was observed: A) Excretion of preformed bile acids present in the enterohepatic circulation during 12 hours following cannulation; B) An increased formation of bile acids resulting in a 10-20 fold increased synthesis of bile acids (40-70 mg/day), as compared to synthesis of bile acids in the intact animal (3-4 mg/day), is present from the second or third day.

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Influence of Thyroid Activity on Excretion of Bile Acids and Cholesterol in the Rat.*† (23019)

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It has long been realized that a relationship exists between plasma cholesterol concentration and thyroid activity(1). In general, hyperthyroidism is associated with decreased plasma cholesterol level and hypothyroidism with elevated concentration. Rosenman, Friedman and Byers(2) found biliary cholesterol in rats, increased in hyperthyroidism and decreased in hypothyroidism. On the basis of turn-over studies, Rosenman *et al.* (3) also concluded that thyroid hormone enhances cholesterol destruction. Marx, Gustin and Levi(4) measuring incorporation of D_2O into cholesterol found cholesterol synthesis increased in thyroxine-injected and decreased in thyroidectomized rats. In recent years the direct importance of bile acid metabolism for quantitative aspects of metabolism of cholesterol has been stressed. Thus, work by Siperstein *et al.*(5) and by Bergström and Norman(6) has indicated that bile acids are the main metabolic end product of cholesterol. Thompson and Vars(7) studied the effects of altered thyroid activity on excretion of cholic acid and cholesterol in bile fistula rats. They expected cholic acid output to be high in the hyperthyroid state and low in the hyperthyroid state. However, they found lower values of cholic acid both in the hyperthyroid and the hypothyroid group as compared to control animals. In their experiments they did not determine taurochenodesoxycholic acid, the second bile acid of quantitative importance in the rat (Bergström and Sjövall(8)).

We have recently investigated excretion of cholesterol, taurocholic and taurochenodesoxycholic acid in normal bile fistula rats(9).

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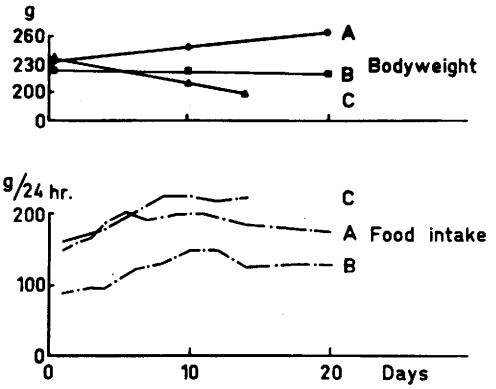

FIG. 1. Total food intake and avg body wt of A, 7 control animals, B, 7 hypothyroid animals and C, 7 hyperthyroid animals.

Using the same technic we have now investigated the influence of thyroid hormone on excretion of these compounds in the bile fistula rat.

Material and methods. White male rats of the institute stock (wt 210-270 g) were fed a synthetic diet consisting of a mixture of concentrate of pig feed and barley meal in proportions 2:1. Hyperthyroid rats were prepared by giving thyroid (Pulv. thyr. sicc. Iodine content 0.225%, AB Leo, Sweden) as .4% of diet for 10 days prior to operation, and after operation. Hypothyroid animals were prepared by giving propylthiouracil (Tiotil, Pharmacia, Sweden) as 0.5% of diet for 3 weeks prior to operation, and after operation. Euthyroid control animals were given the diet without any additions. The common bile duct was cannulated as previously described. The animals were given 0.9% NaCl to drink *ad libitum* during the experiment. Taurocholic and taurochenodesoxycholic acid were determined as previously described(9) using paper chromatographic separation as described by Sjövall. Bile cholesterol was determined as described previously(9).

Results. In Fig. 1 average body weight and food intake of animals in 3 experimental groups are presented graphically. The hyperthyroid rats failed to gain weight in spite of increased food intake. These animals further exhibited such clinical signs of thyrotoxicosis as increased pulse rate and tremors. The hypothyroid rats did not show any weight loss in spite of diminished food intake as compared to controls.

