Short Term Studies of Effect of Heparin upon Cholesterol Excretion in Man.* (25250)

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Ample evidence exists that plasma cholesterol is influenced by the amount of circulating triglyceride, and that cholesterol functions as a component of lipoproteins involved in transport of neutral fat(1,2). Chylomicra and lipoproteins bind cholesterol(3-6). It therefore was interesting to investigate the effect of a marked reduction in serum triglycerides upon serum cholesterol, and upon excretion of cholesterol end-products. This could be accomplished by injection of adequate doses of heparin resulting in production of a lipolytic enzyme, lipoprotein lipase, which markedly enhances removal of neutral fat from the blood but has no known direct effect upon cholesterol *per se*. Fecal bile acids and digitonin-precipitable sterols were determined as both pathways apparently function in elimination of cholesterol in man(1,2,7-10).

Methods. Four males were used in this study. Three were normal individuals and one (Z.T.) was a patient with hypercholesterolemia who had sustained a myocardial infarction several years before. The subjects remained on their normal diets during the experiment. All stools were collected over a 4-day period and for 4-6 days during administration of heparin. The latter was injected subcutaneously as a concentrated aqueous solution† in doses of 150-200 mg every 12 hours depending upon the patient's weight. This amount of heparin is the usual anticoagulant dose and affords substantial triglyceride removal from the bloodstream(11). Postabsorptive blood samples were drawn prior to and at the end of the heparin period, and serum cholesterol(12) and triglycerides(13) determined. Feces were analyzed in duplicate for bile acids(14) and digitonin-precipitable sterols(15). The 4-day control sample was pooled, whereas the stools collected while on heparin were grouped as 2 or 4 day pools.

Results. Average values obtained from the duplicate fecal analyses are shown in Table I. An increase in bile acid and digitonin-precipitable sterol excretion occurred during the period of heparin administration in all 4 individuals. Increase in bile acids varied from 25-96%, in sterols from 19-174%. The decrease in cholesterol end-product excretion found in the last 2 days in subject M.S. is probably misleading. It can be seen from the marked reduction in the stool dry weight that he was constipated during this period. Unfortunately the heparin had been discontinued before this was appreciated. The data presented in Table II illustrates the reduction in circulating triglyceride which occurs following heparin therapy, and the smaller decrease in the serum cholesterol. As had been repeatedly noted with other modalities, when the initial cholesterol level is higher a larger drop occurs (patient Z.T.).

Discussion. During these experiments the possibility was suggested that injected heparin appeared in the stool in increased amounts, and that it was not entirely removed by the

TABLE I. Daily Fecal Bile Acids, Digitonin-Precipitable Sterols and Dry Weight before and during Heparin Administration.

Subject	Analysis	Before heparin	Days on heparin* 2	4	6
H.E.	Bile acids†	220	378	326	268
	Sterols	390	1070	693	775
	Dry wt	82	88	66	69
Z.T.	Bile acids	296		580	
	Sterols	276		352	
	Dry wt	78		96	
E.S.	Bile acids	221		277	
	Sterols	308		368	
	Dry wt	91		87	
M.S.	Bile acids	456	659	143	
	Sterols	662	1440	319	
	Dry wt	109	70	26	

* Before heparin sample analyzed as a 4-day pool. After heparin stool samples analyzed as 2- or 4-day pools.
† Values of bile acids and digitonin-precipitable sterols in mg, dry wt in g.

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† Lipohepin. Supplied through courtesy of Darwin Labs, Los Angeles, Calif.

TABLE II. Fasting Serum Triglycerides and Cholesterol before and after Heparin. Values in mg %.

Subject	Triglycerides		Cholesterol	
	Before	After	Before	After
H.E.	144	53	220	206
Z.T.	131	103	420	336
E.S.	157	69	253	235
M.S.	146	73	237	204

bile acid extraction procedure. In view of its acidic nature heparin, if present, could affect the bile acid titration. However we were unable to demonstrate any metachromatic or anticoagulant activity in the final extract after dialysis. Furthermore, heparin added *in vitro* to a stool sample did not appear in the ethanolic extract which contains the bile acids and lipid substances. It therefore appears fairly conclusive that the increased acidity demonstrated in the bile acid extraction procedure after heparin injection was not due to the presence of heparin itself.

