Slow-wave frequency before and after transection of the colon orad to the *fusus coli* (mean ± SD values for recordings taken during 3 periods of 24 h in 6 animals)

	Proximal colon			*f. coli*	Distal colon		
	3 taeniae		2 taeniae				
Percentage of total colon length	0–10	11–20	21–30	31–40	41–50	51–60	61–70
Slow-wave frequency	14.9	16.4	17.2	21.9	22.1	21.0	20.4
Control	1.3	1.6	0.9	2.1	2.4	2.3	4.6
Slow-wave frequency after section							
1st week	10.7[a]	11.7[a]	12.3[a]	19.6	20.4	18.7	20.4
	2.7	1.4	1.9	2.1	3.6	2.7	2.9
2nd week	12.1[a]	12.4[a]	13.2[a]	19.1	20.4	18.0	18.8
	0.9	0.9	1.1	1.4	1.4	3.2	2.4

[a] $p < 0.01$.

more or less unchanged in intensity. Contractions were propagated to the distal colon from the *fusus coli* either directly or from the proximal colon through the anastomosis.

Discussion. These results show clearly that the *fusus coli* acts as a pacemaker 'pulling up' the slow-wave frequencies of the proximal colon, those of the distal colon maintaining this high level. Thus, the gradient of the slow waves on the proximal colon is the reverse to that seen on the small intestine.

To date there is no valid explanation for the mode of production of the two kinds of faeces. Variable retention of water during the flux and reflux of digesta between caecum and the oral part of the proximal colon has been suggested, but no significant changes in the contractions of the latter region concomitant with production or expulsion of one or other kind of faeces has been detected[4,7].

The polarity of wall movement imparted by the slow waves on the proximal colon demonstrated here would tend to maintain the contents at this level for the optimal period of time. The passage of soft faeces aborad to the *fusus* would simply require a predominance of the spiking activity over the slow-wave counter-current. This work does not explain the dynamics of segregation of soft and hard faeces but suggests that the initial postprandial expulsion of hard faeces situated in the distal colon is the prerequisite for the transit of soft faeces through the *fusus coli*.

High Altitude Influence on the Level and Turn-Over Time of Cardiac Norepinephrine in Rats

M. PRIOUX-GUYONNEAU, J. DURAND, J. R. RAPIN and Y. COHEN

Laboratoire de Pharmacodynamie, Faculté de Pharmacie, Rue Jean-Baptiste Clément, F-92290 Chatenay-Malabry (France), 9 February 1976.

Summary. In rats exposed to an altitude of 2,900 meters the level of endogenous cardiac norepinephrine decreases after the 5th day of exposure. The turner-over time of the amine proceeds in 3 steps which are probably related to periods of stress and adaptation: initial increase, important decrease from the 5th day and return to a normal value from the 12th day.

An insufficient oxygen supply induces hypoxia in man and animals. This state can be provoked by any physiological alterations or by improverished oxygen environment. These conditions are specially realized at high altitude when a decrease of barometric pressure produces reduction of partial pressure of oxygen in the inhaled air (PI 0_2). Most of the studies about physiological consequences of hypobaric hypoxia deal with respiratory and cardiovascular modifications[1–3]. Recently, some authors pointed out that hypoxia, from varioux origins, can be considered as a stress which induces a stimulation of the sympathetic system in adrenals[4–6], heart[7] and brain[8]. Until now, few investigations were made about these effects in hypobaric hypoxia. However it is important to define physiological disturbances under these conditions, for they are likely to be different from those observed in hypoxic hypoxia[9].

To obtain physiological conditions of man living at high altitude, experiments reported in this study were performed at Pic du Midi de Bigorre, France (2,900 m). Influence of hypoxia on noradrenergic system was investigated in the rat by the determination of tissue level and turnover time of cardiac norepinephrine for periods ranging up to 12 days.

