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Metabolism of Human Serum Albumin in Man during Acute Exposure to High Altitude (14,100 Feet) *

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The effect of high altitude exposure on protein metabolism in man has not been fully investigated. In a recent study of eight sea level residents (1), the concentration of plasma total protein and of the specific proteins thyroxine-binding globulin and ceruloplasmin was noted to be increased during the first 2 weeks of exposure to high altitude. Since the electrophoretic distribution of the plasma proteins was unchanged, the observations were interpreted as resulting from marked water loss from the intravascular compartment. In contrast to these changes, the concentration of thyroxine-binding prealbumin (TBPA) was decreased during this period. Alterations in the metabolism of this plasma protein may be manifest rapidly by changes in its concentration due to its rapid rate of metabolism (2, 3). Thus, the reduced concentration of TBPA noted at high altitude was interpreted to reflect possible changes in plasma protein synthesis or degradation in this environment that had been masked by the dehydration of the intravascular compartment.

In the present investigation, the turnover of ¹³¹I-labeled albumin was studied in five subjects during a control period at 5,280 feet and for eight days at 14,100 feet. The method of data analysis allowed an independent estimate of the daily rate of albumin synthesis and degradation during the experimental period. These observations were correlated with simultaneous measurements of gross nitrogen balance, TBPA concentration, and various indexes of thyroid function.

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Methods

Human serum albumin-¹³¹I was obtained commercially¹ and initially contained less than 1 g-atom iodine per g-molecule albumin. It was shipped as a 1% solution (97.2 μc per ml) and was further diluted with 1% human serum albumin immediately after receipt in the laboratory. The preparation contained 4.2% inorganic iodide-¹³¹I as determined by rapid paper electrophoresis (4). After addition to human serum, 1 μc per ml, vertical starch gel electrophoresis was performed for 16 hours in a borate buffer at a potential difference of 125 v. More than 95% of the radioactivity in the starch gel migrated with the albumin band (Figure 1). Sterilization was achieved by two passages through a 0.22-μ Millipore filter. The sterilized material was stored at 3° C (72 hours) and had a concentration of 4.6 μc per ml on the day of injection.

Five soldiers, aged 19 to 23 years, were used as volunteer subjects. They were in good health and had been residents of Denver, Colorado, for at least 3 months before the onset of the study. During the control period, carried out at 5,280 feet altitude, they remained in a metabolic ward where they were offered a diet that supplied 3,000 kcal per day containing 1.1 to 1.5 g protein per kg body weight per day. Lugol's solution, 20 drops per day, was administered on the day preceding the injection of albumin-¹³¹I and daily throughout the study to limit thyroidal uptake of iodide-¹³¹I released from degraded protein. On the first experimental day, 16 to 18 μc albumin-¹³¹I (35 to 39 mg albumin) was injected from weighed syringes into the tubing of a running intravenous infusion of 5% dextrose in water. Subsequent counting demonstrated less than 0.005% of the injected dose remaining in the intravenous tubing. Fifteen ml heparinized blood was withdrawn without stasis 10 minutes after the injection of the albumin-¹³¹I and daily thereafter. All urine and stool was collected and kept at 5° C. Plasma and samples from 24-hour urine pools and from homogenates of 4-day stool collections (delimited by carmine markers) were stored frozen at -20° C until needed for radioactive or chemical assay.

After 10 days at 5,280 feet, the subjects were rapidly transported (2½ hours) to the summit of Pikes Peak, Colorado (14,100 feet altitude). There they were housed in a laboratory trailer in which the temperature was maintained at 18° to 21° C. The environmental tem-

¹ Abbott Laboratories, North Chicago, Ill.

perature varied between -10° and $+14^{\circ}$ C and the relative humidity between 15 and 25%. The diet and collections of blood, urine, and stool were continued unchanged. Efforts were made to maintain a degree of physical activity similar to that at the lower altitude. The subjects remained at high altitude for 8 days and then returned to 5,280 feet for a 4-day postaltitude period.

