mouse renal function was studied. The following dose-related changes were noted 18 hr after the intraperitoneal injection of endotoxin to mice: (i) Elevation of the blood, brain, and liver levels of urea nitrogen; (ii) decreased excretion of urinary urea nitrogen; (iii) diminished output of urine; and (iv) inhibition of the renal clearances of inulin and PAH. These findings clearly indicate that renal function is impaired in mice treated with relatively large doses of endotoxin. It is noteworthy that these doses exceed those usually required to demonstrate nonspecific resistance to experimental microbial infections in mice. Mice were rendered tolerant to the renal inhibitory effects and to the lethal effects of endotoxin by injecting them with a relatively low dose of endotoxin for 8 consecutive days prior to the administration of a high dose of endotoxin, which would ordinarily reduce renal function and produce 85% mortality in 72 hr.

The capable technical assistance of Miss Joan T. Napoli is gratefully acknowledged.

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Received June 25, 1968. P.S.E.B.M., 1968, Vol. 129.

Effects of High Altitude on Lipid Components of Human Serum (33388)

GEORGE J. KLAIN AND JOHN P. HANNON

Physiology Division, U. S. Army Medical Research and Nutrition Laboratory, Fitzsimons General Hospital, Denver, Colorado 80240

A significant decrease in body weight has been repeatedly observed in man during acute high-altitude exposure (1–4), and available evidence seems to indicate this decrease results primarily from a loss of body fat. Thus, Hannon *et al.* (5), on the basis of skinfold and body-weight measurements found an appreciable loss of subcutaneous fat in women exposed to high altitude for a period of 2.5 months. In subsequent studies, Hannon and Chinn (6) employing body-density measurements observed a similar fat loss in men exposed to 14,000 feet for 15 days. Further data on the fat reduction at high altitude are found in the report of Surks *et al.* (7) who estimated body fat content by measurements of body density, creatine excretion, and total body K^{40}. Long-term residents of high terrestrial altitudes exhibit only a slightly reduced body fat content (8, 9); hence, it would appear that the loss of fat at altitude is characteristic of acute rather than chronic exposure. In laboratory animals, Chinn (10) found a decrease in the body fat content of rats exposed to high altitude for several weeks and fed diets containing a high proportion of either carbohydrate, fat, or protein. Somewhat earlier, Cullumbine (11) found a transient decrease in the body fat content of mice very briefly exposed to low oxygen gas mixtures. Since the foregoing reports imply an altitude-induced increase in lipid catabolism, one might expect concomitant alterations in the various lipid components of the serum. In this respect, however, perusal of the literature reveals only a few reports of rather limited scope. Muller and Talbott (12), for example, did not find any changes in concentrations of plasma cholesterol, lecithin, or fatty acids in men after several days' exposure to 10,000 or 14,000 feet. Schmensky (13) reported elevated blood cholesterol levels in some natives of high-altitude regions in Switzerland, but his observation was contested by Guzmann-Barron (14) and Hurtado (15) who claimed that hypercholesterolemia does not occur in acclimated inhabitants of the Andes. In lower animals MacLachlan (16) observed a decrease in the plasma lipid content of rabbits subjected to short periods of reduced atmospheric pressure, but he did not observe this response in dogs or cats. In the study reported here, serum samples were obtained from eight soldiers over a two-week period of exposure to 14,000 feet and were analyzed for several key lipid components as well as glucose and water.

Methods. The subjects employed in this study were eight soldier volunteers (ages 20–24 years) who were in good health and who had resided at sea level for at least one year prior to the start of the study. Initial low-altitude measurements were made over a seven-day period at San Antonio, Texas. The subjects were then rapidly transported by air to Denver and by automobile to Pikes Peak, Colorado (14,100 ft.) where they remained for 14 days. At low altitude army barracks were used for housing while on Pikes Peak, the subjects were housed in a laboratory trailer. Temperature was maintained at approximately 25° in both the barracks and trailer. Each subject was given a standard diet containing approximately 3000 calories per day consisting of Army improved C rations (meal type) supplemented with fruit, milk, cereal, and soup. Daily caloric intakes were recorded.

After an overnight fast, 50 ml of venous blood was drawn from the subjects on day five of the control period at sea level, and on days 1, 3, 7, and 14 at Pikes Peak. After clotting at room temperature for one-half hr the blood was centrifuged at 2500 rpm to obtain serum samples. These samples were immediately frozen and kept at —20° until analyzed.

Serum total lipids were determined gravimetrically after extraction of an aliquot of the serum with choloroform-methanol (2:1 v/v) at 50° as described by Folch (17). Aliquots of the chloroform-methanol extracts were used to determine total cholesterol according to Searcy and Berquist (18), free fatty acids (FFA) according to Dole (19), and lipid phosphorus according to Chen *et al.* (20). The phospholipid concentration was estimated by multiplying total phosphorus by 25. Serum water was determined gravimetrically by drying in vacuo at 55° for 24 hr. Serum glucose was determined enzymatically according to Wasko and Rice (21). Statistical analyses were accomplished on the balanced repeated-measures design by analysis of variance and a critical difference at $p \leq 0.05$ was reported for each of the metabolites analyzed (22, 23).

