ACTH. Using the same type of experiments we have studied the t 1/2 of the 39 aminoacids ACTH in 11 high altitude natives; the results were similar to the ones obtained in the sea level controls.

ADRENAL FUNCTION AND CORTISOL METABOLISM

This part comprises four papers; two have been published and the other two have been accepted for publication. A summary of each one follows:

1.- Endocrine Studies at High Altitude. II Adrenal Cortical Function in Sea Level Natives Exposed to High Altitude (4300 meters) for Two Weeks

Moncloa, F., Donayre, J., Sobrevilla, L.A., & Guerra-García, R.
J. Clin. Endocrinol. 12:1640-1642, 1965.

Ten young men, sailors, sea level natives were exposed for two weeks to 4300 meters of altitude. The ascent to high altitude was associated with a transitory but definite increase in the cortisol secretion rate and in the urinary excretion of 17,21-dihydroxy-20-ketocorticosteroids and in 17 ketogenic steroids. The increase in cortisol secretion rate suggests that the greater urinary excretion of the urinary steroids was due to that increase. Fig. 1.

2.- ACTH Stimulation and Dexamethasone Inhibition in Newcomers to High Altitude

Moncloa, F., Beteta, L., Velasco, I., & Goñez, C.
Proc. Soc. Exp. Biol. & Med. 122:1029-1031, 1966.

We studied 3 groups of young adult males, natives and residents of sea level. The first group was formed by 12 subjects; this group was stimulated with ACTH twice, one at sea level and the other during a trip to high altitude. The increase in urinary steroids was of the same magnitude in both circumstances and significantly higher than the one obtained by simple exposure as reported above (i.e. in another group). The second and third group were formed by 7 subjects each. Both groups were taken to 4300 meters under dexamethasone administration; in the second group the dose was 0.5 mg/6 hours and in the third group it was 2.0 mg/6 hours. The results indicate that when dexamethasone is given the hypoxic stimuli are easily blocked. Fig. 2.

3.- Radiosulfate Space in Humans at High Altitude

Malpartida, M. & Moncloa, F.
Proc. Soc. Exp. Biol. & Med.

We studied 14 sea level natives, 9 of which were observed again after 36 hours of exposure to high altitude (4,300 m). Seven high altitude natives were also studied. The results indicated that extracellular space was significantly decreased (1.4 liters). Body weight was also decreased (1.2 kg.). However, there was no statistical cor-

relation between these variables. This was interpreted as meaning that the decrease in body weight is a result of several changes, the decrease in extracellular fluid being only one of them. Table 1.

4.- Plasma Cortisol Concentration and Plasma Dissappearance Rate of 4-^{14}C-cortisol in Newcomers to High Altitude

Moncloa, F., Velasco, I., & Beteta, L.
J. Clin. Endocrinol.

Plasma cortisol was measured in 10 sea level natives before and during the first day of their stay at 4,300 meters. There was a significant increase in the mean concentration and the normal circadian rythm was altered. In the control observations the lower value was obtained at 12 p.m. but under hypoxia at that time there was a 3.5 fold increase. The plasma dissappearance curve of 4-^{14}C-cortisol was studied in another group of nine sea level subjects. The experiment was done twice; a control observation at sea level and the second one after 36 hours of exposure to high altitude. The curves obtained were double exponentials; therefore, a two-compartment model describes the data. In brief, the results show that the second compartment was smaller in acute exposure to high altitude; this finding may be partially explained by the contraction in the extracellular space. The other indexes, namely the transfer constants and the metabolic clearance rate were not statistically different. Tables 2 and 3.

HALF-LIFE OF CORTICOTROPHIN (ACTH)

This part comprises one published paper and a summary of recent observations.

1.- Biological Half-Life of a Synthetic Corticotrophin in Men
Moncloa, F., Velasco, I., & Beteta, L.
Acta Endocrinologica (Kbh) 52:337-340, 1966.

We studied nine male students of our School of Medicine. Two experiments were performed in each subject. The first time they were intravenously injected with 0.05 IU of ACTH/kg of body weight and plasma samples were analyzed for cortisol after 60, 75, 90, 105, 180 and 240 minutes. The second time, at least three days later, the injection was of 0.25 IU of ACTH/kg; and the plasma samples obtained at 120, 135, 150, 165, 240 and 300 minutes afterwards. The t 1/2 was calculated using the following equation

$$t\ 1/2 = \frac{.693\ (h-h')}{\log a - \log a'}$$

where a and a' were the doses injected; h the time when cortisol starts to fall with dose a; and h' with dose a'. The t 1/2 ranged from 19.4 to 38.7 minutes, the mode being 38.7 minutes, the mode being 32.3 minutes.