Samples of plasma, urine, and stool were counted with appropriate standards in a Packard Auto-gamma spectrometer, series 314E, with a counting error of less than 1%. Plasma volume was calculated on the basis of the concentration of radioactivity in the plasma obtained 10 minutes after injection of the albumin- 125 I. Three subsequent measurements of plasma volume were made photometrically with Evans blue dye (T-1824), one on the sixth day of the control period and one each on the fourth and eighth days of altitude exposure. The subjects were fasting and were required to remain supine for at least 1 hour before each of these determinations. Plasma albumin concentration was calculated as the product of the plasma total protein concentration (5) and the percentage of albumin on stained plasma electrophoretograms.² By this technique the mean \pm standard deviation of eight measurements of the same normal plasma performed on different days was 4.40 ± 0.15 g per 100 ml. Nitrogen was measured in urine, stool, and homogenates of 2-day diet composites by the Kjeldahl technique (6). The completeness of urine collections was checked by creatinine excretion. In some of the plasma samples, total thyroxine concentration (7),³ free thyroxine concentration (8), and the maximal binding capacity of thyroxine-binding prealbumin (8) were also determined.

Data analysis. The data were analyzed on the basis of an open two-compartment mamillary model by the graphic method of Pearson, Veall, and Vetter (9), which is based on the observations of Berson, Yalow, Schreiber, and Post (10) and Campbell, Cuthbertson, Matthews, and McFarlane (11). After radioactive assay the following functions were calculated daily and plotted on semilogarithmic paper: Q_P , the per cent of the injected dose in the plasma (per cent of dose per milliliter plasma multiplied by the plasma volume); Q_B , the per cent of the injected dose remaining in the body (injected dose minus the cumulative losses due to the excretion of urine and stool and withdrawal of blood); and Q_E , the per cent of the injected dose in the extravascular compartment (Q_B minus Q_P). The fractional rate of degradation of plasma albumin (k_d) was determined by dividing the per cent of the dose excreted in the urine by the average Q_P of the same day. The albumin degradation rate was obtained by the product of k_d and the plasma albumin pool. A line with a slope corresponding to k_d was then constructed tangent to the Q_P curve. The point of contact defined that point in time (T_B) when the spe-

² Beckman (South Pasadena, Calif.) electrophoresis membranes, no. 324330.

³ Bio-Science Laboratories, Los Angeles, Calif.

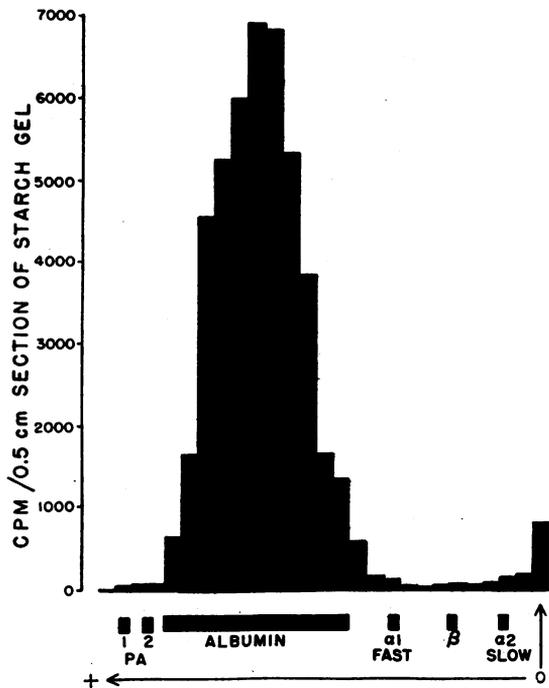


FIG. 1. DISTRIBUTION OF ALBUMIN- 125 I AMONG THE PLASMA PROTEINS SEPARATED BY STARCH GEL ELECTROPHORESIS. The stain of representative proteins is also shown. O = origin, + = anode, PA = prealbumin.

cific activity of albumin was presumed identical in the intravascular (IV) and extravascular (EV) compartments. The magnitude of the total exchangeable albumin pool could then be calculated on the basis of the plasma specific activity and Q_P and Q_B at T_B .