Results. As previously reported (24), high-altitude exposure was associated with a voluntary reduction of the caloric intake. Thus, during the control period, the subjects consumed about 2900 cal per day but by the fourth day at altitude their average daily intakes had decreased to about 1800 cal. Thereafter, caloric intakes improved somewhat, ranging from 2000 to 2300 cal for the remainder of the study. The caloric deficit at altitude was associated with a concomitant loss of body weight that averaged 2.7 kg

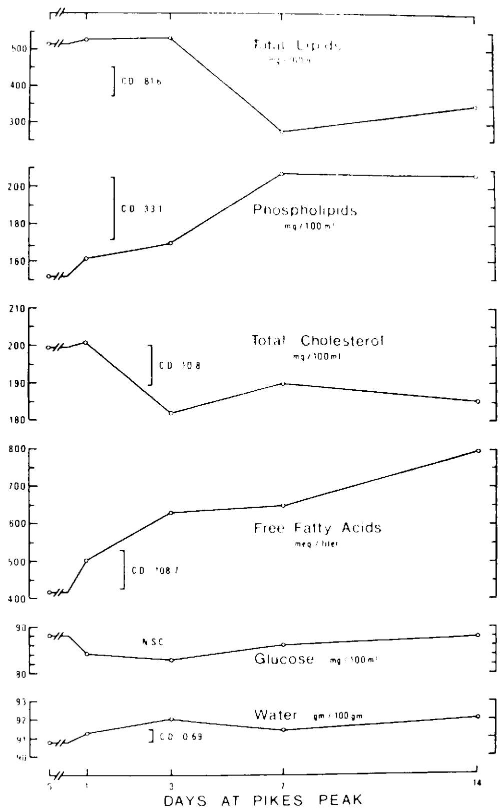

FIG. 1. Effect of high altitude on serum lipid components, plus serum glucose and serum water. Abbreviation C.D. refers to critical difference, $p<0.05$; NSC refers to no significant change.

during the first week and 0.51 kg during the second week of exposure.

As indicated in Fig. 1, exposure to high altitude produced significant changes in the concentrations of all serum lipid components. In the case of total lipids, a rapid decrease was observed between the third and seventh day on the Peak and at the end of the second week at altitude, the values averaged about one-third lower than those seen earlier in San Antonio. A similar, although less pronounced, decrease of total cholesterol was also observed. In this instance, however, the altitude effect was apparent on the third day of exposure. By way of contrast, phospholipid and free fatty acid levels were increased rather than decreased during the period of altitude exposure. The effect on phospholipids achieved significance by the seventh day of exposure at which time the level had risen from 153 mg to 207 mg/100 ml. Of all the components measured in the present study, free fatty acids showed the greatest altitude effect, increasing from a low altitude value of 415 meq/liter to a maximum high altitude value of 795 meq/liter after 14 days on the Peak. Altitude had no effect on serum glucose concentration but caused a slight, about 1%, increase in serum water content ($p\leq0.05$).

Discussion. Impairment of appetite resulting in a decreased intake of calories and protein has been previously reported in both humans and animals exposed to high altitude (7, 24, 25). And since severe caloric restriction is associated with a decrease in serum triglycerides in cholesterol (26) some of the changes in concentration of serum lipid components found in the present study could be attributed to dietary causes. However, it would seem unlikely that the alterations in total lipids and cholesterol are entirely due to this cause. Thus, the daily caloric intake averaged about 2000 cal over a 14-day period of exposure, and in relatively inactive individuals this would not be a severe restriction. Another possibility is an altitude-induced reduction in intestinal absorption. In this respect, Pittman and Cohen (27) suggested that hypoxia of the intestine produced by exposure to 19,000 feet will result in intestinal malabsorption while Van Liere *et al.* (28) claimed that anoxia inhibits propulsive motility of the small intestines. More directly, Van Liere and Sleeth (29) and Van Liere and Vaughan (30) reported a decrease in the intestinal absorption of sodium chloride and water under conditions of mild anoxemia. Finally, a suggestion of fat malabsorption is found in Pugh's report (31) that increased fat intake by Himalayan climbers gave rise to greasy stools.

A marked rise in serum FFA seen in the subjects of this study is probably due to an increased mobilization of FFA from depot fat. Recently, Usjenskii and Chou-Su (32) reported elevated serum fatty acid levels and an increase in the lipolysis of triglycerides in adipose liver and lung tissue of rats acutely exposed to hypoxia. In dogs McElroy and Spitzer (33) reported a hypoxia-induced mobilization of FFA; however, Oro (34) failed to confirm this observation.

It seems likely that an enhancement of adipose tissue lipase activity is responsible for the increase in serum FFA level observed during altitude exposure. Furthermore, it would appear likely that this enchancement of lipase activity is attributable to a concomitant increase in sympathetic nervous system activity. Indeed, several recent reports (35, 36) show that altitude exposure is associated with a progressive increase in urinary catecholamine excretion, particularly, norepinephrine. It is noteworthy that the changes in norepinephrine excretion closely parallels the serum FFA changes seen here.

Summary. Serum lipid components were measured in eight male subjects exposed to an altitude of 14,000 feet for 14 days. Concentrations of total lipids rapidly decreased after the third day of exposure and a similar, although less pronounced decrease was observed in cholesterol levels. By way of contrast, phospholipid and FFA levels progressively increased during the period of altitude exposure. High altitude had no effect on serum glucose concentration but caused a slight increase in serum water content. The data indicate that high altitude has a marked effect on lipid metabolism.

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Received June 25, 1968. P.S.E.B.M., 1968, Vol. 129.