2.- Comparison of t 1/2 of Two Synthetic ACTH Preparations and Further Observations in High Altitude Natives

The method used is described in the previous paper (vide supra). In 10 subjects we have studied the t 1/2 of two different ACTH preparations; the 24 aminoacids ACTH (Ciba 30920) and the 39 aminoacids ACTH (Ferring A B). The results show that the 39 a.a. preparation has the same t 1/2 in four subjects and shorter in the other six. With the 39 aminoacids ACTH we have compared the t 1/2 in 14 natives of sea level versus 11 high altitude natives. The results (Fig. 3) indicate that in high altitude natives the preparation tested has the same t 1/2.

Table 1.- Extracellular space measured with S^{35}

	Body weight kg	Radiosulfate space liters	% body weight
High Altitude Natives (7)	55.8 ± 1.5	9.2 ± 0.5	16.4 ± 0.6
Sea Level Natives Contents (14)	65.6 ± 1.2	9.8 ± 0.3	15.0 ± 0.4

Nine Sea Level Natives

	Body weight kg	Radiosulfate space liters
Before exposure to high altitude	66.3 ± 1.4	10.2 ± 0.4
2nd day of exposure to 4,300 meters	65.1 ± 1.4	8.8 ± 0.2
Decrease	1.2 ± 0.2 [a]	1.4 ± 0.2 [a]

[a] $P < 0.001$

Table 2.- Plasma cortisol concentration in acute exposure to high altitude ug/100 ml

	12 p.m.	8 a.m.	12 m.	4 p.m.	8 p.m.	Mean concentrations
Sea level controls	4.3 ± 0.9	17.7 ± 1.3	10.5 ± 1.5	8.4 ± 0.9	7.6 ± 1.3	9.9 ± 0.6
High altitude exposure	15.1 ± 4.0	20.0 ± 2.2	18.0 ± 4.6	12.5 ± 1.5	8.7 ± 2.1	15.5 ± 2.1
p Values	< 0.05	> 0.20	< 0.20 > 0.10	< 0.05	> 0.20	< 0.05

The figures are the means ± S.E.

Table 3.- Results obtained from the plasma disappearance curve of radio active cortisol using a two-compartment model in 9 sea level volunteers before and during exposure to 4,300 m. Figures are the means ± SE.

	Control at sea level	2nd day of exposure at high altitude
V_m (liters)	5.45 ± 0.59	6.55 ± 1.01
V_n (liters)	11.71 ± 1.47	7.08 ± 0.97 [a]
k_{13} (min^{-1})	0.1032 ± 0.0146	0.0749 ± 0.0163
k_{31} (min^{-1})	0.0476 ± 0.0063	0.0557 ± 0.0088
k_{12} (min^{-1})	0.0321 ± 0.0011	0.0349 ± 0.0062
α (min^{-1})	0.1742 ± 0.0194	0.1534 ± 0.0251
β (min^{-1})	0.00885 ± 0.00116	0.01220 ± 0.00131
MCR liters/24 h	239.5 ± 22.7	259.7 ± 15.7

[a] $p < 0.02$. In all the other instances the differences were not statistically different.