Albumin synthesis was equated to degradation only during the control period. However, analysis of the extravascular to intravascular distribution ratio (Q_B/Q_P) and the rates of change of the Q_B and plasma albumin specific activity curves by the method of Matthews (12) resulted in an estimate of albumin synthesis + net transfer from the EV to IV compartment (k_{12}) (per cent of the IV pool replaced per day) that was independent of changes in pool size and transfer rates. This method involves no assumptions other than those inherent in the method of data analysis described above (9). During the control period the rates of change of these curves were obtained by their slopes. At high altitude, however, the curves were often complex and it was necessary to derive polynomial exponential expressions to adequately describe them. This was accomplished by stepwise regression in an IBM 1044 digital computer (13). The first derivative of the derived polynomial gave the instantaneous rate of change at any point in time. Estimates based on the precision of the plasma albumin determinations and radioactive measurements indicate that the calculated k_{12} may vary by as much as 20 to 30%. Thus, only large changes in this function

TABLE I
Turnover of albumin-¹³¹I during the control period*

Subject	Height	Initial weight	IV albumin pool	Albumin degradation rate		EV/IV distribution	Total exchangeable albumin pool		Biological $t_{\frac{1}{2}}$	
				Fractional	Absolute		g	g/kg		
				day^{-1}	g/day		$g/kg/day$	g/kg		days
J.G.	173	61.28	124.3	0.1164	14.47	0.236	1.40	276.4	4.51	13.24
J.S.	186	75.60	171.3	0.1094	18.74	0.248	1.34	383.2	5.07	15.11
D.T.	173	65.19	133.3	0.1273	16.97	0.260	1.45	283.1	4.34	11.56
L.W.	162	67.73	119.7	0.1231	14.74	0.218	1.31	240.0	3.54	11.28
D.D.	185	83.16	134.2	0.1151	15.42	0.185	1.55	300.8	3.62	13.52
Mean	176	70.59	136.6	0.1183	16.07	0.229	1.41	296.7	4.22	12.94

* Abbreviations: IV = intravascular; EV = extravascular.

should be considered important. Data were expressed as the arithmetic mean \pm standard error, according to the methods of Johnson (14).

Results

General. The nature of the radioactivity in the plasma and urine was determined in each subject during the control period and at high altitude. Equal volumes of cold 15% trichloroacetic acid (TCA) were added to samples of urine, and

plasma and the precipitates formed were washed twice with cold 1% TCA. Radioactive assay of the precipitates and the supernatant solutions revealed that more than 99% of the radioactivity in the plasma and less than 1% of the radioactivity in the urine were protein bound. The effectiveness of thyroidal blockade by stable iodide administration was measured by counting over the thyroid gland preceding and succeeding altitude ex-

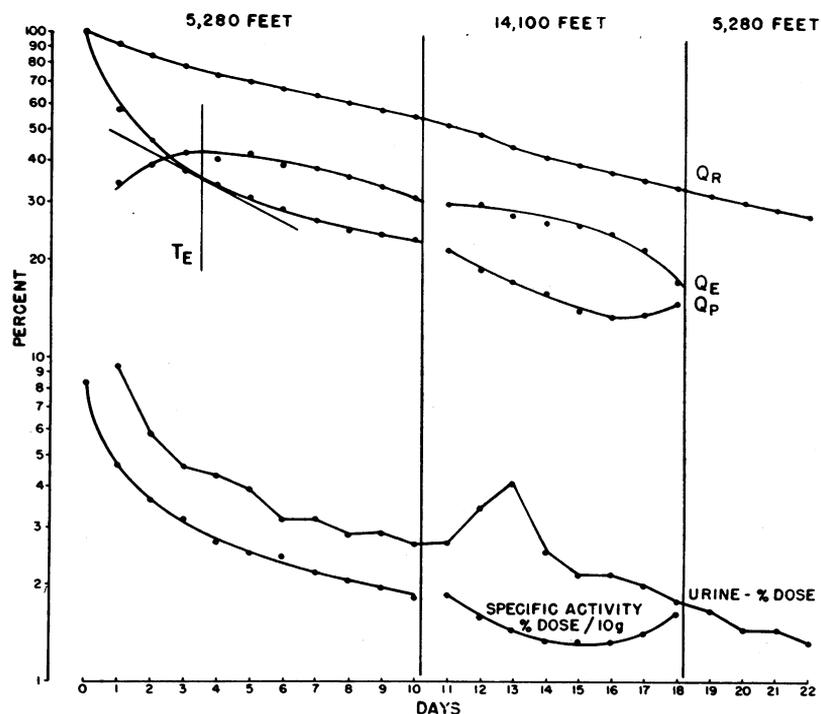


FIG. 2. ALBUMIN-¹³¹I TURNOVER DATA IN SUBJECT J.G. Q_R is the per cent of the injected dose remaining in the body; Q_E and Q_P are the per cent of the injected dose in the extravascular and intravascular compartments, respectively. T_E represents the equilibrium time, i.e., when the specific activity is equal in both compartments.