Material and method. Male Sprague-Dawley rats (average weight 250 g) were reared at sea level and transferred to an altitude of 2,900 m. During 12 days the animals

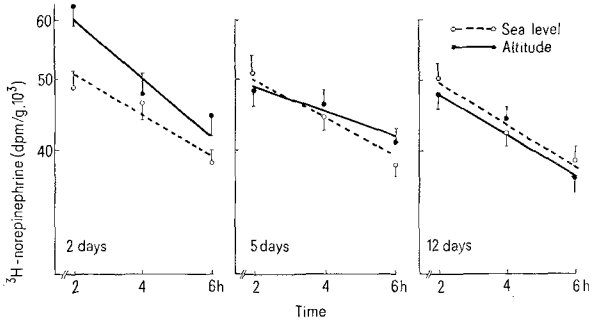
[1] A. HURTADO, Ann. intern. Med. *53*, 247 (1960).
[2] P. MORET, E. COVARRUBIAS, J. COUDERT and F. DUCHOSAL, Acta cardiol. Belg. *27*, 283 (1972).
[3] A. R. FRISANCHO, Science *187*, 313 (1975).
[4] O. S. STEINLAND, S. S. PASSO and G. G. NAHAS, Am. J. Physiol. *218*, 995 (1970).
[5] W. S. MYLES and A. J. DUCKER, Int. J. Biometeor *17*, 51 (1973).
[6] S. R. SNIDER, R. M. BROWN and A. CARLSSON, J. neural Transmission *35*, 283 (1974).
[7] R. H. GOLDMAN and D. C. HARRISSON, J. Pharmac. exp. Ther *174*, 307 (1970).
[8] D. A. HURWITZ, S. M. ROBINSON and I. BAROFSKY, Psychopharmacologia *19*, 26 (1971).
[9] P. D. ALTLAND, H. F. BRUBACH, M. G. PARKER and B. HIGHMAN, Am. J. Physiol. *212*, 142 (1967).

were housed as usual and received habitual food and drink. The temperature of the laboratory was 21 ± 1 °C and the barometric pressure was 720 ± 4 mb. The turn-over of cardiac norepinephrine is appreciated by using the isotopic method[10]. This method consists of surveying the disappearance of radioactivity of a tissue after administration of a tracer doser of labelled norepinephrine; it is assummed that the radioactive compound mixed homogenously with the endogenous amine and the level of the latter being stable, the decline of radioactivity is used to calculate the turnover of the transmitter.

Animals are given, i.v., at determinated periods, 5 μCi/kg of 1-[7-^{3}H] norepinephrine (^{3}H-NE) (specific activity 10,3 Ci/mmol, Radiochemical Center, Amersham). They are killed by decapitation 2, 4 and 6 h after administration of ^{3}H-NE, the hearts are rapidly excised and homogenized at 0 °C in 6 ml of ice-cold 0,5 *M* perchloric acid added with 0.5% sodium metabisulfite and 0.5% EDTA. After centrifugation, the supernatant is removed and frozen at -20 °C.

Norepinephrine contained in the supernatant is separated from *O*-methyl metabolites by adsorption on aluminium oxide[11]. After desorption by perchloric acid 0.05 *N*, the labelled catechol compounds including norepinephrine and its metabolites are measured by liquid scintillation counting (Packard 3380 spectrometer). Acid derivates of catecholamines are estimated by the technique of CROUT[12]; the quantity of these substances, inferior to 5% of total catechol compounds, was judged to be negligible and no correction was made for the expression of final results. The endogenous norepinephrine after extraction on aluminium oxyde, is measured by the fluorimetric method[13].

^{3}H NE is expressed as dpm/g and endogenous NE as ng/g of fresh tissue. Standard errors of the mean are calculated and results are compared by Student's *T*-test.



Influence of various times of exposure to altitude on kinetics of elimination of radioactivity in rat hearts after i.v. injection of 5 μCi/kg ^{3}H-norepinephrine. The regression lines on semi-logarithmic plot were calculated by the least squares method. Points represent mean values ± SEM of 5 to 7 animals.