URINARY STEROIDS AND CORTISOL SECRETION RATE

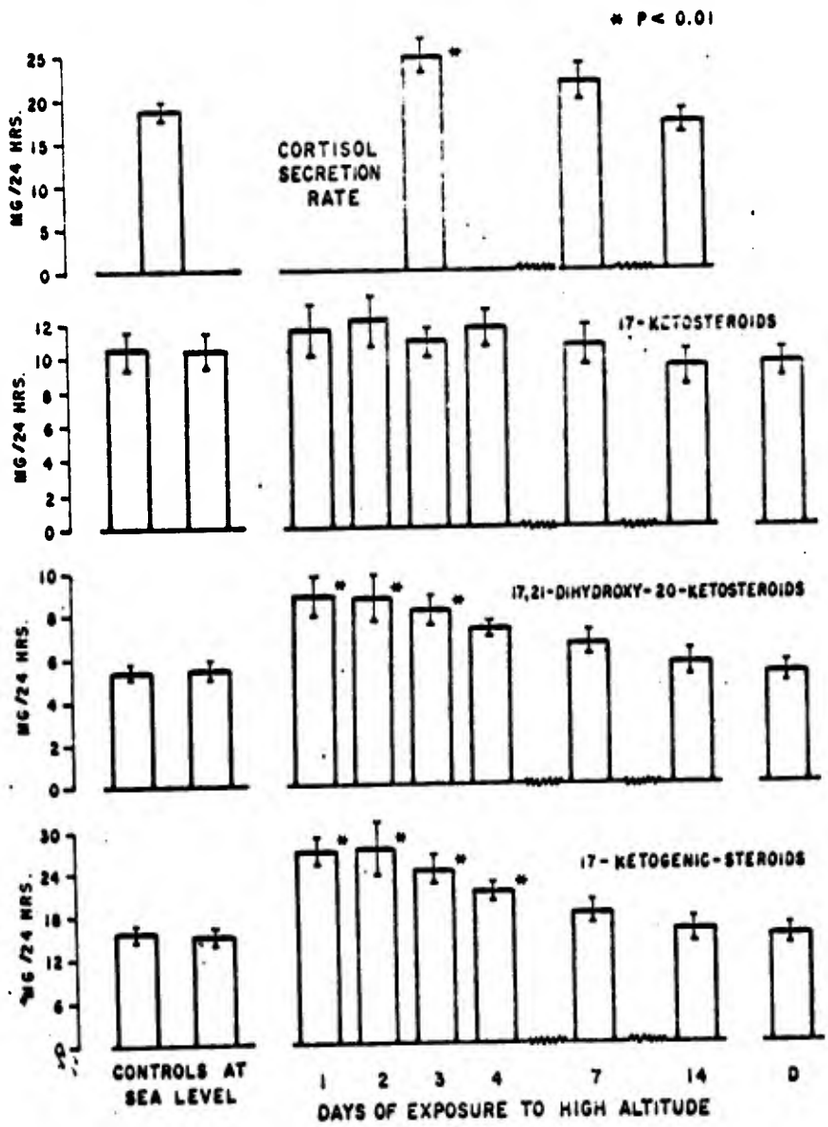


Fig. 1

URINARY STEROIDS IN SEA LEVEL NATIVES TAKEN TO AN ALTITUDE OF 4,300 m. UNDER ACTH & DEXAMETHASONE MEDICATION

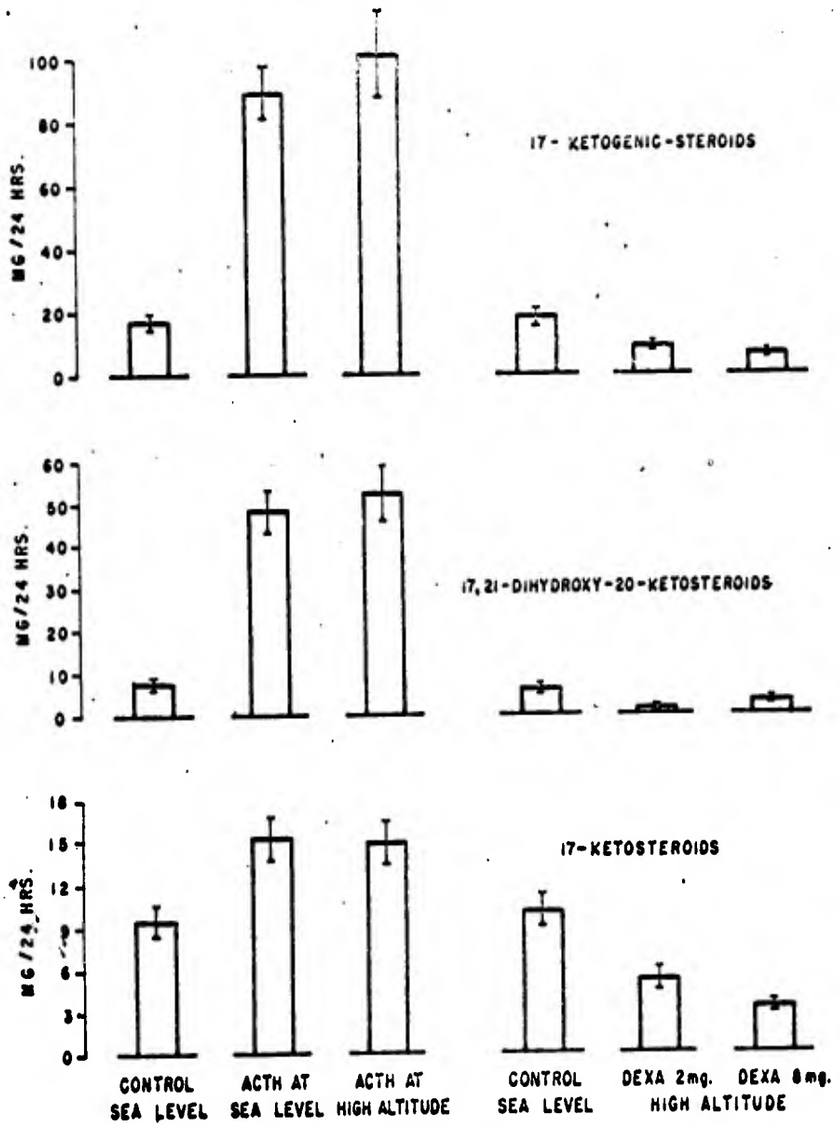
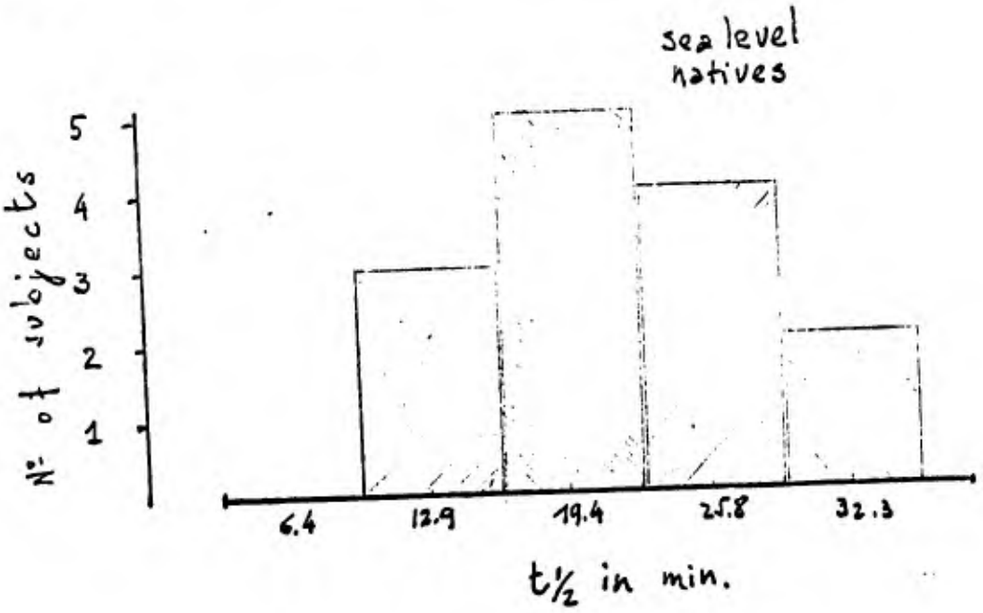
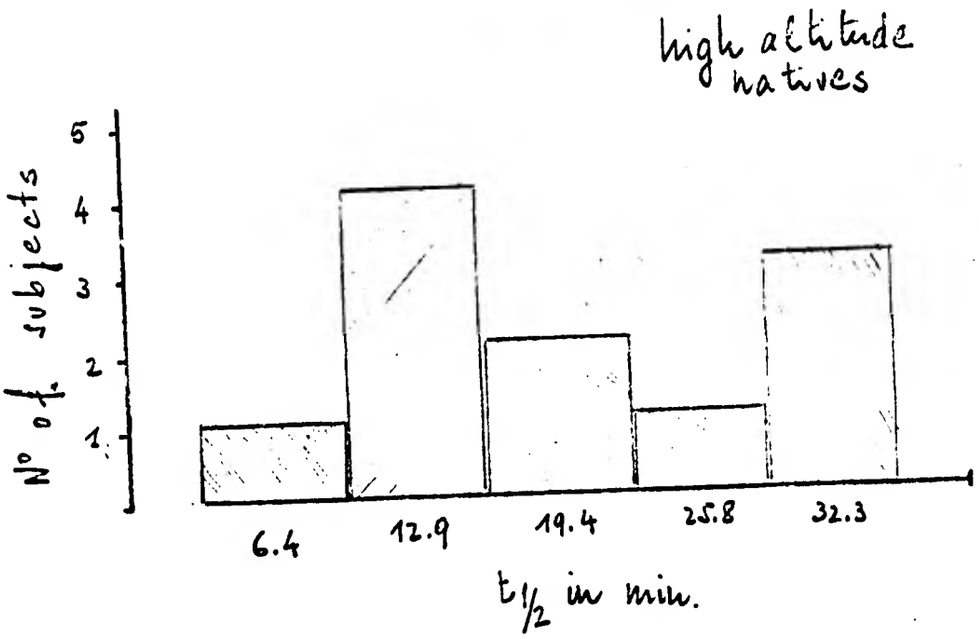


Fig. 2

Fig. 3 BIOLOGICAL HALF-LIFE OF ACTH





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13. ABSTRACT Indexes of adrenal function and cortisol metabolism in acute exposure of sea level natives to 4,300 meters of altitude prepared. a) Cortisone secretion rate is temporarily increased correlating with increases in its plasma concentration and in the urinary excretion of its metabolites; b) Hypoxia does not result in a maximal corticotrophin; c) The adrenocortical response to high altitude can be blocked by administration of dexamethasone; d) Second compartment in which cortisol is distributed is diminished. May be related with the contraction of radiosulfate space observed under same experimental conditions; e) Metabolic clearance rate of cortisol is not significantly altered.

Corticotrophin half-life (t 1/2). Synthetic 24 aminoacid ACTH has t 1/2 slightly longer than synthetic 39 aminoacids ACTH. Using same type of experiments we studied t 1/2 of the 39 aminoacids ACTH in 11 high altitude natives; results were similar to those obtained in sea level controls.

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