posure. All counts revealed less than 1.5% of the injected dose had been accumulated by the thyroid.

Albumin turnover. The size of the intravascular and total exchangeable albumin pools and the albumin degradation rates during the control period are presented in Table I. The data from a representative subject are plotted in Figure 2. The mean fractional rate of degradation in the control period was 0.1183 ± 0.0031 (SEM) per day, which resulted in the degradation of 16.07 ± 0.80 g albumin per day. Calculations based on the total albumin pool and the degradation rate showed that the biological half-time of the preparation of labeled albumin employed varied between 11.28 and 15.11 days.⁴

Plasma volume, the only pool directly measured, was constant in the control period but significantly

TABLE II

Plasma volume, albumin concentration, and total plasma albumin during the control period and at 14,100 feet altitude

Subjects	Control	Days at 14,100 feet	
		4	8
Plasma volume (L)			
J.G.	2.725*	2.140	2.027
J.S.	3.782	3.167	2.911
D.T.	3.065	2.766	2.499
L.W.	2.541	2.414	2.150
D.D.	3.117	2.842	2.591
Mean	3.046	2.666	2.436
Plasma albumin concentration (g/100 ml)			
J.G.	4.56†	4.76	4.57
J.S.	4.53	4.79	4.26
D.T.	4.35	4.37	3.95
L.W.	4.71	4.16	4.51
D.D.	4.31	4.57	4.63
Mean	4.49	4.53	4.38
Total plasma albumin (g)			
J.G.	124.3	101.8	92.6
J.S.	171.3	151.7	123.6
D.T.	133.3	120.9	98.7
L.W.	119.7	100.4	97.0
D.D.	134.2	130.0	120.0
Mean	136.6	121.0	106.4

* Average of two determinations.

† Average of eight determinations.

⁴ $t_{1/2} = [0.693 \text{ (total albumin pool)}] / \text{amount albumin degraded per day}$. This represents an artificial half-time, since its calculation assumes a one-compartment model. It is presented to facilitate comparisons with other studies.

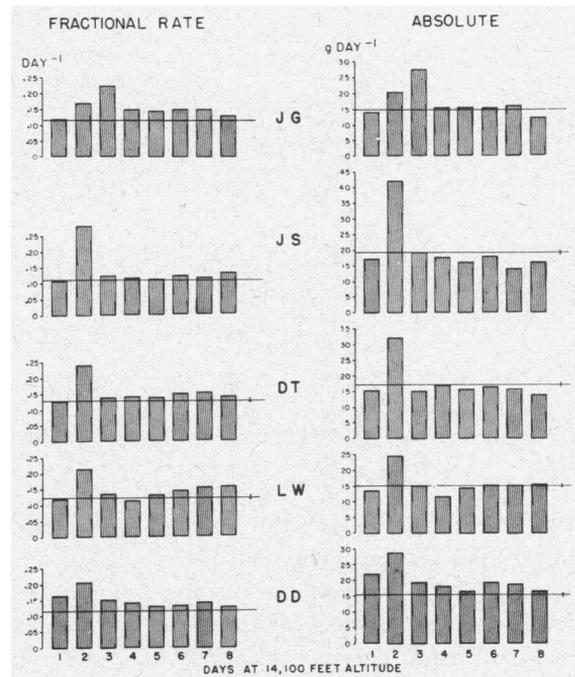


FIG. 3. ALBUMIN DEGRADATION IN MAN AT HIGH ALTITUDE. The horizontal lines show the mean control degradation rates with the standard error shown on the right. Calculations of mean \pm standard error were based on data from 10 days in the control period. When no standard error of the mean is shown, it falls within the thickness of the horizontal line.