There is no known direct effect of heparin or lipoprotein lipase upon cholesterol absorption, synthesis or excretion. It is most likely that the enhanced elimination of cholesterol end-products demonstrated in these subjects after heparin therapy occurred as a result of the decrease in circulating triglycerides. When less neutral fat is present in the bloodstream, less cholesterol is needed for this transport function and the excess is excreted, both as bile acids and sterols. It may also be that some of the increase in digitonin-precipitable sterols resulted from decreased cholesterol absorption secondary to lower serum triglycerides although we have no evidence to support this possibility. In any event the findings of this study confirm that serum triglyceride levels affect cholesterol levels although they are undoubtedly not the only factor involved in the genesis of hypercholesterolemia. Heparin, by reducing the neutral fat content of the blood(16-17), lowers serum cholesterol in those cases where hypercholesterolemia is secondary to hypertriglyceridemia. Since the turnover rate of plasma cholesterol is much slower than that of fatty acids(18), it is possible that longer periods of heparinization would result in more profound drops in cholesterol than were seen in these short-term experiments.

The data indicate that when loss of cholesterol from the body is increased by any modality it cannot be assumed that this has occurred via a primary effect upon hepatic or intestinal excretory mechanisms. Thus this explanation of the decrease in serum cholesterol observed when vegetable oils are substituted for animal fats may not be valid(9,10, 19-21). Fecal losses of sterols are more rapidly affected than serum changes(21) but this is probably due to the slow turnover time of plasma cholesterol as compared to the hepatic conversion of sterol to cholic acids, and does not indicate that excretion of greater amounts of cholesterol end-products is the cause of reduction in serum cholesterol. It is more logical that cholesterol is lost from the body in larger quantities than usual whenever there is a decrease in the requirements for it, in any of its functions throughout the organism. The effects observed after injection of heparin and lowering of serum triglycerides support this point of view. It is possible that the differential effects of saturated and unsaturated fats partially are mediated through similar mechanisms(22).

The present investigation should be extended to involve more subjects, on controlled diets, and with longer observation periods on heparin therapy. It would also be advisable to study individuals with hypercholesterolemia who do and do not have an associated elevation of serum triglycerides, to obtain further information on the interrelationship of these 2 lipid parameters. However, since the fecal analyses are laborious, it was desirable to present the results of this preliminary study.

Summary. 1. Serum triglycerides and cholesterol were decreased, and fecal bile acids and digitonin precipitable sterols were increased, after injection of heparin in 4 human subjects. 2. Evidence was discussed which indicates that this effect of heparin upon cholesterol metabolism is a secondary phenomenon resulting from maintained reduction of circulating triglycerides.

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Analysis of Weight and Height of Apparently Healthy Population, Ages 65 to 94 Years. (25251)

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This paper presents a study of average weights at each inch of height for men and women in successive 5 year age groups from 65 to 94 years of age. A review of the literature has failed to reveal a comparable study and we believe that this constitutes the first comprehensive analysis of height and weight in old age. This study represents one facet of a larger survey of blood pressure and health of this old age white population of the United States. Previous publications have dealt with relationship of blood pressure to age and sex (1) of blood pressure to weight and height (2), etc.

Materials and methods. Detailed information concerning collection and statistical evaluation of the data has been presented (1-3). 2925 males and 2694 females were finally accepted for study. Statistical evidence that the sample was reasonably homogenous and representative of aged, clinically healthy, white population of U. S. has been presented(3). Average weight at each inch of height was computed separately for each sex and 5 year age group. A more consistent progression of weight with increasing height was then obtained from these crude data by use of weighted moving average, a commonly employed statistical procedure for this type of data.* The derived figures were plotted and freehand curves fitted to them. No attempt was made to achieve absolute uniformity in profile of these curves.

Results. Table I presents the crude data and number of observations for each inch of height. Height range in males was essentially from 61″ to 73″; while in females from 58″ to 68″. Females consistently weighed less than

* Weight in lbs for each inch of height represents a weighted average of values for 5 consecutive inches from 2 below to 2 above inclusive. Weighting values of 1, 4, 6, 4, 1, were assigned. Average weights based on fewer than 5 frequencies were omitted. With this technique, weight obtained for every inch of height is actually based upon roughly 5 times as many observations as in the crude data and "weighting" tends to reduce distortion occurring at extremes of height due to unequal frequencies.