Influence of altitude on turn-over time, rate of release and half-life of cardiac noreprinephrine

Time of exposure to altitude (days)	Turn-over time T_r (h)	Rate of release k h^{-1}	Half-life $T_{1/2}$ (h)
0	15.1 ± 1.4	0.066 ± 0.006	10.5 ± 0.9
2	11.3 ± 1.0	0.088 ± 0.007	7.9 ± 0.7
5	19.6 ± 1.7	0.050 ± 0.004	13.9 ± 1.2
12	14.9 ± 1.3	0.067 ± 0.006	10.4 ± 0.9

Values are the means of 15 to 18 determinations ± SEM.

The regression lines are calculated by the least squares method, linearity is verified and the standard error of the regression coefficient is calculated according to SNEDECOR[14]. The slope of regression lines is used to evaluate rate of release kh^{-1}) turnover time ($T_r = 1/k$) and biological half-life ($T_{1/2} = 0.693/k$) of the labelled amine.

Results. The observations made in groups of 15 to 18 rats after 2, 5 or 12 days exposure to altitude concern endogenous norepinephrine and kinetics of elimination of injected labelled amine.

The level of endogenous norepinephrine is significantly reduced (25%) in animals having stayed 5 to 12 days at altitude, when compared to the level of this transmitter in rats studied at sea level (700 ng/g). However, this level is constant inside each group of animals used for determination of the turn-over.

The results concerning kinetics of elimination of labelled norepinephrine is shown in the Figure. From these results it is possible to evaluate the turn-over time, the rate of release and the biological half-life of the amine (see Table). Turn-over time is accelerated in animals which have spent 2 days at altitude (11.3 h) compared to that in control rats of the same strain at sea level (15.1 h); the amine half-life is 7.9 h and the rate of release 0.088 h^{-1}, instead of 10.5 h and 0.066 h^{-1} at sea level. After 5 days exposure at 2,900 meters turn-over increase (19.6 h), which involves an augmentation in a similar way as the half-life (13.9 h) and a decrease of elimination (0.050 h^{-1}). However, after 12 days, the turn-over time, half life and rate of release return to nearly normal values.

Discussion. Exposure at altitude induces biochemical disturbances of the cardiac noradrenergic system in rats. During a 12-day study, 3 consecutive periods can be discerned. Firstly it seems that the variation of barometric pressure produces a stress which results in a decreased turnover time of the amine. The progressive depletion of norepinephrine observed afterwards could be considered as a direct consequence of the initial step, while the concomitant decrease of the turn-over time would be an adaptative reaction. The third step, after a 12-days exposure to altitude, corresponds probably to a period of more complete adaptation, since the half-life of the amine returns to the values observed at sea level; however, even after this time, the level of endogenous norepinephrine remains lower.

Previous work, performed in hypobaric chambers, at various simulated altitudes (5,500 to 8,000 m) showed comparable data: decreased cerebral level of norepinephrine[8,15] increased urinary elimination of the amine[5] and reduced half-life of the transmitter in the brain, during the first hours of exposure to hypoxia[15]. Consequently, it seems that, whatever the intensity of hypoxia and the nature of the organ studied, altitude is able to induce, by means of an initial stress, a relative depletion of the pool of reserve. The reduction of the turn-over time which occurs in a following step could be considered as a phenomenon of economy.

[10] F. BERTI and P. A. SHORE, Biochem. Pharmac. *16*, 2091 (1967).
[11] A. H. ANTON and D. F. SAYRE, J. Pharmac. exp. Ther. *138*, 36 (1962).
[12] J. R. CROUT, Arch. exp. Path. Pharmak. *248*, 85 (1964).
[13] U. S. VON EULER and F. LISHAJKO, Acta physiol. scand. *51*, 348 (1961).
[14] T. SNEDECOR and W. C. COCHRAN, *Statistical methods* (IOWA State University Press, Ames 1967).
[15] A. CYMERMAN, S. M. ROBINSON and D. MCCULLOUGH, Can. J. Physiol. Pharmac. *50*, 321 (1972).