decreased in every subject at altitude (Table II). The mean reduction from the control volumes was 12.5% at 4 days and 20.0% at 8 days at 14,100 feet. Plasma volumes on the days between these determinations were calculated by interpolation. Plasma albumin concentration was stable during the control period but increased transiently in three of the five subjects at altitude. The increased albumin concentration appeared to be due entirely to an increase in total protein concentration, since the electrophoretic distribution of the plasma proteins was unchanged throughout the study. In this study any elevation in plasma albumin concentration was less than the decrease in plasma volume resulting in a decreasing plasma albumin pool in all subjects at altitude (Table II).

The fractional rate of degradation (k_d) of albumin-¹²⁵I was increased in all subjects at 14,100 feet (Figure 3). The changes were most marked during the first 3 days, but the mean percentage increase in k_d remained 11 to 18% higher than the control even during the last 5 days at altitude.

TABLE III
The rate of albumin synthesis + net transfer from the extravascular to intravascular compartments during the control period and at high altitude*

Subject	k_d	Control period	k_{in}							
			Days at 14,100 feet altitude							
			1	2	3	4	5	6	7	8
J.G.	11.64	13.72	12.37	11.42	14.74	15.92	18.25	14.53	5.60	-5.17
J.S.	10.94	10.55	17.69	18.32	12.14	11.33	13.68	13.37	11.16	8.86
D.T.	12.73	15.12	20.24	24.29	12.73	11.54	10.81	10.79	5.97	4.72
L.W.	12.31	13.86	18.19	20.24	14.69	11.43	8.81	10.70	2.09	-5.52
D.D.	11.51	15.55	17.66	16.10	14.23	10.57	12.13	14.14	14.83	3.42
Mean	11.83	13.76	17.23	18.07	13.71	12.16	12.74	12.71	7.93	1.26

* Abbreviations: k_d = albumin- ^{125}I degradation rate during the control period; k_{in} = per cent of IV pool replaced per day.

The absolute degradation of albumin (grams per day) was also elevated early during altitude exposure. Here, however, the changes were smaller in magnitude than those of k_d due to the progressive diminution of the plasma albumin pool. In

the last days at altitude, albumin degradation was increased only in subject D.D.

If we assume that albumin synthesis was equal to degradation in the control period, the mean rate of synthesis was equivalent to k_d (11.83% intravascular albumin pool per day) (Table III). This assumption was not made at altitude because of the lack of knowledge regarding possible changes in the total exchangeable albumin pool. Mean k_{in} , calculated from the $Q_E:Q_F$ ratio and the rates of change of the Q_E and plasma albumin specific activity curves, was 13.76% per day in the control period and was increased to 17.23 and 18.07% per day on the first 2 days at altitude. From the third through the sixth days mean k_{in} was slightly lower than the control, and on days 7 and 8 it was reduced to 7.93 and 1.25% per day despite a marked shift of radioactivity from the EV to IV compartments (Figure 2). In J.G. and L.W. there was a calculated net loss of albumin from the plasma pool on the last altitude day.

Metabolic balance studies. The subjects accepted a diet that provided 3,000 kcal per day during the control period, but they ingested less at altitude. The mean minimal caloric intake was 2,100 kcal per day. The mean protein intake was 1.32 g per kg per day and fell progressively with the caloric intake to 0.90 g per kg per day during the last 2 days at altitude. Three of the five subjects were in nitrogen balance during the control period, L.W. being in slight positive balance (1.25 g per day) and J.S. in slight negative balance (-1.06 g per day) (Figure 4). Altitude exposure induced a mean negative nitrogen bal-