In Fig. 2 the excretion pattern of bile acids in the various groups is presented. In euthyroid animals, total excretion and proportion between taurocholic and taurochenodesoxycholic acids were the same as when the diet consists of oats and white bread(9). In the euthyroid group approximately 15% of total bile acid output is taurochenodesoxycholic acid. The gradual fall in bile acid excretion during the first day of collection is clearly demonstrated. As previously pointed out the amounts excreted during the first 6 or 12 hours represent bile acids present in the enterohepatic circulation. In the hypothyroid group the circulating amount of bile acids as judged from amount excreted during first 12 hours, is somewhat higher than in the control group. Less than 10% of this amount consists of chenodesoxycholic acid. In the hyperthyroid group the circulating bile acid pool is clearly elevated. Thus excretion of bile acids during the first 12 hours is almost twice that found in control animals. Approximately 50% of the amount excreted is chenodesoxycholic acid. Total excretion of bile acids during subsequent days in the hypothyroid group is considerably decreased. As previously pointed out, the plateau level reached on second or third day after operation represents maximal capacity of the liver for bile acid production. In the hypothyroid state this capacity thus seems to be impaired

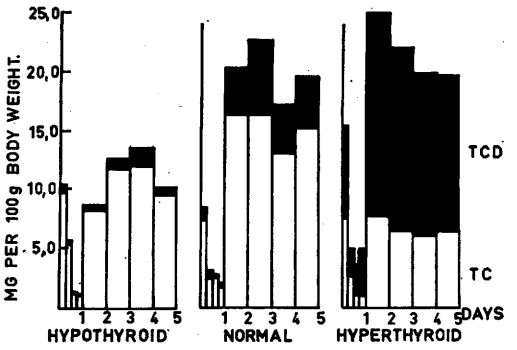

FIG. 2. Excretion of Na-taurocholate (TC) and Na-taurochenodesoxycholate (TCD) in the 3 experimental groups. Values are expressed as mg/100 g body wt. Each column in the diagram represents mean value of 4 animals.

TABLE I. Influence of Thyroid Activity on Excretion of Cholesterol in Bile Fistula Rats.

Hr after operation	Avg excretion of cholesterol (mg/100 g body wt) in rats		
	4 hypothyroid	4 control	4 hyperthyroid
0- 6	.15	.14	1.60
6- 12	.09	.11	2.05
12- 18	.01	.04	.52
18- 24	.03	.09	.64
24- 48	.36	.93	3.44
48- 72	.44	.96	3.91
72- 96	.45	.90	3.70
96-120	.31	.81	2.63

to a considerable degree. In the hyperthyroid animals total amounts of bile acids excreted during the last 4 days of experiment are approximately as large as the corresponding amount in control animals.

From Fig. 2 it also is obvious that the level of thyroid activity has a pronounced influence upon composition of the bile acid mixture formed. In the hypothyroid rats the amount of chenodesoxycholic acid excreted is reduced to less than 10% of the total. On the other hand, in the hyperthyroid state there is a shift towards chenodesoxycholic acid which represents about 70% of total amount excreted as against 15% in normal rats. Thus the decrease of cholic acid output in these rats is fully compensated for by increased formation of chenodesoxycholic acid.

In Table I excretion of cholesterol in the various groups is given. It is seen that hyperthyroid rats excrete far more cholesterol than normal rats. This finding confirms the results obtained by Rosenman, Friedman and Byers(2).

There is a fall in excretion of cholesterol during the first day after operation (Table I). A minimum usually occurs 18-24 hours after operation. This minimum is followed by increased excretion of cholesterol and a plateau is reached on the second day. This minimum can be seen in all groups.

The mechanism behind the findings reported is obscure. It should be stressed that the bile fistula animals are in a highly unphysiological state and further work must be done to be able to compare these results with changes that occur in the intact animal.

Summary. The influence of thyroid activity upon excretion of bile acids in bile fistula rats has been studied. In the hypothyroid state formation of both cholic acid and chenodesoxycholic acid is diminished. In the hyperthyroid state excretion of bile acids is not decreased but the composition is changed in that taurocholic acid is markedly decreased but taurochenodesoxycholic acid increased.

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