SUMMARY.

This study was initiated to try and answer two questions.

1 Can a differentiation be made between alcohol inducible and carbohydrate inducible hypertriglyceridaemia, possibly by a simple test?
2 What is the influence of the regular use of alcohol on hypertriglyceridaemia? Is it possible to obtain data justifying a well defined advice about the use of alcohol in this condition?

The survey of the literature in chapter 1 starts with a description of lipoproteins and hyperlipidaemias. Triglycerides are mainly transported through the plasma packed in large lipoproteins: chylomicrons and very low density lipoproteins. These two classes are produced in the gut and the liver and are cleared from the blood by adipose tissue, muscle and other tissues. The apoproteins that partly form the stabilizing shell of lipoproteins may play a role in regulating the triglyceride transport. When there is a discongruence of lipoprotein production and its removal from the blood, accumulation of one or more classes ensues. This hyperlipidaemia can be classified in different ways. Arguments are presented why the classification according to levels of triglyceride and cholesterol is preferred to that according to lipoprotein electrophoresis. All forms of hyperlipidaemia may be caused by other diseases, then called secondary hyperlipidaemia. The consequences of hyperlipidaemia are separated in direct ones, such as xanthomas and pancreatitis, and indirect ones, such as atherosclerosis. Hyperlipidaemias are mainly treated by changing calorie content and composition of the diet.

In the second part of the first chapter the complex mechanisms involved in triglyceride metabolism are discussed. Disturbances of glucose and insulin metabolism contribute most to an abnormal triglyceride metabolism. Hypertriglyceridaemia sometimes found in obese patients is related to an increased insulin resistance. Carbohydrate induction of hypertriglyceridaemia, which can be translated as the effect of chronic glucose and insulin excess on hypertriglyceridaemia, is a normal phenomenon more clearly expressed in patients with high triglyceride levels at the outset.

The third part of the first chapter deals with alcohol. Alcohol is metabolised in the liver by a specific enzyme, alcoholdehydrogenase. The oxidation of alcohol leads to a change in redox potential causing most of the metabolic consequences of alcohol use.

Overproduction and accumulation of triglycerides in the liver may lead to fatty infiltration. Liver damage may also be caused by a direct toxic action of alcohol and this effect is responsible for pathologic changes such as alcoholic hepatitis and cirrhosis. The triglyceride overproduction in the liver causes hypertriglyceridaemia when alcohol is infused during some hours or when it is given on top of a fixed

amount of calories in the diet. One study reports the separation of two kinds of hypertriglyceridaemia, one ethanol but not carbohydrate inducible, the other carbohydrate but not alcohol inducible. The possibly practical consequences of this differentiation evoked our first question. One of the mechanisms by which alcohol may influence hypertriglyceridaemia, i.e. enhancement of insulin production or glucose intolerance, is discussed in the closing paragraph of chapter 1.

In chapter 2 the patients and methods are described. Seven male hypertriglyceridaemic patients who regularly use more than 100 grams of alcohol per day, form group A. Group B is composed of 8 others using less than 30 grams per day. These two groups were subjected to provocation by carbohydrate rich and isocaloric ethanol rich diets. The performance of a basal glucose tolerance test and one during continuous infusion of alcohol is described. Apart from the usual parameters the corrected insulin response (CIR) is introduced to circumvent the problems of evaluating insulin levels after oral glucose loading. The CIR is deduced from the physiological relation between glucose and insulin after an oral glucose load; it is defined as $CIR = \frac{I.100}{G(G-70)}$. We used the intravenous fat tolerance test as a means to compare the effect of dietary manipulation on the handling of an exogenous fat load.

The results of the dietary provocations are described in chapter 3. The individual fasting triglyceride curves are depicted, accompanied by short case histories. It appears that an increase in the fasting triglyceride level after a carbohydrate rich diet occurs in patients of both group A and B. Thus it occurs irrespective of previous alcohol use. This effect is more pronounced when the initial TG levels are higher. We were surprised to find that the isocaloric ethanol rich diet caused a decrease of fasting TG in the patients tested except in two of seven alcoholics. These two were not CH inducible and may have the 'alcohol inducible' form of hypertriglyceridaemia. They were not separable from the other five alcohol users by other means than dietary provocation, such as a glucose tolerance test during alcohol infusion (ch. 4) or an intravenous fat tolerance test (ch. 5). In conclusion one can say that carbohydrate inducibility does occur in patients with hypertriglyceridaemia who use more than 100 grams of alcohol per day. In most patients isocaloric replacement of nutrients by alcohol leads to a decrease in fasting serum triglycerides. Therefore, ethanol cannot be regarded as a specific hypertriglyceridaemogenic agent in these patients.

The effect of ethanol on glucose tolerance and insulin response is reported in chapter 4. In normal controls ethanol causes an increase of glucose and insulin in the first half hour after glucose loading. This may be due to an increased intestinal glucose uptake. This effect is not present in either of the hypertriglyceridaemic groups. Patients of group A (alcohol users) have a decreased glucose tolerance, probably due to a decreased initial insulin response, during ethanol infusion, while those of group B (non-alcohol users) do not show such an effect.
This might be an expression of beta cell function impairment by chronic alcohol

use, revealed by ethanol. The impaired insulin secretion leading to lipoprotein lipase depletion may play a role in gross hyperlipidaemia during ethanol intoxication.

In chapter 5 the results of the intravenous fat tolerance tests are described. The handling of exogenous fat is impaired in patients with hypertriglyceridaemia irrespective of previous alcohol use. By this test the differentiation between the hypertriglyceridaemic and the normal state is sharper after a carbohydrate rich diet. The negative correlation between serum triglyceride level and removal speed, however, is the same in normals and in patients with hypertriglyceridaemia. After a CH rich diet a decreased removal of triglycerides is a constant phenomenon, whereas the production may either increase or decrease. An ethanol rich diet causes an impairment of exogenous fat removal in hypertriglyceridaemic patients, again irrespective of previous ethanol use.

Regarding the two questions at the beginning of this summary we may conclude

1 Carbohydrate inducibility was observed in both alcohol-using and in non-alcohol-using patients. Two out of seven patients who used more than 100 G alcohol per day showed an alcohol inducibility of the hypertriglyceridaemia. These two could be separated from the others by no other means than dietary (alcohol rich) provocation.
2 Except in these two, isocaloric replacement of nutrients by alcohol led to a decrease of fasting serum triglycerides.

It can be concluded from these observations that it is not necessary to deny the use of alcohol to all patients with hypertriglyceridaemia. When alcohol inducibility is suspected it can be proven by dietary provocation. Apart from this carbohydrate restriction is advisable for all hypertriglyceridaemic patients, irrespective of their previous alcohol use.