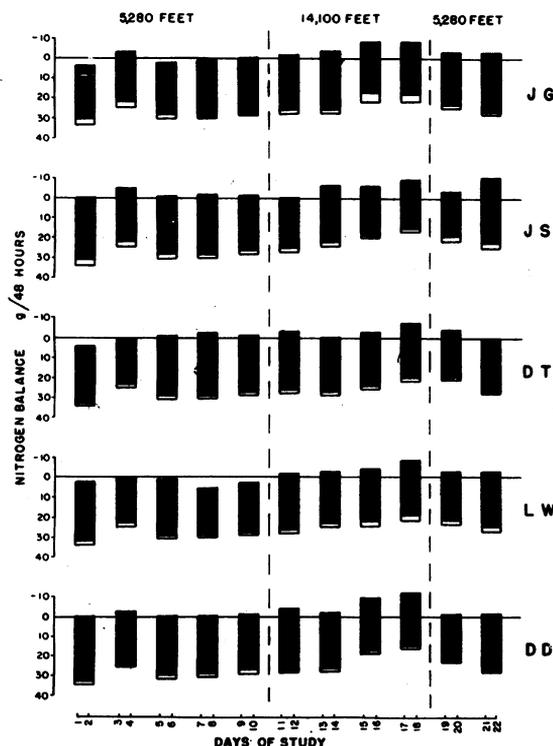


FIG. 4. NITROGEN BALANCE IN MAN AT HIGH ALTITUDE. Intake is plotted downward from the horizontal lines. The open areas represent stool nitrogen and the black areas nitrogen losses in the urine, sweat (estimated at 15 mg per hour), and blood.

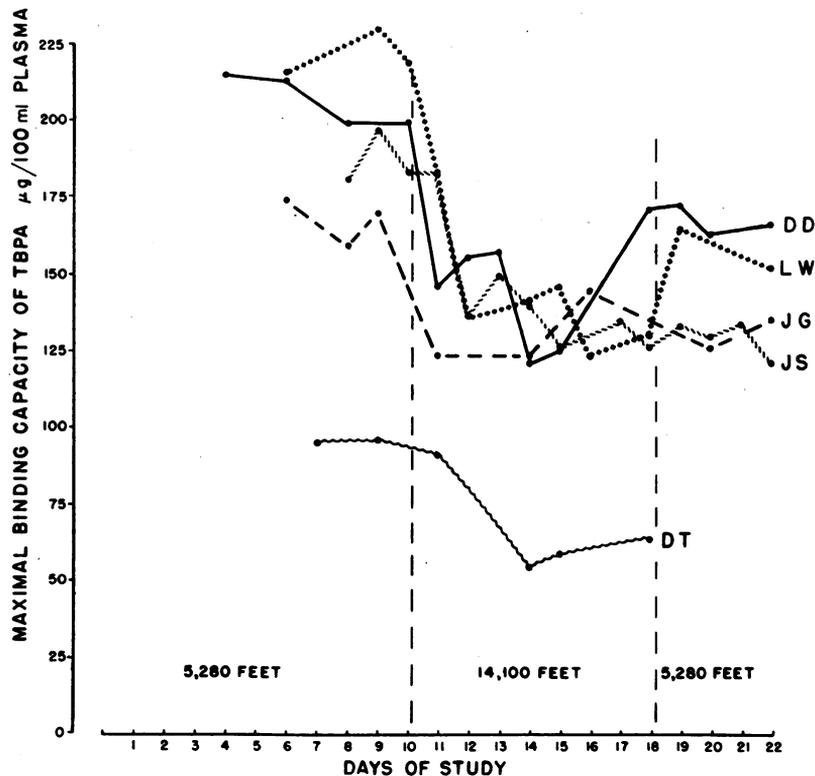


FIG. 5. MAXIMAL BINDING CAPACITY OF THYROXINE-BINDING PREALBUMIN (TBPA) IN MAN AT HIGH ALTITUDE.

ance of 2.33 g per day (range 1.28 to 3.18 g per day). Nitrogen balance remained negative in the recovery period. Body weight, measured daily, was stable initially, but a progressive decrease was observed in all subjects at high altitude. The mean maximal weight loss was 2.14 kg (range 1.37 to 3.75 kg) representing 3.01% of initial body weight. Weight lost at altitude was not regained during the 4-day postaltitude period.

Alterations in thyroxine-binding prealbumin concentration and various indexes of thyroid function. A marked decrease in the concentration of TBPA was observed in all subjects at 14,100 feet (Figure 5). Significant changes were noted on the first altitude day, but the maximal decrease (mean 62% of the control) did not occur until the fourth to sixth altitude days. D.D. and L.W. showed some return toward control values during the postaltitude period, but TBPA concentration remained significantly depressed in all subjects at the conclusion of the study. Although the control TBPA concentration was be-

low the normal range in D.T., the changes due to altitude were similar to those in the other subjects. Plasma free thyroxine concentration was elevated in four of the subjects due to an increase in the plasma total thyroxine concentration as well as diminished thyroxine binding by plasma proteins. The changes were maximal during the last 2 days at altitude. Thyroxine degradation, measured by the turnover of ^{125}I -labeled thyroxine, appeared to be increased during the first 3 days of altitude exposure.

Discussion

A moderate increase in albumin degradation, lasting 24 to 48 hours, occurred in all subjects during the first 3 days after acute exposure to high altitude. This change was accompanied by an increased plasma albumin concentration in all subjects except D.T. Since the electrophoretic distribution of the plasma proteins was unaltered, the data suggest that, like the previous study (1), the plasma proteins were concentrated as a re-

sult of water loss from the IV compartment. The progressive decrease in plasma volume observed at high altitude here and by others (15–17) supports this interpretation. The small increases in plasma hemoglobin concentration and hematocrit (1 to 3%) observed during the altitude period make it unlikely that increased red blood cell formation in this environment was primarily responsible for this change. The fact that plasma protein concentration is initially elevated infers that the rate of IV water loss must temporarily exceed the ability of the proteins to re-equilibrate with the EV compartment. Although this imbalance persisted for only several days in this study, elevated plasma protein concentrations were still noted 2 weeks after 8 subjects were taken to the same altitude from sea level (1). The degree of altitude "stress," therefore, appears to play some as yet undefined role in the magnitude of these changes.

Increased adrenocortical activity during the early phase of high altitude exposure has been reported (18–20) and might influence these data indirectly by increasing the renal clearance of non-protein ^{131}I released from degraded protein (21), or directly by affecting protein synthesis or catabolism. Although it is frequently assumed that labeled iodide, monoiodotyrosine, and diiodotyrosine, which are the principal breakdown products of iodinated proteins, are excreted instantaneously, they are, in fact, distributed throughout the body in low concentration according to the rate of protein catabolism and the size of their individual pools (10). The lag in renal excretion of these degradation products after their release from the protein molecule has been estimated not to significantly affect urinary excretion data in the normal subject (22). The direct effects of excessive concentrations of the glucocorticoids on albumin metabolism have also been studied, either when these compounds were administered to man or animals (23, 24) or in Cushing's syndrome (25). There is general agreement among these studies that cortisol effects an increase in albumin degradation as well as an increase in synthesis, although the latter effect is smaller. The subjects' previous acclimatization to 5,280 feet altitude and almost complete lack of mountain sickness during acute high altitude exposure, however, make it extremely unlikely that increases in cor-

tisol secretion sufficient to alter albumin metabolism directly or indirectly were present in this investigation.

Initially after altitude exposure, a decreased rate of fall of the EV activity curve (Q_E) was accompanied by an increased rate of fall of the IV activity curve (Q_P). Towards the end of the altitude period more marked changes in the opposite direction were observed. The concomitant rise in plasma albumin specific activity indicates that large amounts of high specific activity albumin entered the IV compartment from the EV albumin pool at that time. From this observation and the alterations in plasma volume noted above, it is concluded that marked intercompartmental shifts of fluid and metabolites occur during acute exposure to this environment. The function k_{in} calculated from these curves was increased during the first 3 days at altitude but decreased markedly just before descent to the Denver laboratory. These data must be interpreted with caution because of the small group of subjects employed and the large intercompartmental shifts that were observed. Although the precise relative contributions of albumin synthesis and intercompartmental transfer to k_{in} cannot be ascertained, it appears possible that albumin synthesis may be reduced towards the end of altitude exposure. Since the liver is the site of albumin synthesis (26), alterations in some hepatocellular functions involved in protein synthesis might occur in this environment. The studies of Klain (27), who recently observed decreased incorporation of injected ^{14}C -labeled glutamic acid and alanine into liver protein of rats at 14,100 feet, would be in accord with this hypothesis. The metabolism of immunoglobulins that are not synthesized primarily by the liver is not affected by high altitude. Trapani has reported (28) that rabbits at high altitude (12,000 feet) demonstrate normal or increased antibody production when challenged with antigen. The rate of removal of immunoglobulins determined after passive transfer of antibodies to these animals was unchanged.

A negative nitrogen balance has previously been reported in animals (29, 30) and man (31) at high altitude. In the present study, nitrogen balance was most negative during the latter period of exposure. At that time the intake of calories and protein was reduced due to appetite impairment.

The mean minimal protein intake, 0.90 g per kg per day, was not, however, sufficiently low to alter protein metabolism itself. Alterations in nitrogen balance were minimal during the first 2 days at altitude when albumin catabolism was greatly increased. The probability exists that amino acids released from degraded albumin at that time were reutilized for the synthesis of other plasma or tissue proteins required to meet the new metabolic demands of this hypoxic environment. Thus, conclusions based on the turnover of albumin may not be readily extrapolated to the state of protein metabolism in the entire organism.

The effects of thyroid hormone on albumin metabolism have been investigated in hypothyroid (32, 33) and euthyroid (34, 35) subjects. The results of these studies indicate that thyroid hormone produces an increase in albumin degradation together with an increase in synthesis. No reports are available concerning the relationship of thyroxine utilization and plasma free thyroxine concentration to the parameters of protein metabolism measured in this study. Early during altitude exposure increased degradation of thyroxine paralleled the increased rate of albumin synthesis and degradation. Plasma thyroxine concentrations were unchanged. During the last 5 days at 14,100 feet, however, plasma total and free thyroxine concentrations were elevated. Since free thyroxine presumably represents the hormone available to the tissues (36), and since thyroxine stimulates the incorporation of amino acids into rat liver protein (37), an increased rate of albumin synthesis was anticipated at this time. The opposite may have occurred. Although the fractional rate of albumin degradation remained moderately elevated, the rate of synthesis may have been decreased. The data would appear to show, therefore, possible interference with the stimulation of protein synthesis by thyroxine during acute exposure to this environment. Whether the interference is at the cellular level or related to changes in tissue blood flow or to other factors remains to be elucidated.

As in all studies of this nature, the quality of the tracer employed is of great importance in data interpretation. In the present investigation, the initial degradation rate was more than 4 to 5% of the retained activity per day during the first few days after injection and, in two subjects, the

plasma curve, Q_p , did not decline at a constant rate. According to the criteria of Berson and associates (10), these observations suggest that the preparation of albumin-¹³¹I employed was not entirely satisfactory. If this interpretation is correct, the values presented for the albumin degradation rate during the control period might be falsely elevated. Since the more rapidly degraded components in this preparation would be metabolized before the experimental period, the observations made at that time would still be valid.

The present study emphasizes the difficulties that arise in the analysis of turnover data in the nonsteady state. Other investigators have approached this problem by assuming the constancy of pool sizes (23) or the uniformity of specific activity throughout the body (34), or by using a second injection of labeled albumin to redetermine the size of the total body albumin pool (24). The assumptions implicit in these methods, justified in experimental situations where metabolic events change relatively slowly, would lead possibly to erroneous conclusions in the present study where pool size and plasma albumin specific activity change rapidly from day to day. The frequent measurement of the size of the IV pool as well as the use of the digital computer for the derivation of expressions to adequately describe complex data curves obviates these problems to some degree. However, it should be emphasized that accurate assessment of small transient changes in albumin metabolism in the nonsteady state cannot be achieved by any method currently available.

Summary

The metabolism of human serum albumin was studied by means of albumin-¹³¹I in five young males at 5,280 feet and for 8 days at 14,100 feet altitude. The data were analyzed in a manner that made possible the daily estimation of the rate of albumin degradation and synthesis + net transfer from the extravascular to intravascular compartments.

Albumin degradation was increased markedly for 24 to 48 hours within the first 3 days at high altitude. A large shift of high specific activity albumin from the extravascular to intravascular compartments occurred towards the end of altitude exposure and was accompanied by a decrease in the rate of albumin synthesis + net transfer.

A decrease in the intake of calories and protein (minimum - 0.90 g per kg per day) as well as a negative nitrogen balance was observed during the high altitude period.

The data are discussed in relation to changes in thyroid and adrenocortical function that have been observed in this environment.

Acknowledgments

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